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EDITORIAL

THE DIAGNOSIS OF FLUOROSIS

Advanced fluorosis can be readily diagnosed by the osteosclerotic changes evident upon radiography. Even prior to the development of visible bone changes, new sophisticated methods such as morphometric measurements and photon absorptiometry permit the recognition of the early stage of the disease. Similarly the appearance of dental fluorosis, especially when it involves most of the denture, is so characteristic that a prompt diagnosis can be made by merely inspecting the mouth.

Another diagnostic sign early in the disease, especially in children and women is Chizzola Maculae, the round pinkish-brown skin lesions which clear spontaneously within a week and are occasionally accompanied by muscle pains, gastric upsets and headaches. These lesions are often overlooked by clinicians because of their close resemblence to traumatic bruises. Since they are painless, they can escape the patient's attention so that he fails to report them to his physician.

On the other hand, the initial nonskeletal phase of chronic fluoride intoxication is difficult to diagnose. Like in many other kinds of chronic intoxication, objective criteria are lacking early in the disease. The diagnosis is further hampered because the wide spectrum of symptoms mimics many other diseases. The combination of gastrointestinal and musculoskeletal manifestations, especially the involvement of joints, furnishes a clue for the diagnosis, particularly when accompanied by respiratory symptoms if atmospheric fluoride is involved. Excessive thirst, muscular fibrillation, chest pain and the presence of scotomas often suggest the possibility of chronic fluoride poisoning. Nevertheless, strict avoidance of fluoride and careful observation of the patient _ when he resumes fluoride intake either knowingly or on a double blind basis _ remain the mainstay of the diagnosis prior to development of bone changes. In practice, however, patients are not always willing to submit to such procedures once they have regained their health.

Clinicians have therefore been searching for laboratory methods to pinpoint the disease. The three parameters which at the moment are being considered of value are fluoride assays of urine, plasma and bones. Bone fluoride is obtained by biopsy of the iliac crest. The results of fluoride assays, however, are difficult to interpret. Whereas in large-scale statistics they clearly reflect the degree of fluoride intake of a population, there are wide variations among individuals which interfere with the reliability of these parameters as a diagnostic criterion. They certainly do not constitute proof of damage to any specific organ.

In this issue (p10) Czerwinski has shown how the bone fluoride content varies according to the site from which the bone specimen is obtained. Spongious bone contains more fluoride than cortical bone. Age is another variable which influences bone fluoride levels (1). Obviously the fluoride content of bone cannot be considered an indicator of fluoride damage to muscle tissue or to the gastric mucosa. Furthermore, there is disagreement as to what level of fluoride in bone should be considered normal. Whereas formerly (2) 300 ppm was considered the normal limit, we now know

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that tea drinking persons residing in nonfluoridated London may show levels as high as 2000 ppm. Whether or not such values affect the health of the respective individuals is not known. On the other hand, in advanced skeletal fluorosis, Singh et al. (3) reported levels as low as 600 ppm which some consider to be near, or within, the "normal" range.

Determination of plasma fluoride has been of great interest to scientists. With respect to the degree of damage to the human body, however, it is of questionable value. Here too, there is no final agreement as to what constitutes the "normal" fluoride level of plasma and whether or not this level is being regulated by homeostasis. Even if plasma fluoride should be persistently high as it is in residents of high fluoride areas in India, there is not always a positive correlation with the degree of sickness or health of the individuals.

Similarly, urinary fluoride excretion provides no definite answer with regard to fluoride intoxication. In large scale statistics some correlation between fluoride intake and urinary fluoride has been reported. However, high fluoride values as, for instance, 10 mg or more in urine are not necessarily associated with illness, whereas low urinary fluoride levels have been found in patients with nonskeletal (4) and even with skeletal symptoms (5). Children rarely excrete large amounts of fluoride in the urine during the growth of their skeleton whereas persons, in whom fluoride intake is temporarily discontinued, show urinary excretion in excess of intake.

In this issue Elsair et al. (p 21) have reported that fluoride in nails correlates with that of bones. They suggested that this might be a useful parameter, equally as valuable as a bone biopsy, but involving much less discomfort to the patient. This interesting observation requires further studies.

Other quests for diagnostic criteria for preskeletal fluoride intoxication have not been fruitful, undoubtedly because of the variable nature of the low-grade symptomatology. Serum and urinary calcium, phosphorus, alkaline phosphatase, succinic dehydrogenase and other enzymes as well as hematological studies have been carried out by various investigators of fluorosis but results have not been consistent enough to permit the use of these parameters as precise criteria for the diagnosis. Ferguson in a recent article abstracted on pages 42-3, showed inconsistent values of plasma alkaline phosphatase in a group of thirteen subjects residing in a nonfluoridated area. Such inconsistency is not unexpected because alkaline phosphatase activity is dependent on numerous pathological processes other than fluoride intake. Similarly, calcium and phosphorus levels of the blood have been found to be altered by fluoride intake (6) but the results are too inconsistent to serve as a diagnostic criteria. There is also considerable doubt as to whether hematological findings are helpful in diagnosing fluorosis as shown in the article by Burhan Uslu on pages 38-41.

To the clinician confronted with the diagnosis of the early stage of chronic fluoride poisoning, therefore, a careful history and thorough observation of the patient remains his most effective diagnostic tool.

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FLUORIDE BRIEFS

Through analysis of market basket collections, the total fluoride in-
take for young male adults was estimated to vary from 0.912 mg per day in
unfluoridated Kansas City, Missouri to 1.720 mg/day in fluoridated Atlan-
ta, Georgia in 1975. The 1977 collection from San Francisco, California
revealed a higher fluoride intake (1.636 mg/day) than in 1975(1.213mg/day).

Singer, L., Ophaug, R.H. and Harland, B.F.: Fluoride Intake of
Young Male Adults in the U.S. Am. J. Clin. Nutr. 33:328-332, 1980.

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MATERNAL IONIC PLASMA FLUORIDE CONCENTRATIONS DURING PREGNANCY AND AFTER DELIVERY

by

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SUMMARY: Strong evidence that fluoride accumulates in fetal bone is probably reflected in the maternal fluoride balance. The present study further supports the earlier findings that maternal ionic plasma (IPF) concentrations significantly decrease during pregnancy compared to concentrations in nonpregnant controls of the same age. After delivery the mean IPF concentrations start to return to usual levels despite the onset of the excretion of milk. Normalization takes place in about two weeks. The reason for the inverse correlation between maternal IPF-concentration and the birth weight of the child remains unsolved.

Introduction

In recent years it has become clear that fluoride penetrates the placenta. This has been demonstrated in animals (1-3) and in man (1,4,5). It is characteristic for fluoride to accumulate in human calcified tissues especially in bones and teeth. The same phenomenon takes place in the fetus during pregnancy (6). According to Gedalia et al., fluoride accumulation in the fetus may account for the decrease of maternal urinary fluoride concentrations during pregnancy which is inversely correlated with the increase in fetal bone fluoride (7). Plasma fluoride concentrations as well tend to decrease during pregnancy (7 - 9). In mothers residing in a low-fluoride community (0.1 - 0.2 ppm fluoride in the drinking water), Hanhijarvi et al. found a significant inverse correlation between human ionic plasma fluoride (= IPF) and the duration of pregnancy (8). There was also evidence that after delivery the level of IPF again started to increase towards the control level. Similar observations have been made in pregnant women residing in a community with artificially fluoridated drinking water (9). In this study,however, the selection of patients was inadequate because many women, who had recently delivered a child were not studied more closely but were all incorrectly included in the group called "in labor". Furthermore, interruptions in the artificial fluoridation of the tapwater had occurred. Moreover new data have also become available.

Therefore our aim in this study is to revise and make more precise the earlier findings of IPF in pregnant women residing in a community with 1.0-1.2 ppm fluoride in the tapwater. Does the decrease of IPF concentration during pregnancy still remain significant as compared to nonpregnant controls?

A second question to be explored is how do IPF concentrations be-
have after delivery in a fluoridated area? According to Bercovici et
al., the urinary fluoride concentrations returned to the usual level
within 4 months, when the patient consumed 0.55 ppm fluoride in the
drinking water (10). Our earlier findings indicate a more prompt return
of the maternal plasma fluoride in a low-fluoride (0.1 - 0.2 ppm) area
(8). This portion of the earlier investigation, however, was based on
a few samples only.

The third part of this study was to determine whether or not the
weight of the infant correlates with the IPF-concentration of the mother.

Material and Methods

The study was carried out on pregnant women and mothers who had re-
cently delivered in the Central Hospital of Kuopio. All patients had been
residing inside the City of Kuopio, where the drinking water contains 1.0
to 1.2 ppm of fluoride. Among the 67,000 inhabitants of Kuopio, the home
tap water of approximately 9,000 was not fluoridated. Thus some patients
may have been included who obtained fluoridated water only in the hospital.
IPF-concentrations, serum creatinine levels, age and week of pregnancy or
day after delivery were determined.

The plasma samples were drawn early in the morning while fasting,
following the night's rest in the hospital. The method for the deter-
mination of IPF was electrometric with a slight modification described
elsewhere (11, 12) of that published by Fry and Taves in 1970 (13).Serum
creatinine was analyzed by an autoanalyzer used routinely in the hospi-
tal (Technicon autoanalyzer II apparatus). The limit of normal serum
creatinine concentration was 115 μmol/l in this hospital.

Plasma samples of females of the same age and from the same commu-
nity were used as controls. The final material consisted of 233 hospi-
talized women, 68 of whom were included in the group of pregnant women,
86 had delivered a child recently and 79 were included in the control
group of the same mean age.

Results

Table 1 and Figure 1 present our principal data. Figure 1 reveals
an inverse correlation between the IPF-concentration and the week of
pregnancy; all pregnant women are included. The result of regression a-
nalysis is: intercept 0.99 μmol/l, regression coefficient -0.0036, r =
0.20, n = 68. The regression coefficient does not differ from zero sig-
nificantly (p = 0.1).

When the pregnant women are grouped according to the trimester of
pregnancy (Table 1), the mean IPF concentration of the women of the last
trimester is significantly lower than in the control group (p < 0.01).
The group of the third trimester of pregnancy could be divided into some
subgroups, too, e.g. the IPF concentration of 9 women during the third
trimester who had hypertonia or toxemia, which was known to be medicated

Table 1

Mean Ionic Plasma Fluoride

Trimester of Pregnancy	Weeks mean	Plasma F$^-$ μmol/1 $\pm$ S.D.	Age mean	Serum creatinine μmol/1 $\pm$ S.D.	n
First	10	0.97 $\pm$ 0.22	31	63 $\pm$ 15	12
Second	19	0.90 $\pm$ 0.25	27	62 $\pm$ 14	11
Third	36	0.86 $\pm$ 0.18 **	26	62 $\pm$ 9.4	45
Days after Delivery	Days mean				
0	0	0.92 $\pm$ 0.14	32	62 $\pm$ 9.3	3
1	1	0.99 $\pm$ 0.32	20	64 $\pm$ 2.6	4
2	2	0.95 $\pm$ 0.29	26	62 $\pm$ 6.8	10
3	3	0.84 $\pm$ 0.17 **	26	63 $\pm$ 6.6	14
4	4	0.86 $\pm$ 0.20 *	26	60 $\pm$ 6.7	20
5	5	0.84 $\pm$ 0.25 ^{o}	27	66 $\pm$ 13	14
6	6	0.90 $\pm$ 0.27	27	60 $\pm$ 8.9	24
7 or more	10	0.97 $\pm$ 0.33	28	64 $\pm$ 8.4	14
Nonpregnant control group	–	1.0 $\pm$ 0.30	27	75 $\pm$ 14	79

** = $p < 0.01$, * = $p < 0.05$, o = $p < 0.1$

Figure 1

Maternal IPF Concentration and Week of Pregnancy
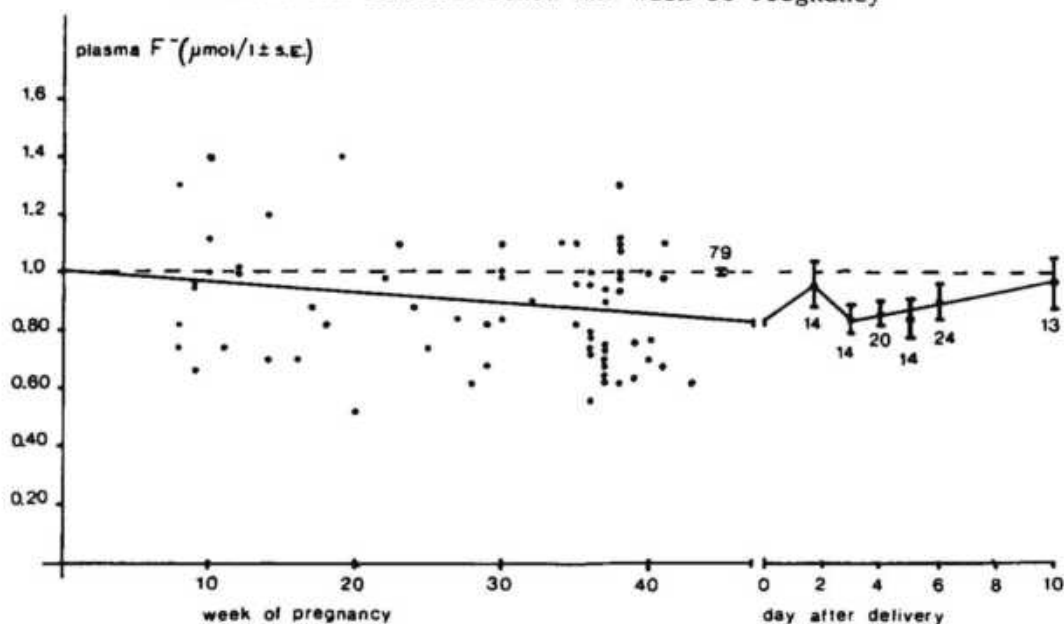
The mean IPF levels each day after delivery (+ S.E.) and number of patients.

with diuretics was 0.89 ± 0.20 µmol/l (± S.D.). This mean value is si-
milar to the mean value of the whole group in the third trimester(Table
1). Only 5 pregnant patients whose edema was recorded and who were not
using diuretics had slightly elevated IPF-concentrations (1.0 ± 0.21
µmol/l) when compared with other women (Table 1) of the same trimester.
When these five patients are excluded, the regression analysis between
the IPF concentration and the week of pregnancy slightly changes (in-
tercept 1.0 µmol/l slope = -0.0046, r = 0.27, n = 63, p < 0.05).

At one and two days after delivery, the maternal IPF-concentration
is slightly elevated (Table 1 and Figure). Three days after delivery,
coincident with the start of milk excretion, the mean maternal IPF-con-
centrations are again significantly lower than in the nonpregnant con-
trols (p < 0.01), after which the mean IPF levels begin to increase
steadily. They reach the control level about ten days after delivery.
The regression analysis between the IPF-concentrations and the day af-
ter delivery was also performed including all plasma samples, which were
drawn on the third day or later following delivery. The intercept was
0.78 µmol/l, the regression coefficient 0.019, r = 0.21, and n = 86.
The correlation coefficient differs almost significantly from zero (p<
0.05).

The regression analysis between the birth weight of the child and
the IPF-concentration is given in Figure 2. The correlation coefficient
differs almost significantly from zero (p < 0.05). The regression co-
efficient = 0.15, intercept 0.28 µmol/l, r = 0.51 and n = 19.

Figure 2

Maternal IPF and Birth Weight of Infant
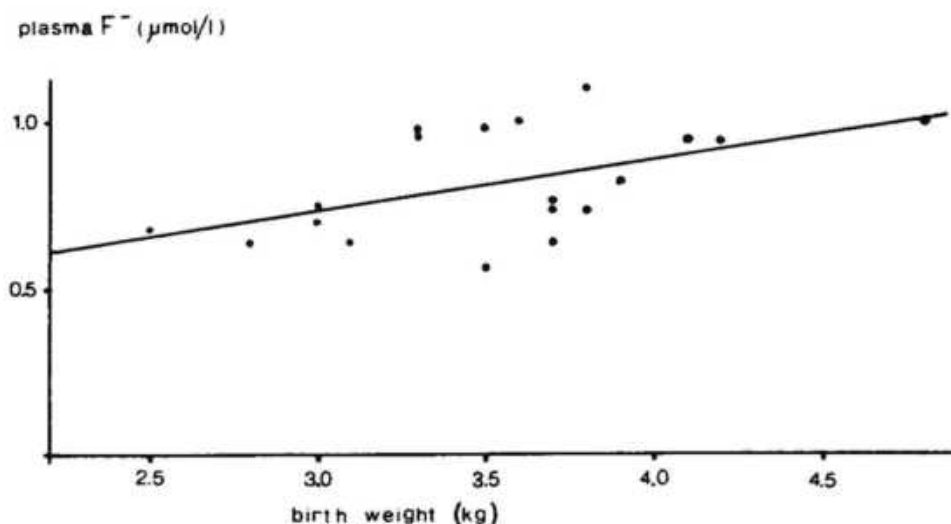
Regression coefficient = 0.15, intercept - 0.28 mol/l, r = 0.51, n = 19

Discussion

As shown previously the present findings demonstrate a significant decrease of maternal IPF during the last trimester of pregnancy. It is probable that this is due to the absorption of fluorides into fetal calcifying tissues. Increased renal excretion of fluoride does not account for the decrease in IPF because the amounts of fluoride excreted daily are lower during pregnancy than in the nonpregnant controls (14). One possibility might be an increased uptake of fluoride in the maternal bone. This however is unlikely because during the last trimester the fetus needs so much calcium that the maternal plasma parathormone levels are higher than usual (15). Furthermore, according to the earlier findings of Ericsson, increasing IPF levels should be expected with elevation of bone fluoride (16).

The significance of edema on IPF levels during late pregnancy remained poorly quantitated. As stated above, five women had edema but did not use diuretics. During late pregnancy edema is very common. The series may contain more such cases, because we lacked clear criteria for differentiation of "normal" and "abnormal" edema. We know that in the five women, the edema was untreated. It is probable, however, that edema, regardless of the cause, may account for slight elevation of IPF concentrations (17). If the edema is controlled by diuretics, the IPF levels also react favorably as our results indicate.   The difference between the IPF-concentrations of edematous and nonedematous pregnancies disappears.

After the birth of the child the material IPF levels start to increase and serum calcium levels return to normal levels. It is probable that maternal bone starts to accumulate calcium and fluoride(15). However, according to the present results the excretion of milk slightly slows down the accumulation of fluoride, because the material IPF levels are slightly higher before the onset of milk excretion than after it. Despite a slight loss of fluoride into the milk, the maternal IPF-concentrations return to the control level after two weeks.

The explanation for the positive correlation between the IPF-concentration and fetal body weight remains unsolved. An inverse correlation would have been expected. This finding should not be overemphasized, because the samples were drawn between 35 and 41 weeks of pregnancy and the weight of the infant was obtained at birth. However, it is possible that women with a large fetus drink more water or their parathormone activity is stronger during pregnancy than that of the women who give birth to a smaller child.

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    44-53, 1974.   **********

FLUORIDE CONCENTRATION IN THE CORTEX AND IN FULL THICKNESS SAMPLES OF THE ILIAC CREST

by

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SUMMARY: The fluoride content was evaluated in iliac crest samples taken from cadavers without previous history of fluoride exposure. Fluoride concentration in the cortex before and after ashing was determined by the Coulomb excitation method using a C-48 cyclotron. Fluoride was then estimated in the same samples by the microdiffusion method. Fluoride assays in full thickness iliac crest samples were also made.

Varying fluoride concentrations in adjacent areas were noted as well as in the cortex and in full thickness samples. The significance of the differences is discussed.

Introduction

The fluoride content of the skeleton is considered to be directly related to exposure to chronic poisoning. It is the most important criterion in the diagnosis of industrial fluorosis. A bone sample is usually obtained by needle biopsy of the iliac crest 2 cm below and posterior to the spina iliaca anterior superior. A cylinder of bone is taken through the full thickness of the ilium, namely the outer compact bone, the cancellous bone, and the inner compact bone (1-4).

In practice it is possible to make only an approximate determination of the site of the percutaneous bone biopsy. Often tissue of the inner cortex cannot be obtained. Individual differences in the structure of the ilium should be taken into consideration, as well as morphological changes in those exposed to the action of fluoride.

The present paper reports an attempt to determine whether or not the macroscopic structure of the sample as well as the site on the iliac crest from which it is taken may influence the determination of the fluoride content of the skeleton in man.

Material and Method

Bone samples were obtained from cadavers of persons aged 42 to 50 years (average 45.9), who had not previously been exposed to fluorides. A section 4 x 4 cm in size was taken from the ilium adjacent to the

spina iliaca anterior superior. Preparations of the full thickness of
the ilium as well as of the cortex alone were made of each sample. The
samples of the cortex were obtained by mechanical abrasion of the can-
cellous layer. In four cases two preparations of the cortex were made
from two adjacent areas of the ilium. In preparation of the cortex,
the fluoride content was determined by the Coulomb excitation method
for further treatment. The cortical preparations as well as the full
thickness samples were ashed and the fluoride content determined by the
microdiffusion method.

Figure 1

Fluoride Content in the Cortex and in the Full Thickness Bone
Samples Estimated by Microdiffusion

347	550	445	580	440	310	148	392	593	407
430	553	586	635	710	389	240	355	726	370
						310	500	559	570
I	II	III	IV	V	VI	VII	VIII	IX	X
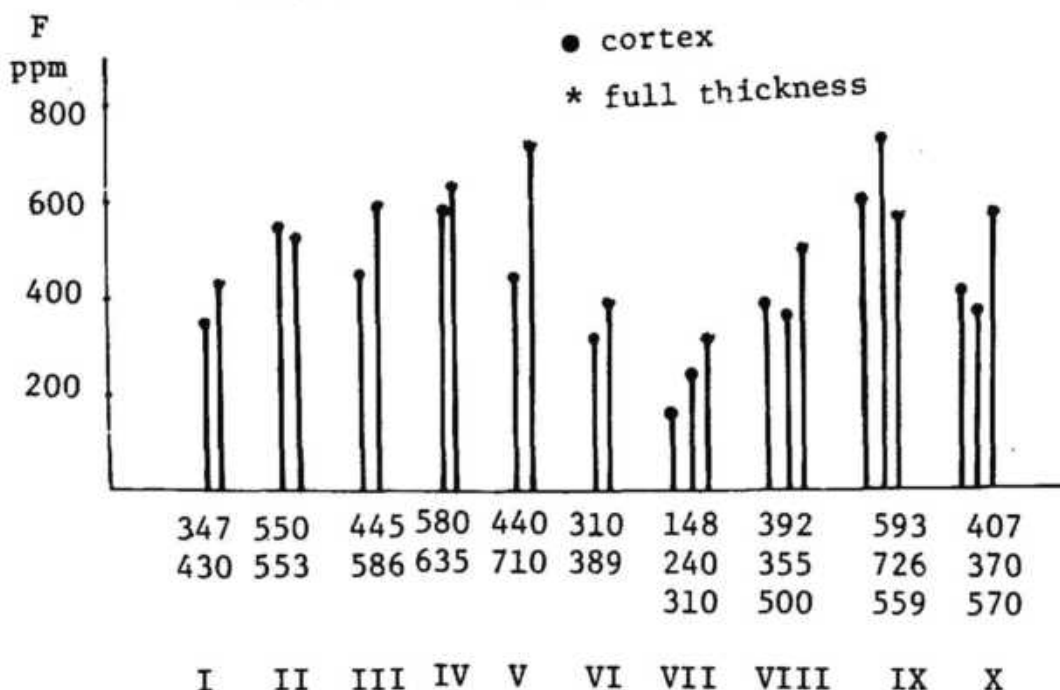
Results

The fluoride content, determined by the microdiffusion method (5),
in the cortex and in full thickness samples from the iliac crest is il-
lustrated in Fig. 1. The fluoride content varied in the cortex from 148
to 728 ppm with an average of 429 ppm, and in the full thickness samples
from 310 to 710 ppm (average 524 ppm). The relation of the fluoride
content of the full thickness samples to that of the cortex was 1.23 ±
0.03. In the cases VII to X the fluoride content in two adjacent areas
of the cortex was determined. The mean difference in the levels in the
two samples was 71.2 ppm, i.e. 16% of the contents determined. In the
same cortex samples, the fluoride content was also determined by the

Coulomb excitation method. Differences of 30% were obtained. The de-
tailed results of measurement by this method together with a description
will be the subject of a separate paper.

Discussion

   The fluoride content found in full thickness samples from the iliac
crest in nonexposed subjects is in agreement with Shelman's report on
the same age group (6).

   Our investigations show that the fluoride level in full thickness
samples is higher than that in the cortex alone. It is known that the
distribution of fluoride in various parts of the skeleton is unequal,
but the data refer rather to individuals charged with an excessive sup-
ply of fluoride (7,8, 9,10). Both Gardner (11) and Weidmann (12)
found a higher fluoride content in the cancellous metaphysis than in
the cortical diaphysis. Wallace-Durbin (8), using F^{18}, observed a
sequential decrease in the fluoride concentrations in the mandibles,the
epiphyses and the metaphyses. In studies on cadavers, Weatherell   (9,
13) observed a similar decrease in the fluoride concentration in the
direction: rib - cancellum, rib - compacta, metaphysis - cancellum, dia-
physis - compacta. The ratio of the fluoride content in the cancellous
and cortical bone of the rib is estimated as 1.5 - 3.5, as is the can-
cellous and cortical bone of the metaphysis (9,13,14). This ratio is
probably the same for the cortex of the cancellous bone of the ilium,
but we have not found any relevant data in the available literature.
The relation of 1.23 which we found between the fluoride content in full
thickness samples and the cortex itself are in approximate agreement
with the factors just given.

   A markedly larger deposit of fluoride in the cancellous bone was noted
by Perkinson (15) in histological autoradiograms when using F^{18}. The
larger deposit of fluoride in the cancellous bone results from the better
blood supply in cancellous than in cortical bone. Similar differences
have been observed in fluoride deposits in the long and flat bones (16).

   The differences in fluoride content which we have found in two ad-
jacent areas of the cortex confirm the observation of the unequal dis-
tribution of fluoride in the bony tissue. These differences appeared
particularly marked when measurements were made by the Coulomb excita-
tion method, which determines the fluoride content solely in the super-
ficial layer of a specimen a few microns in thickness and 0.5 cm^2 in ar-
ea. The fluoride content in two adjacent areas varied much less after
the samples were ashed. Hence the local structure of the cortex, which
is more homogeneous after ashing, may have a decided influence on the
results of measurement.

Conclusions

   The fluoride content in full thickness samples from the iliac crest
in subjects not exposed to fluoride contamination, is more than 1.23
times as high as that in the cortex. Adjacent areas of the cortex may

differ by 16% in fluoride content. Both the macroscopic structure of the
sample and the site from which it is taken may affect the fluoride con-
tent in the skeleton. For the relation between the fluoride content in
the cortical and cencellous bone of the iliac crest in subjects exposed
to fluoride contamination further studies are warranted.

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EFFECT OF LONGTERM FLUORIDATION OF DRINKING WATER
ON MINERAL CONTENT OF THE SKELETAL SYSTEM

by

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Halle (Saale), G.D.R.

SUMMARY: By means of photon absorptiometry the mineral
content of bone (radius) of 1160 residents of Karl-Marx-
Stadt (fluoridated since 1959) was compared with that of
4150 inhabitants of nonfluoridated Halle.

Only in the age group 16-20, among those who had been
drinking fluoridated water since birth, was an increase in
bone mass encountered following longterm fluoridation of
drinking water. In the other age groups, a tendency to
lower values was observed in the fluoridated city.

Introduction

That chronic fluoride intoxication leads to skeletal fluorosis was
established by the work of Møller and Gudjonsson (1) and Roholm (2, 3).
This bone disease is characterized by hyperossification and hypermineral-
ization (4 - 6). Chronic fluoride intoxication is attributable to inhal-
ation of airborne fluoride and to ingestion of fluoride-containing dust
and food. In such industries as aluminum smelting, in production of cry-
olite, of hydrofluoric acid, of magnesium, of fertilizers, and in brick-
works from 15 to 20 years are required for severe fluorosis to develop.

In endemic fluorosis, caused by a 10-30 years' intake of drinking wa-
ter naturally containing fluoride (0.7-46 ppm) mainly in India, osteoscle-
rosis is the major feature (7 - 9). In industrialized countries such as
the German Democratic Republic (G.D.R.) in which osteoporosis is the most
frequent metabolic bone disease affecting approximately 350,000 or 2% of
the population (10), investigators have reported success with fluoride
treatment.* Osteoporosis is reported to occur less frequently in natural
fluoride areas namely, Texas (formerly 8 ppm) (13, 14), North Dakota 4 -
5.8 ppm (15), Sweden 4-6.8 ppm (16, 17), and India 8 - 10.5 ppm (18) than
in areas where water contains little or no fluoride.

The aim of this study is to determine whether or not fluoridation of
drinking water (1 ppm) over a period of 19 years increases bone mass in
normal persons and may thus be of prophylactic value in osteoporosis.

Material and Methods

Normal subjects were examined from two cities of the G.D.R., Halle in-
cluding Halle-Neustadt with 326,000 inhabitants, and Karl-Marx-Stadt with
307,000. In Karl-Marx-Stadt, drinking water has been fluoridated (1 ppm)

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* Editor's Note: Others have been recommending caution because of adverse
side effects (11, 12).
From the Orthopedic Clinic of Martin-Luther-University, Halle (Saale)G.D.R.

since 1959; the fluoride content of the air ranges between 5 and 6 μg/m³. In Halle and Halle-Neustadt fluoride in drinking water ranges between 0.1 and 0.2 ppm and the air contains an average of 5 μg/m³. Bone mineral contents were studied in Karl-Marx-Stadt, 509 men and 651 women (1160 subjects) on the occasion of routine chest x-ray examinations. Only those persons who had been residing in Karl-Marx-Stadt since the initiation of drinking water fluoridation in 1959 were included in the survey.

Figure 1

Bone Mineral Analyzer
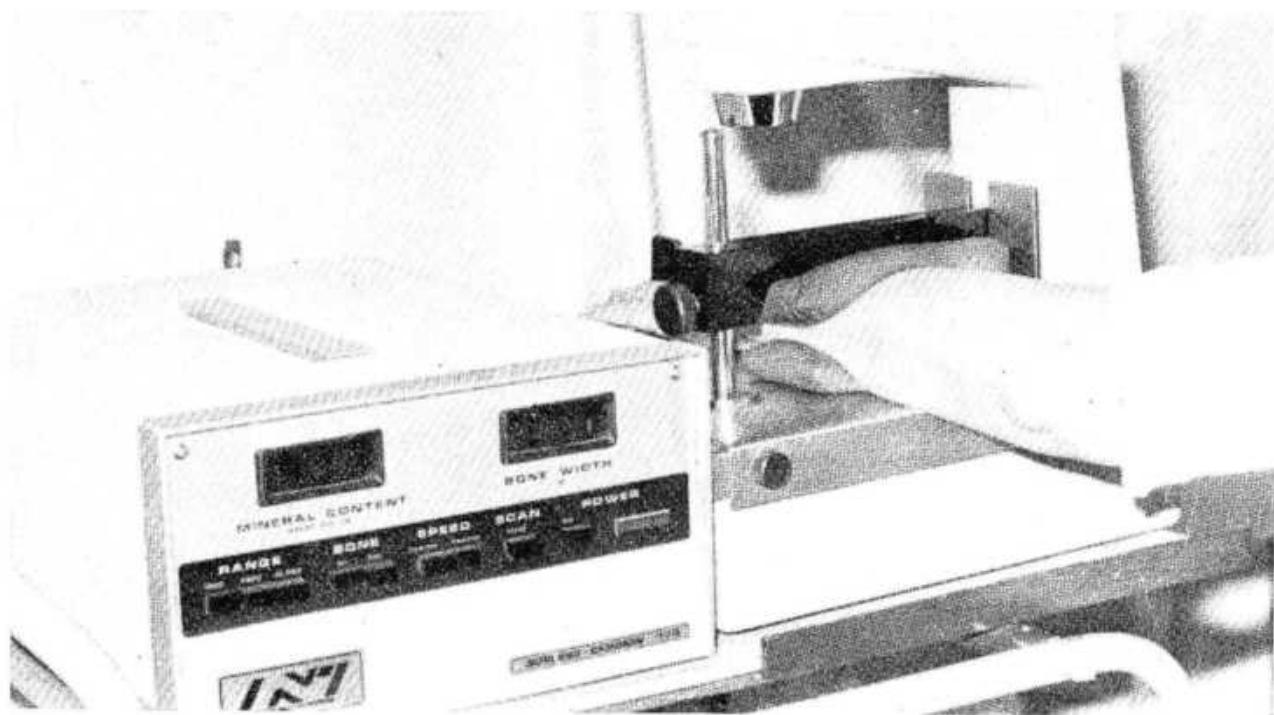
In Halle, 2158 males and 1996 females (4154 subjects), patients of the Orthopaedic Clinic and residents of a home for the aged were included in this study. In all persons a thorough history was taken. Subjects suffering from diseases that can influence bone metabolism were excluded, such as gastrointestinal and hormonal disturbances, liver and kidney diseases, diabetes, intake of steroids and confinement to bed for a prolonged period.

The bone mineral content was determined by photon absorptiometry according to Cameron and Sorenson (19) at the level of the radius, one-third of its length from the styloid process. The transportable Norland-Cameron Bone Mineral Analyzer (USA) comprised of a measuring device and a computer was used. The measuring device consists of a monochromatic radio-nucleide source, iodine [125], and a well collimated scintillation detector in the form of a sodium iodide-crystal (Fig. 1). With the help of a wa-

ter-filled rubber cuff applied around the arm, the irregularities of soft
tissue were compensated. The scanner, which approaches the bone with con-
stant speed, first measures the soft parts' absorption and the area across
the bone. Absorption of the radiated protons is dependent on the bone
mineral content. The impulse rate in the detector is diminished appropri-
ately. The scintillations are transformed into electric impulses.

Resulting from integral of the absorption curve, the computer module
gives a digital read-out of the bone mineral content in g/cm and of   the
width of the bone in cm. In order to make a comparison independent of the
variable bone width and thus of the skeletal size, in accordance with in-
ternational custom, the quotient (index) of measured mineral content and
bone width (Mc/BW in g/cm^2) is presented. Four measurements are carried
out at the "off-handedness" radius, i.e. the left radius for a right hand-
ed person after which the average value is calculated. The reproducibi-
lity and accuracy of repeated measurements are very reliable. They are
at the 2% level for bone mineral content and bone width (20). For the age
groups 16-20 years, 21-30 etc. up to 81-90 years for men and women from
Halle and Karl-Marx-Stadt, the mean values and standard deviations were
calculated for bone mineral content, bone width, and quotient (index) =
$\dfrac{\text{mineral content}}{\text{bone width}}$.

The mean values of the single age groups from Halle and Karl-Marx-
Stadt were compared by means of the Student's paired t-test (variant ac-
cording to Welch) concerning their significant differences.

Results

The results are shown in Figures 2 and 3 and Table 1:

1. Men and women aged 16-20 from Karl-Marx-Stadt show a significant-
    ly higher index ($\dfrac{\text{mineral content}}{\text{bone width}}$) than those in Halle.

2. In the female groups, there were no further significant differ-
    ences in the index. In Karl-Marx-Stadt however, the simple min-
    eral content declines at ages 31-40, 41-50 and 71-80, but de-
    creased bone width compensates for this phenomenon in the index.

3. The male residents of Karl-Marx-Stadt 31-40 and 41-50 years old
    show a significant decrease in mineral content (index and partly
    mineral content). Bones of the 61-70 year old also showed a de-
    crease in mineral content.

Discussion

The expected positive effect of 19 years of fluoridation of drinking
water on bone mass and on mineral content of the peripheral skeleton (ra-
dium) respectively was not confirmed, except in the age groups 16-20years.
In Karl-Marx-Stadt, a tendency to lower mineral values than in nonfluori-
dated Halle was observed, especially in men. One could therefore conclude
that fluoridation of drinking water has a positive effect on the skeleton
only if the persons have been consuming fluoridated water since birth, in

Figure 2

Bone Mineral Index of Males in Karl-Marx-Stadt and Halle

$$index = \frac{BMC}{BW}$$
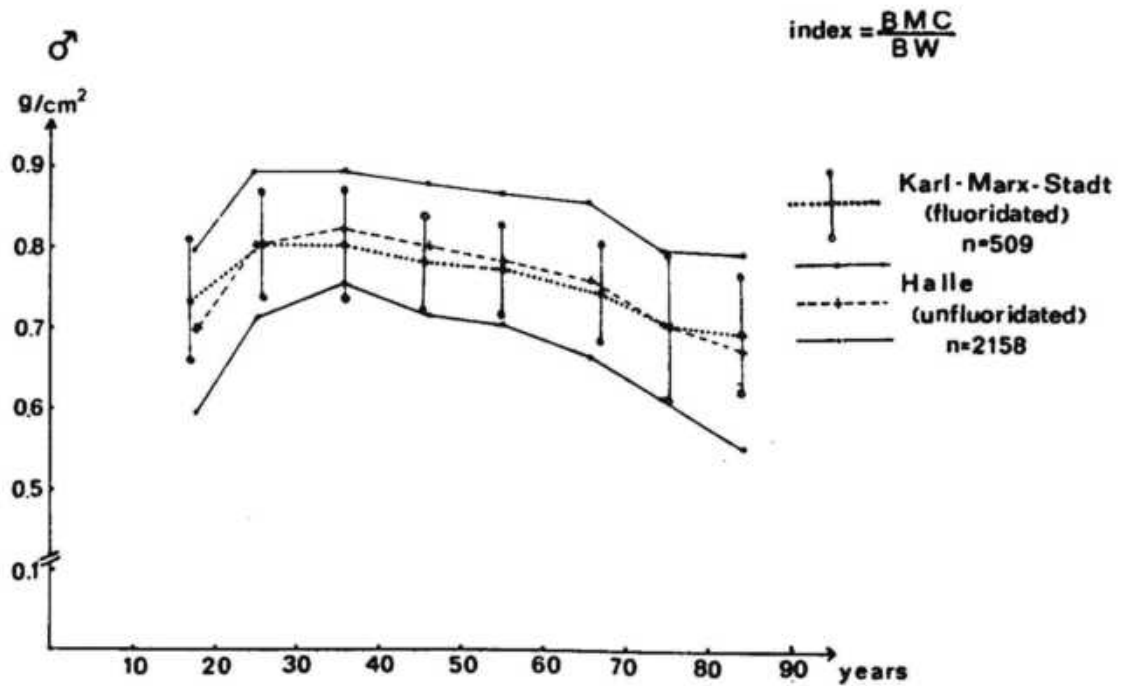
Figure 3

Bone Mineral Index of Females in Karl-Marx-Stadt and Halle

$$index = \frac{BMC}{BW}$$

Franke, et al.
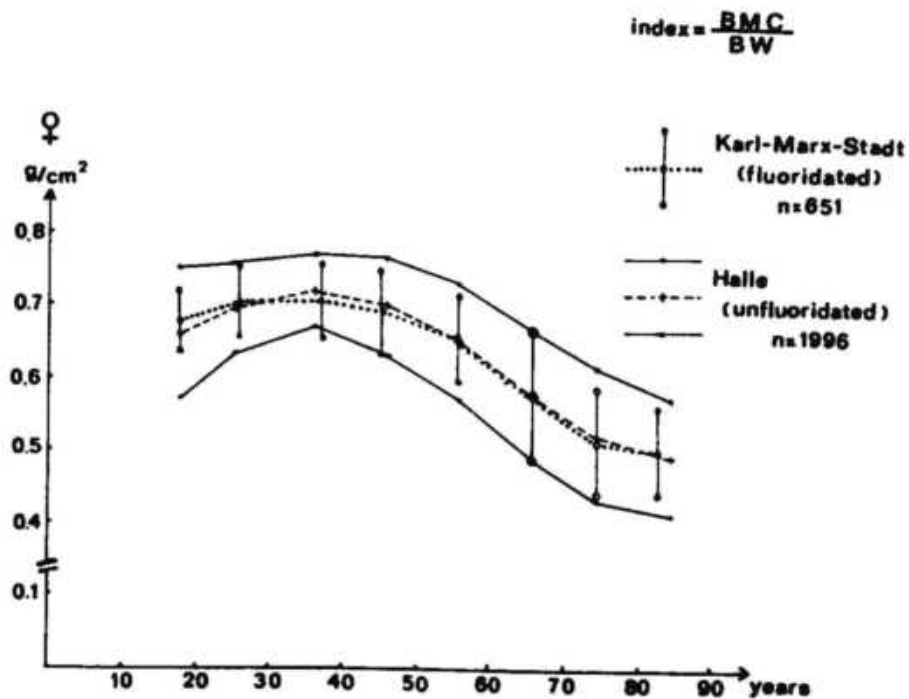
Table 1

Measurements of Bone Mineral Content in Halle and Karl-Marx-Stadt

Age Groups	Mineral Content (g/cm)					Bone Width (cm)			Index (g/cm²)		
	n	Halle	n	Karl-Marx-St.	t-test	Halle	Karl-Marx-St.	t-test	Halle	Karl-Marx-St.	t-test
Men											
16-20	268	0.996±0.233	42	1.030±0.152	–	1.423±0.199	1.409±0.147	–	0.693±0.100	0.731±0.075	1%
21-30	267	1.206±0.212	81	1.190±0.144	–	1.509±0.166	1.482±0.132	–	0.796±0.093	0.802±0.065	–
31-40	394	1.246±0.146	96	1.216±0.152	–	1.527±0.146	1.527±0.147	–	0.817±0.070	0.796±0.064	1%
41-50	450	1.234±0.165	94	1.150±0.132	1%	1.554±0.147	1.482±0.145	1%	0.794±0.079	0.777±0.058	5%
51-60	329	1.196±0.158	62	1.176±0.118	–	1.540±0.143	1.524±0.142	–	0.777±0.079	0.773±0.056	–
61-70	288	1.172±0.169	64	1.126±0.128	5%	1.557±0.154	1.526±0.130	–	0.754±0.094	0.738±0.061	–
71-80	135	1.102±0.155	64	1.059±0.170	–	1.581±0.154	1.505±0.143	1%	0.699±0.087	0.704±0.087	–
81-90	27	1.056±0.164	6	1.067±0.117	–	1.600±0.173	1.558±0.157	–	0.666±0.116	0.687±0.070	–
Women											
16-20	191	0.842±0.191	64	0.838±0.106	–	1.261±0.177	1.232±0.133	–	0.662±0.094	0.680±0.043	5%
21-30	235	0.882±0.119	94	0.869±0.100	–	1.272±0.146	1.235±0.110	5%	0.695±0.061	0.704±0.053	–
31-40	254	0.928±0.113	92	0.869±0.087	1%	1.297±0.140	1.235±0.104	1%	0.717±0.051	0.706±0.053	–
41-50	349	0.911±0.112	94	0.866±0.104	1%	1.306±0.125	1.252±0.119	1%	0.699±0.066	0.692±0.063	–
51-60	390	0.840±0.121	88	0.830±0.098	–	1.293±0.124	1.271±0.124	–	0.650±0.080	0.655±0.063	–
61-70	337	0.746±0.134	119	0.745±0.135	–	1.298±0.126	1.300±0.138	–	0.575±0.086	0.574±0.084	–
71-80	197	0.688±0.122	87	0.655±0.111	–	1.324±0.149	1.293±0.116	–	0.522±0.087	0.507±0.075	–
81-90	43	0.654±0.120	13	0.655±0.058	–	1.326±0.144	1.317±0.100	–	0.494±0.084	0.501±0.061	–

view of the fact that the age groups 16-20 years from Karl-Marx-Stadt were the only ones who showed a significantly increased index.

For the decreased values at higher ages, especially among men 31-50 years of age in Karl-Marx-Stadt, we have no explanation. Nutritional habits and occupation (brain or heavy work) may influence the bone mineral content. In the framework of such an extensive experiment no precise conclusion for these problems was possible.

In the literature likewise the results obtained to date have not been unequivocal.

Whereas Iskrant ($_{21}$) observed a significant decrease in the number of fatal accidents from falls in old people in areas where water contains fluoride naturally, no such effect was encountered from artificial fluoridation of drinking water. After 20 years of fluoridation of drinking water, Korns ($_{22}$) too, found no differences in the frequency of osteoporosis and fractures in comparison with those in a nonfluoridated town. Alffram et al. (17) observed no change in the rate of fractures of the neck of the femur at 0.8 to 1.2 ppm in drinking water compared to lower levels of fluoride in water. Even at 2-3 ppm fluoride in drinking water naturally, Nordin ($_{23}$) found no differences at autopsy in bone volume of the iliac crest in comparison with that in persons without fluoride in drinking water. No change in the lumbar spine other than a decrease in osteoporosis of the cervical spine and of the hands was found by Ansell and Lawrence (24) after five years of fluoridation.

Our investigation can be compared with those of Sluys Veer et al.(25) who determined the mineral content of the radius in residents of two Dutch towns by ^{125}J-photon absorptiometry, the same method that we used: Tiel (21,900 inhabitants) had been artificially fluoridated at 1 ppm since 1953 and in Culemborg (15,600) drinking water contained 0.01 ppm fluoride. They compared five hundred subjects from Culemborg (nonfluoridated) with 518 from Tiel (fluoridated) between 25 and 74 years. The mineral content in all age groups in the fluoridated town had increased. The differences, however, were only significant when all men and women were considered together. Using the same examination method, Donath et al. (26), failed to find any differences between 400 residents of a Swiss village, where natural fluoride content in the drinking water was 10 ppm compared with 3000 residents of low fluoride Geneva.

Obviously the fluoride content of 1 ppm in drinking water, considered optimal for caries prophylaxis, is not sufficient to exert a positive influence on bone metabolism. According to our results an increase in bone mass occurred only in persons who had been drinking fluoridated water since birth. For proof of this thesis, however, another 10-20 years will be required.

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BORON AS ANTIDOTE TO FLUORIDE: EFFECT ON BONES
AND CLAWS IN SUBACUTE INTOXICATION OF RABBITS

by

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SUMMARY: Rabbits were "subacutely" intoxicated by administration of 30 mg/kg/day of fluoride for 3 months followed by 15 mg/kg/day for a subsequent 3 months (F). Boron was given alone (B) as preventive and simultaneously with fluoride prophylactically (F + Bp), as well as therapeutically namely midway during the experimental period (F + Bpc) while fluoride was being administered and after it was discontinued (Bc compared with fluoride interruption F⚡), at a constant F/B ratio. All groups were compared to normal controls.

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Boron, administered during fluoride intoxication
or after its interruption, reduces fluoremia and in-
creases urinary fluoride excretion. Skeletal fluo-
ride levels are directly related to those of claws.
They bear no relationship to fluoride in hair. The
high fluoride content in bone in lot F decreases
with addition of boron. It is still high in lot F♀
but returns to normal in lot Bc. Calcium content
of bones remains normal in all lots. Posterior pad
radiography shows a cortical thickness in lot F
which is less pronounced in lots F + Bpc and F♀ ,
and returns to normal in lot Bc.

Introduction

Boron has been considered an antidote in fluoride intoxication (1,
2). When administered to rabbits preventively at the beginning of sub-
acute fluoride intoxication, boron counters the adverse effects of fluo-
ride upon hemostasis (3) and respiration (4).   During balance studies
with large short-term doses of fluoride, boron administered as a preven-
tive, does not alter the fluoride balance but counteracts the decline of
the phosphorus and calcium balance (5, 6), due to formation of a F + B
complex which is less damaging than fluoride. When boron was given un-
der the same conditions therapeutically after interruption of fluoride
administration, excretion of fluoride increased and residual phosphorus
and calcium disturbances were corrected (6, 7).

In the current study, we determined the effect of boron, adminis-
tered alone as a preventive starting at the beginning of subacute fluo-
ride intoxication, as "preventive-curative" during the course of fluoride
intoxication and as a therapeutic measure after interruption of fluoride.
The following parameters were investigated during the various plans of
administration: Fluoremia, fluoruria, fluoride and calcium content of
bones, of claws and of hair as well as skeletal radiography.

Materials and Methods

Subacute fluoride intoxication was induced in rabbits by addition of
30 mg F/kg/day to their drinking water for 3 months, followed by 15 mg/
kg/day for 3 subsequent months (F). Boron was administered alone (B)
in doses of 11.55 mg/kg/day for 3 months followed by 5.78 mg/kg/day for
the following 3 months. In other groups, boron was given simultaneously
with fluoride for the entire period prophylactically (F + Bp); it was
started midway during the period of intoxication (F + Bpc), or curative-
ly (Bc) after fluoride was discontinued, compared with lot F in which flu-
oride had been given without boron for 3 months. Data on all these groups
were compared with those of normal controls (Fig. 1).

Fluoremia after mineralization (8) and urinary fluoride were meas-
ured by the specific electrode method (9, 10), and related to 24-hr. ex-
cretion of creatinine. Bone, claws and hair fluoride content was deter-

mined after breaking, drying, delipidation and mineralization.Posterior
pad radiography was performed in all lots on the same day at the same
distance and with the same intensity.

Figure 1

Outline of the Experiments
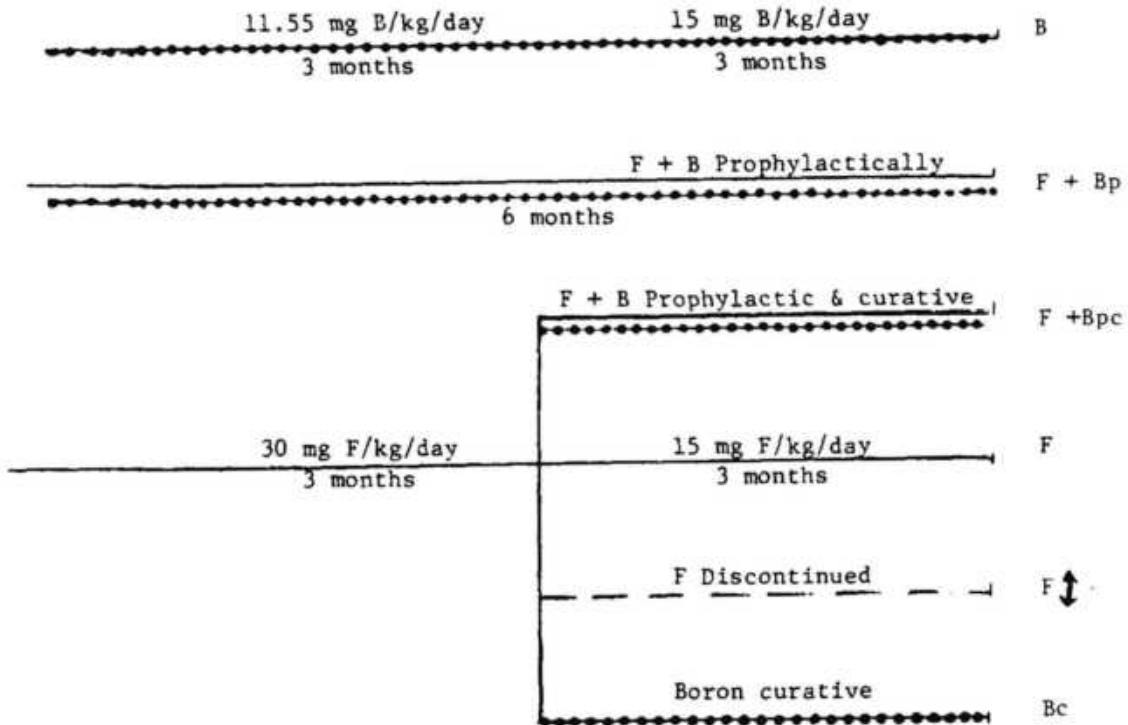
Results

In lot F, the group receiving fluoride alone, fluoremia (Fig. 2)
was very high. In lots of F + Bp and F + Bpc, the elevation of the flu-
oride content in blood was less than in lot F (p 0.05 or p 0.10). After
interruption of fluoride intake in lot F and Bc, fluoremia returned to
normal. Fluoruria (Fig. 2) was very high in lot F (p 0.001) and further

increased in lot F + Bpc as compared to lot F (p 0.10).   After inter-
ruption of fluoride, the urinary excretion of fluoride remained high (p
0.01), but was more pronounced in lot Bc than in Lot F (p 0.10).   When
boron was administered midway during the period of intoxication (F +Bpc)
or after interruption of fluoride (Bc), the blood level of fluoride de-
creased and urinary excretion of fluoride increased.

<div align="center">

Figure 2

F⁻ Levels in Blood and Urine

</div>
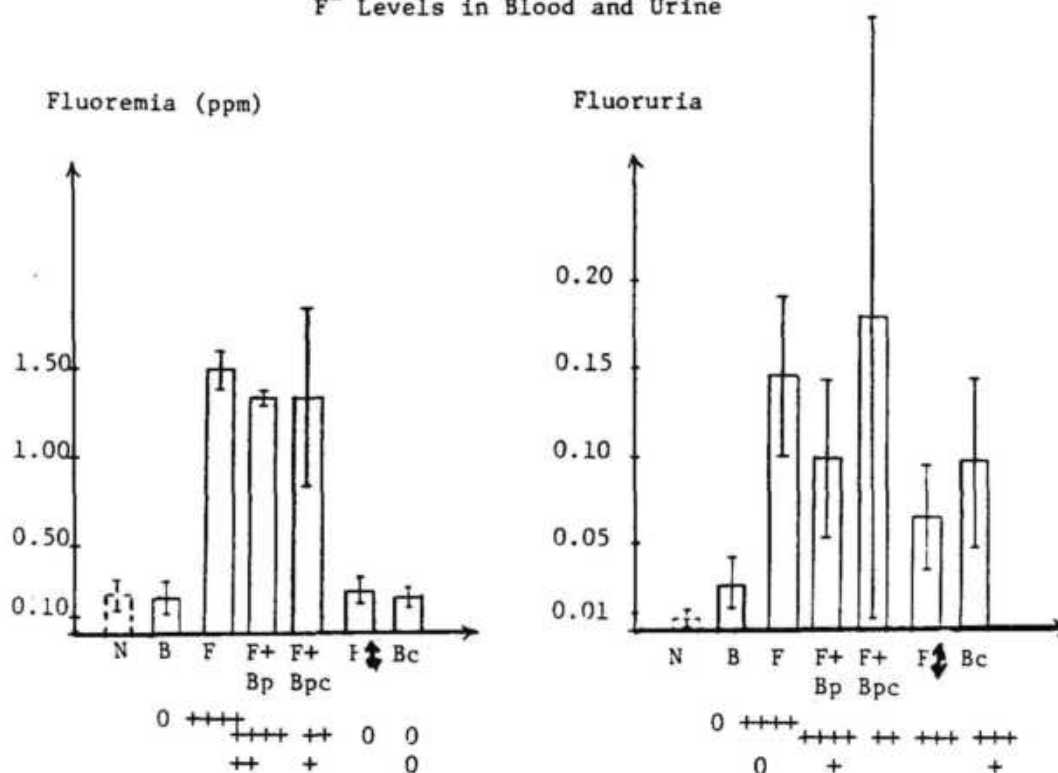
The fluoride content of bones (Fig. 3) remained at normal levels in
lot B.   It was very high in lot F (p 0.01), and seemed to decrease when
boron was added (F + Bpc) (p 0.05).   After interruption of fluoride, the
fluoride content of bones was still high in lot F (p 0.05), but when bo-
ron was administered therapeutically (Bc), bone fluoride remained normal.
The calcium content of bones (Fig. 3) was within the normal range in all
groups without retention or loss with the doses used in this study.

Whereas the fluoride content of hair did not vary, fluoride levels
of the claws paralleled those of bones (Fig. 4).   There was a marked in-
crease of fluoride in claws in all lots, compared to normal (p 0.001),

but a partial reduction when boron was administered midway during the period of intoxication (difference F + Bpc and F: p 0.10), or after interruption (difference Bc and F: p 0.10).

Figure 3

Fluoride and Calcium in Bones
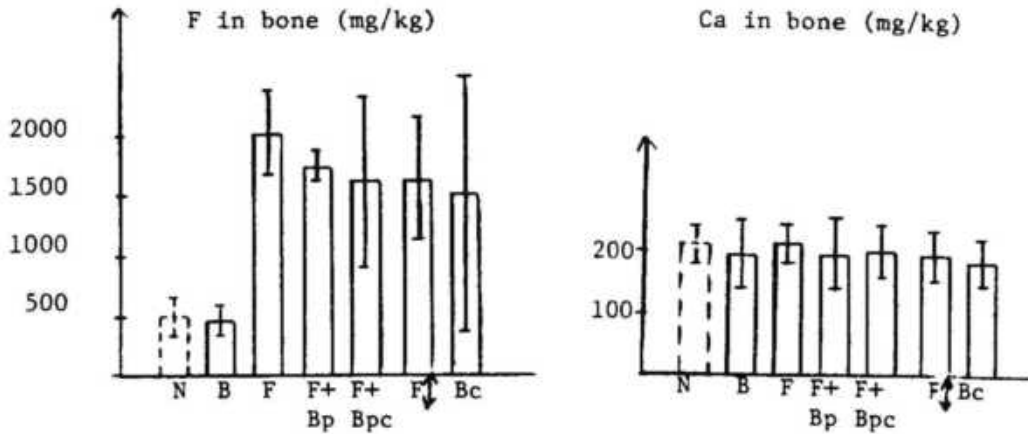
Figure 4

Fluoride in Claws and Hair
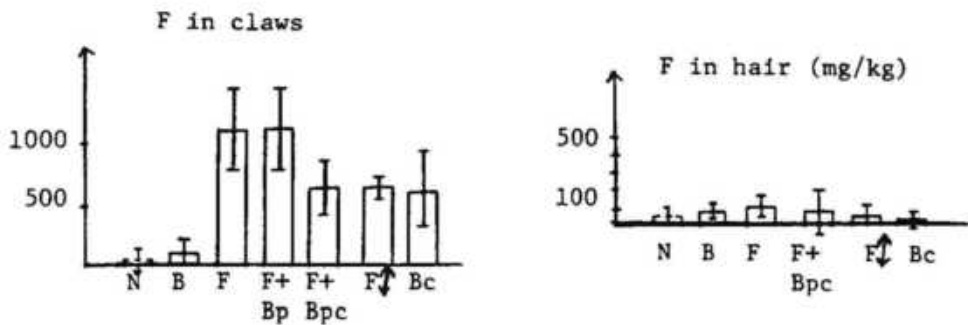
Posterior pad radiography (Fig. 5) was normal in lot B. Thickness of the cortex was less pronounced in lots F + Bpc than in lot F. When boron was administered after interruption of intoxication (Bc), the x-ray findings returned to normal.

Figure 5

X-ray Appearance of Leg

T

B

F

F + Bpc

F

Bc

Discussion

In our experiment, the antagonistic effect of boron to fluoride is

Table 2

Enzyme Activities Following Fluoride Treatment

F⁻ Levels (ppm)	Alk. phosphatase			Acid phosph.			ATPase			LDH			SDH		
	0	10	25	0	10	25	0	10	25	0	10	25	0	10	25
KIDNEY															
Outer cortex Proximal tubules	++++	++++	++	+++ to +++	+++	++	+ to ++	++	+ to ++	++++	++++	++	++++	+++	++ to +++
Distal tubules	++++	++++	++	+++	+++	++	+ to ++	++	++	++++	+++	++ to +++	++++	+++	++ to +++
Glomeruli	±	±	±	+	+	±	+	+	+	+	+	+	±	±	±
Inner cortex	+	+	+	+	+	+	++	+	±	++	++	++	++	++	++
Outer medulla	±	±	±	±	±	±	±	±	±	++	++	++	+ to ++	+ to ++	+ to ++
Inner medulla	±	±	±	-	-	-	-	-	-	±	±	±	±	±	±
LIVER Parenchymatous cells	+++	+++	++ to ++	++++	++++	+++	++	++	++	++++	++++	++++	+++	+++	++

Activity: ++++ very strong; +++ strong; ++ moderate; + low; ± negligible; – none

noticeable mainly when boron is administered midway during the period of
fluoride intoxication or following interruption of fluoride administra-
tion. This confirms the hypothesis of Baer et al. (1) that a B + F com-
plex is formed which follows the same metabolic kinetics as fluoride but
is less toxic. Boron as preventive (F + Bp), reduced fluoremia compared
to lot F (p 0.05) but failed to increase urinary fluoride excretion; nor
did boron decrease the fluoride content of bones and claws (Fig.3 and
4). However, when administered during intoxication (F + Bpc) or after in-
terruption of fluoride administration (Bc) it apparently reduced the body
burden of fluoride by substituting an F + B complex for fluoride. In lots
F + Bpc and Bc, fluoruria was more pronounced than in lots F and F⚡ (in-
terruption: F⚡) (Fig. 2). In lot Bc, boron had a distinct effect upon
the skeletal radiography (Fig.5).   Therapeutically, therefore, boron
seems to be more effective than prophylactically. It could be used as
an antidote after discontinuance of fluoride intake to assure more effi-
cient excretion of fluoride from the body and prompter detoxification.

Our studies also indicate that the claws (but not the hair) repre-
sent an interesting parameter of body fluoride which is more precise but
less injurious than skeletal radiography (11) or bone biopsies (12).
Five milligrams of nails in man could be an indicator of fluorosis if
our observations in rabbits can be extrapolated to those of man. Herman
et al. (13) showed that in human fluorosis nails, hair and skin contain
less fluoride than bone, teeth and aorta, levels which are similar to
those of kidney and urinary tract, but higher than in all other soft tis-
sues.

The fluoride content of bones is elevated in our experiment in the
F lot which is in accordance with the findings of several authors on flu-
orosis (11, 14, 15, 16). Some are treating osteoporosis with fluoride
(17, 18), whereas others have reported adverse effects with this treat-
ment (19). Large doses of fluoride may induce demineralization of bones
due to hyperparathyroidism (20, 21) related to intestinal malabsorption
of calcium (5, 6, 7, 22). Fluoridated bone is a mixture of osteosclero-
sis and demineralization induced by hyperparathyroidism. The total bone
mineral content increases in fluorosis (14, 16, 23) and the calcium bal-
ance improves (24). With large doses in rabbits, we observed an inter-
ference in the calcium balance due to a reduction in the calcium diges-
tive utilization coefficient (5, 6, 7). In the current experiment, with
or without fluoride and boron, the calcium content of bone does not vary
(Fig. 3). This observation provides evidence neither for nor against
fluoride treatment of osteoporosis in doses used in our experiment.

Finally claws or nails (but not hair) represent an interesting para-
meter of the body's fluoride burden similar to radiography and biopsy of
bones. Boron acts as an antidote to fluoride. Administered initially,
boron simultaneously with fluoride had no effect upon the fluoride body
burden, but when added during intoxication or after interruption of flu-
oride a decline in the fluoride content of bone and claws was observed.

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FLUORIDE ABSORPTION BY THE ROOT AND FOLIAR TISSUES
OF THE HORSE-BEAN (CALCICOLE) AND LUPIN (CALCIFUGE)

Preliminary Studies

by

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SUMMARY: In the root and foliar tissues of calcicole
(horse-bean) and calcifuge (lupin) plants, absorption
of fluoride, at least in weak concentrations, does not
appear to be related to the metabolism of these plants.

Nevertheless the comparison of these two tissues
highlights clearly the differences in absorption of
fluoride in the two species. Absorption appears to
be slower and of longer duration in calcifuge plants
whereas between the two tissues, absorption is essen-
tially quantitative, the foliar tissues always showing
higher levels of fluoride than the roots. On the other
hand, fluoride is only weakly attached to the tissues
since most of it can be easily exsorbed into the water.

Our data disclose a great similarity in the ab-
sorption mechanism of fluoride and calcium ions in
calcicole and calcifuge plants.

Introduction

Previous studies of different physiological processes have shown a
strong link between calcium and the transport of fluoride in plants sub-
jected to fluoride pollution. Numerous authors have shown experimental-
ly that the calcium concentration of the culture influences, in most in-
stances, the penetration and accumulation of fluoride in roots and leaves
(1-7) as well as in different tissues (8, 9).

It must also be pointed out that natural variations of calcium in
plants bring about differences in the accumulation of fluoride. Indeed,
the resistance of leaves to the necrotizing effects of fluoride varies
during their development (10 - 12). We have been able to relate these
variations to the changes in the amount of calcium in the leaves during
their aging (13, 14). In polluted trees, fluoride and endogenous cal-
cium concentrations in different parts of the tree (15 - 17) are closely
related.

To follow up these various studies, we investigated whether or not
the calcicole-calcifuge character of certain plants, which naturally in-
volves important differences on the level of calcium absorption (18),

also induces fundamental differences in the absorption mechanism of flu-
oride.

Material and Method

I. <u>Vegetable Material: Source and Preparation:</u> Two leguminous fod-
der-plants were used for the study: the yellow lupin <u>(Lupinus luteus L.)</u>
a calcifuge species and the calcicole horse-bean (<u>Vicia faba</u> var.minor).

Of the two plants, two types of tissues, namely foliar and root tis-
sues were investigated simultaneously. The leaves are the preferential
absorption sites for fluoride at the time of atmospheric pollution, where-
as the calcicole-calcifuge selectivity takes place at root-level.

a) <u>Preparation of the Excised Roots</u>: After germination in distilled
water, the seeds were planted in constantly aired trays; the environment
of the culture contained a very dilute inorganic solution with the fol-
lowing composition:

0.1 mM/l of $Ca(NO_3)_2$, 0.1 mM/l of $MgSO_4$ and 0.1 mM/l of KH_2PO_4

Twenty-four hours before the experiment, this solution was replaced
by distilled water at which time the roots had weak inorganic reserves.
At the time of the experiments, namely eight or nine days after replant-
ing, the roots were excised at collar-level, washed in distilled water,
dried between two sheets of filter paper, and immersed in the fluoride
solutions. Each sample consisted in about five roots.

b) <u>Preparation of the Foliar Discs</u>: The plants had been cultivated
in the constantly aired KNOP environment. For the experiment, i.e. fif-
teen to twenty days after replanting, discs of 4 mm diameter were cut out
trenchant-style from the adult leaves. The cuts were made between the
principal veins. These discs were rinsed in distilled water, dried bet-
ween two sheets of filter paper, and soaked in the fluoride solutions.
Each sample was made up of about one hundred foliar discs.

II. <u>Experimental Techniques</u>: For the fluoride solutions we used
NaF and each one had a volume of one liter so that the concentration of
the surroundings did not vary during the course of the experiment. The
temperature of the solutions was maintained at 26°C and the pH adjusted
to 6. For the excised roots, the solutions were constantly aired during
absorption. At the end of the experiment, the plant material was quickly
taken out of the solution, rinsed in distilled water and dried between
two sheets of filter paper.

III. <u>Analytical Techniques</u>: The plant material was dried in a dry-
ing cupboard at 70°C for three days after which it was finely ground.
The fluoride concentration was obtained by using about 80 mg of the homo-
geneous powder. For fluoride analysis, the method of Levaggi et al.(19)
was used. By this method the mineralization of the samples in a Schöniger
oxygen flask is followed by a measurement of the fluoride which has been
obtained and taken from an absorbing solution by means of a specific e-
lectrode. The results are given in µg of fluoride per gram of dry mate-
rial (ppm).

Figure 2

Fluorine Absorption as a Function of Concentration

Foliar Tissues

Root Tissues

Figure 1

Fluorine Absorption as a Function of Time

Foliar Tissues

Root Tissues

Legend: Lupin (▲) Horse-bean (■)

Results

I. Fluoride Absorption as a Function of Time

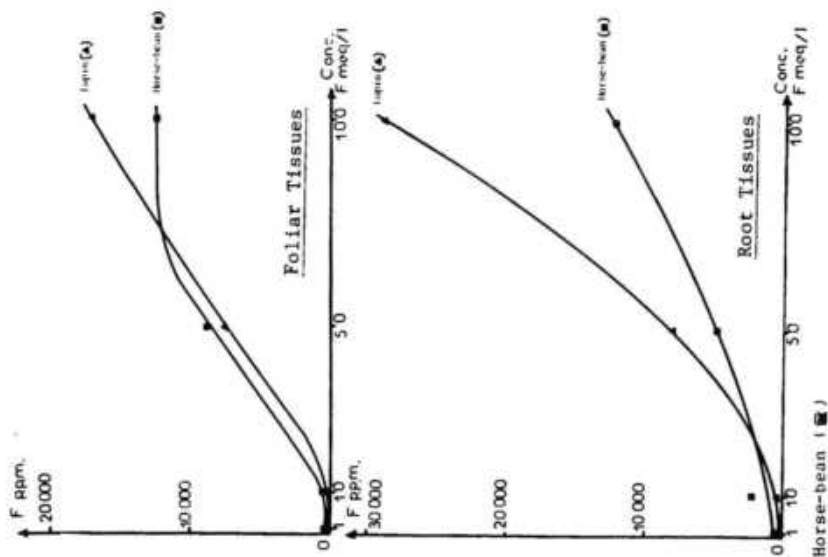a) Experimental Conditions: The fluoride concentration of the ab-
sorption solution was fixed at 50 meq/l, i.e. 950 µg F/g, a strength si-
milar to that of solutions used by other authors (20, 21). The absorption
period was 30 min.,1 hr., 2 hrs., 3 hrs., and 8 hrs. For each experiment
we determined the initial fluoride strength of the tissues.

b) Interpretation of the Curves (Fig. 1): The curves obtained sug-
gest that in the two species and for the two tissues used, fluoride ab-
sorption is a passive phenomenon. As a matter of fact, these curves do
not take the form of a linear phase of a constant gradient indicating an
active phenomenon according to the usual interpretation, but represent a
horizontal straight line corresponding to a constant rate of absorption.

The initial fluoride strengths show little variation (Lupin: roots =
23 ppm, leaves = 108 ppm   -   horse-bean:roots = 33 ppm, leaves = 250ppm).
The amounts of fluoride after absorption are greater in the lupin (calci-
fuge) than in the horse-bean (calcicole), and greater in the leaves than
in the roots. The lupin contain 8200 ppm of fluoride in its roots and
15,000 ppm in its leaves compared to 7200 ppm and 11,700 ppm in the roots
and leaves respectively of the horse-bean.

Above all we noted that the form of the curves for the two species
differ distinctly. For the lupin, the absorption time is longer, namely
5 hrs. for the root tissues and 8 hrs. for the foliar tissues whereas the
respective absorption times in the root and foliar tissues of the horse-
bean are 3 hrs. and 4 hrs. Furthermore, initially the phenomenon is
slower in the lupin, since during the first hour 2,000 ppm and 2,300 ppm
of fluoride is absorbed respectively in its roots and leaves compared
with 3,000 ppm and 4,700 ppm in the roots and leaves respectively of the
horse-bean during the same period.

II. Fluoride Absorption as a Function of the Environment Concentration

a) Experimental Conditions: The concentration range studied was 1 to
100 meq F/1 (20, 21). The absorption time was fixed at 5 hrs. to allow
sufficient time, in the majority of cases, for the curves to reach a
plateau.

b) Interpretation of the Curves (Fig. 2): It seems that the absorp-
tion increases as a function of concentration, slowly in a first step
(between 0 and 10 meq F/1), then more rapidly from 10 meq F/1. The absorp-
tion increase of concentration seems to be identical in the two species
up to about 50 meq F/1. Above this point it becomes much more signifi-
cant in the lupin (calcifuge) than in the horse-bean (calcicole).   The
curves have the same form for the foliar tissues as for the root tissues,
but in this experiment root tissues appear to accumulate more fluoride.

From these curves it appears that, above all, we must distinguish

·between the weak (0 to 10 meq/1) and the strong (10 to 100 meq/1) fluor-
ide concentrations. Effectively, for the weak concentrations the curves
quickly show a horizontal asymptote from 1 meq F/l onwards; in this re-
gion the absorption seems to be slightly more significant in the horse-
bean.

For the strong concentrations, on the other hand, the absorption in-
creases with concentration and it is very marked in the lupin (calcifuge).
The curves have a very different form and the mass absorbed does not tend
towards an asymptotic value.

Figure 3

Fluoride Exsorption as a Function of Time
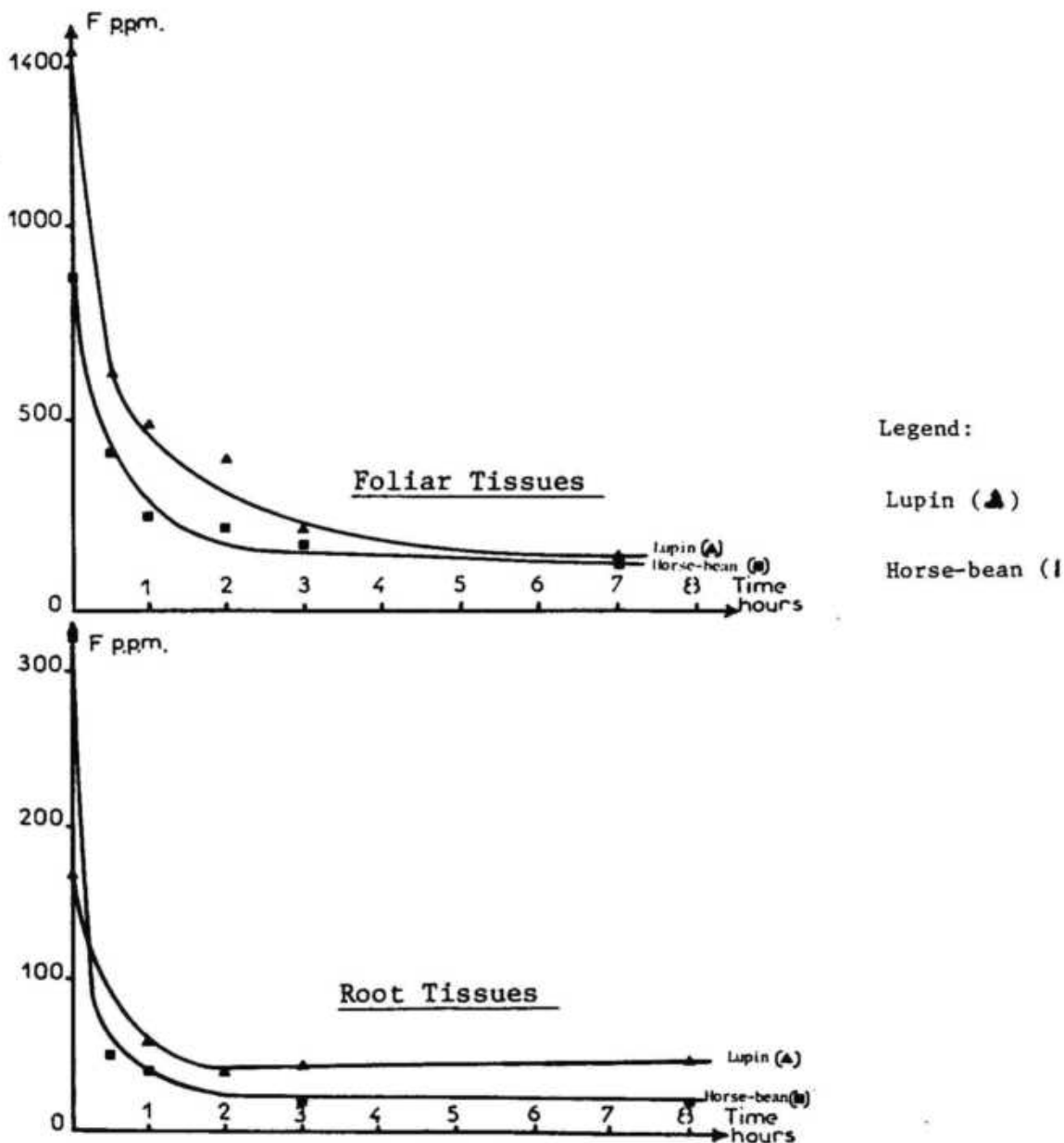
III. Fluoride Exsorption as a Function of Time

a) Experimental Conditions: The excised roots or foliar discs were
left for 24 hrs. to absorb in a fluoride solution of 10 meq/l.   At the
end of this time the plant material was quickly rinsed in distilled wa-
ter and then transferred into a large volume of distilled water for ex-
sorption during periods of 30 min., 1 hr., 2 hrs., 3 hrs. and 8 hrs.

b) Interpretation of the Curves (Fig. 3): These fluoride exsorption
studies allow us to evaluate the extent of the fixation of the fluoride
absorbed during these experiments. For the root tissues, the exsorption
was initially faster in the horse-bean than in the lupin, and the quanti-
ty of fluoride lost by these tissues was greater in the horse-bean than
in the lupin.

For the foliar tissues the exsorption phenomenon is explained by the
same type of curve as for the root tissues, but the lupin appears to have
lost more fluoride than the horse-bean. At the end of the experiment the
fluoride strength is practically the same in both specimens, being slight-
ly more in the calcifuge (lupin) regardless of the kind of tissue.

Interestingly, the quantities of fluoride eliminated by the different
tissues of lupin and horse-bean practically correspond to the quantities
absorbed. Ultimately we found 100 ppm fluoride in the leaves and 40 ppm
in the roots which are of the order of the fluoride test strengths.   So
it seems that little of the absorbed fluoride is strongly fixed inside the
various tissues.

Discussion

The results of the experiments on fluoride absorption as a function
of time in the foliar discs and excised lupin and horse-bean roots indi-
cate that we are dealing with a passive phenomenon independent of meta-
bolism. These results agree with the findings of Venkateswarlu (21) who
used barley roots.

The experiments on absorption as a function of fluoride concentration
show that the absorption mechanism is concentration dependent. In fact
at weak concentrations (<10 meq F/1) fluoride absorption as a function of
the strength of the surroundings seems to be explained by a hyperbolic
curve according to Epstein (22). Beyond this, the shape of the curve
differs and the mass absorbed does not tend to an asymptotic value. More-
over at strong concentrations fluoride accumulates significantly. This
accumulation is much more marked in the calcifuge specimen. If in the
weak concentration regions the process is one of passive absorption we
can hypothesize an active transportation mechanism.

Finally, the experiments on exsorption as a function of time have
shown that practically all fluoride absorbed could be desorbed by water.
This would seem to indicate that very little of the absorbed fluoride is
strongly fixed inside the tissues.

Generally speaking, the independence of the metabolism and the short
time required for the absorption and elimination processes which quickly
tend toward limited values, suggests that fluoride fixes itself on a lim-
ited number of sites essentially located at the cell-medium interfaces.
This fixation of fluoride on these sites is very weak and is easily dis-
placed.

Comparison Between the Calcicole and Calcifuge Species

From our results it appears that respecting fluoride absorption with
time, as well as absorption as a function of fluoride concentration, the
comparison between the two species demonstrates clearly differences in
reaction providing distinguishing criteria between calcicole and calci-
fuge plants. These differences are of limited importance on a quantita-
tive level: the initial fluoride reserves are equivalent and the masses
of fluoride absorbed by the two species are more often of the same order.
A surplus accumulation in the lupin results only in connection with
high levels of fluoride (100 meq/l).

On the qualitative level, on the other hand, differences are marked.
In fact the absorption curves differ for the two species; the phenomenon
appears to be slower and of longer duration in the calcifuge plants.

Comparison Between Foliar and Root Tissues

On the qualitative level, the absorption phenomena in the two tissues
are similar, the forms of the curves being identical. On the other hand,
on the quantitative level, the foliar tissues always show higher fluoride
levels except for the roots when the concentrations are high.

Comparison with Calcium Absorption

By comparison with identical studies carried out on the roots of cal-
cicole and calcifuge plants (18), there were close similarities on the
level of the absorption mechanism of calcium and fluoride ions. Indeed
these curves show exactly the same form. The effect of the calcicole
and calcifuge absorption characteristics can be explained in the same
way. In particular the absorption characteristics at strong concentra-
tions which very clearly distinguish calcium from all other cations are
the same as those for fluoride. Furthermore, the differences in fluoride
absorption for the calcicole and calcifuge species are not very pro-
nounced on the quantitative level but are particularly prominent on the
qualitative level. Only the fixation mechanisms of the two ions seem to
be different. Indeed whereas Salzac (18) has shown that very little of
the calcium absorbed by the excised roots can be exsorbed, our experi-
ments demonstrate that practically all absorbed fluoride can be quickly
desorbed.

The reason for this similarity between this cation and anion absorp-
tion mechanisms is difficult to explain. It requires investigation at
the level of the strong chemical affinity which exists between these two
elements.

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Plants. Nature, 212:1324-1327, 1966.

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EFFECT OF FLUORIDE ON HEMOGLOBIN AND HEMATOCRIT

by

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SUMMARY: Hemoglobin and hematocrit values in
human subjects residing in an endemic fluoro-
tic area were within the normal range.   Rats
that received 30 to 100 ppm NaF in drinking
water up to 45 days showed no significant change
in hemoglobin and hematocrit levels.

Introduction

The effect of fluoride on hemoglobin and hematocrit levels in labor-
atory animals has received considerable attention in the literature (1).
Ginn and Volker (2), observed a reduction of hemoglobin   values in
rats which received 50 ppm of fluoride as NaF in water daily for 150
days. Valjavec (3) noted only a slight reduction in hemoglobin levels
in nine rabbits, which received daily intravenous injections of 10 to
30 mg/kg NaF up to 159 days.   However Greenwood et al. (4) found no
changes in the hemoglobin and blood coagulation time after young dogs
received intravenous injections. In humans, Roholm (5) noted a slight
reduction in the number of erythrocytes but hemoglobin levels were un-
affected. Balazova et al. (6) observed in children living in close prox-
imity to an aluminum factory since birth that hemoglobin values were low-

er, erythrocyte values higher than in the control area. In children in
fluoridated Newburgh, N.Y., the incidence of cortical bone defects   was
significantly greater than in the nonfluoridated control city of King-
ston, N.Y. but the hemoglobin values did not differ significantly (7).

Material and Method

This investigation was made on sixty rats and 241 humans. The ex-
perimental animals were divided into four groups namely, fifteen control
rats which received tap water (0.1-0.6) (Group 1); fifteen received 30ppm
NaF in their drinking water for 15 days (Group 2); fifteen were given 50
ppm for 30 days (Group 3) and fifteen received 100 ppm for 45 days(Group
4).

The group of humans was composed of 62 males, 51 females and 128
children. All of them had been residing in the endemic fluorotic area
of Eskisehir throughout their lives, where drinking water contained 3.8-
4.9 ppm fluoride. They were examined for evidence of skeletal fluorosis
by means of x-rays. The diagnosis of dental fluorosis was established by
a dental surgeon.

Hemoglobin and hematocrit levels were determined in 119 male and
122 females afflicted with fluorosis; their ages ranged between 2 and
70 years. Sixty-eight of the 119 males were below age 16. Of the 122
females, 60 were below age 16. The results were compared with those of
nonfluorotic patients admitted to the hospital for other complaints.

Results

In the fifteen rats of Group 1 with 0.1-0.6 ppm fluoride in drinking
water, the hemoglobin levels ranged between 10.5-12.6 gm % and hematocrit
values were between 39-50 (Table 1). In Groups 2, 3 and 4 the hemoglobin

Table 1

Hemoglobin and Hematocrit Values in Rats

	Hemoglobin gm %	Mean	Hematocrit %	Mean
Group I Control	10.5-12.6	11.38	39-50	45.8
Group II 30 ppm NaF 15 days	10.2-12.4	11.16	37-55	45.7
Group III 50 ppm NaF 30 days	10.4-11.8	11.21	39-50	44.1
Group IV 100 ppm NaF 45 days	9.8-11.8	11.08	39-48	43.2

and hematocrit values revealed no significant differences between the control and the fluorotic animals at the termination of the experiments.

Table 2 presents the hemoglobin and hematocrit levels of the residents of the endemic fluorotic area. No significant differences were observed between the fluorotic and nonfluorotic subjects

Table 2

Hemoglobin and Hematocrit Values in Humans

	No.	Hemoglobin gm %	Mean	Hematocrit %	Mean
Men	51	11.40-14.15	13.18	35-47	42
Women	62	10.50-13.20	11.92	32-45	41
Boys	68	9.12-12.56	11.26	33-42	38
Girls	60	10.10-13.08	12.07	33-40	38

Discussion

In evaluating these data it appears that when anemia occurs in fluorosis, it should be considered a secondary manifestation due either to nutritional imbalance or to partial obliteration of the medullary space because of its reduction due to osteosclerosis. In the series of 55 cases by Singh et al. (8) in which the fluoride concentration of water ranged mainly between 1 and 2 ppm, hemoglobin levels from 8 to 15.5 gr/100 ml were found. Our results compare favorably with those of Agate et al. (1), who noted normal blood counts and hemoglobin levels in industrial fluorosis. Their finding was also supported by our animal experiments in which no difference was noted between the control and the fluorotic rats.

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FLUORIDE BRIEFS

The authors found, in the combined backs and necks of broiler chicks,
about 20 times as much fluoride as in bone-free meat. The range of flu-
oride in various parts of a broiler carcass was 0.9 to 45 ppm (wet weight).

Among the commercial phosphate supplements administered to chicks,
the fluoride content of "soft phosphate" was 17,100 ppm, of defluorinated
rock phosphate 1820 ppm, and of fish meal 188 ppm.

Pool, M.F., Tango, W.J., and Klose, A.A.: The Fluoride Content
of Commercial Broiler Backs and Necks. Poultry Science, 45:1545-
1550, 1965.

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The authors reported in insolated rat hepatocytes significant inhibition
by sodium fluoride and monofluoride enzymes of three glycolytic enzymes
namely, enolase, phosphoglucomutase and pyruvate kinase. This inhibition
appears to take place inside the cells and may be due to cAMP dependent
phosphorylation of the enzyme.

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Rat Hepatocytes. Biochem. and Biophys. Research Communications,
94:901-908, 1980.

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RADIOFLUORIDE DISTRIBUTION IN RAT LUNG, COLON AND HEART

by

G.M. Whitford, R.S. Callan and D.E. Pearson
Augusta, Georgia

In most soft tissues, fluoride enters the intracellular spaces as indicated by the tissue water-to-plasma fluoride concentration ratio which ranges between 0.4 to 1.0.

The authors injected intravenously 8 female Wistar rats with ^{18}F, 9.1 µCi/rat. They sacrificed four rats after 30 minutes and the other four after 60 minutes and collected blood from the neck wound, heart, colon, and lungs. They removed the colon, heart, and lungs. Fecal pellets were removed from the colon and special care was taken to dissect the lung from the major bronchi and trachea because cartilage tends to attract fluoride. Samples were weighed and counted for ^{18}F in a well-type scintillation counter.

The tissue water-to-plasma concentrations were lowest for the heart and colon and highest in the lung and trachea tissue. There was no evidence of ^{18}F binding by colon or by peripheral lung tissue. The authors stated in conclusion that earlier reports of the ^{18}F hi

Thirteen subjects residing in a nonfluoridated area (0.1 ppm in drinking water) on a normal and roughly comparable diet, were divided into experimental groups. Both groups received daily for 6 weeks, two placebo tablets without fluoride. Subsequently, the first group of 6 subjects were given two tablets daily for 7 weeks, one of which was a placebo, the other one contained 1 mg fluoride. The second group of 7 subjects continued on the placebo tablets for another 8 weeks after which they received two 1 mg fluoride tablets daily for 7 weeks.

The plasma alkaline phosphatase showed wide variations within normal limits among the subjects receiving two placebo tablets. The values in those receiving fluoride tablets did not differ significantly from the control values. However, in the subjects receiving 1 mg fluoride daily, the mean reduction in plasma alkaline phosphatase activity was 11% and in subjects receiving 2 mg fluoride daily the reduction was 13% during the first five weeks following the change from placebo tablets. After 5 weeks the mean in the subjects on fluoride tablets was close to that of the controls.

Subjects who received (2 mg F^-) daily after a period on one tablet (1 mg F^-) showed a decrease in alkaline phosphatase below the control levels. In both groups (1 and 2 mg F^-), the plasma alkaline phosphatase was below normal during the first week of administration.

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FLUORIDE INHIBITION OF DNA SYNTHESIS IN ISOLATED NUCLEI FROM CULTURED CELLS

by

R.I. Holland
Oslo, Norway

Fluoride inhibits protein and DNA synthesis in LS cells. The author elucidated the mechanism for this effect by isolating DNA synthesizing nuclei from LS cells and from LS cells resistant to 6 mM (114 ppm) fluoride. Fluoride concentrations of 1.5 mM (28.5 ppm) had no effect, but 3 and 6mM inhibited DNA synthesis in both groups of cells, the sensitive and the resistant cells. In intact cells - as distinguished from their nuclei - fluoride affects exclusively the DNA synthesis in sensitive cells. Their intracellular fluoride concentration is only 30 to 40% of that of the extracellular concentration. Inhibition of DNA synthesis by fluoride is secondary to fluoride inhibition of protein synthesis.

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Abstract

HYDROFLUORIC ACID - A CHRONIC POISONING EFFECT

by

D.A. White
Edinburgh, Scotland

(Abstracted from J. Soc. Occup. Med. 30:12-14, 1980)

The author points to the hazard of longtime occupational exposure to hydrofluoric acid. In three men engaged full time in the department of a plant where glass is dissolved from the surface of metallic platinum by means of concentrated hydrofluoric acid (80%),mean fluoride levels in the urine were as high as 12.02 ppm. This value exceeds the levels known to cause osteosclerosis. However, neither data on the patients' health nor x-ray changes were recorded. One of the employees had essential hypertension.

In the breathing zones in one room where the acid was used, the atmospheric hydrofluoric acid was well within the threshold limit of 2 mg/ m^3. However higher levels (5.1 mg/m^3) were detected in the other room. Following installation of local exhaust ventilation over the positions involved, the mean atmospheric fluoride levels were 0.7 mg/m^3 and the mean urinary fluoride declined to 1.41 ppm.

The author emphasizes that standards of occupational health designed to protect the worker from acute effects of HF, do not protect the worker from chronic exposure at lower levels.   He recommends routine monitoring of urinary fluoride in employees working with hydrofluoric acid.

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Vlijanie ftora okruzajuscej
sredy na zdorov'e uslovijach bucakskoj gidrogeochemiceskoj provinicii

INCIDENCE OF ATMOSPHERIC FLUORIDE UPON THE STATE OF HEALTH OF A POPULATION IN THE HYDROGEOCHEMICAL PROVINCE OF BUCAK

by

A.S. Kas'jenenko

(Abstracted from Vrach Delo 12:105-111, 1978)

The author carried out studies in six different areas of the province of UdSSR in Bucak of the Ukraine, the part of the USSR where water contains the highest levels of fluoride naturally in water.

In each of the six communities 100-200 children were examined. In an
area with 1.2 ppm fluoride in water, dental fluorosis exhibiting small
white spots on the teeth (Stage 1 according to Gabovic) was observed in
13.4%. Above 1.6 ppm, the incidence of dental fluorosis showed an increase
to 52%. When these percentages were compared with those reported by Gabo-
vic 30 years ago in the same area, there was a distinct decline in the in-
cidence of fluorosis at the same fluoride concentrations in water. The au-
thor attributes this improvement to social hygienic conditions which have
enhanced the tolerance to fluoride.

The electrical resistance of the teeth was measured in order to de-
termine fluoride-induced changes of the structure and the chemical compo-
sition of the teeth. With addition of fluoride to drinking water, the
electrical resistance, which normally amounts to 150-200 kΩ declined to 40
kΩ in cases with fourth grade fluorosis.

The caries incidence among children below 16 years, in areas with 1.2
-4.2 ppm fluoride in drinking water showed a 50-70% reduction compared to
that of the control area with water fluoride levels of 0.1-0.35 ppm.

Two thousand female workers aged 50 to 60 were studied in two cities,
one with 1.5-1.6 ppm and the other with 0.1-0.35 ppm fluoride in water.
There appeared to be less caries and less extracted teeth in the fluoride
group drinking the water with a higher fluoride level.

The fluoride concentration above 1.5 was associated with a delay in
eruption of teeth at ages 8-10. In children 13 years of age, however,
there was no difference in delay compared with normal. At age 13, with 8.2
to 10.3 ppm in water, more teeth were erupted than in the control area.

The effect on bones was studied in six localities with varying fluo-
ride levels in the drinking water. Six hundred x-ray films were taken of
the hands of 9-year old children and 600 of the cervical spine of 50-year
olds. In addition, chemical and histological studies were carried out.

At 1.0-2.5 ppm the density of the bones had increased compared with
the controls. At 4.0-4.2 ppm the density appeared to be reduced and at
8.2-10.3 ppm there was a distinct decrease in density to the extent that
osteoporosis occurred. In the last-mentioned group, a delay in ossifica-
tion was observed. Among the 50-year old subjects, "old-age" changes of
the cervical spine appeared to be more frequent and more pronounced than
in controls. Histologically, no clear-cut changes were found in bones of
individuals who had expired as a result of accidents. The citrate con-
tent of their bones decreased when the drinking water contained 2 ppm
fluoride. At 2-2.5 ppm and above in drinking water, children showed an
increase in the threshold for sensitivity of the eye to red color. At the
highest concentration of 8.2-10.3 ppm the degree of this deficiency was
similar to that among workers in fluoride industries.

                                                      J. Franke

                        ****

Ostéose fluorée après 11 ans de traitement
ininterrompu par l'acide niflumique

FLUORIDE OSTEOSCLEROSIS AFTER 11 YEARS OF
UNINTERRUPTED TREATMENT WITH NIFLUMIQUE ACID

by

Bregeon, C., Bernat, M., Renier, J.C.
Rebel, A., and Basile, M.
Angers, France

The first report of fluoride osteosclerosis due to a drug was pre-
sented in 1978 by Prost et al. The current report describes the case
of a 57-year old male afflicted with rheumatoid arthritis which had been
developing gradually since 1945. Mainly involved were the hips and the
left carpal-phalangeal joints. His condition was treated at first with
prednisone which had to be discontinued because of the presence of ane-
mia. It was followed by a fluoride-containing drug Noflumique acid. At
first, 2000 mg/day was administered for 15 days; he then received 1500
mg/day until January 1969 when the patient was subjected to arthroplasty
at the right hip.

Subsequently the patient was taking 6 capsules (1500 mg/day) of the
above-mentioned acid together with Indometacine and Aspirin continuously
up to May 1978. The total dose of fluoride consumed by this patient at
0.3 g/day during 4120 days was estimated to be 1240 grams.

The first signs of osteosclerosis appeared in 1974. By May 1978,
extensive lesions had appeared in the pelvis, spine and ribs, whereas
the skull and other bones remained within normal limits.

Biochemical studies in April - May 1978 and in June 1979, thirteen
months after discontinuance of treatment, revealed a slight decrease in
the serum, calcium and alkaline phosphatase. Urinary calcium had de-
creased to 62 mg/day, urinary phosphorus was 685, plasma ionized fluo-
ride 0.2 mg/liter and 24-hour urinary fluoride 5.6 mg. By June 1979 the
urinary calcium had increased to 114 mg/day, urinary phosphorus to 820mg/
day and hydroxyprolinuria to 43 mg/day. Both urinary and plasma fluoride
were slightly lower than in 1978.

Histomorphometric bone studies in 1979 showed that the volume of
trabecular bone was 40.6% compared to 17.4±5.6% (normal); resorption sur-
face was 10.4% (normal 3.6±1.1%); periosteocytic lacunae 58 μ2 (normal
50.7±5.5 μ2). The structure of bone tissue and of the osteoid was of
lamellar type, the rate of mineralization had decreased and the number
of active osteoclasts had increased.

The authors pointed out that the fluoride doses during 11 years
were as high as the ones reported previously by Prost et al. They also
emphasized that thirteen months after discontinuance of fluoride intake,
the urinary fluoride level remained considerably elevated.
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SOME OBSERVATIONS ON ATMOSPHERIC FLUORIDE CONCENTRATION IN STOKE-ON-TRENT

by

Bennett, A.J., and Barratt, R.S.
Stoke-on-Trent and Birmingham
England

The authors carried out an atmospheric fluoride survey in the industrial city of Stoke-on-Trent, the seat of pottery and brickworks. To collect particulates they used membrane filters; for gaseous fluorides, alkali-impregnated cellulose pads were placed after the membrane filter. Air samples daily during a two-week period in 1978 at two sites, were averaged. At the non-industrial site, with one exception, the total fluoride concentrations were below the limit of detection by the method used, namely 0.1 $\mu gF/m^3$. In the industrial site, the highest concentration was 7.11 $\mu gF/m^3$ air. The calculated weekly mean concentration of total atmospheric fluoride was 2.81 $\mu g/m^3$ during the first week. During the second week however, which coincided with the annual holiday period, it was only 0.48 $\mu g/m^3$. Although a strong correlation was observed between the sulphur dioxide concentrations and those of fluoride, none existed between airborne fluoride and smoke concentrations.

The authors attributed the relatively low amount of particulates to the possibility that particulates were lower during the sampling periods or they may have been deposited before they reached the sampling sites. Smoke concentrations were low during the survey period in the industrial area. The lack of relationship between smoke and fluoride indicates that combustion of domestic coal is not the source of fluoride or of SO_2. Possible sources include industrial processes in which both pollutants are emitted such as firing of clay material using sulphur-bearing fuels.

The authors tabulated data from similar surveys, both in England and in other countries. In the yard of a Japanese aluminum refinery, the concentration of total fluoride in air ranged up to 92.4 $\mu g/m^3$. In the U.S.S.R. near a superphosphate plant, the levels rose as high as 98 to 485 $\mu g/m^3$.

Although the values reported by Bennett et al. are relatively low, the authors suggest that persons residing in areas where atmospheric fluoride levels are elevated, where both locally grown vegetables as well as considerable tea are being consumed and, in addition, the water is fluoridated, the daily fluoride intake may possibly be above 5 to 8 mg, the level of intake at which osteosclerotic changes occur.

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Critical Survey of Stability Constants and
Related Thermodynamic Data of Fluoride Com-
plexes in Aqueous Solution, by A.M. Bond and
G.T. Hefter. IUPAC Chemical Data Series,
No. 27, Critical Evaluation of Equilibrium
Constants in Solution, Part A: Stability
Constants of Metal Complexes. Pp 71 + vii,
3 tables, plus references. Pergamon Press
Inc., Maxwell House, Fairview Park, Elms-
ford, New York 10523. Softcover, $25.00.

This volume is one of the latest in the series of critical compila-
tions being prepared by the Commission on Equilibrium Data of the Analy-
tical Chemistry Division of the International Union of Pure and Applied
Chemistry. Because of the importance of fluoride complexes in many chem-
ical and biological systems, virtually every scientist engaged in fluo-
ride research will find it of great practical value.

In the introductory section the authors summarize and compare how
fluoride-metal ion stability constants are measured and what are some of
the frequently overlooked difficulties and complications in their deter-
mination. They also comment on the measurement and reporting of enthal-
pies of fluoride complexation. Finally, they explain how the extensive
data collected here have been evaluated and arranged.

In the main table, stability (formation) constants of fluoride com-
plexes are assembled with over 70 metal ions and hydrogen ion at various
ionic strengths. The second table lists enthalpy and entropy data for the
more important complexes. Finally, the third table presents what the au-
thors regard as the "best" values for the stability constants given in
the main table. More than 250 references, arranged by year and alpha-
betically by first author, are cited.

For those who need a handy compilation of data on fluoride complexes
in aqueous solution, this volume is warmly recommended, although it is
quite expensive for only 71 pages of typescript printing.

                                                        A.W.B.

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