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EDITORIAL

GASTRIC ULCER AND FLUORIDE

In a recent issue Czerwinski and Lankosz reported that seven out of 60 retired workers (12%) in a Polish aluminum plant, who showed evidence of low-grade skeletal fluorosis, were afflicted with gastric ulcer; five of them had undergone gastric resection (1). Such a high incidence raises the question whether or not certain kinds of ulcers in the stomach and upper intestinal tract, encountered in a physician's practice, might be related to fluoride. Could our daily diet contain enough fluoride to induce this disease?

A cardinal feature of acute poisoning from inorganic fluoride compounds is severe vomiting, extreme pain in the epigastrium and gastric hemorrhages. At autopsy, ulcerations of the stomach and the upper intestinal tract are almost always present (2). These ulcers are believed to be induced by the corrosive action of hydrofluoric acid which is formed when a fluoride compound comes in contact with free hydrochloric acid which is normally present in the stomach at a concentration of about 0.1 molar (0.2 to 0.4%). Whitford et al. (3) observed that at a pH range of 1.85 to 5.50, fluoride penetrates the bladder tissue by nonionic diffusion of HF. This action was suggested earlier by Roholm who quoted the observations of Wieland and Kurtzahn that fluoride and silicofluoride, under the influence of the gastric hydrochloric acid, form hydrogen fluoride which penetrates the gastric mucosa in a non-dissociated state including corrosive changes. "For absorption of fluoride from low soluble compounds such as calcium fluoride, fluoroapatite and cryolite, the acidity of the stomach plays a decisive role" (4).

Roholm elaborates further on this phenomenon as follows: "The corrosive action of fluoride upon the skin and mucous membranes is not likely to be mediated by its acidity but by the fact that the non-dissociated HF molecule penetrates the epidermis and the mucosa and thus damages the underlying tissue. Therefore, not only hydrogen fluoride and silicofluoride have a corrosive action but all other acid solutions of fluoride as well, particularly bifluorides and silicofluorides" (5).

The degree of damage to the gastric mucosa i. e. the severity of the ulceration is therefore dependent on the amount of the fluoride compound ingested, the tightness of the bond of the fluoride ion in the molecule of the compound, and the acidity of the stomach of the individual patient. Other factors undoubtedly play a part in this action as, for example, the simultaneous presence of fat in the stomach which impedes absorp-

tion into the bloodstream (6).

In chronic fluoride poisoning from long-term intake of minute amounts of fluoride, sufficient hydrofluoric acid may be formed in the stomach to induce the symptoms of an "irritable stomach" namely, gastric pain and tenderness in the epigastrium, nausea, and vomiting. In about 1% of 1,100 pregnant women and young children receiving fluoride tablets (about 1.0 mg daily) for prevention of tooth decay, Feltman and Kosel observed these manifestations (7). These doses correspond to those ingested from the average daily consumption of fluoridated water. Roholm has observed gastric symptoms in 55 (80.9%) of 68 cryolite workers with skeletal fluorosis (8). Waldbott in 50 out of 52 cases of preskeletal fluorosis due to artificially fluoridated water (9).

The delicate lining of the gastrointestinal tract in young children and infants seems to be particularly susceptible to injury from fluoride as suggested by the occurrence of hemorrhages in the stomach and bowels of five infants who received 0.5 mg of fluoride/day in drops, an amount equal to the intake from 500 ml of fluoridated water. As soon as this medication was discontinued the hemorrhages disappeared (10). Gastric hemorrhages were also described in five newborn infants whose mothers had been exposed, during pregnancy, to fluoride fumes in a Czechoslovakian aluminum factory (11).

I have had occasion to review the record and the microscopic findings of a similar, rather dramatic, instance of fluoride-induced stomach ulcers. On August 24, 1962, the chief surgeon of the Ochsner Clinic in New Orleans consulted me about a nine-year-old boy, W.B.B., Jr. Gastric hemorrhages had necessitated the removal of a large portion of the stomach. After the boy's return home from the hospital, he promptly suffered another hemorrhage so severe that a part of the upper bowel had to be removed. This time, careful questioning revealed that several hours before the second incident, the boy had taken a fluoride tablet (0.5 mg) for prevention of tooth decay. The attending physician was convinced that the fluoride tablet had caused the hemorrhages. The child had been taking the tablets twice daily for at least six months.

The microscopic sections of his stomach revealed another remarkable phenomenon--the presence of so-called teleangiectasis, areas of widened capillary blood vessels below the surface of the stomach. This unusual finding further supports the causal relationship to fluoride, since teleangiectasis also occurs on the skin of patients treated with fluorine-containing cortisone ointments, but not if the cortisone molecule lacks fluorine (12).

The question arises whether or not the minute amounts of fluoride which are present in food and in drinking water would suffice to induce gastric ulcers and whether fluoride should be considered one of its causes, a possibility which, to date, has not received attention in the medical literature.

In the average person, such small amounts of fluoride would probably not suffice to adversely affect the gastric mucosa, particularly if buffered by the presence of non-acid food. But what about the patient with hyperacidity? Spasticity of the stomach associated with hyperacidity is usually interpreted by the radiologist as "irritable stomach" and attributed to strain and nervous tension. In my own experience, this condition is not uncommon in fluoridated communities. When these patients are placed on nonfluoridated water their symptoms subside. Whether or not such persistent, long-term "irritability" of the stomach may eventually lead to ulcers in an individual with hyperacidity should be of interest to the gastro-enterologist.

G.L.W.

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THE INFLUENCE OF VOLCANIC FLUORIDE EMISSIONS ON THE SURROUNDING VEGETATION

by

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SUMMARY: Studies in the Mount Etna region show that the continuous emission of gaseous fluoride from active volcanoes subject the surrounding vegetation to uninterrupted fluoride pollution. However, intermittent emission of ash, rich in fluoride, exposes vegetation only temporarily to polluted air as in the case of the volcano Soufriere. Rain washes away the accumulated fluoride from the leaves.

It has been known for a long time that volcanoes are emitting SO_2 into the atmosphere. For example, during the course of normal activity, Mount Etna discharges into the air a quantity of SO_2 equivalent to the total amount emitted by industry in France.

On the other hand, the emission of fluoride gases by volcanoes has only recently been taken into consideration. Our research is the first study of the impact of these fluoride gases on the vegetation in volcanic regions.

At the outset, it is necessary to divide the volcanic activity of fluoride into two categories: the continuous gaseous activity which is encountered near an active volcano such as Mount Etna in Sicily (1) and Kilauea in Hawaii (2), and intermittent activity caused by eruptions. Hekla in Iceland in 1970 and Soufriere in Guadeloupe in 1976 are two examples whereby fluoride reaches the plants, mainly through the ash which is rich in this halogen.

With respect to vegetation, to date only the accumulation of fluoride derived from ash has been studied in Iceland (3, 4, 5).

Accumulation of Fluoride in Vegetation of the Volcanic Regions of Mount Etna

This volcano, situated in north-eastern Sicily is 3274 m high. Ap-

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proximately 30 tons of fluoride are emitted each day, principally as HF.

A series of vegetation samples were first taken at different altitudes solely from the eastern face of Mount Etna by Haroun Tazieff's Team in early summer 1976 (Fig. 1).

The analysis for fluoride in the vegetation gave the following results (Table 1).

Table 1
Fluoride Content of Vegetation Related to Altitude

Number	Location of Sampling	Altitude	F^- Concentration
1	Hornitos n° III, Valle del Leone	2450 m	240 µg/g
2	Before dyke	2390 m	295
3	Lava - flows from fissures	2240 m	281
4	Fault	2120 m	251
5	Fracture	2150 m	195
5 bis	Fracture	2150 m	266
5 ter	Fault	2150 m	281
6	Fault (Citelli Face)	2170 m	249
7	Citelli Face	2000 m	176
7 bis	Citelli Face	2000 m	113

For the first time, we showed that vegetation around an active volcano such as Mount Etna obviously always accumulates fluoride. The concentration of fluoride decreases with the distance from the crater of the volcano. Moreover these levels (between 300 and 100 µgF/g) are higher than those usually found in vegetation which vary between 10 to 20 µgF/g.

In summer 1976, a second series of clover (Trifolium sp.) samples were taken from various sites on Mount Etna by Professor Mazzanti (Fig. 1). The analysis of these samples for fluoride gave the following results (expressed in µgF/g of dry matter) (Table 2).

Table 2
Fluoride Content of Vegetation Related to Locality

Number		Altitude	F^- Concentration
A (Oct. 1976)	Serra la Nave (accampamento francese)	1700 m	8
B (July 1976)	Valle del Bove (Rifugio Menza)	1700 m	102
C (Oct. 1976)	Nicolosi (via Fratelli Gemellaro 14)	700 m	14

Figure 1

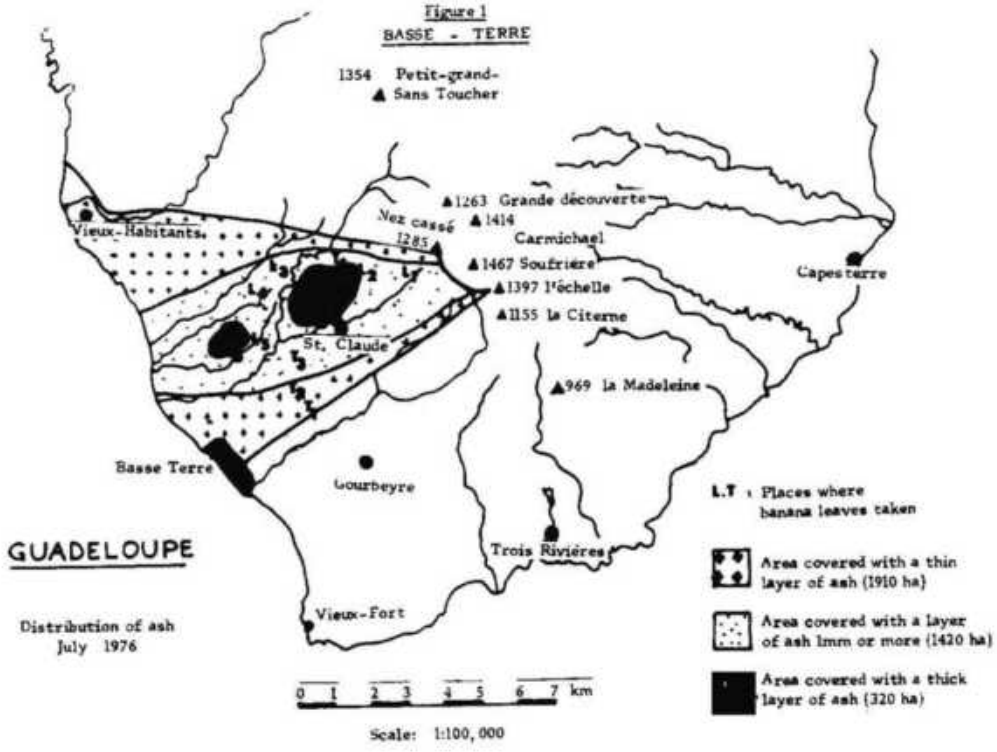
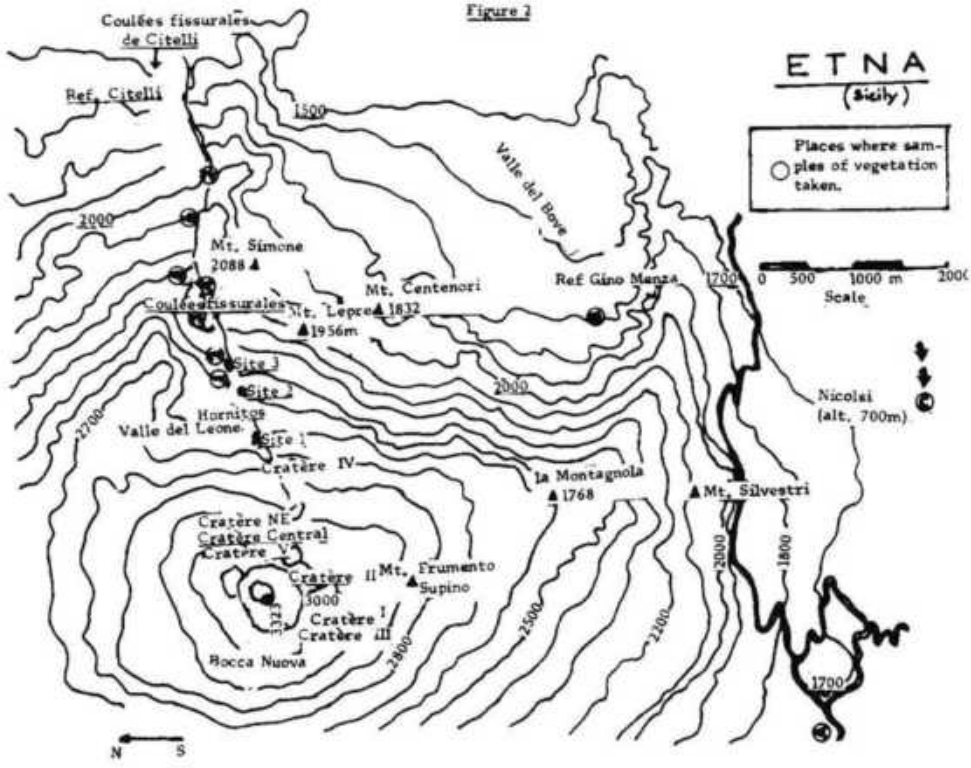


Figure 2



These results show a clear accumulation of fluoride in the vegetation of "Valle del Bove", whereas two other sites were not contaminated by fluoride, although site A is situated at the same altitude.

This difference is explained by the prevailing wind pattern in the Mount Etna region which is northwesterly throughout 300 days of the year, whereas "Valle del Bove" is situated on the southeastern face and is in the direct path of the fluoride fumes. On the other hand "Serra la Nave" and the town of "Nicolosi", situated on the southern face of Mount Etna seem to be protected from the fluoride emanations. "Nicolosi", moreover, is a considerable distance away from the volcano.

La Soufrière (Guadeloupe)

This Guadeloupian volcano is 1484 m high. After large emissions of ash from this volcano in early July 1976, we studied the effects of this ash which was rich in fluoride, on the nearby vegetation, particularly on the banana trees.

Banana leaves as well as bananas were sampled during the summer of 1976 by Haroun Tazieff's Team at different points covered by ash (Fig. 2). The concentrations of fluoride are presented in Table 3 (results expressed in µgF/g of dry matter).

Table 3
F⁻ Concentration in Banana Trees

Places Where Samples Taken	Type of Sample	Fluoride Concentration (µg/g)
L 1	Banana leaf (fourth leaf)	30
L 2	" " "	30
L 3	" " "	8
L 4	" " "	35
L 5	" " "	18
L 6	" " "	20
T 1	" " "	16
T 2	" " "	19
T 3	" " "	27
T 4	" " "	22
T 5	" " "	32
T 6	" " "	33
	Banana peel	24
	Banana pulp	7

At the same time, the volcanic ash contained 727 µgF/g. During the sampling, the quantity of fluoride in the banana trees was normal or slightly higher than normal.

However we think that, immediately after the period when the volcano emitted large amounts of ash rich in fluoride, a certain quantity of this halogen had accumulated in the leaves, but was subsequently washed away by the rain. At the time of sampling, all accumulated fluoride had disappeared.

Two days after the 5/5/70 eruption of Hekla in Iceland, the concentration of fluoride in grass was 4300 μgF/g (3) at sites where the depth of ash was 10mm. Forty days after the beginning of the eruption, the fluoride concentration was less than 30 μgF/g. This decrease was due in part to heavy rain fall during that time. In the first days after the eruption of Hekla, the concentration of water soluble fluoride in the ash varied between 1400 and 2000 μgF/g.

Remarks

The accumulation of fluoride in the vegetation of volcanic regions must be affected by the high proportion of SO_2 present in the atmosphere. In fact, studies carried out in fumigation chambers have shown that in many cases, leaves accumulated less fluoride from air polluted by SO_2 + HF than leaves polluted solely by HF (6). This decrease in accumulation of fluoride could be the result of closure of the stomata of leaves caused by the presence of SO_2 (7). Thus, we are led to believe that the accumulation of fluoride found in the samples of vegetation growing near Mount Etna must be less than that which would have occurred if the volcano had not emitted large quantities of SO_2 along with the fluoride.

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CYTOGENETIC EFFECTS OF HYDROGEN FLUORIDE GAS ON MAIZE

by

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SUMMARY: Maize seedlings of the genotype $\underline{C}^{I}\ \underline{Sh}\ \underline{Wx}$ were fumigated with hydrogen fluoride gas (HF) continuously for 4, 6, 8 and 10 days. Microspore mitosis of the treated plants indicated the presence of fragments and bridges suggesting the occurrence of the phenomenon of breakage-fusion-bridge cycle of McClintock. This phenomenon was later confirmed by the production of endosperm mosaicisms. The period of fumigation was clearly related to the extent of the area resulting from the B-F-B cycle. Recombination values were estimated from F_2 data for the regions C-sh and sh-wx. There was a significant increase in the frequency of crossing over for region I with maximum increase being for the 4 days duration. The recombination value for region II showed no significant deviation from the control. These findings indicate that HF in addition to being a mutagenic agent is also able to reduce crossing over in certain chromosome segments.

Hydrogen fluoride gas (HF), as an air pollutant, has been clearly shown to be a mutagenic agent (1 - 7). In addition to its mutagenicity, HF was reported by Adams (8), and Ledbetter et al (9) to be a cumulative phytotoxicant. The fumigation of tomato plants and maize seedlings with HF in concentrations below those needed to cause visible injury induced permanent chromosomal changes (1 - 7). Recently, Jagiello and Lin (10) showed that the treatment of mouse, sheep, and cow oocytes, in vitro, with different concentrations of NaF produced meiotic abnormalities similar to those reported by Mohamed, Applegate and Smith in onion root-tip chromosomes (5). These findings supported the suggestions of Muller (11) that some toxic substances which occur as air pollutants, such as HF, may give rise to chemical reactions that result in the formation of mutagens.

In view of the cytological results obtained in maize microsporocytes after fumigation of seedlings with HF (3), the objective of the pre-

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sent studies has been to follow such cytological abnormalities in the post-meiotic mitotic division of the microspores in the treated plants, meiosis in F_1 microspores and to determine the effect of HF treatment on recombination values.

Materials and Methods

Maize kernels of the genotypes $\underline{C}^I$ Sh Wx and C sh wx were obtained from the Maize Genetics Cooperation. In all of the studies, the recessive genes, including C, which is recessive to $\underline{C}^I$, were carried by the seed producing plants. The kernels from both genotypes were germinated in the greenhouse in polyethylene pots containing a horticultural soil mixture.

The procedure of fumigation and treatment was described previously (2). The concentration of the fluoride gas was kept close to 3 µg/m^3. The fumigation of the $\underline{C}^I$ Sh Wx seedlings was run for 10 days; the first treated plants were removed after 4 days and subsequently plants were removed after 2-day intervals. Control runs were always made simultaneously with treatment runs. After each treatment period the treated and control plants were transplanted into the field. Microsporocyte samples were collected from the fumigated and control plants for microspore mitotic divisions. At pollen shedding, pollen grains were collected separately from each treated and control plant and used to pollinate the recessive seed carrying parent. After the mature harvested F_1 ears were dried and shelled, the kernels were classified according to the different recognizable pheontypes (12 - 14).

A sample of seeds from each of the F_1 populations was planted in the field to produce F_1 plants. Microsporocytes were collected from each plant for meiotic analysis. At the time of sexual maturity the F_1's from treated and control plants were selfed to determine any change in recombination values for the chromosome nine marker genes under investigation: $\underline{C}^I$-C (colorless vs. colored aleuron), Sh-sh (nonshrunken vs. shrunken endosperm), and Wx-wx (non-waxy vs. waxy endosperm).

Results and Discussion

A. Meiotic Analysis: Anaphase and telophase studies of the microspore mitosis of the treated plants showed the presence of dicentrics with or without fragments as well as fragments alone (Figs. 1 - 3). The presence of such chromosomal abnormalities may well be explained on the basis of reunion of broken chromatin to form the dicentrics. The presence of heterozygous inversions (3) in the treated plants and the occurrence of crossing over within the inversion loop might explain such findings. Fur-

Figures 1-3
First Mitosis in the Microspores

Fig. 1 - Anaphase with a fragment (indicated by arrow).

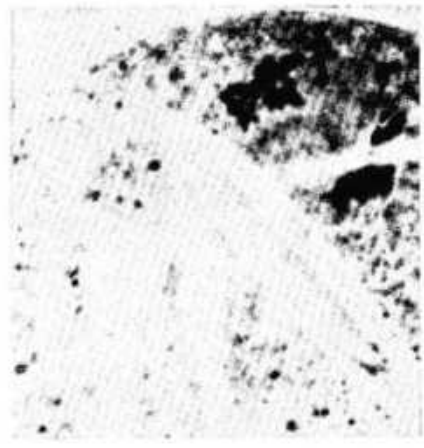

Fig. 2 - Late anaphase with the fragment lying in the equatorial plane.

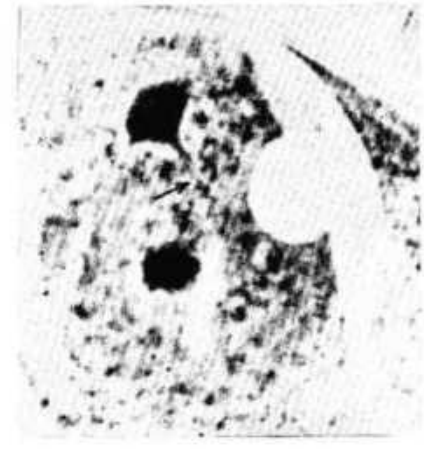

Fig. 3 - Telophase showing a broken bridge.

thermore, the fact that HF affects enzymatic activities in plants (9) might cause a delay in meiotic cycle. According to Rees (15-16) and Darlington and Haque (17), microsporocytes delayed in meiotic activity can exhibit chromosomal breakages. Such breakages may eventually lead to the formation of structural changes and fragmentation. It can be seen from Fig. 1 that the acentric fragment lies in the cytoplasm. This indicated that this fragment was produced either in the first or the second meiotic division and was carried into the telophase II nucleus and later to the post-meiotic division. This would happen if the acentric fragment was close enough to be surrounded by the newly developed nuclear envelope. The mode by which fragments could become included in a telophase II nucleus was explained fully by McClintock (18). Since HF can cause stickiness of chromosomes (3), the acentric fragments may get attached to any chromosome and be included within the nuclear boundry. This is another method by which the acentric fragment might be transmitted to the following generation.

Cytological studies on the F_1 plants microsporocytes confirmed the presence of translocations as well as inversions reported earlier by Mohamed (2).

B. Endosperm Mosaicisms : The cytological basis and behavior for endosperm mosaicisms was provided by McClintock (18-19) with the discovery of the B-F-B cycle. In maize endosperm, this phenomenon is recognized by the different patterns that appear, depending upon the endosperm genic markers in use in the experiment.

The data dealing with endosperm mosaicisms derived from the chromatid B-F-B cycle initiated from the breakages produced in either the pre-meiotic or meiotic cycle by HF treatment is given in Table 1. Illustra-

Table 1
Frequency of Spotted Areas and Mosaics
in Kernels due to the B-F-B Cycle in Percentage

Treatment in days	Spots 1	2	3	>3	Small areas	Medium & Large areas	No. Kernels
4	27	21	11	15	25	1	411
6	11	16	14	40	17	2	597
8	14	17	12	27	26	4	167
10	9	18	13	22	26	12	161

tive mosaic kernel types are shown in Figures 4 - 9. Table 1 shows that the longer the period of fumigation the larger the mosaic area resulting from occurrence of the B-F-B cycle. Such findings agreed with those of Bianchi and Giacchetta (12) in their studies of mutations induced by x-rays in maize. Whereas they reported a linearity with dose, the current studies with HF failed to indicate such an effect, at least after 8 days of continuous fumigation. The regression coefficient was 1.87 unit/treatment. This value holds true for the three shorter periods of treatment but not for that of ten day duration.

The presence of a high frequency of spots (Table 1) was evident in the shorter periods of treatments. This could be attributed to the delayed effect of the B-F-B cycle in the endosperm tissue in the shorter periods of fumigation. Such delayed reactions have been verified cytologically by Rhoades and Dempsey (20) in maize. On the other hand, Neuffer, Jones and Zuber (21) stated the $\underline{C}^1$ gene produces few dots (spots) in combinations with $\underline{C}$ allele. However, in the current studies the number of spots do vary according to the duration of treatments even with the same genic combination.

C. Linkage Intensity: The linkage data was based on F_2 ears in which the different allelic genic markers showed no distortion or significant deviation from the 3:1 ratio. The chi-square test for homogeneity showed that such selected ears from each treatment were homogeneous. Table 2 gives the frequencies of crossing over, using the product method, for the gene markers $\underline{C}$-$\underline{sh}$-$\underline{wx}$. It can be seen from these data that in each treatment for region I ($\underline{C}$-$\underline{sh}$) there was a significant increase in the frequency of crossing over with the maximum increase being for the 4 days (9.7%) (Table 3). The increase was not of a high magnitude for the other

Figures 4 - 9
Kernels Illustrating Endosperms Mosaicisms

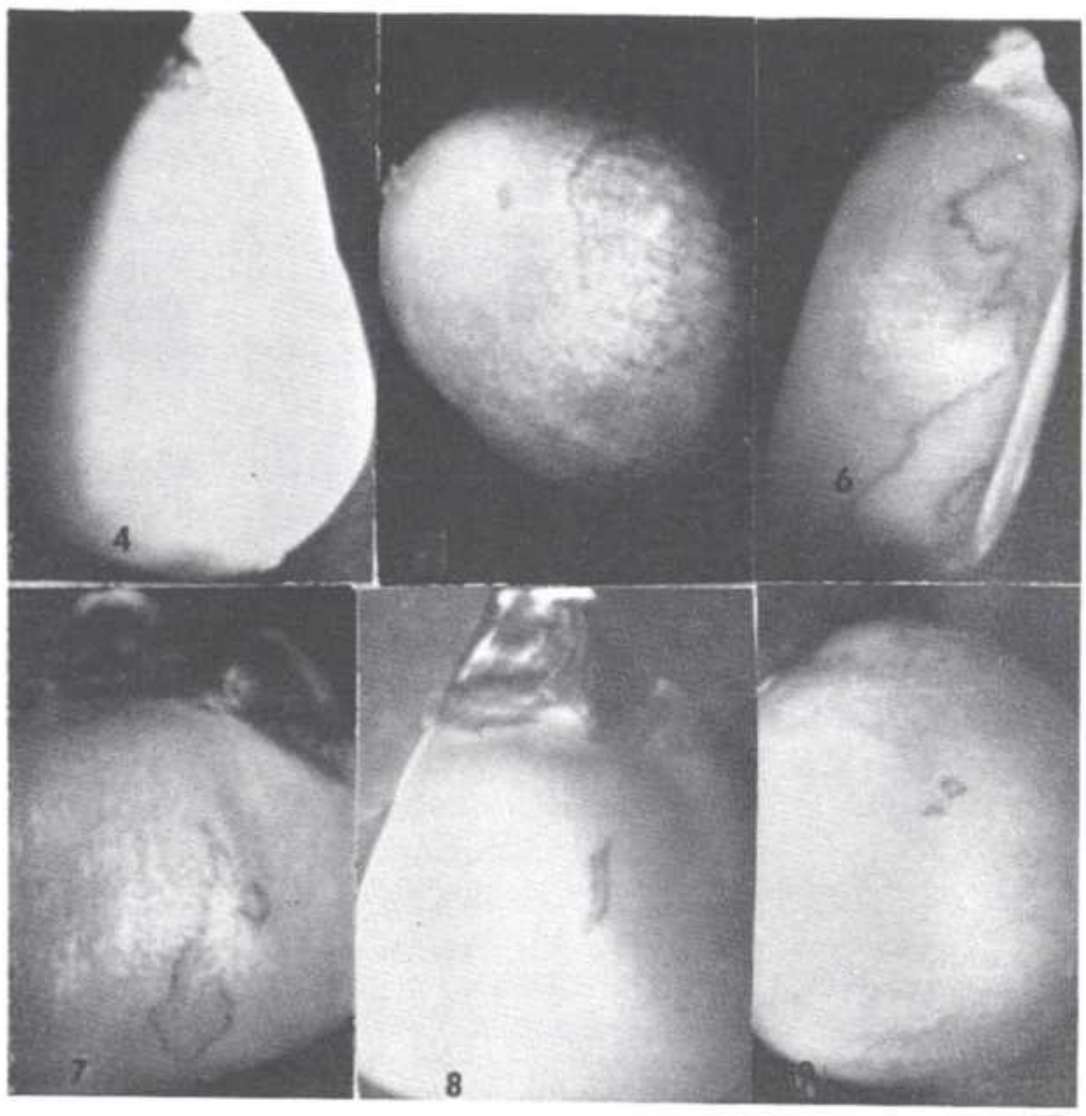

Fig. 4 - Control, kernel is colorless due to the presence of C^I. Figs. 5-7 - Large and medium colored (C). Figs. 8-9 - Small sector or sectors produced by relatively late occurrence of the breaks and the loss of C^I.

treatments, it was nevertheless significant among the different durations of treatments except for the 4 days. The significant reduction in the crossing over frequencies in the 6, 8, and 10 days of treatments, when compared with 4 days fumigation, may be attributed to the induction of minute chromosomal changes or to asynaptic mutants as pointed out by Mohamed (3). On the other hand, the crossover values for region II (sh-wx) did not deviate significantly from the control. According to Mather (22), the total amount of crossing over in the genome is relatively constant. However, a decrease of crossing over in one or more chromosomes due to structural changes would be balanced by an increase in crossing over in other regions. Since the current material exhibits inversions (3), then the reduction in crossing over due to the presence of these heterozygous inversions will be compensated for by the increase in crossing over in another chromosome or

Table 2
Recombination Values, in Percentage, for the Different Treatments

Treatment	Ear No.	Region C-sh	Region sh-wx	Region C-wx	Number of kernels
Control		5.5 ± .8	25.5 ± 1.8	27.0 ± 1.8	851
4 days -	1	13.0 ± 1.9	19.7 ± 2.1	27.5 ± 2.8	379
	2	22.5 ± 3.5	26.5 ± 3.9	30.0 ± 4.1	189
	3	12.7 ± 2.3	21.0 ± 3.0	27.5 ± 3.5	237
	4	12.0 ± 2.6	29.2 ± 4.1	35.5 ± 4.1	178
	5	16.0 ± 1.9	32.0 ± 3.9	31.0 ± 2.8	420
6 days -	1	12.5 ± 1.7	25.5 ± 2.4	25.5 ± 2.4	446
	2	6.5 ± 1.9	22.7 ± 3.7	25.5 ± 3.9	172
	3	8.1 ± 1.6	27.0 ± 3.0	27.0 ± 3.0	313
	4	8.1 ± 1.6	27.8 ± 3.1	25.1 ± 2.9	309
	5	9.1 ± 2.2	24.0 ± 3.8	24.7 ± 3.9	173
	6	7.4 ± 1.3	32.1 ± 2.8	28.8 ± 2.7	427
8 days -	1	10.3 ± 1.8	22.9 ± 2.7	32.0 ± 3.1	338
	2	7.5 ± 1.5	26.7 ± 2.9	31.0 ± 3.2	321
	3	7.1 ± 1.4	22.1 ± 2.6	23.0 ± 2.7	339
10 days -	1	9.0 ± 1.3	32.7 ± 2.7	34.3 ± 2.8	472
	2	5.6 ± 1.2	26.5 ± 2.8	27.1 ± 2.8	361
	3	12.4 ± 1.9	25.9 ± 2.8	30.4 ± 3.0	358
	4	13.4 ± 2.6	27.2 ± 3.7	31.0 ± 4.0	205

* ± Standard Error

region. Similar results were obtained by Redfield (23) in Drosophila. She noticed increases in crossing over in the distal y^2-w^2-spl end of the chromosome when the second and third chromosomes were heterozygous for inversions.

The current data also showed that the region most sensitive to HF is the distal segment involving C-sh. Similarly, Lifschytz (24-25) demonstrated that a rise in temperature increased crossing over in the region car-y^+ in Drosophila melanogaster. He attributed this increase in crossing over to the proximal or intercalated heterochromatin in this region; whether this phenomenon relates to region I, in our present studies, is hard to say. It is well known that DNA replication is somewhat delayed in the heterochromatin region thus reducing the frequency of crossing over under normal conditions. Therefore an alternative explanation for the genetic be-

Table 3
Summary of the Pooled F_2 Data for the Recombination Values (r/c), in Percentage for the Different Treatments

Treatment		Region C-sh	Region sh-wx	Region C-wx	Number of kernels
Control	r/c	5.5 ± .8*	25.5 ± 1.8	27.0 ± 1.8	851
4 days	r/c	15.2 ± 1.0	25.7 ± 1.3	30.3 ± 1.5	1403
	diff.	9.7	.18	3.3	
6 days	r/c	8.6 ± .7	26.5 ± 1.2	26.1 ± 1.2	1840
	diff.	3.1	1.0	-.9	
8 days	r/c	8.3 ± .9	23.9 ± 1.6	28.7 ± 1.7	998
	diff.	2.8	-1.6	1.7	
10 days	r/c	10.1 ± .8	28.0 ± 1.4	30.7 ± 1.5	1396
	diff.	4.6	2.5	3.7	

havior of the region C-sh may be offered. Cytologically this region is composed of contracted chromatin represented by heavy chromomeres (21) and thus will be delayed under normal conditions in DNA replication. Chromosome breakage in this region followed by reunion of broken ends or merely uncoiling of the chromomeres by HF will increase the physical length of this region leading to an increase in crossing over. This occurs within 4 days of fumigation. On the other hand, with longer periods of HF fumigation the same phenomenon might occur. However, the frequency of crossing over would be expected to be less than that obtained within the 4 days of fumigation, since fumigation of longer duration produces minute deficiencies, cryptic structures or asynapsis between homologous chromosomes (3).

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HYDROFLUOROSIS IN THE FLUORIDATED MILWAUKEE AREA

by

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SUMMARY: The histories of 20 patients with preskeletal fluorosis due to artificially fluoridated water were analyzed. Fourteen (70%) complained of polydipsia. All presented a wide spectrum of symptoms among which polydipsia (70%), general pruritus (55%), headaches (60%) and gastrointestinal symptoms were the most prominent. None of these subjects had been aware, while ill, that fluoride was being added to their drinking water. All made a full recovery when they discontinued the use of fluoridated water for drinking and cooking their food.

In a previous report (1) I presented the history of eight cases of preskeletal poisoning from fluoridated water in the Milwaukee area. Another group of 20 patients interviewed August 1972 provided additional data which are herewith reported. The following are some of the case histories:

Case 4, L.Z., a 60 year old housewife of Cudahy, Wisconsin (fluoridated November 7, 1966), developed a pruritic skin eruption whenever she was bathing. This was followed within a few days by pain in the mid-abdomen, nausea, vomiting and frequent watery stools, by dryness in the throat and marked polydipsia and polyuria. She also had intermittent headaches involving the whole head which gradually became persistent. The patient became listless and her energy waned increasingly. These symptoms continued for about 6 weeks. Then she learned that others were similarly affected from drinking the recently fluoridated Cudahy water. She switched to spring water (0.1 ppm) for drinking and cooking and used melted snow for bathing. Within a week she noted marked improvement and shortly thereafter all the adverse symptoms disappeared.

Case 7, K.D., a 31 year old woman moved at age 18 in 1960 to Milwaukee (fluoridated in August 1953). Within a few days she experienced pains throughout the abdomen which gradually increased in severity; she also had persistent painful urination with frequency and urgency. This condition lasted for nine months when she moved back to her parent's home in Cudahy, which, at that time, was unfluoridated. She made a complete recovery within less than 2 weeks. Two years later she returned to Milwau-

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kee. The abdominal pains recurred promptly with increasing severity and persisted day and night independent of eating. She also had experienced episodes of nausea, frequent constipation alternating with diarrhea. She became unusually thirsty and soon was drinking more than 4 gallons of water a day. She had constant headaches, localized bilaterally in the frontal part of the head and pain in the lower back and in the thighs. Physical exhaustion and muscular weakness in both legs made it difficult for her to walk. When she was no longer able to stand up, she consulted a physician who admitted her to a hospital for diagnostic studies where she was under observation for one month. While in the hospital she had a convulsion suggestive of a grand mal seizure, characterized by spasticity in legs and arms, blurred vision and inability to talk. After discharge from the hospital her illness remained undiagnosed and unimproved. At home, the convulsive episodes recurred two to three times a week. In 1968 she learned that others had had the same complaints and had improved upon elimination of city water. She followed the same course. She started to improve as soon as she used low fluoride (0.1 ppm) spring water for cooking and drinking. Within 4 weeks she had fully recovered her health. As an experiment she abandoned the spring water and replaced it with fluoridated water. All the symptoms from which she had suffered during the previous 5 years returned within a few days and she developed another epileptiform seizure during which she was temporarily paralyzed. After she switched back to spring water she regained her health.

Case 20, E.A., age 33, developed the symptoms of chronic fluoride intoxication described in Table 1 soon after Cudahy fluoridated its water supply in November 1966. He drank over 4 gallons of fluoridated water a day. His intense thirst was accompanied by persistent dryness in the throat. He suffered every adverse effect listed in the chart. In 1971, after switching to spring water (0.1 ppm), his thirst was quenched by 2 to 3 quarts of this water daily. Simultaneously all untoward effects cleared up within a week.

In 1972, he was hospitalized several times because of an earlier industrial injury to his back. On each occasion, when he was in the hospital and was drinking fluoridated water all symptoms recurred. As soon as he again obtained and drank only unfluoridated water the symptoms disappeared.

Discussion

The syndrome which these patients described is identical with that recorded previously by Waldbott (2-4) and by the author (1).

This presentation is based entirely upon case histories. No laboratory data or examination findings are available on the 20 cases. It should

Table 1

	Initials, Age, Sex	Polydipsia	Chronic Fatigue	Pruritus	Dermatitis	Headaches	Vertigo	Dysuria	Muscle spasms	Abdominal pain	Nausea	Vomiting	Constipation	Diarrhea	Convulsions	Paresthesias	Additional Manifestations
1	KB 30 F	X	X		X	X				X							
2	DB 10 F			X		X					X	X					
3	DEB 8 F			X		X					X	X					
4	LZ 60 F	X	X	X	X	X				X	X	X		X			
5	GV 50 F			X	X												
6	NB 39 M	X	X	X						X				X			Dry skin
7	KD 37 F	X	X			X	X	X		X	X		X	X	X	X*	Back pain
8	JB 40 M	X	X						X							X	Wt. loss 33 lbs
9	SB 11 F				X												Frequent otitis, Anemia
10	JS 27 F	X	X	X		X		X		X			X			X	Sinus disease Stomach ulcer
11	LK 77 M			X													
12	MW 45 F	X	X		X				X								Anemia, Wt. loss 34lbs
13	EM 48 M	X	X													X	Vertigo
14	JP 40 M	X	X					X	X	X				X			
15	ST 42 F	X	X	X	X	X	X		X								Hypothyroid
16	DD 43 F	X	X			X				X				X		X	Facial neuralgia
17	PA 34 F		X	X		X			X		X	X				X	Hypertension, Chronic glomerulonephritis
18	VG 49 M	X	X			X	X		X							X	Kidney stones
19	MC 30 M	X	X	X	X	X			X	X		X		X		X	Sinus disease
20	EA 33 M	X	X	X	X	X	X	X	X	X	X	X		X		X	Stomatitis

*Convulsions and intermittent paralysis

be noted, however, that in the assessment of any kind of poisoning the history is most significant. The recorded events occurred with such constancy in the 20 cases that their relationship to fluoridated water cannot be questioned. Since none of the patients were aware that their drinking water was fluoridated and since none were familiar with the manifestations of the disease which they described, the account of their illness constitutes evidence as valid as any double blind procedure. Indeed, several patients not thoroughly convinced that something in their drinking water was causing their illness, resumed drinking fluoridated water with the result that their illness promptly recurred.

That the symptoms were not due to any other illness is shown by the fact that complete recovery followed elimination of fluoridated water.

Some of the manifestations noted in Table 1 such as loss of weight, the neuromuscular changes, stomatitis, visual disturbances noted by other authors (3, 5), are of a serious nature of the kind which cannot possibly be induced by malingering. Most remarkable is the polydipsia, a major complaint, which is well documented as the result of fluoride intake (6-8). Fourteen of the 20 cases drank excessive amounts of water, four of them in excess of 4 gallons a day. The patients observed that the more water they drank, the greater was their thirst. The patients with polydipsia appeared to be more debilitated than the six persons who drank only 3 to 4 quarts of water a day. A universal complaint was the extreme chronic fatigue, in some to the point of exhaustion--a feature common to chronic poisoning from many other agents. Twelve had gastrointestinal symptoms.

The seizures described by patient #7 fit the description of tetaniform convulsions due to hypocalcemia as recorded frequently in acute fluoride poisoning and described by Waldbott (9) as a manifestation of chronic poisoning from fluoridated water. The paresthesias in arms and legs in eight patients are indicative of damage to the anterior horns of the spinal cord as described in a case of advanced fluorosis by Franke (10).

Dreisbach's "Handbook of Poisoning: Diagnosis and Treatment" 6th edition 1969 - page 165 (11), a standard text in medical schools states: "B. Chronic poisoning: (From inhalation or ingestion.) Intake of more than 6 mg. (1/10 gr.) of fluorine per day results in fluorosis. Symptoms are weight loss, brittleness of bones, anemia, weakness, general ill health, stiffness of joints, and discoloration of the teeth when exposure occurs during tooth formation."

One quart of water fluoridated at 1 ppm contains approximately 1 mg of fluoride. Fourteen of the above-described cases were drinking between 8 and more than 10 quarts of fluoridated water daily, thereby they were ingesting 8 to more than 16 mg of fluoride daily. According to McClure, 4 to 5 mg per day is the upper limit of safety (12).

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THE AVAILABILITY OF FLUORIDE ION FOR NEWBORN BABIES IN A NONFLUORIDATED DRINKING WATER COMMUNITY

by

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SUMMARY: On ten infants, urinary fluoride determinations were made on day 1, 4 and 7 after birth. The values were compared with those of ten adult patients from the same hospital. During the first few days after birth the mean urinary fluoride concentrations are remarkably constant (3.7 ± 1.5 to 4.6 ± 0.8 µ mol/l), but they increase significantly by the end of the first week (0.97 ± 0.44 µ mol/l). Ionized fluoride concentrations of maternal milk

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also showed a slight tendency to increase.

According to Shen and Taves (1) ionized plasma fluoride easily crosses the placenta, at least at term. Earlier, Gedalia et al,(2) have reported that urinary fluoride concentrations of pregnant women were significantly lower than in non-pregnant controls. Ionized plasma fluoride concentrations of pregnant mothers decrease significantly during pregnancy; they are lowest near delivery (3). After delivery, however, ionized plasma fluoride concentrations of the mothers seem to return, in a few weeks, to the control levels (3).

The decrease in the ionized plasma fluoride concentrations of pregnant women might indicate that the customary diet during pregnancy does not contain enough fluoride to keep the mothers' plasma fluoride at the usual level. The reason for this decrease, in our opinion, is not the increasing plasma volume during pregnancy because we have shown (3) that during edematous conditions ionized plasma fluoride concentrations increase.

It is probable that the availability of the fluoride ion for the fetus is desirable at least during late pregnancy (1), when the teeth have started to retain minerals. However, little is known about the availability of fluorides for newborn infants whose almost only source is maternal milk which, according to Ericsson (4), is low in fluorides. Thus the aim of the current study is to determine the availability of fluorides for newborn babies during the first week of life.

Materials and Methods

As shown many times previously (5, 6) urinary fluoride concentrations correlate with the amount of absorbed fluorides. Therefore, we collected the urine of ten newborn boys on the first, fourth and seventh day after birth. The infants in our hospital are given boiled tapwater with glucose, about 60 ml on the first, 60-180 ml on the fourth and 60-180 ml on the seventh day after birth. All samples were gathered and stored in plastic test tubes, bags or bottles. From the urinary samples we measured the ionized fluoride concentrations and calculated the amounts of fluoride excreted daily. Ten adult patients from the same hospital were used as controls. The samples had been taken 2 to 3 months earlier in connection with another investigation.

We used the electrometric method for urinary fluoride analysis, with slight modification, which was first described by Singer et al. (7). The diluted urinary sample was buffered with acetate buffer (9). The recovery was 96 ± 3% (S.D.) and the accuracy of double determinations ± 0.07 (S.D.) μmol/l. No handling with perchloric acid was performed (8).

We also tried to measure the fluoride concentrations of maternal milk electrometrically, which means that only the ionized form of fluoride could be calculated. One milliliter of maternal milk was pipetted on a microsample disc (Orion cat. no. 92-0014) and two drops (0.06 ml) of acetate buffer (pH 4.5) was added before measurement (9). The recovery of this method was 86 ± 6% (S.D.) and accuracy of double determinations ± 0.08 (S.D.) µmol/l.

Results

The urinary fluoride concentrations and the daily excreted amounts are given in Table 1. The mean urinary fluoride concentrations of the infants are remarkably constant from the very first day following birth (between 3.7 ± 1.5 (S.D.) µmol/l and 4.6 ± 1.8 µmol/l), but the daily excreted amounts of fluoride increase significantly from the first day (0.26 ± 0.20 µmol/24 hours) to the fourth day (0.78 ± 0.37 µmol/24 hours) after birth. At the end of the first week, the infants excreted 0.97 ± 0.44 µmol/24 hours, which is significantly more than on the first day after birth.

The ionized fluoride concentrations of maternal milk also show a slight tendency to increase, which is not statistically significant. The mean ionized maternal milk fluoride concentrations were 0.51 ± 0.23 µmol/l on the third day, 0.59 ± 0.21 µmol/l on the fifth day and 0.61 ± 0.28 µmol/l on the seventh day after delivery. The numbers of samples were 9, 8 and 8 respectively.

Discussion

In the community where the samples were gathered, the drinking water is low in fluorides (about 0.2 ppm or 0.1 to 0.3 ppm from different sources). The mean fluoride concentration in adult urine is about 17 ± 7.9 µmol/l and renal excretion 20 ± 6.2 µmol/24 hours (n=10)(partly unpublished data). The mean age of these adult patients was 38 years. The results obtained from the infants in the current study show considerably lower values than those from adults. When considered pharmacologically the results are not comparable directly. A newborn infant weighs about 1/20 as much as an adult. Thus the daily amount of fluoride excreted by the infants should also be 1/20 of the amount obtained from adults, or 1 µmol/24 hours excreted daily. We found 0.97 ± 0.44 µmol/24 hours at the end of the first week of life. The situation is different, when the urinary fluoride concentrations are compared. The infants excreted 265 ml (mean) of urine on the seventh day, which is about 1/5 of the amount of urine excreted by adults (mean 1263 ml) in the hospital. If this fact is kept in mind, the urinary fluoride concentrations of newborn infants also correlate with the results obtained from adults (3.7 µmol/l in infants and 17 µmol/l in adults).

Table 1
Urinary Fluoride Concentrations and the Daily Amounts of Fluoride Excreted in Ten Newborn Infants

Infant	DAY I Urine Vol. (l)	DAY I Urinary F^- µmol/l	DAY I Excretion of F^- µmol/24 hrs	DAY IV Urine Vol. (l)	DAY IV Urinary F^- µmol/l	DAY IV Excretion of F^- µmol/24 hrs	DAY VII Urine Vol. (l)	DAY VII Urinary F^- µmol/l	DAY VII Excretion of F^- µmol/24 hrs
LA	0.100	1.5	0.15	0.180	2.8	0.50	0.260	0.98	0.25
MA	0.030	4.6	0.14	0.220	4.6	1.0	0.270	3.5	0.95
KU	0.113	4.6	0.51	0.223	6.7	1.5	0.380	4.6	1.7
EN	0.075	3.0	0.23	0.215	3.1	0.68	0.225	2.7	0.62
LE	0.070	9.8	0.69	0.120	8.8	1.1	0.240	7.0	1.7
RO	0.090	3.5	0.32	0.240	3.9	0.94	0.260	3.5	0.91
OJ	0.030	2.9	0.087	0.190	4.2	0.80	0.280	3.9	1.1
SJ	0.050	3.2	0.16	0.175	3.9	0.70	0.210	4.2	0.88
EL	0.099	2.8	0.28	0.122	3.9	0.47	0.270	3.4	0.92
KA	0.022	3.2	0.070	0.046	3.9	0.18	0.250	2.8	0.70
Mean ± S.D.		3.9 ± 2.3	0.26 ± 0.20		4.6 ± 1.8	0.78 ± 0.37***		3.7 ± 1.5	0.97 ± 0.44**

** = the amount of fluoride excreted is significantly higher ($p < 0.01$) than on the first day of life.
*** = the amount of fluoride excreted is significantly higher ($p < 0.001$) than on the first day of life.

The ionized fluoride concentration in maternal milk is probably the same as the ionized fluoride concentration in maternal plasma (4). Thus the mother acts as an efficient "fluoride filter" for the infant. Even in areas, where the drinking water contains more fluoride, the infants obtain only small amounts of fluoride in maternal milk, if ionized fluoride concentrations are the same in plasma as in milk. Although all infants of this study were fed with human milk, which is low in fluoride, nevertheless the infants obtained a suitable amount of fluoride by the end of the first week of life. Thus, the above-mentioned daily amount of boiled tap water is enough to keep the urinary fluoride levels of newborn infants comparable with those obtained from adults.

Acknowledgment

During the investigation the result of one urinary volume was lost. The missing value was replaced by the mean value of the nine other volumes of the same day.

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METHODS OF MEASUREMENT OF MINUTE QUANTITIES OF FLUORINE

A STUDY OF THE DIFFUSION OF FLUORINE SUPPLIED TO DENTAL TISSUES BY AMALGAMS

by

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SUMMARY: Fluoride diffusion in dental tissues was measured by micro-probe analysis. The fluoride supply is carried out in vivo by various compounds of fluorides added to conventional amalgams. This method differs thus from previous work (topical applications, electrophoresis, or fluoride solutions) because fluoride penetrates from amalgams either in dentine or in deep enamel, which are more susceptible to caries than superficial enamel. These experiments reveal a rapid penetration of fluoride into dental tissues, which may be characterized by an apparent diffusion coefficient of about 10^{-10}cm2/s.

Introduction

The number and the diversity of analytical methods of measuring fluorine in minute quantities are indicative of the great interest aroused by this halogen in the practice of dentistry. The analytical procedures vary greatly, starting with polarigraphic techniques (half-wave potential of the Uranium V - Uranium III system) and include amperometry based on Pd, Zr, and other electrodes.

Spectrographic analysis is most commonly used for measurements of the order of one part per million. This method is based on five means of detection, namely discoloration of a reagent (1); formation of a ternary complex; liberation of chloranilic acid; catalytic action of fluoride ions on the slow reaction between methylthymol blue (or xylenol orange) and zirconium IV; and spectrofluorimetry.

The development of ion-specific electrodes during the past years has led to the production of the lanthanium fluoride (LaF_3) membrane e-

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lectrode that provides excellent selectivity (2).

Finally, the techniques provided by the Castaing micro-probe in the field of micro-analysis complete the already numerous possibilities of fluorine measurement. We used this method to study the phenomenon of diffusion of fluorine introduced into dental amalgams in the form of fluoride.

Experimental Methods

Electronic Micro-probe Analysis: Analyses were carried out on a Camebax instrument (Cameca, Courbevoie, France), a modular instrument system by scanning electron microscope (M.E.B.) and electronic micro-probe analysis. This apparatus, which possesses both the characteristics of the micro-probe and of a M.E.B., has the great advantage of inclined X-spectrometers. With very precise focusing the analysis is little disturbed by the shape of the object. Thus we have been able to take measurements of teeth immediately after cutting them, avoiding later polishing the mechanical effect of which might have led to contamination of the constituent structures of the tooth.

The operation of the instrument in micro-analysis is identical to that of the traditional Castaing micro-probe (3).

We used two types of analyses namely, 1) a continuous analysis over a linear trajectory which provides data on the general shape of concentration gradients as a function of penetration, and 2) point by point counting which provides a means of tracing precise concentration-penetration gradients (within corrections for fluorescence and absorption).

Preparation of Samples: Rectangular cavities (6 mm X 3mm X 5 mm) are cut on dog's teeth (in collaboration with the Laboratory of Physiology and the Veterinary School of Lyon) and on human teeth (in collaboration with the U.E.R. of Odontologic Science at Lyon). "Dentoria" (Cachan, France) amalgams are used for obturation. They correspond to two particle sizes (normal and fine grains) and contain varying percentages of several fluoride compounds (AgF, NaF, SnF_2, ZnF_2).

The normal particles correspond to normal-setting amalgams (50 μ X200 μ chips of small thickness not screened) of which the particle size varies between 80 and 20 mesh. Fine grains are screened for a particle size of 200 mesh and correspond to a more rapid setting. In a previous report (4) we emphasized the role of the particle size of the alloy in the setting kinetics of the amalgam and its final expansion.

The first tests were carried out on commercially-available amalgams (Fluoralloy of the Dentoria Laboratories at Cachan), fluoride-enriched with 1% of SnF2 for normal setting and 1% of AgF for rapid setting. The silver fluoride used takes the form of an ocher powder of which the particles tend to agglomerate. A fine particle size (GF) was preferred to the normal one in order to provide a better distribution of fluoride in the alloy, particularly when the percentage is small. All fluorides were, as a general rule, tested with normal setting powders but several supplementary tests were made with AgF rapid setting alloys.

With respect to human teeth cavities were prepared without anesthetic, on premolars which had to be extracted for orthodontic reasons. After cutting through the enamel at high speed (All air turbine, Kavo) and resection of dentine with a Maillefer No. 254 cylindrical cutter, under constant irrigation, the cavity is cleaned with merthiolate, then dried with amadou to limit the iatrogenic effects on the tissues. Amalgams are condensed by hand. In the case of dog's teeth, the experiment is carried out under general anaesthesia and only differs from the former by the method of exeresis of the enamel which is carried out with diamond cutters. (The dogs are fifteen to eighteen months old. Their teeth are numbered according to international nomenclature following the dental formula: 3 1 + 1 C + 4 P M + 1 M).

The teeth are extracted after a given time and then wrapped in a cold resin which neither contains nor fixes fluorine. The sample is then cut with diamond cutters in order to expose a cross-section of the three parts being studied: amalgam, enamel, dentine. Polishing is avoided in order to prevent any possible contamination during this operation. Measurements are made by following the enamel-amalgam transition as well as the dentine-amalgam transition zone.

Choice of Analysis Zone: Previous studies on the natural concentration of fluoride in teeth (5) gave the following results:

1. In enamel, the concentration of fluoride decreases from the exterior, following a very pronounced gradient. 2. In dentine, fluorine is believed to be carried by the blood circulation and its concentration decreases from the pulp chamber to the exterior. 3. Fluorine concentration is greater in dentine than in enamel.

In view of the three observations, the zone of analysis should correspond to regions where the gradient of natural fluoride is low in order to obviate any superimposition with concentrations of fluorine due to the amalgam, i.e. enamel, as far as possible from the periphery and for dentine, as far as possible from the pulp chamber.

The best zone for analysis would thus seem to be along, and on either side of, the enamel-dentine junction. The concentration of natural fluorine in this area may then be considered to be constant and the analyses recorded are characteristic of the amount of fluorine which has penetrated by diffusion from the amalgam. Obturations are, therefore, made to a depth great enough to cover enamel as well as dentine perpendicularly to the enamel-dentine junction.

Quantitative Analysis: Measurements made with the Castaing micro-probe are ordinarily subject to a series of corrections to take into account the effects of absorption and of fluorescence. The complexity of fluorine distribution in dental tissues makes it necessary to prepare standards by adding known quantities of fluorine to synthetic hydroxyapatite.

The results presented here are only semi-quantitative because these standards were not prepared systematically for our first tests: the gradients presented below are graduated, with regard to the ordinates, by the number of pulses per unit of time, providing for comparison between gradients, since they were obtained under the same conditions. Nevertheless, taking account of subsequent standards prepared by fluorine-enriched hydroxyapatite, we found that ten pulses per second are equivalent to 75 ppm of fluorine as a first approximation.

The gradients obtained also provide a means of evaluating the quantity of fluorine which has passed into the dental tissues. It is sufficient, for this purpose, to measure the area of the zone located between the gradient and the ordinate corresponding to the sum of background signals and of concentration of natural fluorine, assumed to be constant. We shall give the sign p to the ratio between the quantity of fluorine present in the dentine (working out the ratio between corresponding areas).

The areas measured may also be reduced to an arbitrary unit defined as a quantity of fluorine which has penetrated into the tooth for an amalgam fluorine-enriched by 1% of SnF_2 for fifteen days. Two standards are, in fact necessary, one for the enamel, the other for the dentine. The values shown under the heading "Quantity of fluorine fixed" in tables 1 to 4 are, therefore, non-dimensional and the ratio of the figures corresponding to the enamel and those corresponding to dentine are different from p since the latter is not referred to standards.

Treatment of Results by Diffusion Theory (Resolution of Fick Equations)

The supply of fluorine by means of amalgams may be considered in two different ways from the point of view of diffusion:

A Constant Superficial Concentration: It may be assumed that the amalgam plays the role of a sponge which continually liberates fluorine in order to maintain a constant concentration at the interface between amalgam and dental tissue. The limiting conditions of the Fick equation satisfy the classical case of diffusion in a semi-infinite medium having constant superficial concentration.

Let C (x, t) be the concentration of fluorine in a time l t, at a distance x (x = 0 at the junction, $x > 0$ in the tooth). The concentration of natural fluorine is given the symbol Co before diffusion ($t \geq 0$) and is assumed to be constant in the tooth. Cs is initial superficial concentration (t = 0) with regard to the junction and D is the diffusion coefficient.

We, therefore, have (Fig. 1):

as t = 0	C = Co	for x > 0
as t > 0	C = Cs	for x = 0
and	$C \rightarrow Co$	for $x \rightarrow \infty$

And then (6): $$\frac{C - Cs}{Co - Cs} = \operatorname{erf}\left(\frac{x}{2\sqrt{Dt}}\right)$$

erf being the error function defined by

$$\operatorname{erf}\left(\frac{x}{2\sqrt{Dt}}\right) = \frac{2}{\sqrt{\pi}} \int_0^{\frac{x}{2\sqrt{Dt}}} \exp(-Z^2)\, dz$$

z being a dumb integration variable.

By drawing $\operatorname{erfc}\left(\frac{C - Cs}{Co - Cs}\right)$ as a function of x, a straight line is, therefore obtained of which the slope is $\frac{1}{2\sqrt{Dt}}$ (Fig. 2).

A Thin Layer Which is Exhausted: It is assumed that only fluorine in contact shares in the diffusion. Therefore, we are dealing with a diffusion from an infinitely thin flat source in a semi-infinite medium. Conditions at the limits are then: (Fig. 3)

as t = 0	x = 0	M total mass of fluorine contact
	x > 0	C = Cn: concentration of natural fluorine

$$\text{as } t > 0 \quad \int_0^{\infty} (C(x) - Cn)\, dx = M$$

The Fick equation allows the solution:

$$C(x, t) = \frac{M}{\sqrt{Dt}} \exp\left(\frac{-x2}{4Dt}\right)$$

$$= Co \exp\left(\frac{-x2}{4Dt}\right) + Cn$$

C (x, t) being concentration at time t, and at distance x.

By drawing $\text{Log}\ \frac{C - Cn}{Co} = f(x2)$ a straight line is obtained with a slope of $\frac{-1}{4Dt}$ (Fig. 4).

Figure 1

Concentration-penetration curves of diffusion in a semi-infinite medium with constant superficial concentration.

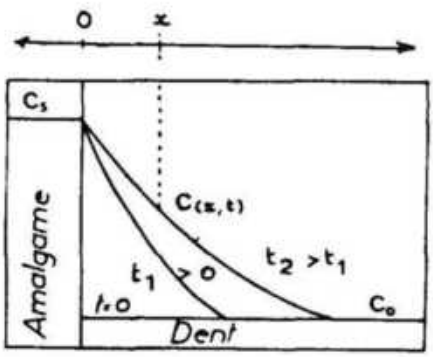
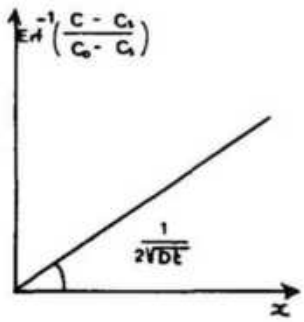


Figure 2

Calculation of diffusion coefficient D for Fig. 1

Slope $\frac{1}{2\sqrt{Dt}}$ of curve erf-2 $\frac{(C - Cs)}{(Co - Cs)} = f(x)$.



The two calculations lead to totally different results. In the first hypothesis in which the fluorine supply is continuously renewed, the quantity of fluorine which penetrates is constantly increasing. In the second case, the gradient concentration is very pronounced at the start and slowly becomes less noticeable to maintain the total quantity of fluorine penetrated constant.

Figure 3

Concentration-penetration curves of diffusion of a thin layer (which is consequently exhausted) in a semi-infinite medium.

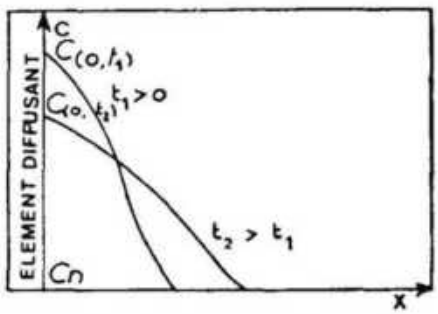


Figure 4

Calculation of diffusion coefficient D - (Slop

$\frac{1}{4Dt}$ of curve Log $\frac{C - Cn}{Co} = f(x2)$.

Results

A Study of Several Fluoride Compounds

This study covers Dentoria amalgams of normal particles to which we added 5% of AgF, SnF_2, NaF or ZnF_2.

Fillings were made on teeth of dogs over a period of fifteen days. Diffusion calculations were based on the thin layer method. The slope is obtained by smoothing curves by computer according to the technique of least squares (Table 1, Figs. 5 to 8).

Table 1

Influence of AgF, SnF_2, NaF, ZnF_2 on Diffusion of Fluorine for a F^- Concentration of 5% of Weight and Constant Obturation Times (15 days)

F^- Compounds	AgF		SnF_2 (5%)		NaF (5%)		ZnF_2 (5%)	
Number of Teeth	13		14		14		18	
Figure Number	5		6		7		8	
Tissue	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.
Diffusion in 10^{-10} cm2/s	0.43	0.20	4.07	1.04	1.1	0.47	0.42	0.20
Quantity of F^- fixed(*)	0.5	0.8	1.15	1.12	0.63	0.81	0.72	0.80
Ratio of fluorine fixed enam.-dent.	0.37		0.63		0.47		0.55	

Figure 5a

F- penetration in the enamel of a dog's tooth (13) from normal particle size amalgam, fluorine enriched by 5% of AgF. Fifteen days. The penetration of silver (Ag) was also followed (in ordinate, number of pulses per time unit, ten pulses = 75 ppm).

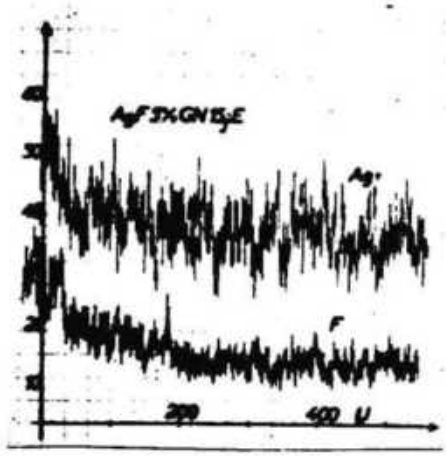


Figure 5b

Same case as in Fig. 5a, but showing penetration into dentine.

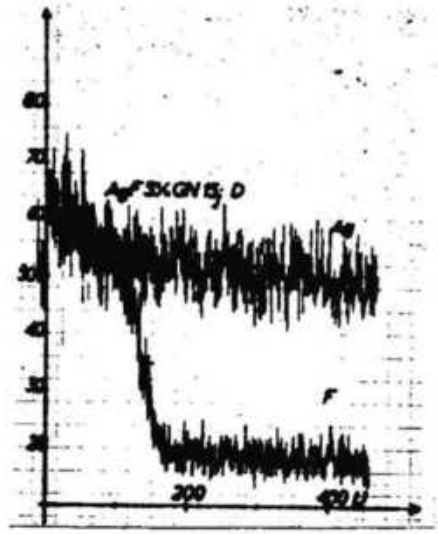


Figure 5c

Smoothing of curves presented in Figs. 5a and 5b.

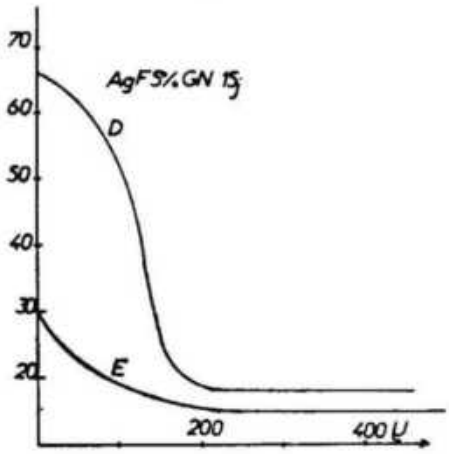
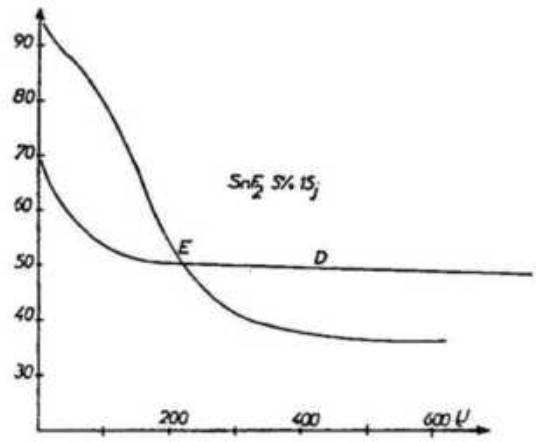


Figure 6

Penetration of F^- into dog's tooth (14) from normal particle size amalgam, fluorine-enriched by 5% of SnF_2. Fifteen days.



E = enamel, D = dentine.

Figure 7

Penetration of fluorine into a dog's tooth (14) from amalgam of normal particle size, fluorine-enriched by 5% of NaF for fifteen days.

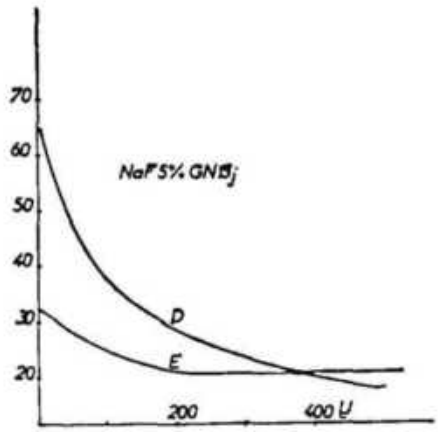
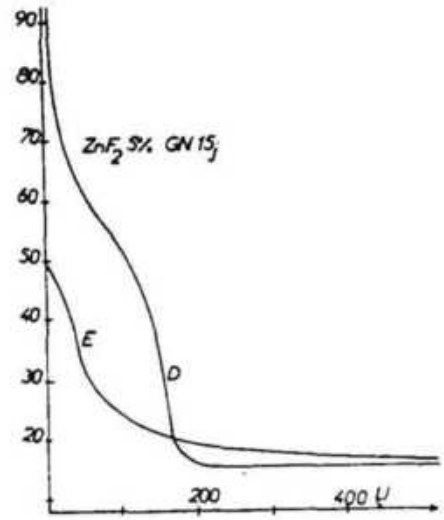


Figure 8

Penetration of fluorine into a dog's tooth (18) from amalgam of normal particle size, fluorine-enriched by 5% of ZnF_2 for fifteen days.



Curves smoothed. E = penetration into enamel, D = penetration into dentine.

Influence of Concentration

We used amalgams at concentrations 1 to 5% of SnF_2 (normal particles) and of AgF (fine particles) in order to study the influence of fluoride content on the penetration of fluorine into teeth (Figs. 6, 4 and 11 and Table 2).

Table 2

Effect of Concentration (1% and 5%) for 15 Days, AgF Added to Fine Particle Amalgam (G. F.), SnF_2 to Amalgam of Normal Particles (G. N.)

F^- Compounds	AgF 1% GF		AgF 5% GF		SnF_2 1% GN		SnF_2 5% GN	
Number of Teeth	24		23		28		14	
Figure Number	9		9		10		10	
Tissue	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.
Diffusion in 10^{-10} cm2/s	2.8	4.2	0.6	0.8	2.06	1.41	4.07	1.04
Quantity of F^- fixed compared to SnF_2 1% Standards	0.51	0.65	0.35	0.87	1	1	1.15	1.12
	0.48		0.24		0.60		0.63	

Influence of Time

The results obtained by 1% and 5% fluorine-enriched amalgams have been compared for two different times (15 days and 1 month) (Table 3, Figures 6, 11 and 14).

The results and the shape of curves obtained at the end of one month show that fluorine does not stay in place but continues its migration so rapidly that the gradient which can be seen very clearly for a period of 15 days has completely disappeared at the end of a month.

It would seem, in addition, that fluorine is not regularly diffused but that it accumulates in privileged spots. This may be compared with the results of Ehrlich and colleagues (3) who arrive at the following conclusions based on a study by microscopic scanning of fluorine supplied by local application:

1. Observation of a gradient of fluorine during periods varying from 1 to 14 days.
2. Gradual disappearance of gradient over longer periods.
3. Accumulation of fluorine in dental canaliculi.

The results which we obtained were therefore similar in every respect and confirmed the results of the second hypothesis (thin layer), with regard to making use of results by the diffusion theory.

Table 3

Effect of Time, Comparison of Results after Fifteen Days and 1 Month, with Amalgams of Normal Particle Size (G. N.) and with Addition of SnF_2, 1% then 5%

F⁻ Compounds	SnF_2 1%				SnF_2 5%			
Time	15 days		1 month		15 days		1 month	
Number of Teeth	28		28		14		14	
Figure Number	10		11		6		12	13
Tissue	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.	Enam.	Dent.
Diffusion in 10^{-10} cm2/s	2.06	1.41	1	1.89	4.07	1.04	0.24	0.65
Quantity of F⁻ fixed, reduced to standards	1	1	0.43	0.51	1.15	1.12		
	0.6		0.71		0.63			

Figure 9

F^- penetration from small particle amalgam, F^--enriched, 15 days with AgF; 1% of AgF for dog 24; 5% for dog 23.

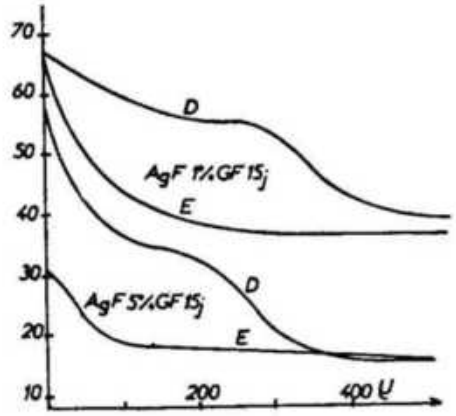


Figure 10

F^- penetration from normal particle amalgam, F^--enriched, 15 days with SnF_2; 1% for dog 23; 5% for dog 14.

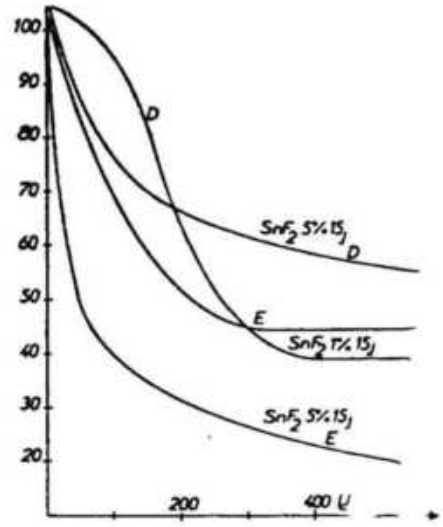


Figure 11

F^- penetration into dog's teeth from normal particle amalgam, F^--enriched by 1% of SnF_2, 15 days on dog 28 (SnF_2, 1%, 15 d) and for one month in dog 28 (SnF_2, 1%, 1 m).

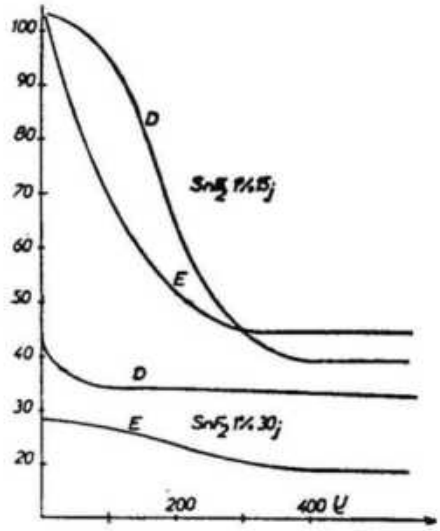


Figure 12

F^- penetration into enamel of dog's tooth (14) from normal particle amalgam, F^--enriched by 5% SnF_2 for one month. Note irregular shape of curve.

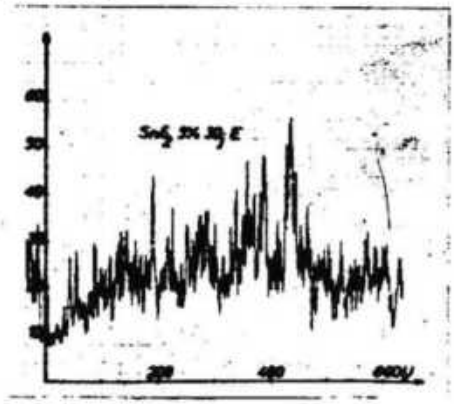


Figure 13

The same case as Figure 12, but penetration into dentine.

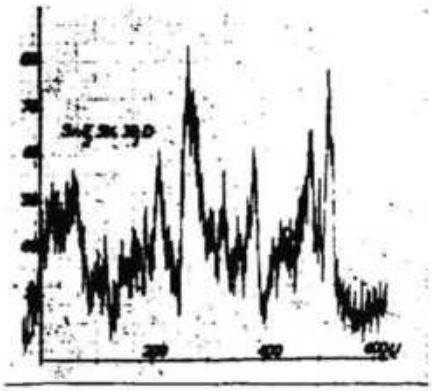
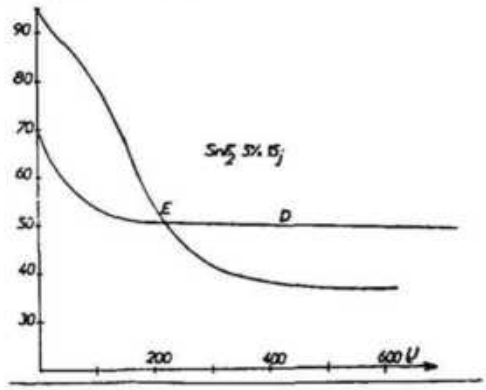


Figure 14

F^- penetration into human tooth (14) from normal particle amalgam, F^--enriched by 5% SnF_2 for 15 days.



Discussion

This preliminary study has enabled us to underline the following:

1. Tin fluoride, SnF_2 should be chosen as the fluoride which penetrates best into dental tissues from an amalgam.

2. In any case, the apparent coefficient of diffusion is of the order of 10^{-10} cm2/s as much into enamel as into dentine (Tables 1 to 3).

The diffusion of fluorine into enamel is characterized by coefficient D, which is often greater than that obtained with dentine. We would recall that this coefficient illustrates the mobility of fluorine particles.

3. On the other hand, the ratio p which depends upon the quantities of fluorine fixed at the time of the analysis shows that there is more of this element present in dentine than in enamel ($p < 1$). This may be explained by the structural differences between enamel and dentine and, in particular, by the presence of canalicules and dental fluid.

The presence of this fluid in fact facilitates the dissociation of fluorine with respect to the dentine-amalgam interface, leading to an increase in the quantity M (see § 11 5 2°) of initial fluorine with regard to dentine (M dentine < M enamel). But this quantity, M, is equal to $\int_0^{\infty} [C(x, t) - Cn]\, dx$, and thus to the area measured between the concentration-penetration gradient and the concentration level C_n (concentration of natural fluorine). As a result of the ratio $p = \frac{M \text{ enamel}}{M \text{ dentine}}$ is less than 1 (Tables 1 to 3).

4. Fluorine does not follow a pronounced gradient, because of its mobility, for a prolonged time and slowly diffuses into the whole tooth, accumulating or becoming trapped in the peri-tubular zones. We have, in addition, observed whitish deposits when dissolving tin fluorides with synthe-

tic saliva. This deposit is primarily caused by the action of fluoride on phosphates mainly resulting in tin fluoral phosphate. This type of deposit might occur on contact of fluoride with dentinal fluid.

5. The quantity of fluorine which penetrates is not at all proportional to the concentration by volume of fluoride incorporated in the amalgam. Transfer by dentinal fluid may, in addition, be superimposed on the mechanism of diffusion suggested.

6. Given the small improvement provided by a 5% concentration of fluoride instead of 1%, one might strongly recommend the use of a 1 or 2% fluorine-enriched amalgam which would modify the mechanical and electro-chemical characteristics of these bio-materials to a totally negligible degree. (8)

7. Finally, Figure 14 gives, as an indication, the first results obtained in vivo with an amalgam fluorine-enriched by 5% of SnF_2 on a human premolar during fifteen days (right upper premolar, child aged 10).

The two curves are quite comparable with corresponding curves in the case of a dog (Fig. 6). (The coefficients of diffusion are $4\ 10^{-10}$ cm2/s for enamel and $0.6\ 10^{-10}$ cm2/s for dentine).

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STUDIES ON FLUORIDE DISTRIBUTION IN INFANTS AND SMALL CHILDREN

by

Ingrid Hellstrom
Stockholm, Sweden

(Abstracted from Scand. J. Dent. Res., 84:119-136, 1976)

The authors determined the fluoride concentrations in bones and blood plasma in biopsy and autopsy specimens from fetuses, infants, and children following exposure to various levels of fluoride. The specimens in newborn autopsy cases consisted of rib, jawbone with teeth, and blood plasma. The fluoride concentrations of bone and dentin were of the same order; the enamel showed somewhat lower levels. High fluoride water increased the fluoride content significantly. The maximal concentration of rib-ash in the bone biopsy material amounted to 400 ppm. The fluoride content of the ribs did not correlate with that of the blood plasma. Of three groups of infants, aged 2 to 6 months, calculated to ingest fluoride in the ratio of 1:10:50 the group ingesting the highest amount of fluoride had higher plasma fluoride values than the two other groups, whereas the alkaline phosphatase was significantly higher than that of the lowest fluoride group. In physically handicapped children, aged 4 to 15 years residing in an artificially fluoridated community, the severely handicapped excreted more fluoride in the urine than the controls.

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FLUORIDE CONTENT OF PREPACKAGED FRUIT JUICES AND CARBONATED SOFT DRINKS

by

A. Enno, G. G. Craig and K. W. Knox
Sydney, Australia

(Abstracted from Med. J. Aust., 2:340-42, 1976)

Enno et al. determined the fluoride content of forty-seven varieties of prepackaged fruit juices and fruit drinks, and sixty-nine varieties

of carbonated soft drinks purchased at retail outlets in fluoridated Sydney, Australia. They noted that in 1973 the Australian population consumed 0.15 litres of carbonated drinks per person per day.

In carbonated soft drinks the fluoride level ranged from 0.3 ppm to 1.5 ppm (mean value 0.75). Prepackaged fruit juices contained from below 0.075 ppm to 0.97 ppm fluoride. The fluoride content of the drinks differed significantly depending on how they were stored.

In drinks packed in metal cans and stored four months, the fluoride concentration dropped by 30% from a mean value of 0.68 ppm to a mean value of 0.52 ppm, which is statistically significant ($P < 0.001$). When stored in glass, however, the fluoride content did not change.

Another factor that influenced the amount of fluoride in these beverages was the water treatment since many of the larger soft drink manufacturers use alum ($KAl(SO_4)12H_2O$) flocculation for water purification. Addition of alum followed by filtration reduced the fluoride concentration in tap water from a mean value of 0.96 ppm to a mean value of 0.62 ppm (35%).

****

BOOK REVIEW

TOXICOLOGY OF ORGANIC FLUORIDE COMPOUNDS AND INDUSTRIAL HYGIENE DURING THEIR PRODUCTION

by

A.I. Korbakova, I.D. Makulova, E.M. Mercenko and T.K. Nikitenko
Akademija medicinskich Nauk SSSR. - Moskva: Medicina,
1975. - 182 S.: 16 Illustrations; 30 Tables; Price, 1 R., 08 K.

During the past four decades the introduction of fluoride-containing refrigerants (Freon) and plastics has become of increasing significance. Furthermore, fluoroacetates were employed in World War II as war poisons. More recently other fluorocarbons and fluorohydrocarbons are being used as refrigerants, fire extinguishers, propellents, dielectrics, stabilizers, lubricants and heat carriers. All of these agents have contributed materially to the rise in production of fluoride compounds. With the steady expansion of the use of fluorocompounds, an increasing number of cases of intoxication have occurred, often with fatal results--especially due to fluoroacetate.

The mode of poisoning and the toxicity of organofluorides, their biological action, the prophylaxis, early diagnosis and treatment of organofluoride poisoning have occupied the attention of industrial hygienists and toxicologists.

The book relates the experiences and results of the Institute for Labor, Hygiene and Industrial Health of the Academy of Science of the USSR in Moscow and of the Leningrad Institute of Industrial Hygiene and Occupational Illnesses. In addition some of the basic American investigations, especially those of the Haskell Laboratory are included as well as the literature available in the USSR and from other countries.

The first chapter deals with measures of industrial hygiene where fluorocarbons are produced. Other chapters discuss the toxicology of fluoroalkanes (Freons), fluoroalkene (Perfluorisobutylen, one of the most dangerous substances), aromatic and aliphatic fluoride derivatives of the fluoropolymeres and their thermoxidative destruction. Chapter 6 is devoted to the toxicity and metabolism of organic fluoride compounds as related to their chemical structure. The last chapter which presents clinical data on poisoning with organic fluorides is subdivided into acute and chronic intoxication, their treatment and prophylaxis.

This book constitutes an attempt to compile all current knowledge on toxicity of the various organofluorides and to outline prophylactic meas-

ures. The index covers 12 pages.

The sole shortcoming of this book in my opinion is the fact that the most recent references to the literature date back to 1971; the book appeared in 1975. Undoubtedly this book will be of considerable value to industrial hygienists, chemical technologists, safety engineers, safety inspectors and to scientists of many other disciplines.

J. Franke

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CORRECTION: The title of the abstract by G.W. Dominok (10:91-92, April 1977) should have read, "Industrial Skeletal Fluorosis and Problems of Treatment, Osteoporosis with Fluorine".

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