October, 1979 Vol. Twelve No. Four

FLUORIDE

OFFICIAL QUARTERLY JOURNAL

OF

INTERNATIONAL

SOCIETY for

FLUORIDE

RESEARCH

Vol. Twelve No. Four October, 1979 Pages 169-220

FLUORIDE

Quarterly Reports

Issued by

THE INTERNATIONAL SOCIETY FOR FLUORIDE RESEARCH

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ABSTRACTS

FLUORIDE is published quarterly by THE INTERNATIONAL SOCIETY FOR FLUORIDE RESEARCH, INC.,

SUBSCRIPTION RATES 1979 — Price per annum in advance including postage $25.00, Single copies $7.00.

MANUSCRIPTS for publication should be submitted in English, double-spaced with generous margins. References should be arranged according to the order in which they are cited in the text, and written as follows: Author, title, journal, volume, pages and year. Each paper must contain a summary of not more than 12 lines.

FLUORIDE is listed in
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EDITORIAL

PRESKELETAL PHASE OF FLUOROSIS

In a recent book reviewed on pages 209-210 and in an article by Girskaya (pp. 214-215 of this issue), the U.S.S.R. authors refer to a large variety of symptoms in conjunction with the widely recognized skeletal changes of fluorosis. Their observations are based on experience with workers in aluminum factories and in cryolite mines. From their description of the disease it appears that gastrointestinal symptoms, mainly gastritis and gastric ulcer dominate the clinical picture. Since the workers were exposed to airborne fluorides, respiratory symptoms also were common. However, judging by the description given by the U.S.S.R. authors no organ of the body is likely to escape adverse effects.

It is noteworthy that as long as 40 years ago the originator of modern fluoride research, Kaj Roholm (1), outlined in detail the same symptomatology. Yet. his findings have been disregarded in the vast USA and British literature. The result has been a gap in knowledge on the biological action of fluoride in these countries. In a series of articles, Waldbott (2) has presented conclusive evidence that even with less intake of fluoride than encountered in industry, the preskeletal phase of the disease is not uncommon. Other investigators have since confirmed the existence of a syndrome associated with intolerance to fluoride in polluted air (3-7) and in water (8-10).

These data have been persistently challenged, mainly by dental researchers. Jenkins (11), for instance, is critical of the technique of the double blind tests designed to confirm the relationship between fluoride and the illness. Schlesinger (12) questions the existence of preskeletal fluorosis because of the sparsity of reports by other investigators.

When Morris (13) described 20 cases of skeletal fluorosis among Arizona Indians, he made no reference to the preskeletal phase of the disease (13). Linsman et al. (14) and Sauerbrunn et al. (15) reported fatalities unequivocally related to fluoride in water (1.2 to 5.7 ppm and 2.2 to 3.5 ppm respectively) but they did not relate the pathological kidney changes and liver damage respectively to fluoride. Even as recently as 1979 Jenkins (16) failed to recognize the validity of numerous clinical observations by authors who confirmed the multisystem phase of fluorosis.

In recent years Kathpalia et al. (17), by animal experiments, have also supported the nonskeletal phase of fluorosis. They found a loss of protein in all organs tested after administering large doses of fluoride. Some of the symptomatology is further explained by Whitford (18) who observed that formation of HF in an acid medium affects the lining of the upper gastrointestinal and the urinary tracts. The occurrence of secondary hyperparathyroidism in fluorosis furnishes a rationale for some of the other symptoms.

It is clear that a reevaluation of our concept of fluorosis is in order. Not only has our understanding of the biological effect of fluoride been blocked, but much suffering could have been avoided had the medical profession been adequately alerted to the symptomatology of chronic fluoride poisoning. A case in point is that of a 27 year old nurse reported by Klemmer and Hadler (19) in the Annals of Internal Medicine who,intermittently for at least 9 years, had been illicitly sniffing methoxyflurane, a fluoride-containing anesthetic. Her symptoms, headache, polyuria, polydipsia, epigastric distress, severe osteoarthritic bone pain, painful nodules on the extremities, disturbed kidney function and generalized osteosclerosis had baffled the attending physicians until skeletal fluorosis had developed and the disease was no longer reversible.

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EFFECT OF FLUORINE AND AN ANTIDOTE (BORON) ON RESPIRATION OF LIVER TISSUE IN RABBITS

by

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SUMMARY: Tissue oxygen consumption of the liver was studied six hours after rabbits were sacrificed following administration of fluoride (F 40 mg/kg/d) for seven months with and without an antidote (boron 4 mg/kg/d). We found no biological and histological changes in the liver, but the oxygen consumption of liver tissue increased in both groups. A single large dose of fluoride (10 mg) was added in vitro to 0.25g liver homogenate. Oxygen soncumption of the tissue increased during the first hour and then declined considerably. Following the addition of 3.85 mg boron, the initial activation did not occur and the secondary decline in oxygen consumption was less pronounced.

Introduction

Fluoride can depress the intracellular metabolism (1). In a previous paper we (2) related that fluoride, added in vitro to homogenate liver tissue of rabbits (0.25g) had no effect on oxygen consumption at a concentration of 1 or 1.5 mg/0.25g tissue but at concentrations of 2.25mg oxygen consumption increased. With doses of 5 to 10mg fluoride, the oxygen consumption of liver tissue (VO_2) increased for the first hour then declined markedly

In our current experimentation, immediately after sacrificing the rabbits which had been previously intoxicated by fluoridated drinking water (F 40 mg/kg/d), we tried to determine whether or not hepatic tissue VO_2 is altered; also whether the simultaneous supply of fluoride and boron will modify the fluoride-induced disturbance of tissue VO_2 when given in a proportion of F 40 mg/kg/d + B 15.4 mg/kg/d in drinking water for seven months; and whether simultaneous administration of fluoride (10mg) + boron (3.85mg) per 0.25g tissue would modify the diphasic action of fluoride upon the hepatic oxygen consumption in vitro.

From the Institute of Medical Sciences, Algiers, Algeria.

Materials and Methods

Hepatic homogenates of fasting rabbits (0.25g) were studied hourly in a respirometer with agitation at 37° temperature for six hours following sacrifice. The oxygen consumption is reported in microliters/g of tissue/hour. Two protocols *in vivo* and *in vitro* were compared to 22 normal homogenates of fasting rabbits.

In the *in vivo* study the fluoride group received 40 mg/kg/day for seven months. Group F + B was given 40 mg/kg/day fluoride and 15.4 mg/kg/day of boron during a seven month period as NaF and as $B_4Na_2O_7 \cdot 10\ H_2O$ in drinking water from the beginning of the intoxication. We had 12 animals in group F and 8 in group F + B.

In the *in vitro* study a large dose of fluoride (10mg) was added to 0.25g normal hepatic homogenate (group F). In group F + B 10 mg fluoride to 3.85mg boron was administered. Group F was comprised of 15 animals and group F + B, of 8 animals.

Results

The absolute values of oxygen consumption (microl/g per hour) during six hours are presented in Figure 1. Figure 2 shows the percentages of the hourly oxygen consumption in the normal controls.

Compared with the oxygen consumption of hepatic homogenates of normal fasting rabbits during the same one hour period, fluoride *in vivo* increases the tissue oxygen ($p < 0.01$) between 3 and 5 hours. Boron administered throughout the experiment (F + B *in vivo*) does not alter this increase which differs from normal ($p < 0.05$), but is similar to the oxygen consumption in the fluoride group. The percentages of decrease are about +68 and +99 respectively in the two groups.

In vitro a single large dose of fluoride increases the tissue oxygen consumption during the first hour compared to normals by 44% ($p < 0.05$), and then decreases it markedly by 64% ($p < 0.01$) between 3 and 5 hours. A single dose of boron given simultaneously with fluoride (F + B *in vitro*) inhibits the initial activation, and slightly limits the secondary depression of tissue oxygen by about 48% ($p < 0.05$) between 3 and 6 hours.

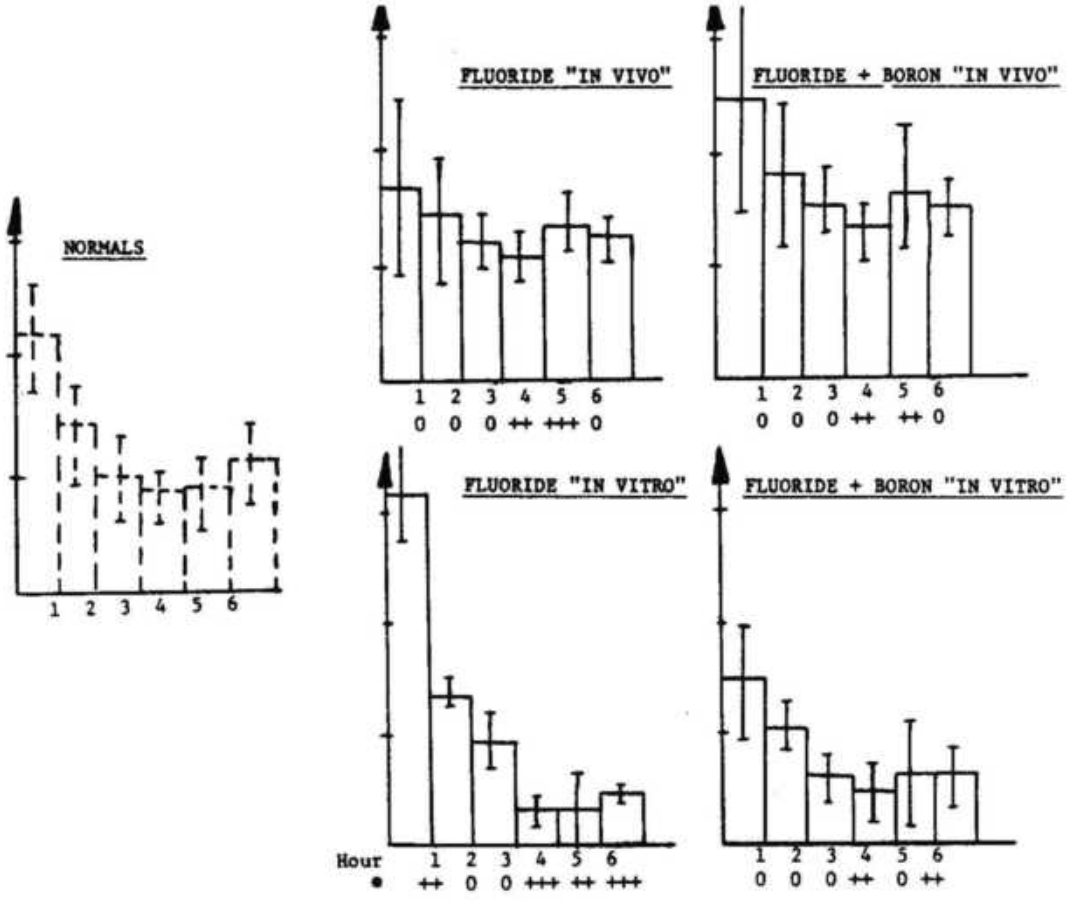
During the *in vivo* experiment, protein electophoresis, triglycerinemia, serum transaminases remained normal in the two groups, F and F + B. The histological findings, according to light microscopy, were also normal. Electron microscopy was not performed.

Discussion

(1). *Effect of Fluoride on Liver*: In our *in vivo* experiment, with F 40 mg/kg/d for seven months, there were no changes in the tri-

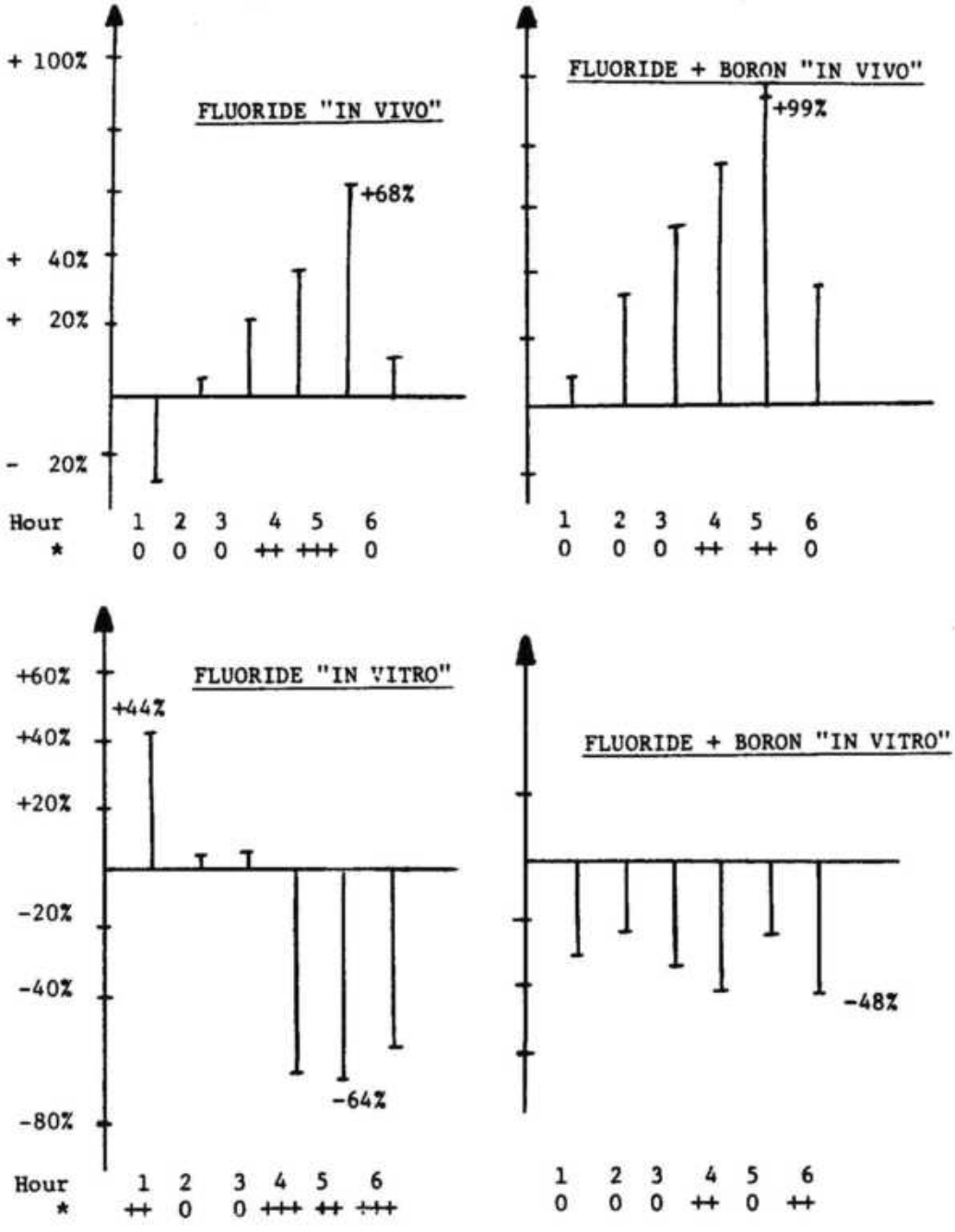
Figure 1
Effects of Fluoride and Boron Upon Hepatic Tissue
Oxygen Consumption In Rabbits

Microliters oxygen/g tissue/hour



* Significant Differences: +++ $p < 0.01$; ++ $p < 0.05$; + $p < 0.10$; 0= nonsignificant

Figure 2
Effects of Fluorine and Boron Upon Hepatic Tissue Oxygen Consumption In Rabbits
(Differences from Normals In Percent)



* Significant Differences: +++ $p < 0.01$, ++ $p < 0.05$, + $p < 0.10$, 0=nonsignificant

glycerides, proteins, serum transaminases nor was there any histological injury to the liver. In experimental fluorosis,an hepatocellular disease has been described with an increase of serum transaminases (4). However fluoride increases the consumption of oxygen in the liver (Figs. 1 and 2). A larger single dose of fluoride (F 10mg/0.25g tissue) in vitro first increases (p 0.05) and then reduces (p 0.01) the oxygen consumption of hepatic tissue (Figs. 1 and 2). Activation followed by depression indicates cellular damage. Fluoride can depress intracellular metabolism, particularly enzymes which are involved in oxidative phosphorylation and in ATPase activity (2). In mitochondria, fluoride can depress the rate of oxidation of some substrates but does not reduce the ADP/O ratio (5).

(2). Effect of Boron on the Hepatic Oxygen Consumption Induced by Fluoride: In our in vivo experiment, when boron was administered together with fluoride throughout the intoxication, it did not affect the oxygen consumption of liver tissue induced by fluoride alone (Figs. 1 and 2). However in vitro when there was an abundant supply of fluoride, boron administered simultaneously with fluoride partially reduced the fluoride-induced oxygen consumption: Boron inhibited the first increase and slightly limited the secondary depression of tissue oxygen consumption (Figs. 1 and 2). Boron therefore seems to act as an antidote in vitro. In future studies, the B/F ratio should be modified by giving more boron for the same fluoride supply in order to determine its possible effect as an antidote upon different metabolic parameters.

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EXPERIMENTAL STUDY OF URINARY FLUORIDE EXCRETION IN DOGS

by

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SUMMARY: Serum and urinary fluoride levels were studied in 20 mongrel dogs, before and after a challenge of fluoride ions. Levels were higher in experimental animals obtained from areas of proven endemicity compared to controls. However the concentration of fluoride in both serum and urine was much greater in animals from an area where, in the past, fluorosis was proven to be endemic but where drinking water now contains 0.6 ppm fluoride. It is suggested that mobilization of stored skeletal fluoride continues over an extended period of time in response to a reduced fluoride content of water.

In humans and animals, urinary excretion of fluoride is one of the most important mechanisms for keeping the plasma fluoride concentration low (1) and for dealing with sustained fluoride ingestion. Approximately half to two thirds of the intake is believed to be removed in this manner. Ericsson (2) administered 1 mg radiofluoride F^{18} to twenty adult humans and recovered 30 percent of the given dose in four hours. A direct relationship has been observed between fluoride intake and urinary fluoride excretion (3-6). Zipkin and Leone (7) investigated the rate of urinary fluoride excretion in adults given a challenge of additional fluoride-containing water. They reported that 97.4 percent of the fluoride was absorbed and later excreted in the urine over a twenty-four hour period. Studies by Chen et al. (8) on dogs gave similar findings.

Hodge (9) observed chronic pathological changes in the kidneys of fluorotic patients but Roholm (10) could find no positive evidence of fluoride-induced kidney pathology.

Yeh et al. (11) from their investigations on urinary fluoride excretion in rats with and without previous exposure to high fluoride-containing drinking water, concluded that the urinary excretory mechanism was more rapidly operative in animals with no previous exposure to fluoride than in those with appreciable tissue fluoride content. Similar observations were made by Zipkin and Leone (7).

Recently we had observed increased fluoride excretion in fluorotic patients compared to volunteers living in non-endemic areas.

From the Lady Hardinge Medical College, New Delhi, India.

The present study was designed to investigate the reason for the variance observed in the urinary excretion of the two groups.

Materials and Methods

Serum and urinary fluoride analyses were made on twenty male mongrel dogs, weighing 8-11 kg. They were collected from areas in and around Delhi and divided into the following groups:

1. Control Group of ten dogs from the Delhi colony of Janakpuri receiving drinking water containing 0.6 ppm fluoride.

2. Experimental Group of ten dogs was further subdivided into two groups: a. Dabri group consisting of five dogs from Dabri village, a zone of endemic fluorosis, and b. Bindapur group consisting of five dogs from Bindapur village, a region of proven endemic fluorosis in the past, where since 1970, a centralized water supply contains 0.6 ppm fluoride.

Animals were kept in the laboratory and given water containing 0.6 ppm fluoride. They were anesthetized by intravenous administration of nembutal. The femoral vein was dissected and cannulated for collection of blood samples. The ureter was exposed and small bore polythene tubing inserted for collection of urine samples.

In the first set of experiments, five control dogs were given an infusion of 10 percent glucose in autoclaved water containing 0.6 ppm fluoride. The infusion lasted one hour and the total urine collected during this period was analyzed for fluoride.

In the second phase of the experiment, five animals of the control group and five each from the two experimental groups were given an infusion of 10 percent glucose in autoclaved Dabri well water containing 2.6 ppm fluoride at a rate of 2.5 ml per minute through a continuous infusion syringe. This procedure maintained the plasma fluoride level constant throughout the experiment and also ensured a urine excretion of 2 ml or more per minute. The infusion was continued for 6 hours and hourly samples of urine were collected.

The fluoride content of serum and urine was estimated by the modified Taves technique (12) by means of the fluoride ion electrode.

Results

Table 1 shows serum and urinary fluoride levels in five control dogs infused with 10 percent glucose in water containing 0.6 ppm fluoride. The range of serum fluoride was 0.065-0.12 ppm with a mean of 0.086 ppm and that of urinary fluoride 1.4-2.28 ppm with a mean of 1.836 ppm.

Table 1
Serum and Urine Fluoride
(5 Control-Mongrel Dogs After Infusion*)

Dogs	Serum F⁻ ppm	Urinary F⁻ ppm
1	0.09	1.80
2	0.12	2.28
3	0.08	1.4
4	0.065	1.6
5	0.75	2.1
Range	.065-012	1.4-2.28
Average	0.086	1.836
S.D.	± 0.023	± 0.36
S.E.	0.01	0.16

* 10% Glucose in Tap Water (0.6ppm F-)

Table 2 gives the comparative data on fluoride levels in serum and urine of the control versus the experimental groups, consisting of five animals in each group infused with 10 percent glucose in Dabri water containing 2.6 ppm fluoride for 6 hours. In the experimental groups of Dabri and Bindapur the mean values as well as the range of serum and urine fluoride are much higher than in the control group of Delhi. In Bindapur animals values were higher than in those of Dabri.

Table 2
Serum and Urinary Fluoride Levels
In Experimental Mongrel Dogs* After Infusion**

	Serum Fluoride ppm			Urine Fluoride ppm		
Dogs	Delhi	Dabri	Bindapur	Delhi	Dabri	Bindapur*
1	0.26	0.38	.46	2.1	9.8	6.8
2	0.35	0.35	0.52	5.2	6.1	10.2
3	0.25	0.63	0.44	2.85	5.3	4.7
4	0.35	0.71	0.53	1.9	4.6	8.5
5	0.33	0.53	0.79	2.1	7.8	12.1
Range	0.25-0.33	0.38-0.71	0.44-0.79	2.1-5.2	4.6-9.8	5.7-12.1
Average	0.308	0.56	0.548	2.83	6.72	8.46
S. D.	0.049	0.012	0.019	± 1.37	± 2.09	± 2.88
S. E.	0.022	0.055	0.008	0.613	0.94	1.29

* Dogs were collected from the area indicated.
** 10% Glucose in Dabri water containing 2.6% ppm Fluoride.

Table 3 shows the fluoride levels in serial urine samples of the control group, collected at the start of the infusion and at hourly intervals thereafter, up to a period of 6 hours. A fall in urinary fluoride excretion in the first 2 hours was followed by a progressive increase which is sustained until the last collection.

Table 3

Serial Urinary Fluoride Excretion In Control Mongrel Dogs*

	Hour 0	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6
1	1.8	1.63	1.55	1.75	1.93	2.08	2.1
2	2.88	2.01	1.9	3.1	3.9	4.98	5.2
3	1.4	1.39	1.39	2.1	2.55	2.7	2.85
4	1.6	1.43	1.38	1.5	1.59	1.79	1.9
5	2.1	1.9	2.05	2.1	2.15	2.1	2.15
Av.	1.84	1.68	1.65	2.15	2.42	2.73	2.84
S.D.	±0.29	±0.33	±0.3	±0.61	±0.89	±1.32	±1.37
S.E.	0.13	0.15	0.134	0.27	0.4	0.59	0.65

* 10% Glucose in tap water (2.6 ppm F^-) infused.

Discussion

It is noteworthy that the serum levels and urinary excretion of fluoride are maximum in the dogs of Bindapur which, though endemic in the recent past, has since 1970 received water containing 0.6 ppm fluoride. This suggests that mobilization of stored skeletal fluoride and its excretion by the kidney can continue over an extended period of time.

Urinary excretion is the main route for elimination of fluoride though a small amount finds its way into sweat, feces and milk. Shupe et al. (13) who analyzed the fluoride content of various soft tissues in dairy cattle with chronic fluorosis stated that—next to bone and teeth—kidney tissue contains the highest concentration of fluoride. Hodge noted changes referable to chronic kidney pathology and Siddiqui (14) observed a decrease in the urea clearance of fluorosis patients from the Nellore district of the Madras Presidency. However Kumar and Kemp Harper (15) did not report any significant change in kidney pathology.

Yeh et al. (11), in experimental studies on rats, observed no difference in the rate of urinary excretion of fluoride in fluoride-exposed and unexposed animals; however, the plasma fluoride content, when presented with a challenge of a fluoride load, was higher in the exposed than in the unexposed group.

In the present investigation, the decrease in the urinary excretion of fluoride by control dogs in the first 2 hours after beginning the infusion (Table 3) may reflect an attempt by the body to spare the kidney from the acute toxic effects of fluoride by a greater rate of deposition of plasma fluoride into the skeleton. However, in the face of the continuous challenge with high fluoride-containing water, the kidney mechanism comes into play to step up the rate of fluoride excretion resulting in the progressive increase observed in the urinary excretion of fluoride.

Acknowledgements

The authors are grateful to Dr. S. Chawla, Principal and Medical Superintendent, Lady Hardinge Medical College and Sucheta Kripalani Hospital, New Delhi, for encouragement and for providing facilities for this work, and to the Staff of the Dept. of Biochemistry and the Dept. of Physiology, Lady Hardinge Medical College for their assistance in the experimental studies.

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EVALUATION OF DAMAGE TO VEGETATION IN POLLUTED AREAS

by

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SUMMARY: For the evaluation of the phytotoxic effect of fluoride, no single parameter by itself would be conclusive in litigation. Contrary to the views of some, one cannot obtain an adequate answer in a given situation by evaluating the appearance of plants in a polluted area in relation to their fluoride content. For the diagnosis, one must include in the investigation a number of other nonfluoride-induced environmental parameters which cause macroscopic appearances of vegetation similar to those due to fluoride. This subject is discussed in this paper with special consideration to the water economy of the plant which is particularly important for its physiological state and for determining the extent of damage.

Presented at the 9th Conference of the International Society for Fluoride Research, Fribourg, Switzerland, July 23-25, 1978.

The determination of fluoride in forage and feed rations constitutes a useful source for the establishment of standards on the basis of which domestic animals can be protected against fluorosis. On the other hand, it is much more difficult to evaluate damage to individual plants, particularly if it is due to long-term effects of low concentrations of fluoride. Furthermore, there is no single parameter for the evaluation of the phytotoxic effect of fluoride which, alone, would be conclusive in litigation. Contrary to the views of some experts, one cannot obtain an adequate answer in a given situation if the appearance of the plant in a polluted area is evaluated in connection with its fluoride content. This is the main subject to be discussed in this paper with special consideration to the water uptake of the plant which is particularly important for the physiological state of the plant and for the extent of its damage.

It is true, the chemical analysis of the plant in conjuntion with its macroscopic appearance form the basis for proving HF damage. On the other hand, many environmental factors affect the fluoride uptake of the plant and therefore excessive fluoride levels are only an indicator of the fluoride effect; they are not conclusive criteria of damage to the plant.

Most significantly, the presence of fluoride in the air rather than in the soil determines the uptake and accumulation of lfuoride in plant tissue. The uptake of fluoride in the plant is dependent on such factors as the kind of plant, its species, its age and the stage of its development, the duration of exposure to the pollutants, conditions of growth and cultivation, climate and many others. Because these conditions are difficult to control, the fluoride content of a plant is subject to wide variations, a fact responsible for the limited value of the fluoride assays of a plant.

Although, basically, the degree of damage is not directly related to the fluoride content of a plant, fluoride-induced damage can be assumed when its fluoride content is very high. Nevertheless, even though the leaves and needles are high in fluoride, they may not be damaged, a fact to be discussed below.

On the other hand, what conclusions can be drawn from visible damage in the form of necoses, chloroses and variations in the habitus of a plant? In association with other investigative methods which must also include other nonfluoride-induced environmental parameters, the symptomatology exhibited by a plant merely gives us a lead in evaluating the degree of environmental fluoride damage. Other sources of damage such as parasites of animal or plant origin, infectious diseases, unfavorable sites, etc. must be investigated. Therefore, the occasional occurrence of certain visible symptoms of damage also must be considered only as an indicator, but not as final proof of smoke damage. This holds true for acute as well as for chronic damage to leaves and needles.

For instance, among various varieties of gladiolas grown in eight

gardens of rural areas of Baden-Wurttemberg in two successive years, we found necroses limited solely to the tip of the leaves; we also found others which extended at different degrees, to 15 cm along the margins of the leaves. The appearance of these lesions was typical of what is described in the literature as fluoride burns. However, the fluoride content of the leaves was within normal limits. Of 94 plants, the mean was 3.4 ppm in dry substance with a range of 2 to 10 ppm. Less than 5% of the surface of the leaves was damaged. No definite cause for this damage could be determined. This observation, however, does not contradict the fact that gladiolas belong to the group of plants which are specifically susceptible to fluoride damage.

Conclusions concerning fluoride-induced damage can be drawn only if other criteria of fluoride pollution and its effect have been established. After ruling out other possible factors, all must be weighed together before arriving at the conclusion that the damage to vegetation is fluoride-induced. Clues for the diagnosis are the recognition of species-specific differences in resistance, the age of the leaves, their stage of development and the effect of these factors on the distribution of the toxic symptoms in the plant. We repeatedly observed that conifers, especially spruces which are planted close together, can manifest considerable differences in individual resistance, one being severely damaged, the other appearing almost normal. What is decisive is not the symptomatology of an individual plant, but the general appearance of different plants and the overall aspect of the whole area, especially their proximity to the source of emission or of impact. Many kinds of natural environmental factors can precipitate the deterioration of the physiologic state of a plant. In spite of this, it is difficult to arrive at a final proof because even the recognition of natural factors damaging to vegetation in a polluted area requires much skill. Hilkenbaumer, for instance, writes in his book, "Obstbau", 1964 (1): "It is difficult to differentaite nutritional disturbances from the symptoms which originate through disease, viruses, climatic and spray damage". Others also point to the uncertainties and to errors in the evaluation of pollution damage resulting from environmental and pathological sources (2-11).

For a healthy plant metabolism certain mineral nutrients are required. Otherwise abnormal changes appear such as necroses, chloroses, spoon-like curling of leaves similar to those caused by fluoride. Of particular significance is a lack of potassium in leaves and needles.

In the following discussion, we shall illustrate how faulty conclusions can be drawn concerning the fluoride content of leaves and the symptomatology on the basis of data obtained from apricot orchards situated close to a fluoride-emitting factory in Wallis, Switzerland (12). The sandy, calcium-containing soils of that region tend to dry out easily because of the high temperatures prevailing during the summer and because of strong winds, frequent violent storms and lack of moisture in the mountainous area. In a neighboring fluoride-exposed apricot orchard, irrigation and good care reduced the foliar damage from 70% to about 5% compared with the previous

year when there was no irrigation and there were tall weeds. Yet, it is noteworthy that the fluoride content of the leaves rose from 255 ppm to 450 ppm in dry substance compared with that of the previous year.

In bordering orchards which were poorly tended during both years, and where leaves showed considerable fluoride damage, the leaves contained about 250 ppm fluoride during the same years. The main reason for the marked increase of the fluoride levels in the first-mentioned orchard is the fact that the stomata of the leaves remained open longer because the water supply was more adequate. Therefore, in contaminated areas the optimal supply of water and nutrients plays a decisive part in reducing the damage to agriculture and forestry. Especially during extremely dry summer months, changes in leaves or needles due to dryness can occur even without pollution; they cannot be differentiated from those induced by pollution. In a dry climate or during dry years, grass and highly extensive growth of weeds between fruit trees is indicative of damage and of physiological weakening of the trees. On the other hand, in areas with much precipitation or during so-called "wet years" or high levels of ground water, cultivation of fruit orchards located on grassland is not only possible, but actually necessary. In addition to the climate, conditions at the site of the plant and the kind of the plant determine its demand for water. As to the climate, it should be mentioned that higher average yearly temperatures entail greater evaporation from the plant and from the soil.

In a polluted area, the uptake of sufficient mineral nutrients from the roots, which depends on adequate water balance, facilitates greater transpiration of calcium, magnesium and aluminum through the stream of the plant. Thus, the noxious ion is transformed into a less soluble compound.

This fact explains why, at the sedimentation pond of the aluminum smelter in Rheinfelden, unexpectedly certain wild plants developed normally. The effluent water of the sedimentation pond, with a fluoride content of approximately 20 ppm, is derived from the scrubbing equipment by means of which the air of the halls is cleansed of HF. Experimentally, we immersed a number of plants in pots up to 1/3 into the pond. The location of the experimental study was in the immediate neighborhood of the electrolysis hall where there was excess pollution. In spite of the extremely high fluoride levels, the leaves showed no visible damage (Table 1) but their growth was retarded. The latter may have been due to the surplus of water.

In another study, at a fluoride-emitting source in the Neckar Valley, we observed no visible damage to the leaves of trees and spruce needles in spite of relatively high fluoride content (Table 2). The favorable supply of water and climatic conditions, mainly precipitation, moisture of air and conditions of soil, particularly its capacity to retain and conduct water, were held responsible.

Table 1
Fluoride Content of Several Plants Derived From Sedimentation Pond of an Aluminum Smelter

Kind of Plant	Total Tests	Mean F^- Content (ppm dry substance)
Ryegrass	4	1790
Forsythia	1	1800
Privet	2	3100
Lilac	1	3400
Ash	2	3980
Margarita	2	4980
Poplar	1	5300
False Jasmine	2	13000

For ryegrass, we assayed the total supraterraneous organs of the plant; for all others, the leaves.

In the same area, we assayed a number of vegetables and found the highest fluoride levels in leaves of string beans and tomatoes, namely 642 ppm and 678 ppm in dry substance, respectively. These plants, too, showed no evidence of damage.

Table 2
F^- Content of Undamaged Leaves and Needles in the Environment of a Fluoride-Emitting Source up to a Distance of 1.5km

Kind of Plant	Total Tests	Mean F^- Content (ppm dry substance)
Fir Needles-age 1		184
Fir Needles-age 2		290
Apple	3	309 (95-561)
Pear	3	376 (263-603)
Sweet Cherry	5	265 (159-397)
Sour Cherry	1	103
Plum	2	425 (259-590)
Nut	1	425
Reneclaude	1	189
Chestnut	1	355 (202-471)
Red Beech	1	279
Birch	3	264 (219-314)
Hazelnut	1	705
Black Currant	1	505

Therefore in a polluted area a number of factors, especially the optimal water and nutrition, tend to reduce the damage to agriculture and

forestry. Every factor which disturbs the water supply, including a surplus of water* in the soil, leads to the physiological weakening of the plant. Due to this stress situation resistance towards fluoride emissions is lessened. Therefore, even at relatively low fluoride levels in the organs of a plant, symptoms of damage may arise.

Stress situations such as dryness, lack of nutrition, poor ventilation of the soil and salting of highways are often responsible for the sudden appearance of necroses on various kinds of trees and on leaves at the sides of highways in areas with, and without, pollution.

*Excess water interferes with the ventilation of the soil and therefore with the respiration of the roots.

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URINARY FLUORIDE EXCRETION IN ENDEMIC FLUOROSIS

by

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SUMMARY: Urinary fluoride is generally regarded as an index of fluoride ingestion. Urinary fluoride excretion was studied in fifty fluorotic patients living, since birth, in an endemic area. The results were related to the severity of the disease and the duration of exposure. A statistically significant correlation was present between the severity of the disease and the duration of exposure and also between the severity of disease and urinary fluoride excretion. In persons belonging to the same socio-economic status and involved in the same occupation, urinary fluoride levels varied grossly with the duration of exposure.

Introduction

Urinary fluoride levels are widely regarded as one of the best indicators of fluoride intake (1). Various workers have emphasized that there is an extraordinary linear relation between the concentration of fluoride in drinking water and urinary fluoride excretion (2). Largent's cases showed such a balance after a minimum exposure to fluoride of ten years (3). A correlation between the level of fluoride in water, duration of exposure, and the occurrence of fluorosis has also been reported (3). Data on the whole body burden of fluoride is difficult to obtain.

We studied whether or not urinary fluoride excretion can be used as an index of the fluoride level in the body as related to the severity of the disease taking into consideration various factors which influence the deposition of fluoride in the body such as concentration of fluoride in drinking water, total duration of exposure and occupation of the patient.

Materials and Methods

In 50 patients the diagnosis fluorosis was confirmed radiologically. They had been residing since birth, in natural fluoride areas where drinking water contained 5-6 ppm fluoride (Table 1). Their daily intake of fluoride was estimated to be 12-15 mg.

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Table 1

Distribution of Patients

Duration of Residence in Endemic Area	Male	Female	Total	Manual Labor	Sedentary
25-34	7	5	12	11	1
35-44	16	5	21	19	2
45-54	9	6	15	13	2
55-64	2	0	2	0	2

After admission to the hospital a careful history was taken and a meticulous physical examination was carried out. The degree of dental changes was charted according to the criteria of Singh (4). X-rays of the entire skeleton were made to classify the radiological changes due to fluorosis (5).

Urinary Fluoride Estimation: Urine collection was started the day after the patients were admitted. The 24-hour urine was measured accurately and fluoride estimates were done immediately after collection for three consecutive days. The fluoride ion electrode was employed for these estimations (6). The mean values were taken as representative readings.

The coefficient of correlation and linear regression were calculated to study the effect of duration of exposure on the fluoride level in the urine (Table 2).

An analysis of the various features observed on dental and physical examination in relation to urinary fluoride excretion is shown in Tables 2-5. The Chi-square test was used to determine the relation between duration of exposure, degree of the disease, and urinary fluoride level.

All patients observed in this study were moderately nourished and not suffering from any other disease. Most patients (42%) belonged to the 35-44 year age group, with the males predominating. In relation to the other age groups, this disparity was less marked.

Results

The minimum age at which the first manifestations occurred in our series was 25; the mean age was 40.2 years. The disease was more prevalent in manual laborers who formed 86% of the total number of cases. Even among the manual laborers, 64% developed clinical features of the disease only after they had been residing in endemic areas for thirty-five years.

No statistically significant correlation was found between the

Table 2

URINARY FLUORIDE EXCRETION IN ENDEMIC FLUOROSIS

Patient Number	Years in Residence in Endemic Area	Duration in Years of Symptoms	Back Stiffness	Neck Stiffness	Paresthesias	Root Pains	Limb Weakness	Muscle Wasting	Muscle Power	Muscle Tone	Sensory Deficit	Planter Reflex	Flexor Spasms	Dental Changes	Exostoses	F⁻ in Urine (mg/day)
1	50	3/12	+	+	+	+	+	-	3/5	H	+	E	+	2	3	4.8***
2	40	1 1/2	+	+	+	+	+	-	3/5	H	+	E	+	2	2	6.6
3	30	1 1/2	+	+	+	+	+	-	3/5	H	+	F	-	2	2	5.4
4	40	1	+	+	+	+	+	-	4/5	H	+	E	-	3	8	4.6
5	40	1	+	+	+	+	+	+	3/5	H	+	E	-	2	2	14.1
6	25	1	+	+	+	+	+	+	2/5	H	+	F	+	2	1	17.9
7	40	1¼/12	+	+	+	+	+	-	3/5	H	+	F	-	2	1	27.0
8	35	6/12	+	+	+	+	+	+	2/5	H	+	F	+	2	1	13.0
9	38	6/12	+	+	+	+	+	+	0/5	H	+	E	+	2	2	15.7
10	50	1/12	-	-	-	+	+	-	3/5	H	+	E	+	2	2	20.0
*11	40	1/12	+	+	+	+	+	-	4/5	N	+	F	-	2	2	5.7
12	35	3	+	+	+	+	+	-	4/5	N	+	E	-	2	10	6.3
13	50	5/12	+	+	+	+	-	-	5/5	N	-	F	-	2	4	8.1
14	50	6/12	+	+	+	+	-	-	5/5	N	-	F	-	2	2	6.3
15	25	3/12	+	-	-	+	+	-	0/5	H	+	E	-	2	2	9.1
16	40	-	-	-	-	-	-	-	5/5	N	-	F	-	1	1	3.9
17	45	6/12	+	+	-	-	-	-	5/5	N	-	F	-	2	1	3.8
18	35	8/12	+	-	+	+	-	-	2/5	H	+	E	+	2	1	7.2
*19	40	8	+	+	+	+	-	-	5/5	N	-	F	-	-	-	3.0
20	36	6	+	-	-	-	-	-	5/5	N	-	F	-	2	3	4.4
21	30	1	+	+	+	+	-	-	5/5	N	-	F	-	1	-	1.5
22	30	3/12	+	+	+	+	-	-	5/5	N	-	F	-	2	2	6.8
23	30	7	+	+	-	-	-	-	5/5	N	-	F	-	2	4	2.8
*24	55	1	+	+	+	-	-	-	5/5	N	-	F	-	2	5	1.5
25	32	1/12	+	-	-	-	-	-	5/5	N	-	F	-	1	-	6.8
*26	63	2/12	+	+	+	+	-	-	5/5	H	+	E	-	1	2	2.8
*27	31	6/12	+	-	-	-	-	-	5/5	N	-	F	-	1	1	1.5
28	35	6/12	+	+	+	+	+	-	3/5	H	+	E	+	3	3	4.9
*29	53	6/12	+	-	-	-	-	-	4/5	N	+	F	-	2	2	2.6
30	35	1/12	+	-	-	-	-	-	5/5	N	-	F	-	1	-	13.0
31	45	1/12	+	-	-	-	-	-	5/5	N	-	F	-	1	2	9.5
32	30	3/12	+	-	+	+	-	-	5/5	N	-	F	-	1	-	1.2
33	35	2/12	+	+	+	-	-	-	5/5	N	-	F	-	3	-	4.7
34	35	3/12	-	-	+	-	-	-	5/5	N	-	F	-	1	2	2.7
35	45	2	+	+	+	+	+	-	4/5	N	+	F	-	1	4	3.2
36	45	10	+	+	-	-	-	-	5/5	N	-	F	-	2	4	2.0
37	50	1	+	+	+	-	-	-	5/5	N	-	F	-	2	2	6.5
*38	50	3	+	+	-	+	-	-	5/5	N	-	F	-	4	4	8.2
39	45	4/12	+	+	+	+	-	-	5/5	H	+	F	-	4	6	10.2
40	42	1/12	+	-	+	-	-	-	5/5	N	-	F	-	2	2	6.0
41	40	6	+	-	-	-	-	-	5/5	N	-	F	-	1	-	1.2
42	30	2	-	-	-	+	-	-	5/5	N	-	F	-	-	-	2.1
43	54	8	+	+	+	+	+	+	4/5	H	+	F	-	4	3	4.5
44	30	1	+	+	-	+	-	-	5/5	N	-	F	-	1	-	1.9
45	40	2	+	+	-	-	+	+	4/5	N	+	F	-	3	4	7.6
46	35	1	+	+	+	-	+	+	3/5	H	+	E	+	2	6	5.8
47	30	3/12	+	+	-	-	+	+	4/5	N	+	F	-	2	4	9.2
48	40	4	+	+	+	+	-	-	5/5	N	+	F	-	1	8	8.6
49	45	1	+	-	+	-	-	-	5/5	N	-	F	-	1	-	1.5
50	50	1	+	-	+	-	-	-	5/5	N	-	F	-	1	-	1.8

* = Sedentary; N = Normal Tone: F = Flexor; H = Hypertonic; E = Extensor
** Mean Duration of Stay = 40.2; S.D.± 9.1 *** Mean Urinary F⁻ = 6.5; S.D.±5.2

duration of exposure and the fluoride excretion in the urine.

In the only two cases without dental changes, the excretion of fluoride was 1 ppm (4.4mg and 2.1mg respectively). Grade 1 changes were associated with an excretory level of 1.2-2.7 mg/day. Grades 2 and 3 showed no correlation with the urinary fluoride levels. Of the five patients who exhibited Grade 1 mottling associated with a high fluoride excretion in urine, one person had genu valgum, another showed gross kyphosis.

The earliest symptoms of fluorosis were stiffness of the back and of the lower limbs and pains in one or both knee joints. Difficulty in squatting, the first complaint of the affected persons, occurred when the excretion was as low as 1.2 mg/day. Paresthesias of hands and feet were also present early in the disease either as a single complaint or combined with stiffness of the back. Urinary fluoride was low in these cases.

Radiculopathy, particularly in the cervical region, was the most common neurological symptom. In 27 out of 29 patients with radiculopathy, the urinary fluoride level was above 3 mg/day. In the other two, both aged 30, urinary fluoride excretion was 1.2 and 1.9 mg/day.

Myelopathy was observed in 75% of the patients with radiculopathy; three cases had paraplegia; the other eighteen complained of weakness of both upper and lower limbs at varying degrees. In most individuals the sensory symptoms preceded the motor symptoms, but at the time of examination both were invariably present in all patients. The spinal cord was involved only when fluoride excretion was 4.5 mg/day or above. Wide variations in urinary fluoride levels were noted in individuals exhibiting the same clinical picture.

Table 3
Stage of Fluorosis Related to Urinary Fluoride

F⁻ Excretion mg/day	1.2-3	3.1-4.5	4.6-6.5	6.6
Crippling Disease	0*	0	0	11
Radiculomyelopathy	0	1	8	4
Radiculopathy	5	1	1	2
Early Symptoms	9	5	2	1

*Number of patients $x^2 = 24.245$ $P = < 0.01$

Crippling fluorosis, which is indicative of the advanced stage of the disease, was seen in eleven patients all of whom were manual laborers. It was associated with urinary fluoride levels as low as 6.6 mg/day. However, some cases have shown the urinary fluoride elvels up to 20 mg/day. There was significant correlation between the excretion rates of fluoride in urine and the severity of disease (Table 3). Though

the urinary excretion of fluoride did not show significant correlation with the duration of exposure (Table 4), the severity of disease correlated well with the urinary fluoride levels (Table 5).

Table 4
Duration of Exposure In Relation to Urinary F^- Level

Duration in years	Urinary F^- mg/day			
	1.2-3	3.1-4.5	4.6-6.5	6.6
55-64	1	0	1	0
45-54	2	4	5	4
35-44	4	3	5	9
25-34	6	1	1	4

$x^2 = 10.022$ $P = > 0.3$

Table 5
Duration of Exposure Realted to Stages of Disease

Number of patients with	Duration of exposure in years			
	25-34	35-44	45-54	55-64
Crippling Disease	1	9	1	0
Radiculomyelopathy	0	4	8	1
Radiculopathy	5	1	3	0
Early Symptoms	3	9	4	1

$x^2 = 23.289$ $P = < 0.01$

In all fifty cases, increased bone density was obvious roentgenologically. Even in persons who were excreting only 1.2 mg fluoride per day in the urine, roentgenological features typical of fluorosis were seen. However, Grade 3 changes were observed only in patients whose excretion of fluoride was above 6 mg/day.

Discussion

Fluoride is excreted from the body throught different routes. Elimination through the feces and sweat is of minor importance and its significance in the fluoride balance has not been adequately established. According to Largent persons who are in a state of fluoride balance ultimately excrete each day an amount of fluoride essentially equivalent to that taken into the body.

The mean duration of exposure at which the disease becomes symptomatic, namely 40 years, is comparable with that reported by Shortt et al. (7) and Leone et al. (8). However, they found no significant correlation between the duration of exposure and the urinary fluoride excretion.

The prevalence of the disease among manual laborers has also been recognized by other workers (3); but the advanced age of onset -- even among those residing in hot climates under conditions of malnutrition -- is a feature at variance with the findings of Siddiqui (9).

Dental mottling was present even in persons excreting as little as 1.2 mg fluoride per day in urine, a finding which agrees with that of Sid-

diqui (9). But minor (grade 1) dental changes seen also in patients with high urinary fluoride excretion may have to be explained by the presence of osteal deformities in persons in whom fluoride deposition in the teeth may have been less than in bones.

Our X-ray findings are in contrast to those of Largent (3) who reported that at Stage 3 the minimum fluoride concentration in the urine is 10 ppm. Moreover, osteoporosis, which has been reported by some workers (10) is not evident in our study.

Stiffness of the back and paresthesias are the earliest manifestations of this disease as was also noted by Siddiqui (9) and Singh et al. (11). Even in persons showing manifestations of advanced disease, the urinary fluoride level was less than their estimated intake of fluoride, thus indicative of a stage of positive fluoride balance. Largent (3) recorded a balance in three individuals ingesting 2, 5.5 and 6.1 ppm fluoride for ten, twenty-nine and thirty-four years, respectively. In our experience, however, persons were in positive balance even after much longer periods of consumption of water with higher levels of fluoride. Furthermore, the degree of the excretion does not vary with the duration of exposure, nor is it to the occupation of the person, considering various factors which hasten the deposition of fluoride in persons doing manual work. Nevertheless, the relation of the stage of the disease with urinary fluoride excretion as well as with the duration of exposure, is noteworthy.

Our studies demonstrated that urinary fluoride excretion is not a reliable indication of the total body exposure to fluoride. At the same time, the severity of the disease can be predicted according to the urinary fluoride level. Furthermore, our findings are comparable with those of many workers (12) who reported that urinary excretion of fluoride is directly related to the level of fluoride intake. Duration of exposure also affects the disease process, there being a significant distribution of the patients in different age groups. The urinary fluoride appears to be a better indicator of the stage of the disease than duration of exposure. This phenomenon suggests that body saturation with fluoride is governed by factors other than exposure to fluoride.

On the other hand, the manifestations of disease at various stages are a clear indication of the total body saturation with fluoride, the symptoms depending on the degree of saturation. Further, the lack of correlation between the duration of exposure and the urinary fluoride may indicate that the rates of equilibrium for fluoride differ from person to person. The mechanism by which fluoride is metabolized in the body, if known, could throw light on the diverse fluoride excretion rates of those residing in endemic areas where the level of fluoride in drinking water remains constant.

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SPECIAL REPORT

A NEW CONCEPT OF THE EFFECT OF FLUORIDES ON BONE

by

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SUMMARY: Chronic fluoride intoxication in humans and animals can produce four distinct bone diseases: osteosclerosis, osteomalacia, secondary hyperparathyroidism and osteoporosis (partly combined). On the basis of own experience and a review of the literature a theory is presented in an attempt to explain these four contrary findings. According to this theory, the dosage of fluoride, the deficiency of calcium and vitamin D, differences of species, duration of fluoride intake and individual sensitivity play an important role. Fluoride acts upon three bone constituents: osteoblasts, osteoclast and bone mineral.

In chronic fluoride intoxication in humans and animals the pathological picture of the skeletal system varies. Four distinct pathological bone conditions occur namely, 1. osteosclerosis i.e. in humans; 2. osteomalacia i.e. in humans and ruminants; 3. secondary hyperparathyroidism i.e. in humans and sheep; and 4. osteoporosis i.e. in rats.

These contradictory findings, severe osteosclerosis on the one hand, osteoporosis or osteomalacia on the other, have been the basis for confusion respecting the effect of fluoride on the skeletal system. Roholm (1-3) was first to propose a rational explanation for the discrepancies in the above findings. He observed that small doses of fluoride in old rats and in humans cause osteosclerosis, whereas large doses lead to osteoporosis and osteomalacia, especially in growing animals with a great demand for calcium.

Kellner (4) believed that precipitation of calcium in the bone is the primary mechanism leading to the development of a rachitic-like picture. Thus, periosteal bone formation might represent a functional com-

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pensation for decline in bone strength induced by rachitis. Osteosclerosis is the healing stage of rachitis.

DeSenarclens (5) also recognized that resorption (osteitis fibrosa) is the first phenomenon of the effect of fluoride related to fluoride tissue acidosis. The second stage would be formation of new bone, especially when low doses of fluoride are involved. Weinmann and Sicher (6) believed that changes of the matrix represent the primary damage by fluoride due to its toxic action upon the cells and upon formation of apatite. According to their observations the initial phenomenon is increased resorption of bone substance. The compensatory newly-formed bone is immature and, therefore, readily resorbed which accounts for the development of osteoporosis.

According to Johnson (7) the main effect of fluoride is its impact on the osteoblasts through alteration of the lipid chemistry. The periosteal bone formation develops proportionally with the mechanical weakening of the old bone due to primary acceleration of cortical remodeling. High fluoride concentrations cause osteomalacia and damage the osteoblasts.

Nichols et al. (8) assume that new bone formation is merely the result of stimulation of the parathyroid glands. The other effect of the parathyroid glands, stimulation of resorption, is blocked.

According to Brearley and Storey (9) and Malcolm and Storey (10) disturbed and delayed mineralization combined with increased resorption, the initial effect of fluoride, is followed by intermittent calcification with hyper or hypomineralization, proliferation, and increased bone remodeling. These contradictory pathological findings in the literature can be explained by the fact that they were dealing with different stages of the disease.

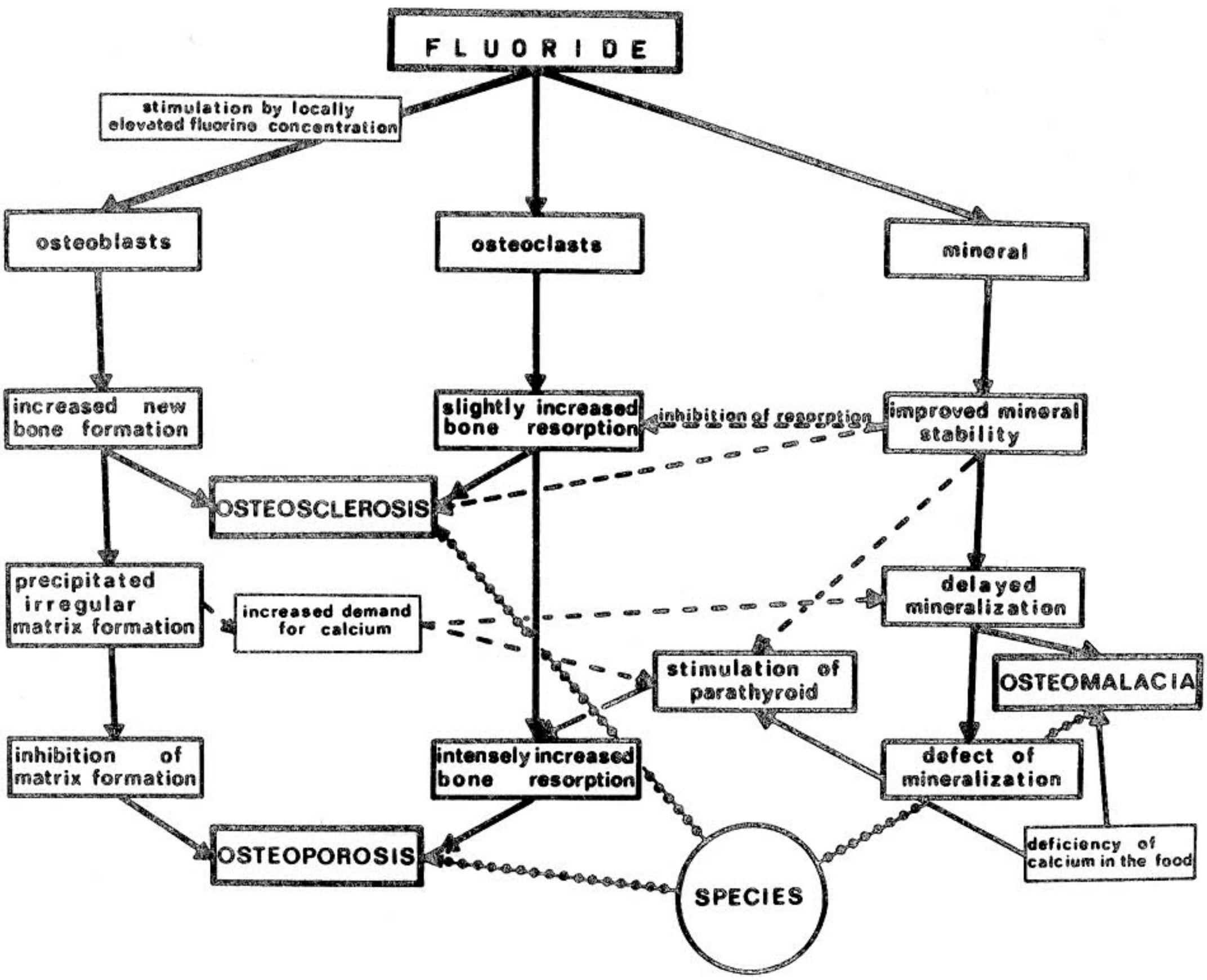
Jowsey et al. (11, 12) proposed the following theory: Fluoride stimulates the osteoblasts. Consequently, the increase in matrix formation enhances the demand for calcium. The resultant reduction of the blood calcium and calcium deficiency leads to impaired mineralization (osteoid formation) and to excess bone resorption.

Shupe et al. (13, 14) emphasize the abnormal activity of osteoblasts which accounts for an abnormal matrix with defective mineralization. Rich and Feist (15) and Rich (16) hold the high localized concentration of fluoride in newly-formed bone and on the bone surface responsible for the fluoride-induced changes. Increased concentration of fluoride involves the osteoblasts, osteocytes and, by resorption, also the osteoclasts. With the enhanced stability of bone mineral the osteoclasts are inhibited.

According to Weatherell (17, 18) and Weatherell et al. (19) the high local concentration of fluoride near the newly-formed crystallites in areas of active mineralization provides the main clue for the action of fluoride. An excessive response of the osteoblasts accounts for disturbance of the matrix and mineralization ensues. Because osteoclasts are stimulated by fluoride, resorption of bone also increases. Resorption is further enhanced by an increased demand for mineral.

Figure 1

F^- Action on Bone



We, too, believe that fluoride exerts a direct stimulation of osteoblasts, probably through stimulation of enzyme activity (Fig. 1). In this manner we can explain the strong osteoblastic effect of fluoride, especially in humans (Figs. 2 & 3). In therapy for osteoporosis, for instance, fluoride blood reaches a concentration of 10^{-6}M (.019ppm)

Figure 2
Extreme Sclerosis in Fluorosis (Stage III)

Figure 3
Extreme Sclerosis of Spongiosa of Body of Lumbar Spine in Fluorosis (Stage III)

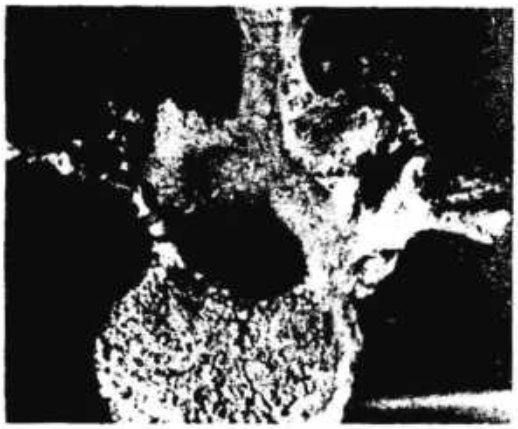
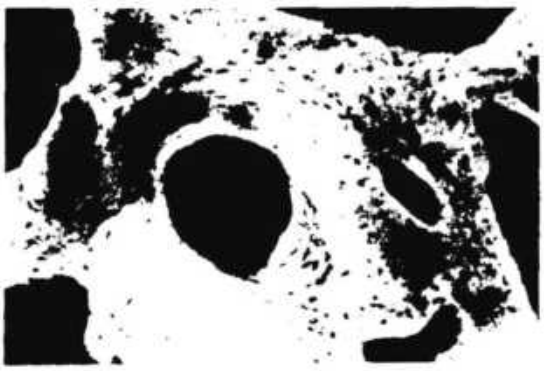
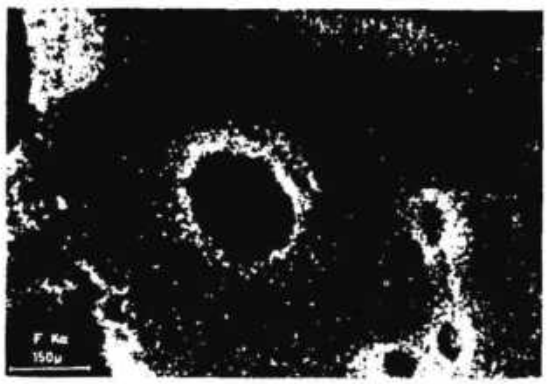


Figure 4
Iliac Crest after NaF Therapy

Microradiography



F^- Deposition in Bone
Electron Probe X-ray Microanalysis according to BANG (3)



(20) whereas in vitro concentrations of 10^{-2} to 10^{-5}M (0.19 ppm) are required to influence enzyme activity (21). Fluorides are deposited at the surfaces of bone, near the blood vessels, and in the newly-formed crystallites (22) (Fig. 4). This enhances the fluoride concentration near the bone cells making stimulation of certain enzymes possible even from low doses (23).

Figure 5
Iliac Crest Bone in Incipient Fluorosis

Periosteal New Bone Formation (x 102)

Figure 6
Femur Section in Fluorosis (left)
Stage III

Periosteal Bone Apposition and Narrowing of Bonemarrow Canal

Figure 7
Iliac Crest after 24 Months NaF Therapy

New Bone Formation on previously existing Trabecula (x 200)

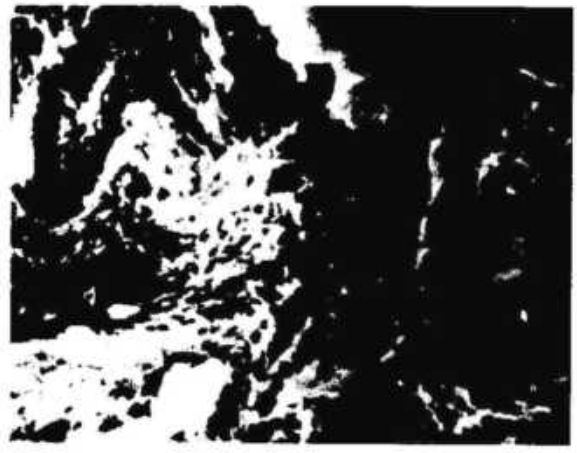
This stimulation of osteoblasts induces new bone formation especially at the periosteum -- where fibrous bone is formed which later becomes lamellar bone (Fig. 5) — endosteally (Fig. 6), and by apposition on previously existing trabeculae (Fig. 7). Such stimulation takes place with doses of 40-60 mg NaF/day.

Further increase in dosage -- either relatively short-term high dosage or low doses over a prolonged period of time -- results in higher concentration of fluoride in the bone and leads to inhibition of certain enzymes (23). Irregular matrix formation (Figs. 8 & 9) and, with still higher doses, even inhibition of matrix formation ensues.

Figure 8
Iliac Crest Fluorosis (Stage III)

Irregular Cancellous Bone (x 5)

Figure 9
Scanning Electron Microgram



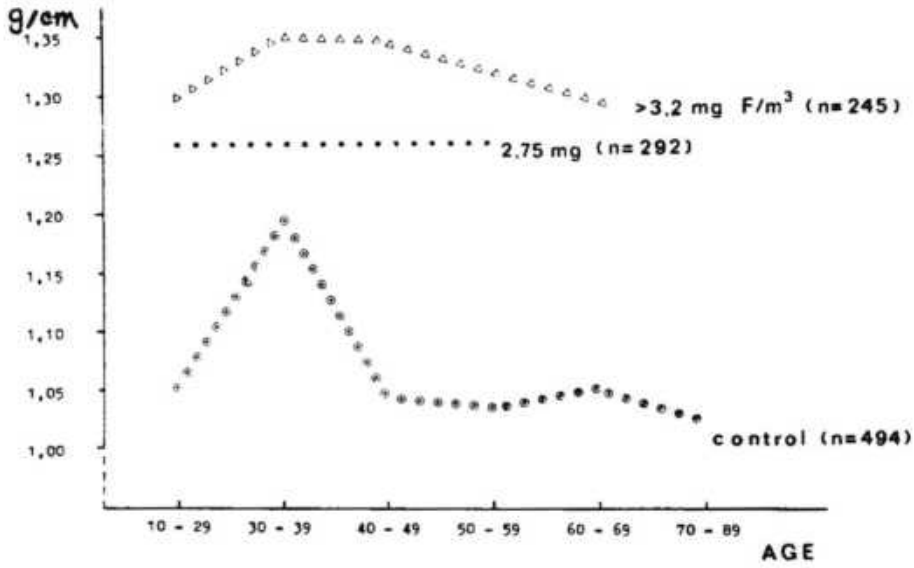
Rib Surface in Severe Fluorosis

The following constitutes evidence of a disturbance of bone cell metabolism at high dosages: a decrease in glycosaminoglycanes and total hexosamines, fluoride concentrations in bone of more than 4,300 mg F/g (25), a decrease of total lipids, of citrates, and exogenous consumption of glucose (26,27), electron microscopically observed disturbances of cell organelles which are responsible for the synthesis of proteins and production of energy (28,29) and completely irregular orientation of collagen fibers in severe fluorosis upon electron microscopy (30,31).

In addition, fluoride primarily stimulates the osteoclasts. The degree of this stimulation is dependent on the individual reaction from person to person. Localized high fluoride concentrations by the degradation of fluoride-containing minerals induce bone resorption. They also account for direct action of fluoride on enzyme activity. The parathyroid hormone (PTH) affects the bone; it stimulates adenylcyclase, which catalyzes cyclis AMP (32). According to Hardeland (33) the adenylcyclase is also directly stimulated by fluoride, which explains the increase in bone resorption without an increase in PTH. In industrial fluorosis we have never found signs of hyperparathyroidism in spite of evidence of increased bone resorption (spongiozation of corticalis) (Fig. 10) and of increased bone remodeling.

Figure 10
Spongiozation of Corticalis of the Iliac Crest
in Fluorosis (Stage II) x 18.5

Figure 11
Increased Mineral Content of Radius
in Aluminum Workers



F^- Concentration of Dust at Place of Work (2.75 and above 3.2mg F/m^3) determined by means of Direct Photon Absorption Technique

At low dosage, bone formation predominates over resorption and osteosclerosis ensues. In industrial fluorosis resulting from long-term exposure, hyperossification and hypermineralization develops (Fig. 11) (22, 34-37). Both processes improve the physical properties of the bone in the initial stages of the disease (38).

The third effect of fluorides on bone is concerned with the bone mineral. By means of X-ray diffraction analyses others (29,35,39-41) and ourselves (42) observed improvement of the crystallinity of mineral through perfection of the crystal lattice (43,44), through formation of fluorapatite, or through turning brushite and octocalciumphosphate into apatite (22,45).

It could be demonstrated, by means of small angle X-ray diffraction analysis, that the improved crystallinity is accompanied by an enlargement of the crystals (39,46). Enlarged crystals react more slowly, inhibiting resorption. Studies pertaining to in vitro dissolution showed that fluorotic bone ismore stable than normal bone in resisting resorption induced by parathyroid hormone (47,52). However, contrary results have also been recorded (53-55).

Many authors consider the improved stability of mineral and the consequent inhibition of resorption the main effect of fluoride (56-59). Inhibition of resorption then causes secondary hyperparathyroidism by interfering with the homeostatsis of calcium (60-70).

Rich (16) and Rich and Feist (15) share our view that reduced crystal solubility of the mineral is not the main effect of fluoride on bone. Too much time is required for turning a large quantity of hydroxyapatite into fluorapatite in view of the fact that it takes 10-20 years to replace half of man's bone mass. The fluoride effect begins after a few weeks or months. Accordingly the improved mineral stability can only partly contribute to the pathological picture of chronic fluoride intoxication.

At higher doses, mineralization cannot keep pace with the precipitated irregular matrix formation resulting in mottled bone and increased osteoid formation (Fig. 12) as for instance, during the treatments of osteoporosis with doses above 80 mg NaF/day. Genuine osteomalacia has only been found in grazing animals, especially in dairy cows (14,71-73), and in endemic human fluorosis (74,75) in South India. In both instances very high doses were involved namely, up to 4 mg F^-/day solely from drinking water (76). We (77) observed a severe osteomalacic component in a case of fluorosis, stages 2 to 3, (Fig. 13) associated with an advanced kidney disease. In severe fluorosis we saw old hyper and young hypomineralized irregularly arranged osteons (Fig. 14).

Deficiency of calcium further aggravates the condition. Human fluorosis with osteomalacic component occurs only in the southern part of India where, in addition to malnutrition, vitamin D and calcium deficiency is likely to prevail. Jolly et al. (75) did not find osteomalacia in northern India where nutrition and calcium intake is adequate. In dairy cows, the calcium balance is under stress because of lactation. After 2-3 periods of

lactation soon after new calving, so-called "milk fever" with severe hypocalcemic states can develop. This alimentary deficiency of vitamin D and calcium, the increased demand for calcium at precipitated matrix formation, as well as improved mineral stability causes secondary hyperparathyroidism at this high dosage. Cases of secondary hyperparathyroidism associated with endemic human fluorosis have been reported frequently from South India (74,76,78-81).

DeSenarclens (5), Faccini and Care (62), Faccini (60,61), and Yates et al. (82) observed in experimental animals on over-activity of the parathyroid glands. We, too, found increased parathyroid activity leading to osteoporosis (36) in experimental rats which received 10 and 20 mg NaF/kg/day (Fig. 15) (83). The osteoporosis could likewise be explained by inhibition of matrix formation due to general intoxication of the organism from such high doses.

In industrial fluorosis, when calcium intake was adequate, we found no signs of secondary hyperparathyroidism even in the most advanced stages (37,42), nor in our patients with osteoporosis treated with NaF (40-80 mg NaF/day). Doses up to 100mg NaF/day failed to increase PTH, determined by the radioimmunological method, during therapy for osteoporosis (84).

These processes are decisively influenced by differences in the species. According to Greenwood (85) and Shupe and Alther (86), cattle are most sensitive to fluoride followed by sheep, pigs, horses, rats, rabbits, guinea pigs and poultry. The reason for the high sensitivity of cattle is undoubtedly the above-mentioned deficiency of calcium and the prolonged period that fluorides remain in the stomach of ruminants, which provides much time for resorption and disintegration of even strongly-soluble fluorides. Human sensitivity is about half-way in between. According to our investigations (83) rats are extremely resistant to fluoride and are, therefore, not suitable for experimental models (61,87). Furthermore, young animals deposit more fluoride in bone and do so more rapidly than older animals.

Many morphological differences in fluorosis can be explained by variations in doses, duration of fluoride intake, species, nutritional state, and compostition of food. In all processes, individual differences play an important role. Dose, age, and species are important in the development of fluorosis as pointed out by Jovanovits (88) as early as 1944.

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BOOK REVIEW

PROISWODSTWENNYJ FLJUOROS (INDUSTRIAL FLUOROSIS)

by

N.A. Bogdanow and E.W. Gembizkij
(Medizina, Leningrad 1975, 95 pp., 24 tables, 10 figures [Russian])

In the introduction, the authors point to the wide expansion of fluoride-containing compounds in our current economy. Chapter 1 describes the clinical features of acute fluoride poisoning based mainly on a review of the literature.

Chapter 2 deals with the usual features of chronic fluoride intoxication. It refers to the literature, particularly with reference to chronic changes in addition to those of the skeletal system. The authors quote primarily authors of the U.S.S.R., with a predominance of early publications, the most recent citations having appeared in 1971. Chronic inflammatory changes of the skin, the eyes and the upper respiratory tract (chronic rhinitis, laryngitis and pharyngitis) are reported; moreover functional disturbances of the central nervous systems ("asthenovegetative syndrome and diffuse damage of the CNS"), circulatory disturbances (bradycardia, hypotension and changes in the EKG), gastric and intestinal disorders, damage to liver and kidneys and dysfunction of endocrine organs, particulary of the thyroid, the parathyroid and the adrenal cortex. In the conclusion of this chapter alterations of the mineral metabolism are discussed.

In Chapter 3, the authors present their own studies on human chronic fluoride intoxication as observed mainly in the production of hydrofluoric acid. In the very early stage of the disease they noted "diastolic hypertension (45%), bradycardia and a decrease in peripheral resistance of the blood vessels, an increase of the minute volume and increased velocity of the blood volume expulsion". In the next phase of the disease, arterial hypertension and myocardial dystrophies occur in 43% of the cases. In the gastrointestinal tract the authors observed gastritis, at first with increased and later reduced production of acid; furthermore, duodenal ulcers. Toxic hepatitis occurred in 10% of the 201 cases observed.

With respect to the skeletal system, the authors described regional sclerosis and bone destruction which they consider early symptoms. In the accompanying illustrations, however, typical bone cysts and cortical islands can be identified which, in the opinion of the reviewer, are not related to fluoride intoxication.*

*Editor's Note: The editor, however, has observed bone cysts repeatedly, particularly in the mandible and in the distal part of the clavicle, early in the disease.

Hypocalcemia, reduced phosphorus and magnesium levels, and increased alkaline phosphatase in the serum have been observed. Radioactive iodine tests revealed, in the first phase of the intoxication, hyper function of the thyroid gland but later hypofunction; however, no clinical symptoms were observed. In the adrenal cortex, a suppression of the production of glycocorticoids was noted. These changes are nonspecific and are considered merely a reaction of the organism to any damaging agent (Sely's adaptation syndrome).

Chapter 4 presents the pathology and pathogenesis of chronic fluoride poisoning. The symptoms are attributable to the aggressive action of fluoride at localized sites, to disturbances of the calcium, carbohydrate and phosphorus metabolism to anti-cholesterase effect of fluoride, to neurovascular changes and to enzyme disturbances.

Chapter 5 covers the diagnosis, prophylaxis and therapy of chronic fluoride poisoning. Diagnostically specific is the following symptom complex: Changes in the mineral composition of serum, increased excretion of fluoride in the urine (5 mg F/1), focal and diffuse osteoporosis and osteosclerosis as well as dysthyreosis.

A new classification of fluoride intoxication is presented, namely:

Early: Minor functional changes of individual organ systems.

Moderate: Mild organic changes and pronounced functional disturbances which are responsive to therapy mainly asthenic conditions, neurocirculatory dystonia, toxic hepatitis, chronic gastritis, focal osteoporosis and sclerosis.

Severe: Major disturbances of numerous organs and systems which are not readily reversible by treatment and are only partially curable. They are protacted asthenic conditions, gastroduodentis, gastric and duodenal ulcer, osteosclerosis.

As prophylaxis, the authors recommend mechanization of work which involves fluoride compounds; adequate ventilation of working halls; control of the atmospheric fluoride content; individual protective equipment such as masks; permanent supervision of workers through otorhinolaryngology specialists; routine X-ray studies of the skeleton after three years' exposure and increased intake of calcium, Vitamin D, C and phosphorous. A change of work is desirable after five years' exposure.

Finally, the authors make certain recommendations concerning therapy of acute and chronic fluoride intoxication. The chronic form is treated with calcium and magnesium compounds as well as Vitamins C, D, B and P. Pyruvic and lactic acid preparations are also recommended.

J. Franke

IATROGENIC FLUOROSIS

(Case Report)

by

D.M. Grennan, D.G. Palmer, R.S. Malthus, M.F. Matangi and R.T.D.de Silva

(Abstracted from the Austral. New Zealand J. of Med., 8:528-531, 1978)
Dunedin, N.Z.

The authors reported a case of moderately advanced skeletal fluorosis in a sixty-nine-year-old female who developed a sudden attack of pain in the left hip and, three weeks later, similar pain in the right hip. She also had pain in the lower back, ankles, knees and shoulders. For about seven years she had been receiving prednisone in doses varying between 2 and 20 mg for the treatment of asthma; during the three previous years she had received elsewhere 60 mg of sodium fluoride and three calcium tablets (about 1g) daily in an attempt to minimize the steroid-induced osteosporosis. Prior to the fluoride therapy she had shown normal thoracic vertebrae and normal serum creatinine, serum calcium and serum alkaline phosphatase.

The examination revealed tenderness over the right iliac crest and limited movement of the cervical vertebrae on lateral flexion. Bone X-rays showed increased density of trabeculae in the lumbar and thoracic vertebrae and pelvis, gross degenerative changes of the cervical spine and a partially healed fracture of the left femoral neck. Ten days after calcium and fluoride tablets were discontinued and while the patient was placed on a daily low calcium (150 mg) diet she had a slight leukocytosis (11,000), a high serum alkaline phosphatase (280 units); serum calcium was 2.46 mmol (9.84 mg%) and the serum inorganic phosphate 1.18 mmol (3.66 mg phosphorous/100 ml). The 24-hour urine collection contained 0.8 mmol (32 mg) of calcium, 26.2 mmol (81 mg%) inorganic phosphate and 3.26 mmol (7.8 mg%) of magnesium. Tubular reabsorption of phosphate was 73% (normal 85%). The iliac crest bone biopsy showed evidence of osteomalacia with widespread uncalcified osteoid seams. The Haversian systems seemed normal and there were no enlarged osteocytic lacunae. The ashed specimens contained 10,640 ppm fluoride in cancelleous bone and 4060 ppm in cortical bone. The fracture of the left femoral neck, after fluoride treatment, was considered consistent with a pseudo-fracture of osteomalacia.

The authors cited a recently reported death by E.G. McQueen in the New Zealand Medical Journal (86:248, 1977) from renal failure which developed while the patient was being treated with 44 mg/day sodium fluoride.

DETERMINATION OF FLUORIDE IN DEBONED MEAT

by

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(Abstracted from Assoc. of Official Analytical Chemists, Inc., 61:4, 1978)

The fluoride content of mechanically deboned meat was measured by a new rapid analytical procedure by means of the specific ion electrode. Deboned comminuted meat is defatted with petroleum ether. Disodium EDTA is added in order to complex calcium and a total ionic strength adjustor to complex interfering ions such as aluminum and iron and to provide a constant background ionic strength to decomplex fluoride and to adjust the pH of the solution. The fluoride is then determined by comparison to a standard curve on semilogarithmic graph paper of fluoride ions vs millivolt readings.

The method is applicable to pork, beef and poultry which has been deboned either by hand or mechanically. Levels above 25.0 ppm are measured by analyzing additional standards and extending the curve into a third cycle. Samples less than 0.7 ppm can be estimated by extrapolation. The average recoveries amounted to 92 ± 4.2 %. The standard deviation of duplicates within the laboratory was 0.5 ppm in the above-stated range.

The analysis of deboned meat (beef, pork and poultry) by the conventional diffusion method and the one reported here gave very satisfactory comparable results in the range from 0.7 ppm to 35 ppm. Mechanically deboned meat contained much more fluoride than that deboned by hand. The highest concentrations recorded were 33.8 and 35.0 ppm.

THE EFFECT OF FLUORINE AND LEAD IONS ON THE CHROMOSOMES OF HUMAN LEUKOCYTES IN VITRO

by

D. Jachimczak and B. Skotarczak
Szczecin, Poland

(Abstracted from Dept. Biol., Inst. Biostruct., Pomeranian Med. Acad., ul. Dunikowskiego 6:70-123)

The authors studied human leukocytes in vitro to which they added lead ions at concentrations of 10^{-3}M (19 ppm) and 10^{-5}M (0.19 ppm) and fluoride at concentrations of $3.15 \cdot 10^{-3}$M (59.85 ppm), $3.15 \cdot 10^{-4}$M (5.98 ppm), $3.15 \cdot 10^{-5}$M (.598 ppm). Both agents induced structural and quantitative aberrations in the chromosomes of the kind indicative

of the mutagenic property of fluoride and lead. The lowest concentration of fluoride ($3.15 \cdot 10^{-5}$M or .598 ppm) was equal to that in the water supply of the city of Szczecin, Poland where water is fluoridated for the prevention of tooth decay. The authors expressed concern about the suitability of this measure.

EFFECT OF FLUORINE ON CALCIUM ABSORPTION IN THE TREATMENT OF OSTEOPOROSIS

by

J. Kocián, P. Macháček and V. Marat

(Abstracted from Cas. lek. ces, 117:619-622, 1978 [Czech])

In treating osteoporosis with sodium fluoride many authors recommend the addition of calcium. However, there is a possibility that insoluble CaF_2 is formed in the gastrointestinal tract leading to decreased absorption of calcium and fluoride. The authors therefore determined the absorption curves for calcium by measuring the calcium level in the blood 30, 60, 90, 120, 180 and 240 minutes after uptake of 10 mg Ca^{++}/kg body weight as calcium lactate among healthy and among osteoporotic patients in its relation to the dose of sodium fluoride.

In healthy persons, 40 mg NaF reduced the absorption of calcium up to minute 120 but between minutes 180 and 240 the NaF + Ca^{++} curve was higher than the pure calcium curve. When sodium fluoride was given in an acid-resistant coating there was reduction of calcium absorption up to minute 60 but, after minute 120, absorption increased more distinctly than with normal NaF doses. The reduction of the calcium absorption is dependent on doses up to 20 mg NaF. With larger doses (40 mg NaF) no further changes of the absorption curves were found.

Among patients with osteoporosis, the simultaneous administration of NaF and calcium also reduces considerably the absorption of calcium from the gastrointestinal tract. Here, too, the reduction is less pronounced when acid-resistant coatings are used.

The negative effect of NaF upon the absorption of calcium can be reduced when sodium fluoride is given at least 1, or even better, 2 hours following the administration of calcium, since then the absorption curve is only slightly altered by sodium fluoride.

J. Franke

THE FLUOROSIS IN ALUMINUM AND CRYOLITE WORKERS

(Fljuoroz u rabocich aljuminievych i kriolitovych zavodov)

by

E. Ja. Girskaja

(Abstracted from "Fluorosis and its Prophylaxis" [Fljuoroz i ego profilaktika] Sverdlovsk, 1967 pp 47-53 [U.S.S.R.])

The author presents extensive clinical studies on 113 cryolite workers from Polevo and Juzno-Uralsk and from the Electrolytic Facility of the aluminum factories in Uralsk, Bogoslovskij, Volgograd, Sumgait and Novo-Kuzneck.

The cases were divided into three clinical groups which the author believes present the three major stages of fluorosis:

1. The earliest manifestations of fluorosis involve the skin, the upper air passages and the gums. At this stage of the disease, vesicular and ulcerative dermatitis, atrophic rhinitis, pharyngitis, laryngitis and periodontal disease appear. Disorders of the stomach and duodenum are not infrequent, associated with pronounced motor and secretory changes which consist at first of a hyperacid and later of an achylic gastritis. In addition, the author observed a fluorogenic decreased activity of several important liver enzymes, especially enolase, cholesterase and serum GOT. Kidney damage is another early symptom as indicated by microalbuminuria and microhematuria. Changes in the nervous system occur, according to the author, by vaso-vegetative dystonia with pronounced hypotonia and bradycardia. Polyneuropathies and radiculitis are common manifestations suggestive of involvement of the peripheral nervous system. The first stage of the disease usually occurs after 4 to 7 years' exposure.
2. With progressive exposure, the disease turns into its second stage which is characterized by changes in bones and tooth enamel, by toxic nephropathias, hepatitis and gastritis. According to the author both osteoporosis and osteosclerosis occur early in the disease. The osteoporosis can become so extensive it may give rise to cystic bone cavities. The long bones of the forearms and of the legs exhibit mainly osteosclerosis. Characteristically, these changes show symmetrical localization. Bony apposition at the endosteum decreases the width of the medullary portion of these bones.
3. The third stage of fluorosis is characterized by generalized osteosclerosis, joint deformities and, at the vertebral column, by ossification of ligaments and tendons. The author considers osteosclerosis the least reversible sign of fluoride intoxication. Even after an interruption of exposure to fluoride of 10 to 12 years, she observed further progression of the toxic processes. Therefore it is imperative that exposure to fluoride be terminated at the first indication of osteosclerosis.

Determination of urinary fluoride among 300 workers revealed no

uniform findings. Even among completely healthy workers in an aluminum facility urinary levels were higher than those of workers afflicted with fluorosis in the same facility.

In concluding, the author expresses her views concerning the pathogenesis of fluorosis. She considers a functional involvement of the anterior lobe of the hypophysis, combined with a marked insufficiency of the adrenal cortex, the principal mechanism of the disease. As proof for the funcitonal impairment of the hypophysis, she cites her observation that fluorotic patients are intolerant to corticosteroids. With respect to therapy, fluorotic workers in the cryolite and aluminum industry are treated with infusions of magnesium sulphate combined with glucose, vitamin B, ascorbic acid and novocaine. Physiotherapy and certain dietary measures are desirable. The most important part of the prophylaxis of fluorosis, however, is the reduction of the atmospheric fluoride concentration at the work place and the incorporation of individual sanitary hygienic measures.

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