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EDITORIAL

The Research of A.K. Susheela on Fluoride Changes in Bone

In the mid 1930s, skeletal fluorosis in India became the subject of widespread attention. Previously osteosclerosis from industrial exposure to fluoride had been recorded in 1932 by two Danish workers, Moller and Gudjonsson (1). In 1937 Shortt and colleagues described endemic fluorosis in the Madras Presidency (2,3). Dagmar Wilson, who after leaving India joined the present author's department, reported in 1939 (4) her observations on the distribution of fluorosis in England and in India where, in the previous few years, she had examined more than 9000 children in the Punjab. Elsewhere in India, other investigators (5-9) presented their findings on skeletal fluorosis to the scientific community. In 1960, an article by Amarjit Singh (10) Professor of Medicine in Patiala in collaboration with S.S. Jolly and B.C. Bansal on skeletal fluorosis with neurological complications in the Punjab appeared in the Lancet. A series of papers which originated in that Department of Medicine has been continued, after the death of Singh, by his successor, Professor Jolly, who has made some of the most careful investigations. Much subsequent work by Teotia, Krishnamachari and others has been reported in this journal.

It is appropriate that the 13th Congress of the International Society for Fluoride Research convene in India with Professor Jolly as President, and with Dr. A.K. Susheela as Organizing Secretary. Through Dr. Susheela's dedication and indefatigable energy, the 13th conference promises to be a milestone in the history of the society at this crucial period. This editorial will summarize briefly Dr. Susheela's outstanding research carried out in the All-India Institute of Medical Sciences, New Delhi.

About ten years ago, she and her colleagues discovered that, in muscle mitochondria in rabbits given 50 mg/kg sodium fluoride daily, creatine kinase (EC 2.7.3.2) was greatly increased (11) as occurs in human muscular dystrophies. Protein synthesis was also inhibited in all soft tissues investigated (12). In bone, about 90% of its organic matter is present as collagen. Using carbon-labelled proline, she showed that synthesis of collagen was diminished resulting in inadequate hydroxylation and cross-linking (13). Subsequently she paid particular attention to the noncollagen proteins of bone which can be divided into glycoproteins and glycosaminoglycans. The former were decreased in fluorotic patients. Some glycoproteins contain sialic acid, which was diminished in rabbits given 10 mg/kg NaF daily. She suggested that estimation of sialic acid might constitute a test for fluorosis (14). However, sialic acid was increased in cancellous bone. Because fluoride binds calcium ions, poor mineralization might result. Cancellous bone contains about twice as much fluoride as cortical bone.

Dr. Susheela next studied the glycosaminoglycans of which there are up to 100 chains in a molecule of proteoglycans (admirably studied in extracellular matrix by Helen Muir). The former are sulphated forms of the latter (such as condroitin sulphates). She made the important discovery that, in rabbits given 10 mg/kg of NaF daily, chondrocytes appeared in cancellous bone trabeculae. Dermatan sulphate also appeared. Whereas glycosaminogly-

cans are not found in normal calcified tissues, they are present in normal tendon, skin and ligaments. The chondrocytes produce cartillagenous islands in cancellous bone (not in cortical) which remain as cartilage (osteoid; if calcified they would be true bone) (15-17). Periosteal tissue increases, thus the girth of bone increases. This increase is found in fluoride treatment of osteoporosis; x-rays show that the new shadows are cartilage. Since in plasma, glycosaminoglycans are increased, estimation of them might constitute a prognostic test of fluoride toxicity (18).

Dr. Susheela also studied the activity of the enzyme adenylate cyclase (EC 4.6.1.1), which is known to be increased by fluoride. In rabbits, which recived 10 mg/kg of NaF daily, its activity increased in cortical bone, liver and kidney, but not in skeletal muscle (19).

At the 12th conference, in St. Petersburg Beach, Florida, Dr. Susheela with her colleagues presented five papers summarizing the above-described work. The importance of understanding the action of fluoride upon bone cannot be over-emphasized. At the 13th conference in New Delhi, India, further advances from Dr. Susheela and her colleagues are anticipated.

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THE INCIDENCE OF MOENCKEBERG CALCIFICATIONS IN PATIENTS WITH ENDEMIC FLUOROSIS

by

E. Tuncel
Bursa, Turkey

SUMMARY: This study is comprised of 106 male patients over age forty from a high fluoride water (3.5-12.5ppm) area. These patients have been matched by age and sex with 106 patients from a low fluoride water (0.00-0.45 ppm) area.

All patients had radiograms of the chest, pelvis and both femora; 21 in the fluorotic group underwent a skeletal survey. All plain films were examined for skeletal fluorosis changes; pelvis and femur radiograms for Moenckeberg arterial calcifications.

Over age 60, patients in the high-fluoride group showed a significantly higher incidence of Moenckeberg calcifications. A highly significant correlation ($P < 0.001$) was observed between the severity of these calcifications and the severity of skeletal changes within this group.

KEY WORDS: Moenckeberg arterial calcifications; Endemic fluorosis; Turkey, fluorosis in

Introduction

Endemic fluorosis or chronic fluoride intoxication is characterized by mottled enamel, increased density of the skeleton, and ligament calcifications resulting from prolonged ingestion of fluoride in drinking water.

Many of the effects of fluoride on human health are well-known. A review of the literature indicates that, in skeletal fluorosis, arterial calcifications are common (1-10).

The main purpose of this study was to investigate the incidence of Moenckeberg calcifications in patients with fluorosis in Turkey.

Materials and Methods

Radiograms of the chest, pelvis and both femora were taken of 106 male patients over 40 years of age, residing in a high fluoride water area and 106 others in a low fluoride water area, 212 patients in all. Moenckeberg calcifications were investigated in the iliac and femoral arterial area. Skeletal changes of fluorosis were evaluated on the basis of all roentgenograms by the following method:

From the Radiology Department, University of Uludag, Bursa, Turkey.

1. Moenckeberg calcifications: a) none, b) slight—calcifications seen in only one femoral or iliac artery, and only a small region affected , c) marked— in both arteries with calcifications affecting a large portion of the arteries .

2. Skeletal changes: a) none or slight (normal or slightly increased bone density, but not significant enough by themselves to indicate skeletal fluorosis, b) mild fluorotic changes, c) marked fluorotic changes. Evaluation mainly followed Roholm's calcification, 1937 (11).

Results

I. Moenckeberg calcifications of iliac and femoral arteries (Table 1) were discovered in 28 of the patients with fluorosis(26.4%),17 of which were slight, 11 were marked. Two of the slight cases were under 60 years of age. In the control group, 12 cases of Moenckeberg calcifications (13.3%) were found, 9 of which were slight, 3 were marked.

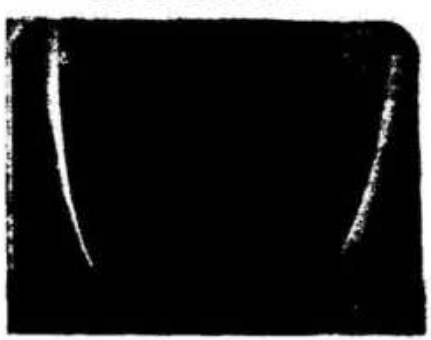
Table 1

Distribution of Moenckeberg Calcifications in Two Groups Based on Age

Age	Number of Cases	Fluorotic		Control	
		Slight	Marked	Slight	Marked
40-59	31	2	-	2	-
60-	75	15	11	7	3

Figure 1

Marked Moenckeberg Calcifications
Severe Fluorosis



II. Table 2 compares Moenckeberg calcifications with skeletal findings in fluorosis patients. Of all patients with fluorosis, 24 (22.6%)showed skeletal findings of fluorosis (15 mild, 9 marked). Only 3 of the 24 patients were under age 60, 21 were older than 60. In five patients with marked skeletal fluorosis, acetabular protrusion, bowing, rough and coarse trabeculations in distal femora were observed. There were "Sandwich vertebrae" appearances in two of them.

Statistical assessment of findings:

1. That Moenckeberg calcifications are more frequent in cases of fluorosis than in the control

Table 2

Comparison of Moenckeberg Calcifications and Skeletal Findings in Fluorotic Group

Moenckeberg Calcifications	Skeletal Changes Marked	Mild	None	Total
Marked	7	3	1	11
Mild	1	4	12	17
None	1	8	69	78
Total	9	15	82	106

Figure 2

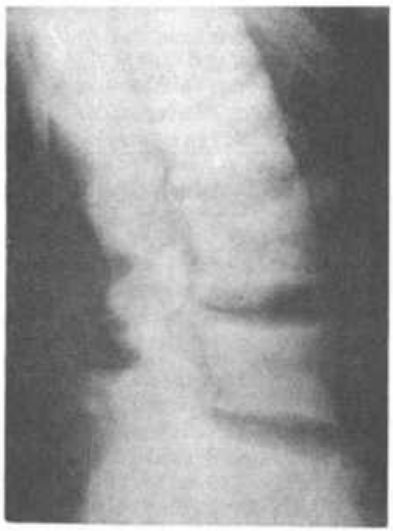
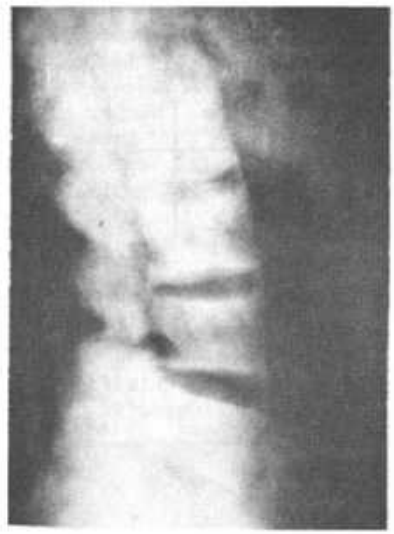


Figure 3



Sandwich Vertebrae Appearances in Severe Fluorosis

group over 60 years of age is statistically significant ($P<0.01$).

2. A close relationship was observed between the distinctness of the findings regarding the skeletal system and the appearance of Moenckeberg calcifications. Moenckeberg calcifications, always found associated with changes in the skeleton, increase in direct relation to the progress of the skeletal changes. This result has a high statistical significance ($P<0.001$).

Discussion

Drinking water in the endemic fluorosis area of DOGU-BE-YAZIT, where our patients were residing, contains 3.5-12.5 ppm fluoride (12-14). In ERZURUM, whence members of the control group came, the concentration of fluoride in drinking water ranged between 0.00-0.45 ppm (12).

All patients were male over 40 years of age. Both skeletal changes of fluorosis and Moenckeberg calcifications were prominent in elderly male patients (15,16). Thus we believe that the conditions of this study were suitable to determine whether Moenckeberg calcifications and skeletal fluorosis are related.

The earliest and most distinct radiological changes of fluorosis were seen in the pelvis, thorax and vertebrae (11,17,18). Moenckeberg calcifications were seen most often in the popliteal and femoral arteries and their appearance in plain radiographs was characteristic (19). They are multiple ring-like calcifications and generally affect a long segment, whereas atheroma calcifications are seen as irregular plaques. Therefore, the radiological study of our patients was sufficient to show skeletal fluorosis changes and Moenckeberg calcifications. According to statistical evaluation of the findings, these calcifications were more frequent in patients with fluorosis over 60 years of age than in the control group, and the degree of calcification and skeletal findings in the patients with fluorosis was closely related.

Speder in 1936 (1) was first to mention involvement of arteries in skeletal fluorosis. Subsequently many others have described the Moenckeberg type of calcification of arteries (2-10). Whereas arteries store more fluoride than any other soft tissue organ, the levels of fluoride and calcium deposition in them are not related (9).

Many studies suggest that parathyroid hyperplasia develops from high fluoride intake (20-22) and that secondary hyperparathyroidism occurs in the skeletal system of patients with fluorosis (23-27). Moenckeberg calcifications and sandwich vertebra appearances are frequently seen in cases of hyperparathyroidism. The high incidence of Moenckeberg calcifications in cases of fluorosis may reflect the development of secondary hyperparathyroidism in these patients. For proof, however, further biochemical, histopathologic and radiographic studies are warranted.

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FURTHER OBSERVATIONS ON RADIOLOGICAL CHANGES OF ENDEMIC FOODBORNE SKELETAL FLUOROSIS

by

Huo Daijei
Guizhou, China

SUMMARY: Among radiological changes in 396 cases of foodborne skeletal fluorosis, from four endemic areas in Guizhou, China, the author has observed osteoporosis, osteomalacia and impaired bone growth in addition to previously recorded findings of osteosclerosis, bone prominences, joint changes, and calcification of peripheral arteries. The deformity of genu valgum, a manifestation of osteomalacia, was encountered in one of the endemic areas. Radiographic appearances varied between individuals, from one area to another, and depending on age.

KEY WORDS: Fluorosis, skeletal; China; Osteosclerosis; Osteoporosis; Osteomalacia; Skeletal fluorosis, foodborne.

Introduction

Since his preliminary findings on radiological changes of foodborne skeletal fluorosis appeared in 1981 (1), the author has made additional observations.

Material

In this report of 396 cases of skeletal fluorosis, 240 were males, 156 were females. They ranged in age from 3.5 to 70 years; 45 were under 19 years old.

The patients came from endemic areas I, II, III, and IV, in Guizhou, China, with different degrees of prevalence. The fluoride levels in drinking water and in some food items in the four areas are tabulated in Table 1.

Table 1

Fluoride Levels in Different Areas

Area	No. of Cases	F^- (ppm) in Water	mgF^-/kg in Rice	Corn	Potatoes
I	92*	0.15-0.18	3.3	5.2-6.6	0.7-0.8
II	70	0.1	2.4-8.1	4.4-13.5	1.2-5.1
III	23	0.51	4.9-8.3	5.0-17.8	Unassayed
IV	211	0.07-0.33	11.8-32.1	16.7-17.2	16.4-45.3

*34 cases previously reported (1) are included.

From the Dept. of Radiology, Guiyang Medical College, Guizhou, People's Republic of China.

The above cases were diagnosed as skeletal fluorosis based on mottled enamel, radiological changes, and the high fluoride levels in food.

Results

The radiological findings are summarized under headings and subheadings as shown in Table 2.

Table 2

Radiological Findings in 396 Cases of Endemic Skeletal Fluorosis

1. Axial osteosclerosis
   a. Thickening of trabeculation
   b. Thickening of cortex
   c. Encroachment of the medullary cavity by compact bone
2. Osteoporosis
   a. Generalized osteoporosis
   b. Peripheral osteoporosis
3. Osteomalacia
   a. Peripheral osteomalacia
   b. Regional osteomalacia
4. Bony prominences
   a. Ectopic ossification of ligaments, tendons, aponeuroses, interosseous membranes, and muscular attachments
   b. Periosteal new bone formation
5. Joint changes
   a. Narrowing of articular spaces
   b. Periarticular osteophytes
   c. Intra-articular free bodies
6. Impaired bone-growth
   a. Growth arrest lines
   b. Multiple compact contours
   c. Failure of modelling
7. Others
   a. Calcification of peripheral arteries
   b. Cyst-like radiolucences

Osteosclerosis and formation of bony prominences on surfaces of bones, which are recognized characteristic changes of fluorosis and the mainstay for establishing the diagnosis, were noted in most of the patients. Osteosclerosis was especially prominent in axial bones of the spine, pelvis, and ribs, although peripheral bones were not spared.

Osteoporosis was either generalized or peripheral according to the sites involved. Generalized osteoporosis, encountered in 20 cases above age 40, involved the whole skeleton. Its radiological features were similar to those of senile osteoporosis. Associated characteristic bony prominences were the basis on which the diagnosis of fluorosis was established. However, the possibility of fluorosis complicated with senile osteoporosis cannot be excluded. Peripheral osteoporosis, which was encountered frequently, was prominent chiefly in peripheral bones, where trabeculae were partially thinned or disappeared; but the remainder, usually the lines-on-force trabeculae, were prominent and coarsened, forming intertwining networks. In these patients, mild osteoporosis was also fre-

quently found in axial bones showing patchy porotic areas, usually in bilateral iliac wings.

According to the sites involved, osteomalacia was either peripheral or regional. In peripheral osteomalacia, the lower extremities were chiefly affected, but the upper extremities and other bones were not spared.

The cortex was thinned or laminated, trabeculae were blurred, density was decreased and was often associated with genu valgum (Fig. 1), which usually began in childhood and progressed over many years. In 10 children, osteomalacia involved the pelvis, forming tri-foliative deformity due to intrapelvic protrusion of bilateral acetabula. The peculiarity of peripheral osteomalacia was its frequent association with axial osteosclerosis. Increased weight of sclerosed axial bones was a factor aggravating the deformity of the lower extremities. Regional osteomalacia was manifested by a radiolucent zone in metaphyses adjacent to epipheses, or by an arcuate radiolucent zone just below the iliac crests (Fig. 2). Presumably, because the rate of new bone formation is too rapid to keep pace with subsequent calcification, a zone of poorly calcified osteoid seam is formed.

Figure 1

Male aged 39, Marked Bilateral Genu Valgum

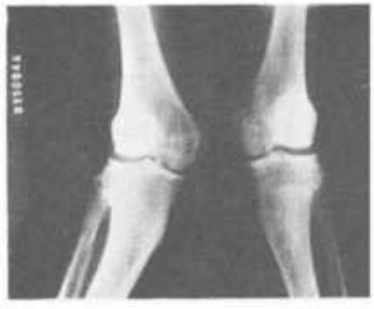
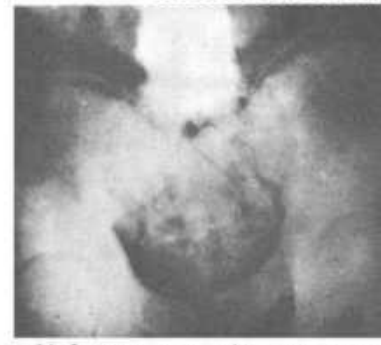


Figure 2

Male, aged 30, Marked Osteosclerosis of Lumbar Vertebrae and Pelvis

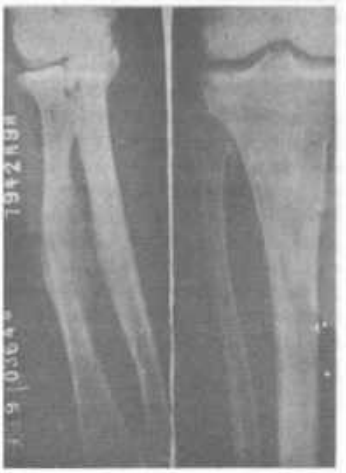


Broad radiolucent arcuate zone at ilium on each side, just below iliac crest.

Radiological features of bony prominences (Fig. 3) and joint changes have been described previously in detail (1). Often growth arrest lines occurred in the lower end of the femur and in the upper end of the tibia (Fig. 4). Sometimes, multiple dense arcuate lines were distinguished just below the brim of the ilium. Multiple dense contours were often noted in the ilium just around the end plate of the acetabulum (Fig. 5). These changes indicate repeated arrest of osteoblastic activity during bone growth. Failure of modelling was occasionally seen, resulting in expansion of shafts and metaphyses (Fig. 6). Moreover, calcification was en-

Figure 3

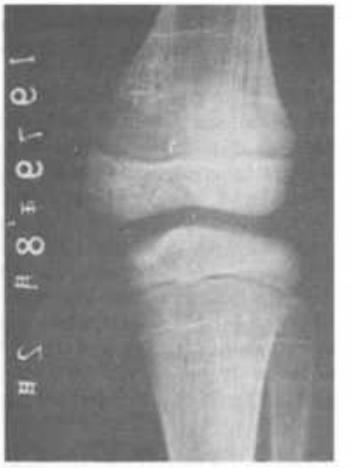
Male, aged 40



Multiple bony prominences on radius and ulna.

Figure 4

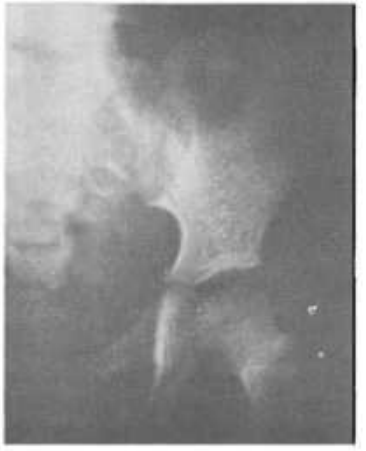
Male, aged 11



Multiple growth arrest line in the metaphyses of femur and tibia.

Figure 5

Male, aged 15



Multiple contours around end plate of acetabulum.

Figure 6

Male, aged 9

Multiple cyst-like radiolucences in metacarpal and phalangeal bones. Note expansion of these bones.

countered in one case, with cyst-like radiolucences in four cases (Fig. 6).

Radiographic appearances varied in different areas. Osteosclerosis, bony prominences, and joint changes were noted in all areas, whereas osteomalacia and impaired bone growth appeared only in Area IV where the fluoride levels in rice, corn and potatoes were much higher than in the same produce from other areas. The appearance of osteomalacia and impaired bone growth in a fluorosis area suggests intake of large amounts of fluoride.

Radiographic appearances varied between individuals. Conflicting changes such as both decreased and increased density, coarsened, thinned and blurred trabeculae, coexisted not only in different bones of one individual, but also in one and the same bone. Some cases showed axial osteosclerosis exclusively, others axial osteosclerosis in association with peripheral osteoporosis or osteomalacia. In the pelvis, patients often showed decreased density with coarsened, rarified trabeculae intertwining in bilateral iliac wings and increased density in regions adjacent to articular surfaces and acetabula. Combinations of various changes produced a wide spectrum of radiographic patterns.

Radiographic appearances also varied from age to age. In younger cases osteosclerosis, bony prominences and joint changes were less marked. Impaired bone growth and regional osteomalacia were encountered chiefly in children and youth. In children below age 5, osteosclerosis was manifested as coarse trabecular striations or networks mixed with scattered dense spots of about 1-3 mm diameter found in iliac bodies, metaphyses of long tubular bones and elsewhere. These spots resulted presumably from en-face view of coarsened trabeculae. The striations, networks, and spots tended to increase in number, become progressively thicker, denser and hazier until sclerosis of spongiosa began to obliterate the demarcation between them and the cortex after about age 10. Below age 15, bony prominences and joint changes were never noted which explains why limitation of movement was rare in children.

Discussion

The present report substantiates the author's observation that,in endemic areas of Guizhou, China, food is an important source of fluoride. According to Li Ribang et al. (2) fluoride in food is higher than usual in a Guizhou fluoride area, because coal is used when baking food. Li Xianji (3), who studied the geological and environmental conditions in Guizhou. believes that fluoride in food can come from soil as well as from baking with coal. Obviously the practice of addition of fluoride to water supplies where it contains less than 1 ppm, is unfit for Guizhou.

Although fluorotic genu valgum, a world-wide problem, has been reported in India (4) and South Africa (5), this is the first report of it in China, where it is confined to certain endemic areas. After studying the four areas, the author concludes that the dose of fluoride influences its occurrence. Whereas in this series, a 3.5 year old child was the youngest with

skeletal fluorosis, fluorosis might begin even earlier, perhaps during the fetal period. Radiographs of the 3.5 year old child and other children showed mild osteosclerosis with trabecular thickening. Among them, osteoporosis, which has been regarded as an early manifestation of fluorosis was not prominent. It seems unlikely in our cases.

Acknowledgement

The author wishes to thank the Guizhou Office for Prevention and Treatment of Endemic Diseases and the Guizhou Sanitation Monitory Station for their radiographs and for data on fluoride levels in Area IV; the Department of Hygiene, Guiyang Medical College, for their data on fluoride levels in Areas I, II, and III.

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ENVIRONMENTAL FLUORIDE AND METABOLIC BONE DISEASE AN EPIDEMIOLOGICAL STUDY (FLUORIDE AND NUTRITION INTERACTIONS)

by

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SUMMARY: Epidemiological, clinical, nutritional, biochemical and radiological surveys were performed in nonendemic fluorosis areas to determine the relationship between endemic skeletal fluorosis and accompanying metabolic bone disorders.

In individuals with inadequate nutrition, en-

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demic skeletal fluorosis is more severe, and metabolic bone disease is more frequent in such individuals in endemic areas. Metabolic bone disease occurred more frequently in residents of endemic areas than in residents of nonendemic areas whose nutritional status was comparable. Common metabolic bone disorders, associated with endemic skeletal fluorosis, were osteoporosis (bone resorption), rickets, osteomalacia, and parathyroid bone disease. In assessing the biological impact of the toxic effects of fluoride, its action on bone becomes more complex when one considers such nutritional factors as calcium, vitamin D and protein.

KEY WORDS: Fluoride (plasma, water, urine), endemic, nonendemic, nutritional status, dietary calcium, vitamin D, alkaline phosphatase; Skeletal fluorosis (mild, moderate, severe); Metabolic bone disease.

Introduction

The use of sodium fluoride in the treatment of osteoporosis by various workers (1-4) and our previous reports that osteoporosis and other metabolic bone disorders are often associated with skeletal fluorosis (5-7), prompted us to carry out a field and clinical study in the following two groups of rural population:1) persons residing in nonendemic areas with fluoride in drinking water < 1.0 ppm, and 2) residents in endemic areas where levels of fluoride in drinking water are high (7.5 ppm). The aim of the study was 1) to find out the prevalence of the metabolic bone disorders accompanying endemic skeletal fluorosis. 2) to study the severity of the toxic effects of fluoride on the bone under differing nutritional conditions and 3) to discover whether natural fluoride in drinking water provides any protection against osteoporosis.

Material and Methods

After geographical location of the villages and analysis of drinking water samples from these areas for their fluoride content, the two groups of the rural population 1) nonendemic and 2) endemic were identified. The field team made a complete house-listing of the population residing in nonendemic and endemic areas. Clinical examination for skeletal fluorosis and accompanying metabolic bone disorders and the nutritional assessment for fluoride and dietary intakes per day were performed by the trained staff on all subjects who had volunteered for examination. The diagnosis of skeletal fluorosis and accompanying metabolic bone disease was confirmed in each individual by a thorough history taking, clinical examination, laboratory and radiological investigations.

The severity of skeletal fluorosis was classified as mild, namely asymptomatic- skeletal radiographs showing generalized increase in bone density; moderate- symptomatic, stiffness, rigidity, pains and aches, restricted movements, osteosclerosis and calcification of interosseous membrane and ligaments; severe- symptomatic with features of moderate fluoro-

sis and exostoses, osteophytosis, marked limitation of movements at the spine and joints, crippling deformities/bed ridden. Metabolic bone disorders especially cases of rickets, osteomalacia, osteoporosis and parathyroid bone disease were included.

Laboratory investigations which were performed included plasma calcium (Atomic Absorption Spectrophotometry)(8), phosphate (Fiske and Subbarow)(9), alkaline phosphatase (King's method) (10), plasma, water and urinary fluoride (fluoride select ion electrode using Radiometer PHM 64) (11).

The radiological criteria for the diagnosis of skeletal fluorosis and accompanying metabolic bone disease are given in Table 1.

Table 1

Endemic Skeletal Fluorosis and Metabolic Bone Disease
Diagnostic Radiological Criteria

Endemic Skeletal Fluorosis

1. Osteosclerosis
2. Irregular periosteal bone formation
3. Calcification of interosseous membrane
4. Exostoses and osteophytosis
5. Dense epiphyses and growth plates

Rickets and Osteomalacia

1. Ricketic metaphyses
2. Deformed pelvic cavity
3. Biconcave vertebrae
4. Looser's zone (pseudo-fractures)

Osteoporosis and Parathyroid Bone Disease

1. Bone resorption with trabeculations
2. Cod-fishing and wedging of vertebrae
3. Thinning of cortex and microcystic expansion of cancellous bone
4. Parahaversian canal resorption
5. Subperiosteal phalangeal resorption
6. Erosion of lamina dura and resorption of alveolar bone

Results and Discussion

Epidemiological, clinical, biochemical and radiological studies were performed in two groups of a rural population. Subjects of Group I had been residing in villages with < 1.0 ppm F^- in drinking water and of Group II had been drinking water containing 7.5 ppm fluoride. The clinical details of the subjects studied are summarized in Table 2.

Table 2

Clinical Details

	Mean water F^- (ppm)	Mean F^- intake/ day(mg)	Total Cases	Age Range	Volunteers for clinical examination	Nutritional Status*	
						Adequate	Inadequate
Nonendemic	0.5	1.8	4700	10-35	800	519	281
Endemic	7.5	21.0	3692	10-35	590	290	300

*Based on Indian Council of Medical Research Standards

On the basis of dietary intake of nutrients, all subjects were classified into adequate and inadequate nutritional status. Mean daily dietary intakes are summarized in Table 3. Dietary deficiencies were similar in all subjects whose nutrition was inadequate. Dietary deficiency of calcium was more specific and severe, the mean daily intake being <200 mg per day (Table 3). In all, vitamin D intake was normal; skin exposure to sunlight was adequate since the subjects spent most of their day time outdoors.

Table 3

Mean F^- and Dietary Intakes/Day

Inadequate	Calories	Protein (g)	Calcium (mg)	Phosphorus (mg)	Vit.C (mg)	Vit.D (IU)	F^- (mg)
Nonendemic 281 cases	1026	31	194	800	25	20	1.8
Endemic 300 cases	1138	33	170	785	35	25	21.0
Adequate 809 cases	2200	56	750	1050	65	75	2.2

Table 4 summarizes pertinent biochemical findings. Plasma and urine fluoride and plasma alkaline phosphatase levels were increased in subjects whose drinking water contained high levels of fluoride. The increases were greater in subjects whose dietary intake of calcium was deficient.

Skeletal radiographs revealed that the toxic effects of fluoride on bone were severe and complex in persons having inadequate intake of calcium (Table 5). The incidence and severity of metabolic bone disorders, which included rickets, osteomalacia, osteoporosis and parathyroid bone disease, were greater in persons exposed to high intake of fluoride and whose nutrition was inadequate (Table 6 and 7). Thus the action of fluoride on bone is more complex when its biological action on bone in relation to its interaction with nutritional factors is considered. Our results have shown that the biological toxicity of fluoride on bone is closely related to in-

Table 4

Laboratory Investigations

	No. of Cases	Plasma (Mean and Range) Fluoride (μM/l)	Calcium (mg%)	Phosphate (mg%)	Alk. Ptase (KAU/100ml)	Urinary F^- (ppm)
Nonendemic						
Nutrition Adequate	105	1.2 (1.1-2.0)	9.5 (9-11)	3.8 (4-5.6)	8 (3-16)	0.6 (0.6-0.7)
Nutrition Inadequate	110	1.2 (1.1-2.0)	10.0 (9-11.2)	3.5 (4-5.7)	15 (9.5-20)	0.6 (0.6-0.7)
Endemic						
Nutrition Adequate	90	8.8 (6.4-12.1)	9.6 (9-11)	3.8 (4-5.8)	16.5 (12.5-23.0)	3.8 (2.6-25.0)
Nutrition Inadequate	115	11.3 (7.5-20.0)	10.2 (9-11)	3.2 (3-5.5)	38 (14-67)	7.5 (3.8-40.0)

take of nutrients, particularly of calcium, by the individuals irrespective of the amount of fluoride taken in.

Table 5

Severity of Endemic Skeletal Fluorosis

	No. of Cases	Mild %	Moderate %	Severe %
Nutrition Adequate	290	91	8	1
Nutrition Inadequate	300	11	56	33

Chronic excessive fluoride ingestion is the primary cause of bone disorders. However, in nutritionally deficient persons, the toxic effects of fluoride become manifest and severe even at lower levels of fluoride intake. Skeletal fluorosis in persons with adequate nutrition was mainly mild and asymptomatic, whereas in those with inadequate nutrition the disease was moderate to severe.

During our survey we found that several factors had affected the severity of skeletal fluorosis and associated metabolic bone disease, such as: 1) the amount of fluoride ingested per day, 2) the solubility of the fluoride ingested, 3) the duration of fluoride ingestion and continuous residence in the endemic area, 4) fluctuations in the amount of fluoride in-

Table 6

Clinical and Radiological Survey of Metabolic Bone Disease Associated with Endemic Skeletal Fluorosis

	Total No. of Volunteers	Dental/Skeletal Fluorosis %	Nutrition Adequate		Nutrition Inadequate	
			Cases X-rayed	% with Metabolic Bone Disease	Cases X-rayed	% with Metabolic Bone Disease
Nonendemic	800	0	300	1.0	281	8.0
Endemic	590	100	290	10.0	300	33.0

Table 7

Incidence of Metabolic Bone Disease Accompanying Endemic Skeletal Fluorosis (Radiological Survey)

Nutrition Adequate				Nutrition Inadequate			
Total Cases	Cases with Metabolic Bone Disease	Rickets/ Osteo-malacia	Osteoporosis/ Parathyroid Bone Disease	Total Cases	Cases with Metabolic Bone Disease	Rickets/ Osteo-malacia	Osteoporosis/ Parathyroid Bone Disease
290	29 (10%)	6 (2%)	23 (8%)	300	99 (33%)	40 (13%)	59 (20%)

Figure 1

Radiograph: Pelvis Showing Osteosclerosis, Triradiate Pelvic Cavity and Coarse Cystic Trabeculations in Ischio-pubic Ramii

Suggests associated osteomalacia and hyperparathyroidism with skeletal fluorosis.

Figure 2

Radiograph: Knees

Showing genu varum deformity, osteosclerosis and ricketic metaphyses.

gested, 5) age at the time of exposure to high levels of fluoride intake, 6) nutritional status, particularly dietary intake of calcium, 7) alkalinity and hardness of the drinking water, 8) climatic factors.

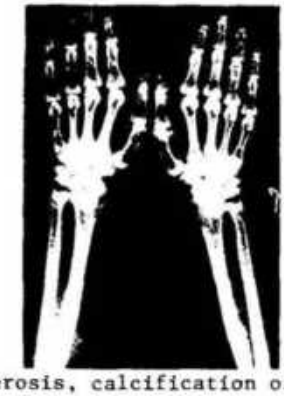
Figure 3

Radiograph: Spine

Osteosclerosis, calcification of ligaments, osteophytosis and compression of vertebrae.

Figure 4

Radiograph: Forearm and Hands



Osteosclerosis, calcification of interosseous membrane, subperiosteal resorption in phallanges, due to associated hyperparathyroidism secondary to fluorosis.

Over 90% of the persons affected with severe skeletal fluorosis, bone disease and deformities (Figs. 1-7) belonged to the low socio-economic group of the farming community and they had generalized nutritional deficiencies. Calcium intake in the severely affected individuals was very low (< 200 mg per day) compared to the daily requirement of > 600 mg.

Figure 5

Endemic Skeletal Fluorosis
Genu Valgum Deformity

External rotation and torsion of bones of leg.

Figure 6

Varying Degrees of Genu Varum and Valgum Deformities

Residents of endemic fluorosis areas.

Figure 7

Radiograph: Pelvis

Osteosclerosis and resorption of bone around iliac bones due to osteoporosis associated with skeletal fluorosis in child with dietary calcium deficiency.

Thus, excessive fluoride intake in individuals whose dietary calcium was deficient, caused severe morbidity and crippling deformities leading to physical, social and economic handicaps.

On the basis of our comprehensive observations, we recommend that whatever measure is adopted to prevent or eradicate fluorosis at the national level be accompanied by correction of the nutritional status of the affected population through appropriate nutritional supplements of calcium, vitamin D and protein.

Acknowledgement

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FLUORIDE CONTENT OF BONES OF RETIRED FLUORIDE WORKERS

by

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SUMMARY: Seven skeletons from former fluoride workers with signs of severe osteofluorosis were analyzed. All had been employed in a fluoride plant for more than 20 years up to age 65. From each skeleton 4 to 15 samples from different bones were analyzed by the potentiometric method with an ion selective electrode.

The average F^- content per skeleton ranged between 3,500 and 9,910 ppm and for single bones between 2,500 and 12,900. The vertebrae and ribs contained the highest, the distal long bones the lowest amount of fluoride. The fluoride content of the bone tissue correlates with the severity of the osteofluorosis - not with the length of life, working time in the plant or the duration of the interval following termination of work in the fluoride-emitting plant.

KEY WORDS: Fluoride workers, retired; Bone fluoride content

Introduction

The fluoride content of bones has been the subject of many investigations. For the current study, bone samples were derived from men working in fluoride-emitting plants. Research on bone fluoride from factory workers, years after termination of the period of exposure, are sparse. According to Fritz (1) skeletal fluorosis can clear up years after termination of exposure.

In the past, fluoride assays were made mainly from one or two bones. Because our material was derived from autopsies, we were able to analyze samples from several bones of the skeleton and thus evaluate the distribution pattern of skeletal fluoride.

Another problem of interest to us is environmental osteofluorosis in subjects residing for prolonged periods in areas of ambient fluoride pollution. For screening cases of skeletal fluorosis, the bones which regularly contain the highest fluoride levels, must be known.

Our material came from skeletons of seven former fluoride factory workers, all of whom were males with signs of severe osteofluorosis (stage III). At death, they ranged in age from 71 to 86 years. All had been employed in a fluoride facility for more than 20 years up to age 65 except case #4, whose work terminated at age 51 when he became disabled.

From the Pathologisches Institut, Bezirkskrankenhaus, Cottbus, GDR. Presented at the 11th International Society for Fluoride Research Conference April 8-10, 1981, Dresden GDR.

Table 1

Postmortem F^- Content (ppm) of Bones in Five Cases of Osteosclerosis

Case No.	1	2	3	4	5
Age	71	86	82	56	80
Osteosclerosis Stage	III	III	III	III	II
10th th. vertebra	11,300	10,600	12,900	11,000	5,000
10th th. vertebra	10,600		11,900	10,200	4,400
2nd l. vertebra	9,900	11,000	12,800	9,500	5,200
2nd l. vertebra	9,800	10,100	11,300	9,100	4,700
1st rib r.	9,900	9,600	12,900	11,000	3,400
1st rib l.				9,600	4,100
3rd rib r.	9,100	7,100	12,700	10,900	4,400
3rd rib l.				10,500	4,000
7th rib r.	9,900	9,000	9,500	10,800	3,900
7th rib l.				10,600	3,700
iliac crest r.	10,000	9,100	12,700	8,700	4,300
iliac crest l.				8,600	4,700
clavicle r.	9,000	5,700	9,700	10,800	3,000
clavicle l.		4,200		8,500	2,800
patella	11,700	7,400	10,800	12,400	
humerus r.	10,500	8,300	10,300	10,200	3,100
humerus l.				10,300	2,800
radius r		6,500	10,800	9,600	2,600
radius l.				8,700	2,700
ulna r.		6,300	11,100	10,300	2,600
ulna l.				8,700	2,800
femur r.	10,100	7,500	8,500	9,200	2,900
femur l.				10,500	3,100
tibia r.	9,500	6,100	7,600	7,500	2,500
tibia l.				8,500	2,500
fibula r.	9,910	6,000	8,900	8,500	2,800
fibula l.				7,900	2,900
calotte		7,200	8,400		

Two to 15 samples from each skeleton, from different bones, from the long bones (even from the middle of the diaphysis) were analyzed for their fluoride content. The potentiometric method with an ion selective electrode, described in detail by Seifert (2), was used.

Results

Composite results of the seven cases are presented in Table 1. In case #1 (14 bones) no significant differences between the fluoride content of the bones were observed. In case #2, however, differences were noted in the long bones of the lower extremities and the clavicle contained less fluoride than the other bones.

Tables 2 and 3 present the results of symmetrical pairs of bone in cases #6 and #7. No significant differences in the fluoride content of bones on one side compared to those on the other side were revealed.

Table 2

F^- Content (ppm) in 10 Bones of 82-Year Old Retired F^- Worker

Case No.	6
Age	82
Osteosclerosis Stage	II
10th vertebra	10,500
2nd l. vertebra	11,100
1st rib r.	8,200
1st rib l.	6,700
3rd rib r.	8,300
3rd rib l.	7,700
7th rib r.	7,600
iliac crest r.	8,800
iliac crest l.	8,900
clavicle	4,900

Table 3

Symmetrical Pairs of Bone in Cases #6 and #7

Case No.	7
Age	80
Osteosclerosis Stage	II
humerus r.	4,400
tibia l.	2,900

Differences in fluoride content of bones between the right and left were not significant.

Conclusions

1. Even many years after termination of occupational exposure, it is possible to diagnose osteofluorosis.

2. In contrast to the findings of Baud et al. (3) who stated that bone fluoride gradually decreases after cessation of exposure, our data show that the morphological signs of osteofluorosis and the fluoride content of the bones are still manifest for 21 years and longer after exposure to fluoride has been terminated.

3. Certain differences were found in the distribution of fluorides in the bones of the skeleton, although they are not significant.

4. The vertebral bodies, ribs and iliac crest contained the highest levels of fluoride.

5. In the iliac crest, the fluoride content remains highly constant.

6. According to our material, a high correlation was found solely between the fluoride content of the bones and the severity of osteofluorosis. No correlation was observed between the fluoride content of bones and the person's age or the number of years he had worked in the factory or the length of time since the termination of his work in a fluoride-emitting plant.

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MICRODETERMINATION OF TOTAL FLUORIDE IN SERUM BY ALUMINUM MONOFLUORIDE MOLECULAR ABSORPTION SPECTROMETRY AND ITS SIGNIFICANCE

by

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SUMMARY: The AlF molecular absorption spectrometry was applied to the determination of serum fluoride samples of which were made of a mixture of equal volumes of serum, 0.05 M $Sr(CH_3COO)_2$, and distilled water. Total fluoride was determined by measuring the molecular absorption intensity of AlF. The sensitivity which gave 1% absorption was 0.028 ng of fluoride and the C.V. was 3 to 9%. The AlF method was used to estimate the normal value of total fluoride in serum.

Determinations were done for 221 healthy individuals who were residing in a rural area. The mean value for total fluoride was 20 ± 9.8 S.D. ng/ml. Fluoride concentrations in serum were determined by both the AlF method and ion electrode method. Values of total fluoride were higher than values of ionic fluoride, which suggests the existence of nonionic fluoride.

KEY WORDS: Fluoride microdetermination; Serum fluoride; AlF molecular absorption spectrometry; Japanese

Introduction

In order to evaluate the effect of fluoride on human health, a number of studies have been carried out with various biological samples such as hard tissues, urine, saliva and blood. Fluoride concentrations in urine and bones are considered by many investigators valid indices of body burden of fluoride.

However, in the case of human serum, no reliable method had been available for determination of fluoride because of its extremely low concentrations. Thus, reported values (1) vary over a wide range. Consequently, with no agreement on the normal value, serum fluoride concentrations have not been of practical value.

Recently, a new analytical method was developed by Tsunoda et al. (2) for the determination of subnanogram fluoride based on aluminum monofluoride molecular absorption spectrometry (AlF method). By this method, levels of serum fluoride were determined satisfactorily. Fluoride values in healthy human serum were investigated by this method and the existence of nonionic fluoride was shown.

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In the AlF method, fluoride is determined by measuring the molecular absorption of AlF, which is produced by fluoride in sample and aluminum at about 3000°C in a graphite cuvette.

Methods and Materials

The authors used, for the measurement of AlF absorption, a Nippon Jarrel Ash atomic absorption spectrometer AA-855 with simultaneous background correction and deuterium lamp, a carbon rod furnace FLA-100 and a platinum hollow cathode lamp L-233 (Hamamatsu TV Co. Ltd.). For the determination of fluoride ion, fluoride electrode (Orion 96-09) and a digital ionalyzer (Orion 801 A) was used. All chemicals were analytical grade commercial materials. Fluoride standard solution was made by dissolving sodium fluoride in distilled water. Serum samples of high fluoride concentrations were used for the experiments.

Procedures are shown in Figs. 1,2. In a graphite cuvette after 10 µl aluminum solution was pipetted and dried, 10 µl fluoride standard solution or serum sample was pipetted. They were atomized by three heating steps: drying, ashing and atomizing, then AlF molecular absorption intensity was measured. In order to estimate the normal value of fluoride in serum, 221 serum samples were obtained randomly from healthy individuals residing in a rural area with less than 0.1 ppm fluoride in drinking water and 0.05 µgF/m^3 in air. Fluoride concentrations were measured both

Figure 1

Procedures and Conditions

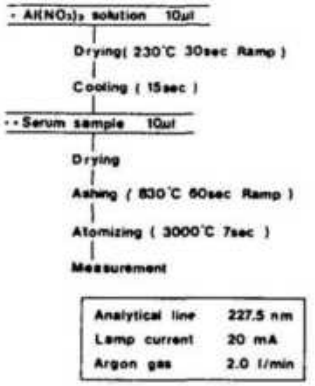
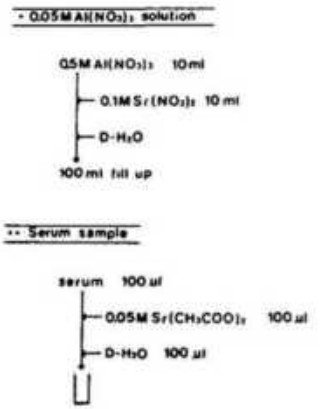


Figure 2

Procedures



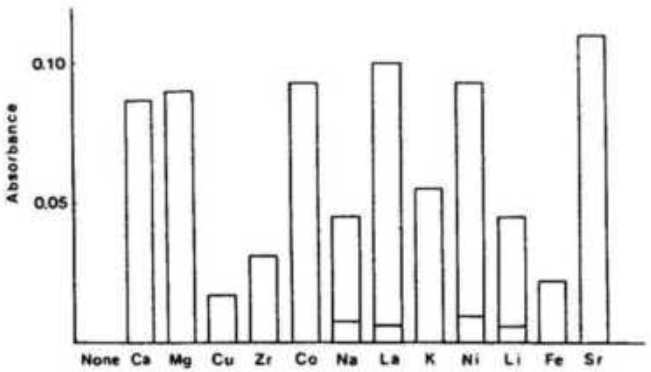
by the AlF method and the electrode method. Serum samples were of three kinds: patients' serum from the hospital, and those obtained from healthy adults who received 2 mg F$^-$ as NaF in single oral doses and rabbits which received intravenously 4 mg F$^-$ as NaF.

Results

The effects of various cations on AlF molecular absorption were investigated (Fig. 3) because 1 to 150 mM Na, K, Ca, Mg are in serum and some cations were reported to enhance AlF absorption (3). When the sample had only aluminum solutions, it gave no peak in spite of the addition of fluoride. However, each solution containing a cation gave a peak and, of 12 cations tested, addition of Sr gave the highest peak without any blank. Therefore, we decided on the addition of Sr to the aluminum solution at a concentration of 0.01 M because AlF absorption was the highest within a range of 0.005 to 0.01 M Sr.

Figure 3

Effect of Various Cations on AlF Molecular Absorption

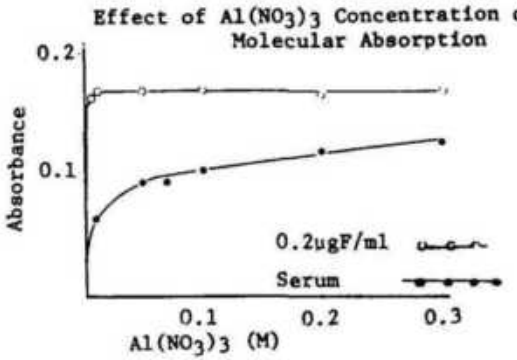


The upper levels represent absorptions when 0.1 μgF/ml is added and the lower levels, without it. Each sample solution contains 0.01M $Al(NO_3)_3$ and 0.01M of each cation. All cations are in the form of nitrates.

The dependence of AlF absorptions on Al concentrations is shown in Fig. 4 in both cases of fluoride standard solution and serum. The net absorption was given by subtracting the blank values from the observed ones, since the blank values increased with the increase of Al concentrations. In serum diluted 3 times AlF absorption was increasing in direct relation to increase in Al concentrations. This differs from the case of standard solution, which was constantly above 0.01 M Al and suggests spectral interference from coexistent materials.

Therefore, in order to eliminate this interference, serums diluted up to 6, 10, and 20 times were investigated in the same way as shown in Fig. 5. AlF absorption of the serum, 6 times diluted, kept increasing in the same

Figure 4

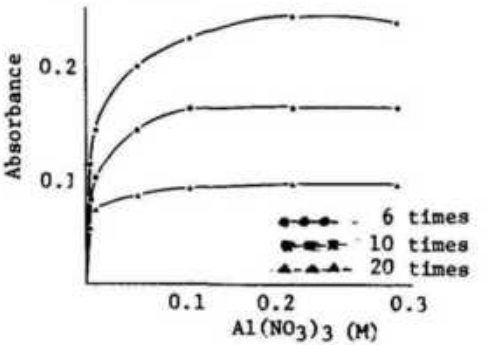


way as that which was diluted 3 times. When serum was 10 and 20 times diluted, it became constant above 0.1 M Al. However, detection of fluoride was difficult when diluted 10 times because the level of fluoride in healthy human serum is extremely low. The serum tested here was that of hospital patients which had a considerably higher concentration level. Therefor, a more valid method with the least dilution was needed.

The effect of various reagents on AlF absorption when added to serum is shown in Fig. 6. Samples were made by mixing equal volumes of serum, each reagent and distilled water. The least dilution is thus obtained because background level is beyond correction if it is the mixture of serum and each reagent only. Some reagents enhanced the the AlF absorption, the best being Sr $(CH_3COO)_2$. This enhancement was not seen in Fig. 7 with standard solution. These results suggest that an addition of coexistent materials in serum is effective against volatilization of fluoride in serum during ashing. Optimal concentration of $Sr(CH_3COO)_2$ was investigated and 0.05 M was used because the highest peak was observed over the range of 0.03 to 0.05 M.

Figure 5

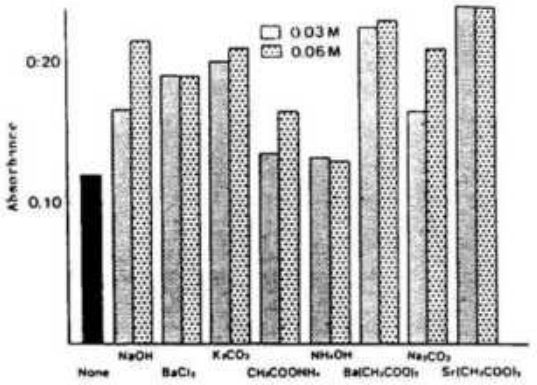
Change in Effect of $Al(NO_3)_3$ Concentration on AlF Molecular Absorption Through Dilution of Serum



The effect on Al concentrations on AlF absorption was re-investigated to determine whether absorption would become constant if we used the following: a mixture of equal volumes of serum or standard solution 0.05 M $Sr(CH_3COO)_2$ and distilled water. The result is shown in Fig. 8. The AlF absorption became constant above 0.03 M Al in both cases of serum and standard solution. This result differed from that seen in Fig. 3 in the case of serum where AlF absorption kept increasing as Al concentrations increased. Consequently, this method could be used with least diluted serum. Fig. 2 shows the procedures obtained as described above.

Figure 6

Effect of Various Reagents on AlF Molecular Absorption
- Each Reagent is Added to Serum -



Sample solutions are mixtures of equal volumes of serum, each reagent and distilled water.

Calibration curves for 0 to 0.25 µg/ml fluoride in distilled water and in serum are shown in Fig. 9. Both of them were linear but differed in slope. Therefore, standard addition method was applied to the determination of fluoride in serum. The sensitivity which gave 1% absorption was 0.028 ng of fluoride and the coefficient of variation was 3 to 9%. Close agreement was shown between fluoride values determined by the AlF method and an ashing-distillation-ion-electrode method (Table 1).

The AlF method was used to determine the normal value of fluoride in human serum (Table 2). The mean value of 221 individuals was 20±9.8 ng/ml. No sex related difference was found but it was significantly lower in individuals 14 to 15 years old than in older age groups ($P < 0.01$), the former was 14.0 ± 6.1 ng/ml and the latter ranged from 20 to 23ng/ml.

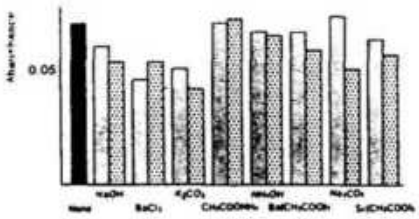
Table 1

Comparison of F^- Concentrations in Serum by Different Methods

Method	Fluoride concentration (µg/ml)	Mean ± S.D. (µg/ml)
open ashing, distillation, fluoride ion electrode	0.35 0.58 0.36 0.49 0.27 0.33 0.39	0.38 ± 0.10
AlF molecular absorption spectrometry	0.39 0.38 0.32 0.36 0.37 0.38 0.42	0.37 ± 0.03

Figure 7

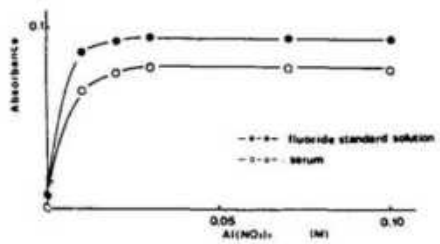
Effect of Various Reagents on AlF Molecular Absorption
-Each Reagent is Added to 0.3μgF/ml Standard Solution-



Sample solutions are mixtures of equal volumes of fluoride standard solution, each reagent and distilled water.

Figure 8

Change in Effect of $Al(NO_3)_3$ Concentration on AlF Molecular Absorption Through Addition of $Sr(CH_3COO)_2$

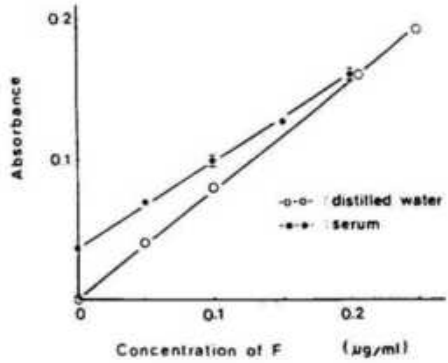


Sample solutions are mixtures of equal volumes of fluoride standard solution or serum, 0.05M $Sr(CH_3COO)_2$ and distilled water.

Fluoride concentrations measured by two methods are shown in Table 3. Total fluoride was measured by the AlF method and ionic fluoride was measured by the fluoride electrode method. Samples were of three kinds: pooled serum of hospital patients, that obtained from healthy human adults who received 2 mg F^- as NaF in single oral doses, and that from rabbits which had received 4 mg F^- as NaF intravenously. The rate of ionic fluoride to total fluoride was 70.5 to 90.2% in humans and rabbits administered

Figure 9

Calibration Curves of Fluoride



NaF; it was higher than that of pooled serum from hospital patients, which was 47.5 to 55.7%. These results suggest the existence of nonionic fluoride in serum. Concentrations of ionic fluoride and nonionic fluoride in serum reflect different sources of intake.

Table 2

Total F^- in Healthy Human Serum

	Age range (years)	N	Mean SD (ng/ml)	50% ile (ng/ml)
Male	14 - 15	30	14 ± 5.6	14
	17 - 18	29	22 ± 9.8	22
	40 - 49	26	23 ± 9.9	22
	60 - 69	27	22 ± 13	21
	TOTAL	112	20 ± 10	19
Female	14 - 15	27	14 ± 6.7	13
	17 - 18	27	22 ± 7.6	23
	40 - 49	28	21 ± 8.2	19
	60 - 69	27	22 ± 10	21
	TOTAL	109	20 ± 9.0	19
TOTAL		221	20 ± 9.8	19

Table 3

Ionic and Total F^- in Serum

Serum	No.	Ionic F^- (µg/ml)	Total F^- (µg/ml)	Ionic/total %
Patients	1	0.89	1.6	55.6
	2	0.78	1.4	55.7
	3	0.27	0.50	54.0
	4	0.16	0.34	47.0
	5	0.090	0.19	47.4
NaF Humans	1	0.046	0.050	92.0
	2	0.043	0.061	70.5
NaF Rabbits	1	4.6	5.5	83.6
	2	3.0	3.6	83.3

Discussion

No reliable method had been available for the determination of fluoride in human serum because of its extremely low concentrations. Since fluoride ion electrode was developed, ion electrode method has been the

most reliable one. However, more than 90% of fluoride concentrations determined in serum of healthy human adults are less than 10^{-6}M (4),which is a limit of fluoride electrode detection.

Recently Tsunoda et al. (2) reported fluoride determination by AlF molecular absorption spectrometry at high temperature cuvette with high sensitivity and a microvolume. Considering these characteristics, the AlF method seems to be satisfactory for the determination of fluoride in serum which contains various inorganic and organic materials, usually available in small quantities and at low fluoride concentrations. However, the original method could not be applied directly to human serum because of spectral interference from coexistent materials and volatilization of fluoride in serum.

Therefore, to eliminate these defects and to enhance the AlF absorption,various cations and reagents were added to the aluminum solution or serum. Regarding the effect of cations, our findings agreed with Tsunoda et al. (2) about the best enhancing effect of Sr on AlF absorption. Chiba et al. (5) determined fluoride in serum by the AlF method using serum diluted 10 times. However, they obtained serum from hospital patients with a considerably high concentration. Our findings also showed that fluoride could be determined with serum diluted 10 times but, with the normal human serum in which the concentration is usually much lower, it could not be detected. Addition of $Sr(CH_3COO)_2$ to serum, however, enabled us to determine fluoride without as high dilution.

Taves (6) suggested that so-called nonionic fluoride was bound to albumin . On the other hand, Singer et al. (7) reported that a large part of serum fluoride was ultrafilterable and not bound to the protein. Ekstrand et al. (8) also reported no binding of fluoride to macromolecules. Ubel et al. (9) recorded the presence of organic fluoride in the serum of workers exposed to fluorochemicals, levels of which appeared to be related to the degree and duration of exposure. Our findings that total fluoride concentrations were higher than ionic fluoride concentrations signifies the existence of nonionic fluoride. Extremely high concentrations of nonionic fluoride in pooled human serum suggest the intake of organic fluoride such as anesthetics and/or the existence of organic fluoride in serum. However, extraneous ionic fluoride may be bound to some organic matter in the living organism, since nonionic fluoride is found in serum of NaF-administered humans and rabbits. Levels of ionic fluoride and nonionic fluoride seem to reflect different sources of fluoride intake.

In conclusion subnanogram fluoride in serum can be determined quantitatively by the AlF method and the normal value of total fluoride in healthy human serum has been proposed. The AlF method is useful for examining the significance of serum fluoride as an index of the body's fluoride burden and for examining nonionic fluoride.

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RENAL FUNCTION IN RESIDENTS OF AN ENDEMIC FLUOROSIS AREA IN SOUTHERN ALGERIA

by

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SUMMARY: Kidney damage (1) in distal and proximal tubular function, (2) in glomerular filtration, occurred in 40 to 60 year olds residing in El Oued an endemic fluorosis area in Southern Algeria compared to normals from Algiers. Functional renal disturbances are proportional to the degree of fluoride accumulation which increases in relation to: a) the level of fluoride in drinking water (areas ABC), b) the fluoride level in nails and c) the radiological grade (0 I II III) of fluorosis.

KEY WORDS: Renal function; Endemic fluorosis; Algeria, endemic fluorosis in

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Introduction

Renal function is affected by fluoride (1,2). In 1976, the biological evolution of fluorosis was correlated with a few renal parameters in adults residing in an endemic fluorosis area. Radiological changes were designated grades 0, I, II, or III (3). In 1982 (4) we recorded in adults, inside the same endemic zone, a correlation between fluoride concentration in drinking water, the degree of fluoride accumulation in nails and the radiological grade. A recent renal function exploration was performed but the results have not been published. In the following, renal disturbances investigated during these two studies are correlated with the degree of fluoride injury in areas with increasing levels of fluoride in water (A,B,C) in relation to radiological grades (0, I, II, III) compared with normals residing in Algiers.

Material and Methods

During the first period (3) renal function was studied in groups 0, I, II, III. Radiological skeletal fluorosis was established according to Pinet et al. (5) wherein 0 = radiologically negative and I, II, III indicate increasing skeletal damage.

In a second study, renal function was correlated with the level of fluoride in drinking water in various areas inside the endemic zone namely, A where the fluoride level in drinking water is 1 - 2 ppm, B (2-3.5 ppm), C (4.5 ppm) with fluoride content in nails which appears to be a good index of F^- accumulation (4) and with the radiological grade. Compared with normals from Algiers (F^- in drinking water 0.2 ppm) fluoride damage to the skeleton appears to increase as the fluoride level in the water rises AI BII CIII (Table 1).

Table 1

Classification in F^- Endemic Zone According to F^- Level in Drinking Water and Radiological Grades

	F^- in Drinking Water	Radiol. Grade Frequencies		Radiological Grade 0 (53)
Area A (29)	1-2 mg/l	0	34%	
		I	52%	Radiological Grade I (23)
		II	14%	
		III		
Area B (18)	2.3.5 mg/l	0	28%	
		I	29%	Radiological Grade II (19)
		II	43%	
		III		
Area C (22)	4.55 mg/l	0	5%	
		I	40%	Radiological Grade III (22)
		II	55%	
		III		
Normals: Algiers (20)	0.20 mg/l	0	95%	

Fluoride in water and urine was measured according to the specific electrode technique (6); and fluoremia, after mineralization (7), by the same method. The classical technique was used to measure urea, creatinine and phosphorus in blood and urine: blood urea, using diacetylmonoxime; urinary urea, using hypobromite; blood and urinary phosphorus, using ammonium molybdate; blood and urinary creatinine, using alkaline picrate, after tungstate-induced deproteinization.

The following renal explorations were performed:

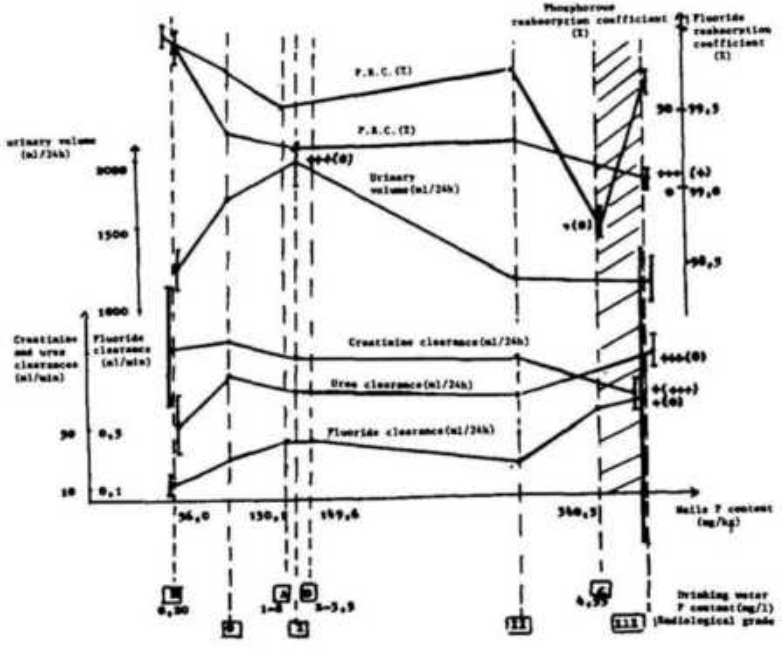
a) Proximal and distal tubular:urinary volume (ml/24h), urea and fluoride clearances (ml/min), fluoruria (mg/24h), F^- reabsorbed mass(mg/24h), fluoride reabsorption coefficient (F.R.C.) (%),

b) Glomerular: creatinine clearance (ml/minute), fluoride filtered mass (mg/24h).

Results

Tubular and, subsequently, glomerular dysfunction, correlated with fluoride in nails, with fluoride in drinking water and the radiological state (Fig. 1) were maximal, most frequently, in groups C and III.

Figure 1



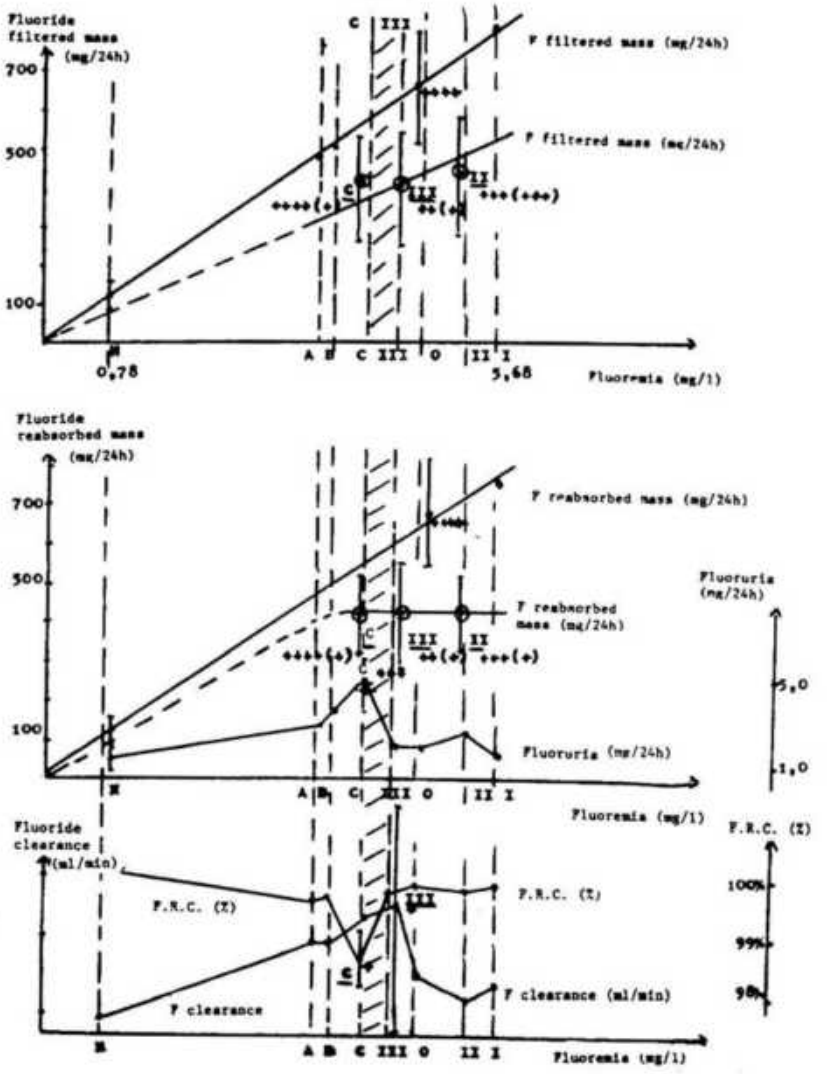
Tubular dysfunction seems to begin in grade I. Urinary volume increases, at this time, compared to N (p 0.01). Abnormalities are considerable in grade II, maximal in groups C and III.

Increases occur in urea clearance (p 0.01), fluoruria (p 0.01), fluoride clearance (slight p 0.10), F.R.C. is slightly decreased (p 0.10). These facts indicate impairment in reabsorption concerning free or Na-bound water, urea and fluoride.

Glomerular dysfunction (filtration impairment) is more evident in grade II and, principally, in C and III. At this time, in grade III, urinary volume is normalized, and creatinine clearance is decreased (difference from N=p 0.10; difference from grade 0 = p 0.01).

In Figure 2, fluoride filtered mass and fluoride reabsorbed mass are plotted against fluoremia. In our experience, fluoremia is not maximal in the highest fluoride group III and C. Both F^- filtered mass and F^-

Figure 2



reabsorbed mass increase in all fluoridated groups, when compared with normal (p 0.01 or p 0.001). Graphic presentation of fluoride filtered mass correlated with fluoremia increase is linear, a) in groups N O A I B, the slope corresponds to the normal creatinine clearance rate, b) in groups II C III a more gradual slope corresponds to a decrease in the creatinine clearance rate. Graphic presentation of fluoride reabsorbed mass shows two curves: a) in groups N O A I B, fluoride reabsorption mass values increase with fluoremia, without any dimunition of the ascending curve, b) in groups II C III, the curve reaches a plateau, whereas fluoremia is only 4 to 6 mg/l. There could be a pathological impairment of maximal transfer in active reabsorption of fluoride, when renal fluoride damage occurs in the last three groups (Fig. 1 and 2. Table 2).

Table 2

Tubular and Glomerular Renal Aberrations

1) Tubular	Comparison with Normals (Algiers)	Possible Abnormalities
Urinary Volume Increase (ml/24h)	P < 0.01 (soon grade I)	Free water (distal) or Na bound water (proximal) impairment
Urea Clearance Increase (ml/min)	P < 0.01	Urea reabsorption impairment (proximal) or collector tube diffusion
Phosphorus Reabsorption Coefficient Decrease (P.R.C. %)	P < 0.01	Proximal tubular impairment (or hyperparathyroid reaction with normal renal function)
Fluoride Clearance Increase (ml/min)	slight p < 0.10	
Fluoride Reabsorption Coefficient Decrease (F.R.C.%)	slight p < 0.10	
Fluoruria Increase (mg/24h)	P < 0.001	Fluoride reabsorption impairment
Fluoride Reabsorbed Mass (mg/24h) 1) continuing increase as F^- filtered mass increases A B O I 2) pathological tubular maximal transfer when F^- filtered mass increases C II III	P < 0.05 to P < 0.001	
2) Glomerular		
Urinary Volume Returning to Normal (ml/24h)		
Creatinine Clearance Decrease (ml/min)	slight p < 0.10 (difference with grade O p < 0.01)	Glomerular filtration impairment
Fluoride Filtered Mass Linear Increase (mg/24h) with a fluoremia increase 1) normal slope: A B O I 2) decreased slope: C II III (creatinine clearance decreased)		

Discussion

In animal and man, fluoride affects renal function (1,2). Tubular dysfunction appears first. Polyuria is present (1,2,8) because of free water reabsorption by distal tubule, namely urinary loss of water (9). Polyuria is also present because of sodium-bound water reabsorption by proximal tubule, namely urinary loss of sodium and water (8). Reabsorption of aminoacids (1), glucose and phosphorus (8) is impaired. Urea clearance increases (1). Proximal damage occurs. Fluoride clearance increases (1,2) for the same reason. The appearance of glomerular dysfunction is delayed. Creatinine clearance decreases (10,11), fluoride and urea clearance first increase, then decrease (1,2). Fluorosis effect on renal tissues: proximal tubular necrosis (12), cytoplasmic vacuolation in distal tubules (11). Fluoride content is highest in soft tissue of kidneys (13). Fluoride increases gamma GT urinary elimination (14). In renal tissue, it affects cAMP intracellular level (15) and mitochondria ATPase activity (8).

Results of our investigation, concerned with 40 to 60-year olds residing in an endemic fluorosis area, are synchronized in Table 2. Renal dysfunction is first tubular, with special attention for fluoride reabsorption impairment and second glomerular, with a slight decrease of glomerular filtration.

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FLUORIDE STANDARDS AND PREDICTING WILDLIFE EFFECTS

by

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SUMMARY: Federal and state clean air laws for the permitting of fluoride emission sources require evaluation of potential adverse ecological effects including those to wildlife and wildlife habitat. Although air quality permits and environmental assessments for fluoride emitting sources often cite compliance with various fluoride standards as demonstration of no adverse effects to wildlife, such use of these standards is inappropriate. A review of the literature regarding fluoride standards and ecological effects of fluoride reveals that adverse effects can occur to wildlife at or even below accepted fluoride standards. Alternative wildlife assessment methods including monitoring, predictive modeling, and sensitive receptor analyses are discussed.

KEY WORDS: Fluoride standards; Wildlife effects; Impact assessment

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Introduction

Fluoride emitting sources are subject to regulatory review and permitting under the Federal Clean Air Act and its 1977 amendments as well as under state clean air laws. Permitting involves documentation of compliance with accepted air quality standards as well as evaluation of potential adverse ecological effects, including effects on wildlife and wildlife habitat (1).

Although no national air quality standards exist for fluoride, environmental assessments for fluoride-emitting sources in the United States routinely cite compliance with state or other recommended fluoride standards to demonstrate no effect or no adverse effects to the environment. The objective of this paper is to assess the appropriateness of using fluoride standards to evaluate air quality impacts of fluoride emissions on wildlife.

Permitting Process

According to the Clean Air Act, as amended on August 7, 1980, any new or modified air pollution source, exceeding specified regulatory emission potential, is subject to a pre-construction Prevention of Significant Deterioration (PSD) review process (2). Currently, fluoride is one of several pollutants regulated under the Clean Air Act. The Act designates that certain fluoride-emitting sources such as primary aluminum ore reduction plants, hydrofluoric acid plants, and phosphate rock processing plants are major sources and therefore subject to pre-construction review (1). States are required to develop their own air quality implementation plans. If the U.S. Environmental Protection Agency (EPA) approves the proposed plan, a state can then implement its own PSD permitting process.

The goals of the PSD review are to protect the public from any adverse effect that might occur at emission levels higher than the national ambient air quality standards; and to preserve, protect, and enhance air quality in areas of special natural, recreational, scenic, or historic value, such as national parks and wilderness areas. Major steps involved in the preconstruction review process are: demonstration of compliance with Ambient Air Quality Standards (AAQS); analysis of impacts on soils, vegetation, and visibility; and analysis of impacts on Class I areas (1).

Significant deterioration requiring detailed ecological assessment occurs when the amount of new air pollution exceeds the applicable maximum allowable increase ("increment") over a baseline concentration for a designated area. The amount of air pollution permissable or increment allowable varies with the classification of the area affected. Class I areas such as national parks and wilderness areas have the smallest PSD increments.

Fluoride Standards

Air quality standards are legal limits on levels of air emissions allowable in the ambient air or in other media for a given period of time. At least thirteen countries have national fluoride standards (3). Although the U.S. has no national fluoride standards, particulate fluoride is regu-

lated under the National Ambient Air Quality Standards (NAAQS) for total suspended particulates (TSP). PSD increments for TSP have been established. Secondary standards for TSP are designed to protect public welfare including wildlife and wildlife habitat.

Twelve states have specific fluoride standards (4) including ambient air quality and forage tolerance standards (Table 1). Most of these states (i.e., Idaho, Kentucky, Maryland, New York, Montana, Texas and Washington)

Table 1

States with Specific Fluoride Standards

State	Type of Standard		
	Ambient Air Quality	Forage	Particulate Deposition
Idaho		X	
Kentucky	X	X	
Maryland	X	X	X
Montana		X	
New Hampshire*	X	X	
New York*	X	X	
Pennsylvania	X		
South Carolina	X		
Tennessee	X		
Texas*	X	X	
Wyoming	X	X	
Washington	X	X	

have forage standards which on a dry weight basis, are 40 ppm F^- as a maximum annual average and 80 ppm F^- as a maximum monthly average in or on vegetation. Wyoming has the lowest forage standard (25 ppm F^-). Maryland has the most comprehensive fluoride standards of any state. Eleven different vegetative standards for maximum allowable fluoride levels have been adopted (5). State ambient air quality standards for gaseous fluoride are generally less than 1.0 ppb F^- as a maximum monthly average and 4.5 ppb F^- as a maximum 12 hour average (4).

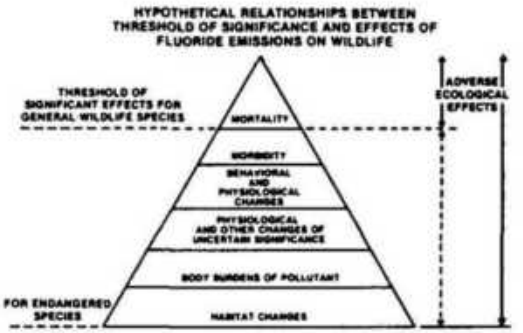
Relationship of Fluoride Standards and Wildlife Protection

Often compliance with fluoride standards is used to claim no effect on wildlife. This was not the intended purpose when these standards were set. Although the effects of fluoride on wildlife are known, studies on their tolerance to given fluoride levels are few (6). Forage standards were developed to minimize the occurrence of economic damage of fluorosis in livestock (7), but in fact, there is evidence they do not (8-10). Fluorosis in wildlife has been reported even when compliance with state forage standards has been met (11).

Numerous reviews (6, 12-15) have described a variety effects of fluoride in domestic animals and wildlife including acute exposure leading to gastroenteritis, muscular weakness, pulmonary congestion, respiratory and

cardiac failure; and chronic exposure leading to dental lesions, osseous lesions including fracturing, lameness, appetite impairment, poor reproduction, bioaccumulation, and behavioral changes. The primary route of fluoride exposure to animals is assumed to be by ingestion of fluoride-contaminated food or water (7). Fluoride is known to be more toxic to younger segments of animal population exhibiting bone growth and tooth development than in mature or older animals (12). Animals which are stressed or on low nutritional planes are more susceptible to fluoride toxicity than healthy animals (11,12). This observation is important when evaluating wildlife populations which are often exposed to greater natural or man-induced stresses, or on lower nutritional planes than their domesticated counterparts. These fluoride effects in wildlife can be grouped into five categories: mortality, morbidity, behavioral and physiological changes, body burdens of pollutants, and habitat changes (Fig. 1).

Figure 1



A comparison of the various state air quality standards for fluoride (5), (i.e., Kentucky, New Hampshire, New York, Texas, and Washington) with vegetation which was exposed to fluoride emissions (16-19) at or below these state air standards shows that vegetation injury can occur, and that the fluoride concentration in vegetation can exceed the recommended state vegetation standards. From a wildlife assessment perspective this means that habitat changes are possible even when ambient air quality compliance is achieved. In addition, studies on the setting and use of air quality standards including fluoride standards have shown that there is a great deal of variability in the response of organisms to air emission, in ambient air concentrations of fluoride for a given time period, and for concentrations of fluoride in or on vegetation (20-23). Because of these facts, air quality standards including forage standards for fluoride cannot be used as indicators of absolute protection. They may in fact not be indicators of even acceptable levels of wildlife protection.

Fluoride Impact Assessments

A more appropriate assessment of the impacts of fluoride emission on

wildlife in the PSD process involves evaluation of the significance of the potential adverse effects. The significance of these effects depends upon the value society places upon the particular wildlife group affected by air emissions. For general wildlife species such as unprotected species, the threshold of significant effects may be considered to occur only at the highest level of effect, i.e., mortality. For highly valued species such as endangered species, the level of significance may be viewed by society to include all potential effects to the species (Fig. 1).

Proper wildlife impact evaluations require site-specific baseline evaluations of air quality (i.e. air monitoring and modeling) and more species-specific evaluations (i.e., sensitive receptor and pollutant fate analyses). If the value society places on potentially affected wildlife is high, i.e., endangered species, the number of significant adverse effects considerations increase (Fig. 1) as well as the scope of the required impact assessment. Where natural or man-made sources of fluoride already exist or are suspected to occur, monitoring of fluoride in air, water, soil, vegetation and wildlife will be needed to establish pre-existing conditions. Evaluation of other pre-existing stresses to wildlife and their habitat including natural stresses such as diseases, or man-induced stresses such as pesticide use is also desirable. This analysis is necessary to differentiate any conditions which may be attributed to fluoride such as vegetation damage due to insects.

For fluoride-emitting sources, both gaseous and particulate fluoride need to be modeled. Predicted fluoride concentrations for 1 hour, 3 hour, 24 hour, weekly, monthly, and annual average and maximum levels should be developed. Short term values should be reported on a seasonal basis. The selection of the reporting period should be a function of the growing season for vegetation in the area. Description of nocturanl and diurnal variations in ambient air concentrations of fluoride as well as the frequency of occurrence of the maximum levels may be necessary because of activity patterns of certain wildlife groups. Isopleths drawn on a wildlife resource map showing predicted concentrations of fluoride are recommended.

Fairly good information exists on effects of fluoride on vegetation to evaluate the potential changes to important wildlife habitat used for cover, shelter and food. The seasonal use of this habitat by key wildlife groups as well as the component of the habitat which is used, i.e. foliage for cover, fruits for food, etc., need to be identified. Lacking species-specific exposure response information, the use of analogous species responses or general vegetation responses may be required.

The wildlife sensitive receptor analysis used to determine potentially sensitive species is often most difficult because of incomplete wildlife effects information. The exposure potential for a given wildlife group may vary with the time of day or season, or with the habits of the species, i.e., resident or transient. With a transient species there may be a low likelihood of significant exposure. If the risk of exposure or exposure potential is low, then the significance of potential adverse effects may also be considered low. If the risk of exposure is high, monitoring of that particular wildlife population may be warranted for granting PSD permit approval.

In summary, the assessment of the effects of fluoride emissions on wild-

life and their habitat, as required by Federal or state regulations, should be based on baseline monitoring, modeling, and sensitive receptor analyses, rather than demonstration of compliance with fluoride standards. The level and complexity of analysis is a function of the importance of the potentially affected wildlife species. Currently, regulatory review required by law, relies on existing fluoride research studies for predicting future effects. Most of these studies were not designed for such predictive purposes. Additional fluoride research that can be used in regulatory review for predicting the transport, fate and effects in wildlife and other biological groups is needed.

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ENDEMIC FLUOROSIS: CHANGE TO DEEPER BORE WELLS AS A PRACTICAL COMMUNITY-ACCEPTABLE APPROACH TO ITS ERADICATION

by

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SUMMARY: Endemic fluorosis remains a challenging national health problem in India. In this study, several methods have been suggested for its control and eradication. The possibility that drinking water obtained through deep bore hand pumps would be an effective and practical measure for eradication of fluorosis was explored. Whereas water samples from 40 to 50 feet underground were high in fluoride content, low in total hardness, low in calcium and magnesium and high in alkalinity, fluoride in waters from a depth of 56 to 110 feet decreased to <1.0 ppm.

The fluoride and iodine content in drinking water were in direct relationship: the higher the fluoride, the higher its iodine content and vice versa in confirmation of our previous observations of lower prevalence rate of iodine deficiency goitre in individuals residing in endemic fluorosis areas where fluoride, naturally in drinking water, was high.

KEY WORDS: Endemic fluorosis; Eradication; Fluoride; Iodine; Water hardness; Calcium; Magnesium; Alkalinity; Deep bore hand pumps; Underground level; Depths

Introduction

Fluorides, which are widely distributed in nature, are universally present in various amounts in soils, water, air, vegetation, seafoods and animal tissues.

Several kinds of fluoride-bearing minerals have been identified in India, the commonest being fluorides, phosphates, silicates and mica groups. Organic fluorides do not present a significant environmental health hazard. The high natural content of fluoride-bearing minerals in the rocks, irregularly distributed all over the country, cause endemic fluorosis. The world's fluorite levels are estimated to be 85 million tons of which nearly 12 million tons are located in India. Sedementary, metamorphic, country rocks and earth's crust are formed from igneous rocks. Through the processes of lithification, remobilization, hydrothermal reactions, weathering and leaching, the fluid phase, rich in the fluoride-containing minerals, is released. By dissolution, dispersion and distribution, fluoride is released in high amounts in ground waters, sea water, subsoil waters, surface waters, surface

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dusts and soils.

Villages in India use the subsoil and ground water for drinking purposes, obtained through drilling of wells and hand pumps. Thus, largely through drinking water, fluoride finds its way into the human body where it causes crippling skeletal fluorosis.

Whereas several workers place the maximum permissible safe limit of fluoride in drinking water at 1.0 ppm, our studies indicate that the safe permissible level should be below 0.5 ppm. The fluoride content in water in different parts of the country ranges between 0.5 ppm and 50 ppm. Zones have been identified where fluorosis is endemic due to high natural fluoride content in drinking water. However, for effective prevention and control, systemic surveys of endemic fluorosis areas are required. The most seriously affected are Andhra Pradesh, Punjab, Haryana, Rajasthan, Gujrat, Tamil Nadu, and Uttar Pradesh. Excessive ingestion of fluoride for 6 mos. to several years causes chronic fluoride toxicity in the form of dental and skeletal fluorosis leading to crippling bone diseases and deformities.

Nearly one million individuals in India are afflicted with skeletal fluorosis. Several million are exposed to the risk of developing fluoride toxicity. Once crippling bone disease has developed, no specific treatment is known and it is largely irreversible.

For control and eradication of fluorosis, surface waters with <1.0 ppm fluoride content have been diverted or piped from neighboring urban areas to endemic villages. Also, small and large scale defluoridation plants have been installed. The first measure is difficult, tedious, time-consuming and expensive. Defluoridation is largely unacceptable to communities because it appears to be mass medication through chemically-treated water. It is impractical because of the cost of chemicals and of plant maintenance. Output of defluoridated water from such plants is insufficient to meet the demands of the community and trace elements of the chemicals used, such as aluminum and magnesium, may enter the defluoridated waters and prove harmful on long-term consumption by human beings.

Therefore, the fluoride content and the chemical composition of drinking water collected at various underground depths in endemic villages was studied to determine whether the depth from which water is collected involves any change in its fluoride content and in that of other constituents.

Material and Methods

Two endemic fluorosis villages - Sikri and Uzera - where the fluoride content in drinking water ranges from 2 to 12 ppm were selected for this project. Complete epidemiological surveys and house-listing of the population was performed in these villages. Each drinking water source (hand pump) was located and numbered house-wise. Seventeen hand pumps were selected at random to increase their depths with locations remaining unaltered. A minimum of 4 samples of drinking water were collected for analysis from each source, at the original 40 to 50 feet depth and subsequently at vary-

Table 1

Composition of Drinking Water Collected from Same Location of Hand Pumps at Original (High F^-) and Deep Bore (Low F^-) Depths

Hand Pump House Location No.	Hand Pump Depth (Feet)		Ca mg/l	Mg mg/l	F^- mg/l	I µg/100 ml	Cl mg/l	Total Hardness mg/l (as $CaCO_3$)	Total Alkalinity mg/l (as $CaCO_3$)
14	Original	40	64	52	3.8	7.0	177.5	386	662
	Deep bore	74	80	25	1.3	1.92	47.3	240	382
29A	Original	40	60	20	3.0	10.00	47.30	148	464
	Deep bore	57	84	30	1.0	3.60	59.20	300	346
109	Original	40	20	8	3.8	10.00	47.30	124	480
	Deep bore	110	112	34	1.0	2.24	47.30	360	404
18	Original	40	88	34	3.8	9.10	82.80	260	562
	Deep bore	56	92	28	0.8	2.90	47.30	296	324
19	Original	42	88	34	3.8	9.10	82.80	260	562
	Deep bore	57	76	25	1.0	1.80	47.30	262	364
22	Original	40	52	36	3.8	6.30	82.80	228	558
	Deep bore	60	76	30	0.8	1.90	71.00	254	284
108	Original	41	36	23	2.4	6.80	41.90	220	440
	Deep bore	80	96	35	1.0	1.70	59.20	314	332
43	Original	42	60	48	4.5	7.80	201.20	332	860
	Deep bore	70	36	30	1.0	6.20	35.50	204	330
101	Original	40	36	22	4.5	12.60	106.50	234	572
	Deep bore	75	68	10	1.0	4.60	70.98	192	180
48	Original	40	48	13	6.3	7.80	82.80	88	924
	Deep bore	60	40	20	2.5	4.24	165.60	186	790
81	Original	40	48	8	5.5	10.20	59.20	90	558
	Deep bore	65	60	18	1.3	3.40	35.50	180	442
85	Original	40	56	33	6.3	11.70	201.20	386	1012
	Deep bore	60	44	34	0.8	6.80	213.00	210	354

Table 1 cont.

Hand Pump House Location No.	Hand Pump Depth(Feet)		Ca mg/l	Mg mg/l	F^- mg/l	I µg/100 ml	Cl mg/l	Total Hardness mg/l(as $CaCO_3$)	Total Alkalinity mg/l (as $CaCO_3$)
106	Original	40	28	4	11.5	7.20	47.30	70	528
	Deep bore	80	84	32	0.8	0.80	59.0	320	326
104	Original	50	28	10	11.0	12.60	106.5	72	762
	Deep bore	56	48	18	0.75	5.50	79.0	96	552
3	Original	40	40	15	10.0	1.50	165.0	126	562
	Deep bore	70	44	18	1.4	1.12	23.7	122	358
7	Original	40	60	5	9.0	1.60	47.3	46	910
	Deep bore	70	40	16	0.8	0.36	23.7	110	232
6	Original	41	60	5	9.0	1.60	47.3	46	910
	Deep bore	66	36	9	1.0	1.60	23.6	60	458

ing depths during the process of deep bore drilling of the hand pumps until the accepted level of fluoride in drinking water was reached. Community co-operation was easily available since residents of the villages were well aware that only drinking water which contains less than 1.0 ppm can alleviate their symptoms. Analyses were done according to standard published procedures (1-3).

Discussion and Results

The results of analysis of drinking water collected from original and deep bore underground depths are summarized in Table 1. The water from the original 40 to 50 feet depths was high in fluoride and iodine, low in calcium, magnesium and total hardness and was highly alkaline. In drinking water from successively deeper levels, fluoride and iodine concentrations decreased continuously. Lower concentrations of fluoride (<1.0 ppm) and iodine in drinking water collected from deep bore (56 and 110 ft) depths were associated with other changes in water constituents. Although not uniform, in the majority of the samples, as depths of water collection increased, water hardness and levels of calcium and magnesium increased, alkalinity fell.

The importance of our finding, of <1.0 ppm in drinking water collected from 56 to 110 ft. underground, is stressed since deep bore hand pumps or wells would be an effective and lasting measure in control and eradication of endemic fluorosis; a simple, convenient, and inexpensive procedure readily acceptable by the community. Although the facts which have emerged are based on a limited number of water sources, only deep bore hand pumps and wells would be effective for eradication of fluorosis at a national level until endemic areas have access to municipal community water supplies. Work on this project is in progress in endemic areas around the country. Epidemiological, clinical, radiological and biochemical studies of the population, which had been drinking high fluoride water since birth followed by one year on <1.0 ppm fluoride in drinking water supplied through deep bore hand pumps are underway. The results will be reported separately.

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FLUORIDE BALANCE STUDIES IN HEALTHY MEN DURING BED REST WITH AND WITHOUT A FLUORIDE SUPPLEMENT

by

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(Abstracted from Amer. J. of Clin. Nutrition, 36:211-218, 1982)

A significant proportion of cases of post-menopausal and senile osteoporosis may be related to decreased physical activity and to the reluctance of older individuals to ambulate. Because skeletal mineral loss is associated with prolonged bed rest osteoporosis, induced by bed rest, is an excellent reproducible human model. After one month of inactivity, the human skeleton loses an average of 1/2% of its total body calcium each month. Specific weight-bearing bones may lose 10 times that amount each month. The purpose of this study was to determine whether doses of F^- lower than those previously used in osteoporotic patients would prevent disuse osteopenia.

Fluoride balances were determined during bed rest in men, on a controlled basal diet and on the same diet supplemented with 10 mg F^- as NaF. Fluoride and calcium were measured in diets, urine and feces. Serum ionic F^- levels were also measured. The results from this study have been compared with those from a previous study of the same subjects during ambulatory periods.

Fluoride has been tested as a possible agent for treating or reducing crippling osteoporosis. Doses of 40 mg and more of F^- daily produced such side effects as "intolerable bone pain or gastrointestinal disorders" in some subjects. To determine whether smaller doses of F^- would improve the calcium balance without causing severe side effects, ambulatory subjects receiving 5 and 10 mg F^- daily for 6 to 17 weeks were studied.

Calcium balances remained in the same steady state in both control and F^- treated subjects. F^- balances were uniformly negative ranging from -0.25 to -0.69 mg F^-/day, in the nine control subjects in which the F^- intake on the unsupplemented diet was very low, namely 0.4 mg/day. When 10 mg F^- were given, ambulatory subjects immediately showed positive balances of 2 or 3 mg F^- daily. However 10 mg F^- daily did not protect against bed rest-induced calcium loss.

Normal serum F^- concentrations, in subjects drinking fluoridate water, average about 0.01 to 0.02 ppm. Average serum ionic F^- ranged from 0.012 to 0.018 ppm for the five control subjects tested and 0.042 to 0.050 ppm for the four subjects given the supplement; the data are comparable with those from ambulatory periods. In both groups calcium balance declined significantly during bed rest, calcium loss being about equal from both urine and feces. During the ambulatory period (5 to 9 weeks), both control and F^- supplemented subjects remained in a steady state of calcium balance. It is apparent that there is no relation be-

tween calcium balance and F^- balance during bed rest at an intake of 10 mg F^-/day.

The authors conclude that 10 mg F^-/day did not protect against bed rest-induced calcium loss.

KEY WORDS: Fluoride, balance, serum, calcium, bed rest, disuse osteopenia

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FLUORIDES IN MECHANICALLY DEBONED CHICKEN

by

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To determine the advisability of using mechanically deboned poultry as a food source for children, at least three major factors must be considered: (1) the likelihood of adverse dental influences following the ingestion of small quantities of fluoride, (2) the amounts of fluoride likely to be taken into the body from food, water, environmental and other sources, (3) the fluoride content of various types of poultry following mechanical deboning.

Because of the small margin of safety for fluoride ingestion, the amount consumed should be well below that which may cause harm. Likewise contributions of fluoride from a variety of sources such as chewing gum, medicaments, soot, fertilizers, asbestos, and tobacco products should not be overlooked. Furthermore, significant biologic differences exist among individuals respecting their response to fluorides.

In mechanically deboned poultry, the fluoride content of mature female fowl is very much higher (average 14.38 µg/gm) than that of young chicken (average, 2 µg/gm) or young turkey (average, 1.7 µg/gm) whereas in mature male stags (roosters) fluoride is low (average 1.2 µg/gm) similar to young birds. Following hand-deboning,on the other hand, fluoride concentrations have averaged only 0.7 µg/gm for (mature female) fowl and 0.32-0.9 µg/gm for young chicken parts. Comparison of mature versus young birds revealed that the daily fluoride consumption of infants was projected to be 200-279 µg from mechanically deboned mature poultry; but only 41-57 µg from mechanically deboned young poultry.

Experimental feeding of high fluoride-containing phosphate to young turkeys resulted in high fluoride concentrations (22 µg/gm) following me-

chanical deboning. Fortunately, the United States governmental regulations help minimize the likelihood of generalized use of such feeds in this country.

Poultry is a good source of dietary protein. It has another desirable nutritional feature: it is lower in saturated fatty acids and higher in polyunsaturated fatty acids than beef or pork products.

At present, mechanically deboned mature female fowl should not be ingested by children. Mechanically deboned poultry intended for consumption by children in strained baby, junior, or toddler foods should be obtained exclusively from roosters, young chickens or young turkeys. Only mechanically deboned poultry from birds raised on low-fluoride feeds should be used in such food products. Despite its high fluoride concentration mechanically deboned poultry from mature female fowl may be used, if necessary, in foods prepared for adult consumption exclusively, provided that such mechanically deboned poultry is only a minor ingredient of such food products.

KEY WORDS: Poultry, mechanically deboned; Chicken, fluoride in; Turkey, fluoride in

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THE SPECTRUM OF RADIOGRAPHIC BONE CHANGES IN CHILDREN WITH FLUOROSIS

by

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(Abstracted from Pediatric Radiology 136:85-90, 1980)

In Tanzania, 298 persons, 251 below 16 years of age, residing in an endemic fluorosis area have presented a new form of bone disease among children much akin to that described by Krishnamachari et al. (endemic genu valgum) and Jackson et al. (Kenhardt bone disease, named after the village where the children were studied). The disease was predominent among male children, most of whom were undernourished with marginal protein deficiency. In spite of plentiful exposure to sunlight, these children developed rickets-like manifestations, such as genu valgum, genu varum and sabre tibia. No biochemical finding was obvious. Some of the children developed severe forms of crippling skeletal deformities and incapacitating pain in bones and in several joints.

Radiographically, even at an early age, the pelvis gave the impression

of varying combinations of osteoporosis and osteosclerosis. Coarsened trabeculae sometimes approached a pseudomozaic pagetoid pattern. The femoral shafts showed increased diameter of the condyles. Coxavara deformities of the hip joints and occasionally coxavalgum deformities were observed. Subperiosteal resorption was associated occasionally with cortical thickness reduction. In a few children, epiphysial lines were widened and mineralization was lacking. Wide seams of osteoid were seen in the femora, small beaking in the femoral condyles, multiple transverse stress lines of Park in the lower ends of the femur shaft. The cortex in the metacarpals and metatarsals was thin with varying degrees of osteoporosis and coarse intertwining trabeculae. Dental mottling was not proportional to the outstanding bone changes.

The author attributed these changes to hyperparathyroidism, although the circulating levels of the hormone could not be estimated. Whereas serum calcium and phosphorus levels were within normal limits, serum alkaline phosphatase levels were considerably elevated. Renal diseases, sicklecell anemia, syphilis and thalassemia were excluded.

Vitamin D deficiency, as a cause of the disease, was excluded in the present investigation. As in India, a combination of high fluoride, low calcium and low protein may play an important role in causation of the disease.

In contrast to classical osteosclerosis, there is now evidence of osteoporosis and osteomalacia in fluoride toxicity as described by earlier investigators from India and South Africa. The present investigation confirms their observations. Steyn and Jackson (South Africa) found skeletal changes in children with bone deformities (Kenhardt bone disease) from exposure to fluoride as low as 2.6 ppm in drinking water. More recently, Teotia, et al. and Krishnamachari and Krishaswamy have reported endemic fluoride-induced osteopathies in Indian children; they reported secondary hyperparathyroidism in endemic fluorosis areas and extremely high levels of immunoreactive parathyroid hormone in genu valgum patients which implicate hyperparathyroidism.

KEY WORDS: Bones, diseases, dysostoses, primary disturbances of growth; Children, skeletal system; Fluoride; Skeletal system, fluoride poisoning.

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Abstracted by K.A.V.R. Krishnamachari

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ENAMEL CHANGES AND DENTAL CARIES IN 7-YEAR OLD CHILDREN GIVEN FLUORIDE TABLETS FROM SHORTLY AFTER BIRTH

by

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(Abstracted from Caries Res. 13:265-276, 1979)

In a caries preventive program, initiated in 1969 in Denmark, a positive association was observed between the number of tablets prescribed and the amount of dental fluorosis in erupted permanent teeth. In all four study groups, which were determined according to the number of tablets ingested, localized enamel opacities were similar in frequency.

A significant inhibition of dental caries in the primary dentition was recorded only for those who received a total of more than 1600 tablets and who had used them continuously through the years. No difference in caries was observed in the permanent dentition. In accordance with current theories, topical effects of fluoride rather than systemic effects prevent dental caries.

By statistical analysis, a direct association between the number of undecayed first molars and previous exposure to fluoride tablets was found. Concomitantly, a positive association was recorded between the duration of tablet ingestion and dental fluorosis. The more pronounced enamel changes observed among children given fluoride supplements in the study of Aasenden and Peebles (Arch. Oral Biol. 19:321-326, 1974), may be ascribed to their higher daily dosage.

Histologically, enamel opacities appear as localized porous areas. When ascertaining the etiology, localized and generalized enamel defects may be due to more than 90 different factors which should be taken into consideration. Longterm use of fluoride tablets is likely to be associated with more positive attitudes toward dental care.

The present results indicate that distribution of tablets to families for use by children from shortly after birth is an unsatisfactory method of fluoride administration because few continue administration of tablets after teeth have erupted.

Current evidence indicates that fluoride confers protection against caries of primary teeth without being incorporated into the enamel.

KEY WORDS: Caries; Clinical trial; Fluoride tablets; Dental fluorosis

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ENAMEL MINERALIZATION DISTURBANCES IN 12-YEAR OLD CHILDREN WITH KNOWN EARLY EXPOSURE TO FLUORIDES

by

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(Abstracted from Community Dent. Oral Epidemiol., 10:335-339, 1982)

Enamel changes and caries experience were studied in 134 12-year old children with a known early exposure to fluoride tablets and/or fluoride-containing toothpaste. This investigation is a continuation of earlier studies of an original cohort of children, born in 1967, living in the town of Umeå and examined at 3, 4, 5, and 8 years of age.

All children had stopped using fluoride tablets by age 6. Enamel mineralization disturbances were recorded in good lighting after air drying followed by an interval of 1 minute. Only permanent first molars and incisors were included. Since various forms of prophylactic treatment, namely fillings or fissure sealing, could have been carried out on occlusal surfaces, only caries and fillings on smooth surfaces were included in the statistical analyses.

Mineralization disturbances, classified as enamel fluorosis, were found in 45% of the children. Buccal surfaces of the maxillary central incisors were the ones most commonly affected by fluorosis, followed by buccal and occlusal surfaces of the permanent first molars. Localized opacities or hypoplasias were found in 39%. 35% of the children with enamel fluorosis likewise had opacities or hypoplasias; 42% of the rest of the group had opacities or hypoplasias.

The increase in the percentage of children with enamel fluorosis, when consumption of fluoride tablets started at 6 or 12 months of age was statistically significant compared to children with only sporadic or no use. The relative risk run by this group was calculated to be 5.4 times that run by children who had not consumed fluoride tablets. The relative risk run by children beginning to take the tablets at 12 months was calculated to be 3.9 times and at 24 or 36 months 2.3 times that in children who had not consumed fluoride tablets.

Early use of fluoride-containing toothpaste did not seem to induce clinical changes in the enamel. Nevertheless, 15% of the children who neither ingested fluoride tablets nor used fluoride toothpaste displayed mineralization disturbances which were classified as enamel fluorosis. When an early use of fluoride tablets and fluoride toothpaste coincided, the prevalence of enamel fluorosis was not higher than in the group of children in whom use of fluoride toothpaste began somewhat later.

Only 2% of the group had no caries or fillings. Caries was reported on smooth surfaces in 37% of the children and in only four children on the incisors or canines. No statistically significant difference or decrease was ob-

served in the prevalence of smooth surface caries or fillings in children with an exposure to fluoride tablets.

KEY WORDS: Enamel fluorosis; Fluoride tablets; Fluoride toothpaste

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FLUORIDE PHARMACOKINETICS IN THE DOMESTIC PIG

by

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(Abstracted from J. of Dental Research, 61:1099-1102, 1982)

Plasma fluoride concentrations were studied in 11 pigs following single oral or intravenous doses of fluoride. When administered with calcium-rich food a bioavailability of fluoride was less than 20% according to pharmacokinetic analyses. The plasma half-life varied from 0.6 to 1.4 h, depending on diet and route of fluoride administration.

This study, to obtain basic quantitative information on some of the factors affecting variations in plasma fluoride levels in the domestic pig, showed that the basal plasma level was more than twice that reported for rats and four times higher than that for humans in low-fluoride areas. This can be explained by the relatively high F^- content of the diet. The difference in background levels of plasma fluoride between and among animals receiving the same diet which was statistically significant, was taken into account when calculating pharmacokinetic parameters.

Plasma concentrations from intravenous and peroral doses have been compared, thus permitting quantitation of the extent of fluoride absorption in studies enduring five hours. The well-known effect of dietary calcium on fluoride bioavailability has been confirmed. Since the half-life of fluoride is very short, the high frequency of plasma sampling is essential for accurate estimation of plasma data.

Background concentrations of plasma fluoride in pigs was shown to be constant for each individual animal. The pharmacokinetic behavior of the drug in relation to route of administration and calcium content of the diet was comparable to data previously reported from human studies. Thus, as far as fluoride pharmacokinetics is concerned, the pig is suitable for investigating effects of fluoride on hard tissue mineralization.

KEY WORDS: Pig, F^- pharmacokinetics in; Plasma F^- in

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EARLY SUPPLY OF FLUORIDE AND ENAMEL FLUOROSIS

by

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(Abstracted from Scand. J. Dent. Res., 85:22-30, 1977)

In a study of enamel fluorosis on 1094 children, carried out in areas where the water fluoride content ranged between <0.2 mg/l and 2.75 mg/l with and without supplementary fluoride, fluorosis was correlated with different infant diets and with the calculated supply per kilo body weight. As in cattle 0.1 mg F/kg body weight, daily, appears to cause fluorosis.

Aasenden and Peebles reported that 7 to 12-year olds, in low F^- areas, had a higher incidence of fluorosis in their permanent teeth following fluoride supplementation since early infancy than children in areas with so-called optimal water F^- content.

In Eskilstuna, with so-called optimal F^- content, in children who had ingested formula powder mixed with water, the groups of teeth which mineralized early were more fluorotic. However, fluorosis was more severe in those cases where 2-3 months every summer were spent in areas where the water fluoride content was greater than that at home. A few findings in F^- districts indicate that a corresponding exposure to lower F^- content results in milder fluorosis.

In both districts, with a low F^- content in domestic water, 32% of the formula-fed children with F^- supplement had mild fluorosis whereas fluorosis increased markedly in both severity and frequency when F^- supplementation had been commenced at birth.

To avoid fluorosis, the higher the F^- content in domestic water, the longer breastfeeding is necessary. In districts with 1 ppm F^- in water, 4-5 months of breastfeeding is necessary. In low F^- districts, fluorosis occurs on the very earliest mineralized parts of the teeth, sometimes on first molars. With increasing F^- content in water, fluorosis was discernible on an increasingly larger area of the incisal or occlusal parts of the teeth. The more severe fluorosis in Lenhovda in 1976 with 1.5 mg F/l compared with that in 1968, in children born just after a change in the water supply from

0.2 ppm, is in agreement with observations in high F^- districts and is further indication of prenatal influence via the mothers. According to Armstrong et al. the child is born with the same F^- content in the blood as the mother.

In Laholm (0.8 mg F/1), where 81 children who still had their primary teeth were examined, 40% had Grade 1 and 3% Grade 2,"very mild" and "mild" fluorosis according to Dean's index. In many cases,both the first and second primary molars were affected.

In Skurup (2.75 mg F/1), where 103 children still had their primary molars, fluorosis of these teeth occurred in 76% of the children; 4% were Grades 3 and 4, according to Dean. In children in the low fluoride districts who received water-diluted formula powder from infancy, none of the children with higher birth weights, but a little over half the children with lower birth weights, developed fluorosis.

Fluorosis was markedly more frequent and severe in children in Eskilstuna who received water-diluted formula powder from an early age (0 - 5 months) compared with those who had been breastfed at least 6 months and/or had received milk-diluted gruel. The difference was significant at the 0.1% level.

The unexpected finding of fluorosis in the non-fluoride groups in the Stockholm district gave rise to the investigation of children in Vaxjo where domestic water has the same low F^- content. Formula powder diluted with water might increase F^- intake to the extent that even high-weight infants could also exceed the threshold value. With a water fluoride content of 2.75 mg F/1 a very mild fluorosis is difficult to avoid.

KEY WORDS: Dental fluorosis; Fluorides; Fluorosis; Mottled enamel

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A MECHANISM FOR THE ANTICARIES ACTION OF FLUORIDE

by

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(Abstracted from Caries Res. 14:298-303, 1980)

Among the many attempts to explain the anticaries action by the fluoride ion are its anti-enzyme and bacteria-modifying properties. For many years the view was held that the reduction in enamel solubility produced by fluoride, accounted for caries reduction but other compounds, which also reduce enamel solubility, did not reduce caries.

The action of fluoride has also been attributed to the greater perfection of fluoride-containing enamel crystals, to the reduction in carbonate content, to changes in cusp, pit and fissure morphology and even to the effect of fluoride on the surface energy of enamel. More recently attention has focussed on the phenomenon of remineralization of early lesions which is favored by fluoride through its effect on apatite crystal growth.

When fluoride interacts with hydroxyapatite, the halide ion displaces the hydroxyl ion. In the partially fluoridated hydroxyapatite, hydrogen bonding interactions provide an energy decrease. Thermochemical experiments have shown a decrease in enthalpy when quite dilute aqueous fluoride interacts with hydroxyapatite. The caries process causes a preferential depletion of calcium ions from the mineral and the action of fluoride is to reverse this process. This means that the function of fluoride can be seen as assisting the repair process at even the earliest stages of a caries attack.

KEY WORDS: Apatite, Calcium, Depletion, Fluoride

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INVESTIGATION ON THE TOTAL DAILY FLUORIDE INTAKE IN COLLEGE STUDENTS IN WUHAN

by

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(Abstracted from Chung Hua Yu Fan I Hsueh Tsa Chih, 16:364-366, 1982)

By means of the weighing method a dietary survey was conducted in May 1980 in one of the colleges in Wuhan.

The total amount of daily fluoride intake per person was calculated to be 1,294.62 µg; 840 µg (about 65% of total intake) came from drinking water, 417.32 µg (about 32% of total intake) from food and 37.30 µg (about 3%) from air. The incidence of dental caries and dental fluorosis in native children who drank the same source of water was 25.38% and 5.69% respectively and the mean output of urinary fluoride was 1.00 mg/l.

KEY WORDS: Fluoride intake; Wuhan, China; Dental caries; Dental fluorosis

Author's Abstract

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