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Contributors will receive 20 reprints of their paper free of charge.
EDITORIALS

NEW OBSERVATIONS ON FLUOROSIS

This issue presents data on fluorosis which originated in different parts of the world where this disease is endemic. A perusal of these reports reveals certain heretofore unrecognized facts:

Soriano's description of the osteoporotic and osteomalacic phase of fluorosis opens the door to an entirely new area of exploration. Osteomalacia due to fluoride was first recognized by Kaj Roholm in his classical work. Other authors have only touched upon it casually. The skeletal changes described by Soriano differ materially from the typical picture of skeletal fluorosis. This difference might be due to the simultaneous consumption of alcohol present in the F-contaminated wine, to liver damage resulting from chronic alcoholism, to Spanish nutritional habits or to climatic factors. Whatever the explanation, osteoporosis due to fluoride presents a challenging problem for further research.

Additional variations in the clinical picture of fluorosis have been encountered by other contributors to this issue. In N. Africa, for instance, Pinet failed to observe paraplegia and quadriplegia, the neurological manifestations which are so common in skeletal fluorosis in India. Perhaps this difference manifests is due to dietary habits as suggested by Pinet or to certain geological conditions which determine the composition of water and food in that area. Freda's description of gastro-intestinal symptoms, especially chronic gastritis, enteritis and liver damage due to fluoride in water is significant. These manifestations have been reported in the incipient stage of fluorosis in the U.S.A. They were also recognized in India. According to Siddiqui the degree of gastric acidity might be a determining factor in the development of gastric symptoms.

Jolly observed rheumatoid pains and arthritis early in the disease, a condition which has been recognized by several authors in industrial fluorosis and in fluorosis due to air pollution ("neighbourhood fluorosis").

Calcification of arteries of the Mönkeburg type in conjunction with skeletal fluorosis is another area of research which needs further investigation. Soriano and Pinet are the fourth and fifth investigators, respectively, who have reported this disease in association with skeletal fluorosis.

Jolly demonstrated a significantly higher incidence of fluorosis in one of two Indian communities with the same F content (3.3 ppm) in their drinking water. This observation points up the importance of minerals associated with fluoride in water and of F intake from sources other than water. The effect of such constituents as magnesium, phosphorus and calcium in water has been dealt with by several contributors to this issue. That fluoride in food, especially in tea, may be a source of "crippling" fluorosis is suggested by the paper of Webb-Peploe and Bradley who observed this disease in Hampshire where the F content of drinking water was negligible.

The reliability of F determinations in bones as an effective diagnostic tool must be questioned on the basis of Jolly's data. He and his predecessor,
EDITORIALS

the late Amarjit Singh, encountered advanced skeletal fluorosis in persons the F content of whose bones was 700 to 1000 ppm, a level previously accepted as "physiological" or "normal". F is present in nearly every living organism and tends to accumulate with advancing age.

The data presented in this issue will undoubtedly have a considerable impact upon many heretofore little understood phenomena.

A GAP IN FLUORIDE RESEARCH

Fluoride is taking on an ever increasing significance in industry and science. New compounds are being synthesized, new industrial uses created, unexpected effects of the fluorine ion on plant and animal life are being recognized. Although fluoride research is expanding more than ever, relatively little knowledge is reaching the scientific community especially the practicing physician and veterinarian. There is a lack of rapport between scientists from city to city, from discipline to discipline and even from one scientist to another at the same university.

Numerous factors account for this dilemma: The recognition of fluorine as an element occurred relatively recently. Assays for fluoride have been tedious and are not always reliable. They are not readily available in hospitals or to practicing physicians. Litigation due to air pollution by fluoride and political implications associated with fluoridation of drinking water often preclude adequate reporting in scientific journals. Usually scientists involved in law suits, who have had the most research experience with fluoride, hesitate to communicate with their finding to the professions lest it jeopardize the interests of those whom they represent in court.

"Fluoride" - Quarterly Reports seeks to bridge this gap in communication.
PERIOSTITIS DEFORMANS DUE TO WINE FLUOROSIS

by

M. Sariano
Barcelona, Spain

In 1952, I (1) described a new bone disease, which I called periostitis deformans. In 1965 (2) I was able to identify this disease with chronic intake of F due to habitual drinking of wine containing fluorine. I termed it "Wine Fluorosis".

This kind of chronic fluoride intoxication is rare. It differs materially from skeletal fluorosis. During a 15 year period we observed 29 cases. Fluoride was originally added to wines to retard fermentation in contravention of existing health laws. The F concentration in wines ranged between 6 and 72 mg/l (ppm). Large-scale consumption of such wines in certain areas has permitted us to study the bone changes thus produced. The most typical form is the development of periostitis deformans. In only one case did we encounter a purely osteomalacic pelvic form. Biopsy of the coxal bone revealed quantities of fluorine greater than 4000 ppm (ash basis). Table I presents the F analyses of bone in 6 patients.

### TABLE I

**F Content of Bones in 6 Cases of Wine Fluorosis**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Bone</th>
<th>PPM F</th>
<th>Consistency of Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Pelvic bone</td>
<td>11,800</td>
<td>Very dense</td>
</tr>
<tr>
<td></td>
<td>Tibia (cortex)</td>
<td>4,500</td>
<td>Very hard</td>
</tr>
<tr>
<td></td>
<td>Femur (cortex)</td>
<td>3,809</td>
<td>Very hard</td>
</tr>
<tr>
<td></td>
<td>Tibia (spongiosa)</td>
<td>11,200</td>
<td>Very soft</td>
</tr>
<tr>
<td></td>
<td>Femur (spongiosa)</td>
<td>11,900</td>
<td>Very soft</td>
</tr>
<tr>
<td>5</td>
<td>Femur (cortex)</td>
<td>905</td>
<td>Very dense</td>
</tr>
<tr>
<td></td>
<td>Pelvic bone</td>
<td>9,770</td>
<td>Very porotic</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>8,090</td>
<td>Spongy</td>
</tr>
<tr>
<td></td>
<td>Humerus</td>
<td>2,680</td>
<td>Dense cortex</td>
</tr>
<tr>
<td></td>
<td>Pelvic bone</td>
<td>8,504</td>
<td>Very soft</td>
</tr>
<tr>
<td></td>
<td>Rib</td>
<td>7,320</td>
<td>Very soft</td>
</tr>
<tr>
<td></td>
<td>Radius</td>
<td>7,690</td>
<td>Soft</td>
</tr>
<tr>
<td>6</td>
<td>Femur (cortex)</td>
<td>1,537</td>
<td>Very hard</td>
</tr>
<tr>
<td></td>
<td>Tibia (cortex)</td>
<td>1,216</td>
<td>Very hard</td>
</tr>
<tr>
<td></td>
<td>Tibia (head)</td>
<td>1,549</td>
<td>Slightly hard</td>
</tr>
<tr>
<td></td>
<td>Trochanter</td>
<td>2,937</td>
<td>Slightly hard</td>
</tr>
<tr>
<td>11</td>
<td>Newly formed bone</td>
<td>11,750</td>
<td>Reticular, spongy</td>
</tr>
<tr>
<td></td>
<td>Marrow</td>
<td>2,376</td>
<td>Hard</td>
</tr>
<tr>
<td>12</td>
<td>Osteophyte (rib)</td>
<td>11,700</td>
<td>Slightly hard</td>
</tr>
<tr>
<td></td>
<td>Osteophyte (finger)</td>
<td>13,580</td>
<td>Soft</td>
</tr>
<tr>
<td></td>
<td>Osteophyte (elbow)</td>
<td>11,400</td>
<td>Soft</td>
</tr>
<tr>
<td></td>
<td>Pelvic bone</td>
<td>10,900</td>
<td>Hard</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>5,519</td>
<td>Very hard</td>
</tr>
<tr>
<td>13</td>
<td>Pelvic bone</td>
<td>13,400</td>
<td>Soft</td>
</tr>
</tbody>
</table>

Chairman, Faculty of Medicine, University of Barcelona, Spain.
Soriano

Pathology in Periostitis Deformans

Four typical phases of F-induced periostitis deformans were noted:

1. **Endosteal** changes lead to a condition which we termed sclero-atrophic osteitis. An initial, slowly developing osteosclerosis gradually leads to osteoporosis and bone atrophy.

2. **Periosteal** changes develop in the course of repeated episodes of hyperostotic periostitis deformans. During these outbreaks the affected bones exhibit zones of periosteal hyperostosis which grow prodigiously, until they resemble bone tumors. On the fingers, they reach the size of an almond (Fig. 1). On forearms and femur they can grow as large as an apple (osteoblastic stage Fig. 2). Usually after a period of about three to five months when the lesions cease growing, the osteoclastic stage (Fig. 3) sets in, and their size decreases (atrophic stage). If the lesions fail to clear up entirely, they leave permanent deformities in the affected bones (Fig. 4 and 5). The periosteal lesions are typical of the disease.

3. **Invading osteophytes** cause soft-tissue changes in periostitis deformans, a condition which we termed "invading osteophytosis." Osteophytes develop in tendons, fasciae, and muscles at the areas where they are attached to bone. This condition can become widespread. Like the other hyperostotic changes observed in the disease, the osseous lamellae of osteophytes undergo atrophy and become osteoporotic during the late stage of the illness, although they do not decrease in size.

4. **Joint** changes or fluoric arthrosis may be very severe especially in the hip, knee and elbow joints (Fig. 6).

**Radiological Diagnosis**

In each group of periostitis deformans, the x-ray changes are characteristic.

1. **Sclero-atrophic Osteitis:** At the onset of the disease osteosclerosis occurs in the vertebral column, the pelvis, and the shafts of the long bones. Subsequently osteoporosis develops at these original sites. The osteoporotic zones tend to expand toward the adjacent areas and eventually affect the cortex and the whole pelvis. In the final stage, osteoporosis invades the vertebral column and all remaining bones (Fig. 7, 8, 9, 10).
Fig. 2

Periosteal ossification simulating bone tumors.

Fig. 3

a. Osteoblastic phase of periosteal growth in forearms in two stages of development.
b. Lamellar appearance of osteophyte. Deformity of both bones 1 year later.

Fig. 4

Advanced periosteal growth in forearm (osteoclastic phase) in another patient. Osteosclerosis in diaphysis.

* All illustrations except Fig. 2 represent radiographs.
Fig. 5

Striation of compact bone (femur) with large osteophyte.

Fig. 6

Marked osteosclerosis in pelvis; intense osteophytic periarticular proliferation of hip joints; "Blocking" arthrosis. "Feathery" outline of os ischium.

Fig. 7

Areas of intense sclerosis coexist with those of marked osteoporosis in the same bone. This is highly characteristic of the disease.

2. Periosteal changes: During the early growing or osteoblastic period, pseudotumors appear which originate in the periosteum. They are composed of projecting nodules of newly formed bone demarcated by round or multicircular margins, which present a radial structure in the shape of a fan or cockade (Fig. 11, 12). During the osteoclastic stage they assume the form of a fine
reticular structure which subsequently merges into progressive osteoporosis. Eventually the osseous lamellae become atrophic and appear honey-combed in the X-ray picture. When new areas of periostitis develop on top of the earlier ones, each layer of the newly formed bone corresponds to a new outbreak of activity. They go through the same stages as do the previously described lesions.

Periosteal proliferations of immature bone, Osteoclastic phase (forearm).

Periosteal growth in the forearms (pseudotumors) involving the interosseous membrane (invading osteophytosis). Osteosclerotic cortices.

During subacute outbreaks endosteal bone may also be invaded. The osseous lamellae of the compact endoosteum will undergo an expansive outburst of activity and produce a bone tumor. The osseous lamellae develop quickly, thicken, separate from each other and leave wide spaces between them (Fig. 10). Later, the lamellae of the endosteal tumor undergo atrophy and form large pseudotumors in the endosteal bone. Frequently, the endosteal bulges are covered by periosteal bone structure which becomes intimately fused with them.
3. Inflamed osteophytes: Osteophytes of endosteal or periosteal origin may proliferate and acquire bizarre forms. The osseous lamellae with irregular margins at the interosseous membrane of the forearm (Fig. 12) are typical of wine fluorosis. Equally characteristic are the harpoon-shaped changes in the tibia and the rostrum-like osteophytes in the calcaneum. There may also be large thin plates which expand deeply into muscles. Occasionally, isolated bony nodules are seen within the sheaths of tendons and muscles which present the radiological feature of fibrositis and of myositis ossificans (Fig. 14). Calcifications in arterial walls are also frequently observed (Fig. 7).

4. Fluoric Arthropathies: Around joints, thick marginal osteophytes develop. In some instances, they grow to such an extent as to block joint movements ("blocking arthrosis") (Fig. 6). The joint block can also be induced by calcification of the periarticular ligament. The most common sites of articular involvement are the hips, the sacroiliac, elbow and knee joints. In older persons, the vertebral column is commonly affected. Advanced stages of the disease show atrophy and ulceration of joint cartilage. All changes of periostitis deformans tend to be symmetrical.

Latent Forms

At the onset of the disease, the vertebral column and the pelvis show only insignificant osteosclerotic together with a slight periosteal reaction and minor porotic lesions in the shafts of the long bones. The periosteal lesions regress eventually, leaving only thin porotic layers of periosteal bone. The most conspicuous finding in such patients is sclero-atrophic osteitis with invading osteophyosis and arthritic changes.

The areas of atrophic osteitis are likely to become the sites of spontaneous fractures. Osseous deformities remain, some of which are produced by residual hyperostoses of periosteal or endosteal origin. Less frequent are curvatures of the diaphyses (Fig. 3). New subacute episodes of periostitis deformans can occur at any stage of the disease.

The radiologist should suggest the fluoric origin of the disease and emphasize the need to search for the toxic substance in the patient's environment, i.e. the habitual intake of contaminated wine.

In order to confirm the diagnosis, a fluorine bioassay should be performed on a biopsied bone specimen taken from the iliac crest.

Fluoride Action on Bone Tissue

Fluoride stimulates osteogenesis. This causes the initial osteosclerotic stage as well as periosteal and endosteal reactions of proliferating bone tissue which resemble bone tumors. If the irritating action of F is intense and persistent the early osteoblastic reaction is followed by osteoporosis and bone atrophy. The osteoporotic stage of the disease occurs only when fluoric intoxication is very severe.

A most striking feature of the osteoblastic action of F is the fact that it can also result in osteoblastic metaplasia in tissue other than bone and cause fibrositis and myositis ossificans. Fibrositis ossificans is usually localized
Endosteal lesions of femur. Fracture in an osteoporotic zone of the striated compact bone; atrophy of femoral head; osteosclerosis of pelvis.

Ossification of muscle of thigh (myositis ossificans) with marked osteosclerosis of femur.

Myositis ossificans in "Wine Fluorosis" (knee).

Orifices in ossified musculature due to arteries passing thru them.

Terminal case of periostitis deformans with invading osteophytosis; atrophy of head of femur. Osteoporosis alternating with osteosclerosis.
WINE FLUOROSIS

near the affected bone, but is nevertheless completely independent of it. The extension of invading osteophytosis into soft tissue encountered in periostitis deformans, appears to be due not only to endosteal and periosteal proliferation, but to a progressive fibrositis ossificans of membranes, tendons and fasciae which are attached at the sites of proliferating osteophyte activity. This "invasive osteophytosis" is another characteristic feature of the disease.

According to our observations the prolific growth in periostitis deformans continues as long as daily amounts greater than 8 to 10 mg of F are ingested no matter through what vehicle. If F intake is intermittent subacute outbreaks will occur coincidentally with increased F ingestion.

The development of the lesions is influenced by such predisposing constitutional factors as osteogenesis imperfecta and probably by impaired nutrition. In "wine fluorosis", alcohol contributes to the severity of the fluorosis, since chronic alcoholism induces anorexia, gastritis and liver damage and thus leads to malnutrition.

Summary

On the basis of 29 cases observed during 1948 to 1968, the author reports a disease termed periostitis deformans which was caused in alcoholics by sodium fluoride added to wine in concentrations of the order of 8 to 72 ppm. Four different phases of the disease are described which are associated with osteosclerosis and osteoporosis. They lead to marked disability and may terminate fatally.

Bibliography

AN EPIDEMIOLOGICAL, CLINICAL AND BIOCHEMICAL STUDY OF ENDEMIC, DENTAL AND SKELETAL FLUOROSIS IN PUNJAB

by

S. S. Jolly
Patiala, India

Since 1958 the Department of Medicine, Patiala, has been actively engaged in epidemiological, clinical and biochemical studies of endemic fluorosis in Punjab, one of the most highly endemic areas in the world. Extensive data on dental, skeletal and neurological aspects of fluorosis have been fully reported in our earlier studies (1-5). The object of the present communication is to evaluate the role of various factors associated with F toxicity. Even where F levels in the water are identical, variations in the incidence of F intoxication clearly point to the existence of causative factors in addition to fluoride.

Material and Methods

An epidemiological survey to determine the incidence of dental fluorosis was carried out in 358 villages of Punjab. Children between 5 to 17 years of age were examined for dental mottling and characteristic dental pigmentation.

Besides the above dental survey, ten villages from the endemic fluorotic area of Punjab each with a different F concentration in drinking water were selected to assess the effect of various factors in F intoxication. Children and adults (both males and females) in these villages were subjected to thorough clinical and radiological examination. Interosseous membrane calcification had been taken as a definite index of skeletal fluorosis.

The waters of the ten villages were analyzed for various important chemical constituents such as total hardness, calcium and magnesium hardness and alkalinity. In an Indian village there is no central water supply. Almost each house has its own hand pump. The F concentration at these pumps shows a wide variation in the same village because of the different depths of the wells. Moreover, the farmers and laborers (the subject of this study) work in the fields. They imbibe water from the places wherever they are during the day. It is, therefore, not possible to evaluate precisely the incidence of fluorosis according to a particular F concentration in the sample of water. However, the mean F concentration of all water samples has been computed for the purpose of determining the incidence of fluorosis.

Dental Fluorosis

About 46,000 children were examined in 358 Punjab villages. The incidence of dental involvement as correlated with fluoride concentration is tabulated in Table 1.

From the Government Medical College, Patiala, India
FLUOROSIS PUNJAB

TABLE 1

<table>
<thead>
<tr>
<th>Number of Villages</th>
<th>Maximum F Concentration in Water (ppm)</th>
<th>Incidence of Dental Mottling</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>1.4</td>
<td>0 – 10%</td>
</tr>
<tr>
<td>96</td>
<td>2.3</td>
<td>10 – 30%</td>
</tr>
<tr>
<td>52</td>
<td>Above 2.3</td>
<td>Above 30%</td>
</tr>
</tbody>
</table>

The incidence of dental fluorosis rises with increasing F concentration but no linear relationship between F levels in water and the incidence of dental involvement is noted. In the ten villages selected for the special study, the incidence of dental mottling in children and adults is given in Table 2.

TABLE 2

<table>
<thead>
<tr>
<th>Name of the Village</th>
<th>Fluoride Concentration (ppm)</th>
<th>Incidence of Dental Mottling in Children (Percent)</th>
<th>Incidence of Dental Mottling in Adults (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gharachaon</td>
<td>1.4</td>
<td>22.6 (124)</td>
<td>13.8 (87)</td>
</tr>
<tr>
<td>Laluwaia</td>
<td>2.4</td>
<td>30.6 (49)</td>
<td>60.2 (74)</td>
</tr>
<tr>
<td>Dharpaia</td>
<td>3.0</td>
<td>24.5 (57)</td>
<td>47.6 (107)</td>
</tr>
<tr>
<td>Bhodipura</td>
<td>5.0</td>
<td>55.9 (34)</td>
<td>31.2 (64)</td>
</tr>
<tr>
<td>Rajthal</td>
<td>3.3</td>
<td>47.0 (133)</td>
<td>10.0 (160)</td>
</tr>
<tr>
<td>Bhikki</td>
<td>3.5</td>
<td>53.4 (146)</td>
<td>52.5 (160)</td>
</tr>
<tr>
<td>Sanghera</td>
<td>3.6</td>
<td>27.4 (137)</td>
<td>49.4 (154)</td>
</tr>
<tr>
<td>Ramasara</td>
<td>5.0</td>
<td>52.7 (95)</td>
<td>56.6 (90)</td>
</tr>
<tr>
<td>Gangugulabsingh</td>
<td>6.5</td>
<td>61.4 (43)</td>
<td>55.6 (58)</td>
</tr>
<tr>
<td>Kahara</td>
<td>9.7</td>
<td>66.0 (50)</td>
<td>70.7 (232)</td>
</tr>
</tbody>
</table>

(Figures in parenthesis denote the number of cases examined.)

The incidence of dental fluorosis in a locality with mean F concentration of 1.4 ppm was about 22.6%. Comparison of this percentage with that in Table 1 shows that it is impossible to attribute the incidence of dental fluorosis solely to the F content of drinking water.

Skeletal Fluorosis

During the epidemiological survey of the villages of Punjab, we examined 1065 cases of skeletal fluorosis, the largest series ever reported. In addition, detailed examinations were carried out on cases which were admitted to the hospital from time to time during the last 10 years. Table 3 gives the overall results of this survey.

Volume 1, Number 2
October, 1968
JOLLY

TABLE 3

Results of Survey

<table>
<thead>
<tr>
<th>Skeletal fluorosis detected by x-ray:</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent with symptoms</td>
<td>835</td>
<td>60.3%</td>
</tr>
<tr>
<td>without symptoms</td>
<td>210</td>
<td>19.7%</td>
</tr>
<tr>
<td>Without crippling</td>
<td>624</td>
<td>58.6%</td>
</tr>
<tr>
<td>With crippling deformities</td>
<td>142</td>
<td>13.3%</td>
</tr>
<tr>
<td>With neurological complications</td>
<td>89</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

Whereas dental fluorosis is easily recognized, the incipient skeletal involvement is not clinically obvious until the disease has advanced to the state of crippling. However, radiological changes are discernible in the skeleton much earlier and provide the only means of diagnosing the disease in its early and relatively asymptomatic stage. These cases are usually young adults whose only complaints are vague pains most frequently in the small joints of the hands and feet, the joints of knees and spine. Such cases are common in an endemic area. They are misdiagnosed as rheumatoid arthritis or ankylosing spondylitis. In the more advanced stages, there is an obvious stiffness of the spine with limitation of its movements followed by kyphosis. Patients experience difficulty in walking, partly because of stiffness and limitation of movements of various joints and partly because of neurological defects in the advanced cases.

The skeletal changes in endemic fluorosis are best described under the following headings:

**Gross Changes in Skeleton**

The gross skeletal changes in cases of endemic fluorosis are quite distinctive and characteristic. They have been described in detail in our earlier publications (4).

We had the unique opportunity to study the complete macerated skeleton of a person affected by endemic fluorosis. The bones were heavy and irregular, their dull color was due to irregular deposition of F. The sites of muscular and tendinous insertions were rendered abnormally prominent by excessive periosteal reaction with development of multiple exostoses. Irregular bone was laid down along the attachment of muscles and tendons in the extremities as well as in joint capsules and in interosseous membranes. The latter is particularly helpful as a diagnostic feature in borderline cases where the density of the bone is not markedly increased. Maximum changes were detected in the spine, particularly in the cervical region. The vertebrae showed altered proportions and measurements in all planes, but the most striking abnormality was the gross reduction of the antero-posterior diameter of the spinal canal, which in the case studied at autopsy was reduced to 2 mm at the level of third and
fluorosis Punjab

**Fig. 1**
Dental Fluorosis in Endemic Area. Note Characteristic Pigmentation of teeth.

**Fig. 2**

fourth cervical vertebrae (Fig. 2). Since the average antero-posterior diameter of the spinal cord in the cervical enlargement is about 8 mm and the bulge of the ligamentum flavum has also to be accommodated, compression of the cord is almost inevitable. The vertebrae were fused in many places, which explained the marked limitation of movement and the resemblance of the disease to spondylitis ankylopoietica. The intervertebral foramina were narrowed and irregular, which accounts for radicular manifestations. In the skull there were no conspicuous changes, but the margins of the foramen magnum were irregular and its diameter reduced as a result of deposition of new bone. The other small foramina were not significantly affected. Therefore, there was no cranial nerve involvement.

The irregular bone deposition was obvious clinically in a large percentage of cases as bony excrescences of varying size. They were noted near the knee joints, along the anterior border of the tibia and near the olecranon. The skeletal changes resulted in limitation of movement, particularly of the cervical and lumbo-dorsal spine and the joints of the lower extremities. The crippling deformities were due partly to muscular dysfunction and partly to immobilization necessitated by pain.

**Radiological Changes**

The most pronounced radiological changes were seen in the vertebral column, particularly in the cervical region (Fig. 3). Osteosclerosis and irregular osteophyte formation were noted in the vertebral body, the transverse and spinous processes and in the pedicles and laminae. Beak-like lipping and a chalky white ground-glass appearance of the entire vertebral column were the characteristic radiological features, along with calcifications of the intervertebral ligaments (Fig. 4). As a result of the irregular exostoses, there was encroachment on the intervertebral foramina and the spinal canal. Next to the spine, osteosclerosis was most evident in the pelvis, along with calcification of sacro-tubercous and sacro-spinous ligaments.

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Irregular periosteal bone formation was observed along the tendons and the fascial and muscular attachments, including the interosseous membranes of forearms and legs (Fig. 5), lines aspera, the deltoid tuberosity, the lower margins of the ribs, the attachment of the Achilles tendon, the tibial tubercles and the greater trochanter. Chest X-rays revealed a peculiar contrast of the marble white, bony cage with the radiolucent lungs. The changes in the skull were not striking, although there was thickening of the vault with sclerosis near the suture lines. The sella turcica and the nasal sinuses were normal and there was no significant narrowing of the basal foramina.

**Histopathology**

Bone biopsy was obtained from the tibia or iliac crest in 21 cases and in one autopsy. In general, the compact bone showed disordered lamellar orientation and an enlarged, poorly formed Haversian system resembling the changes described in experimental animals. In the spongy bone, areas of osteoid tissue were found among well formed trabeculae. Some of the irregular deposits of osteoid tissue extended into the attached muscles. The bone trabeculae were very dense in places and contained a considerable amount of calcium. The areas around the vascular spaces stained deeply with eosin. In two additional cases tissue procured at biopsy consisted of calcified muscular attachment. It showed skeletal muscle infiltrated with areas of irregular calcification. Several trabeculae of osteoid tissue and occasional bony trabeculae were also seen.
Chemical Composition

In 20 patients fluoride content of the bone tissue ranged from 700 to 7000 ppm dry weight compared with a “normal” of 1100 ± 200 ppm in a person from a non-fluorotic area.

Deformities and Crippling Fluorosis

In addition to high fluoride water, other sources of F ingestion in the area surveyed by us were vegetables grown in the fluorotic soil and food processed in water contaminated with F. Therefore, it was not surprising that we encountered 142 cases of crippling fluorosis.

Crippling is due partly to mechanical factors and partly to immobilization necessitated by pain and paraplegia. The most common deformities are kyphosis, flexion deformity of hips, flexion deformity of the knee and fixation of chest in position of inspiration due to calcification of cartilages. The picture of advanced crippling fluorosis was strikingly uniform (Fig. 6 and 7). The quadriplegic patient provided a grim picture of the ravages of the disease bent with kyphosis, with markedly restricted movements of his spine, contractures and flexion deformity of hips and knees. The chest was usually fixed, with minimal expansion. Due to the extreme fixation of the spine the body moved as a single unit when an attempt was made to straighten any portion of it.
JOLLY

In ten villages with varying fluoride concentration the incidence of skeletal fluorosis was correlated with the water’s F concentration (Table 4).

TABLE 4

Incidence of Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Name of Village</th>
<th>Concentration of Fluoride in Water (ppm)</th>
<th>Incidence of Skeletal Fluorosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gharachon</td>
<td>1.4 (0.9-2.5)</td>
<td>2.4 (82)*</td>
</tr>
<tr>
<td>Laluwala</td>
<td>2.4 (1.0-5.5)</td>
<td>23.0 (74)</td>
</tr>
<tr>
<td>Dhupai</td>
<td>3.0 (1.5-5.2)</td>
<td>19.6 (107)</td>
</tr>
<tr>
<td>Bhodipura</td>
<td>3.0 (1.0-5.5)</td>
<td>42.2 (64)</td>
</tr>
<tr>
<td>Rajthali</td>
<td>3.3 (0.5-6.5)</td>
<td>10.0 (160)</td>
</tr>
<tr>
<td>Bhikhi</td>
<td>3.3 (1.0-5.9)</td>
<td>45.6 (160)</td>
</tr>
<tr>
<td>Sanghera</td>
<td>3.6 (1.1-5.8)</td>
<td>33.1 (154)</td>
</tr>
<tr>
<td>Ramuana</td>
<td>5.0 (1.5-11.5)</td>
<td>60.0 (90)</td>
</tr>
<tr>
<td>Ganjigulab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh</td>
<td>8.5 (3.7-14.0)</td>
<td>58.9 (56)</td>
</tr>
<tr>
<td>Khara</td>
<td>9.7 (6.0-16.2)</td>
<td>70.7 (232)</td>
</tr>
</tbody>
</table>

*Figures in brackets denote the total number examined.

At a mean concentration of 1.4 ppm F, the incidence is practically nil. It rises with increasing F concentration in water. However, like in dental fluorosis, the concentration of F is not solely responsible for the incidence of skeletal fluorosis.

Table 4 illustrates two interesting observations. Cases of crippling fluorosis do occur in endemic proportion where the mean fluoride content of water is as low as 3 ppm.

Whereas we encountered crippling fluorosis in some villages with a mean F concentration of 3 ppm, the same concentration did not cause crippling in two others. Therefore, factors other than fluoride must have a modifying role upon the disease.

Neurological Complications of Fluorosis

According to our earlier studies some cases of skeletal fluorosis exhibit neurological complications of radiculomyelopathy due to compression of the spinal cord and roots because of irregular bone deposits in and around the spinal canal. This was convincingly demonstrated by us in a macerated skeleton (4). So far we have studied in detail 62 proven cases of skeletal fluorosis with neurological manifestations, the largest series in the world. The details
FLUOROSIS PUNJAB

of neurological manifestations are to be presented elsewhere. A summary is shown in Table 5.

**TABLE 5**

**Neurological Manifestations in 57 Cases**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Males/females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical radiculomyelopathy</td>
<td>31 -</td>
</tr>
<tr>
<td>Cervical radiculomyelopathy with deafness</td>
<td>1 -</td>
</tr>
<tr>
<td>Cervical radiculomyelopathy with cerebellar involvement</td>
<td>1 -</td>
</tr>
<tr>
<td>Cervical myelopathy (uncomplicated)</td>
<td>4 -</td>
</tr>
<tr>
<td>Cervicodorsal myelopathy</td>
<td>2 -</td>
</tr>
<tr>
<td>Dorsal myelopathy</td>
<td>12 -</td>
</tr>
<tr>
<td>Cervical radiculopathy</td>
<td>1 -</td>
</tr>
<tr>
<td>Peripheral neuritic type</td>
<td>3 -</td>
</tr>
<tr>
<td>Fluorosis associated with cerebrovascular accidents</td>
<td>2 -</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57 - 5</strong></td>
</tr>
</tbody>
</table>

Vertebral artery is compressed as it passes through the cervical spine.

An additional 27 cases were detected at the time of surveys but have not been studied thoroughly by hospitalization. Therefore they are not included here.

**Factors Influencing Toxicity**

1. **Fluoride Content of Drinking Water:** It is universally agreed that fluoride ingestion produces toxic effects, but the concentration which may produce deleterious effects is the subject of controversy. The minimal threshold has not yet been established definitely. In some studies from India, very low F concentrations have been shown to be associated with marked fluorosis. According to our extensive survey of villages an F concentration of 0.9 ppm to 2.5 ppm is associated with an incidence of only 2.4% with a range of 1.3 to 5.2 ppm F in water. The incidence of skeletal fluorosis is not solely dependent on the F concentration of water. Upon comparing the two villages, Rajthal and Bhikhi, with practically the same mean F level of 3.3 ppm, a marked difference in the incidence of skeletal fluorosis is noted, namely 10% and 45.6% respectively. In Bhikhi, a large number of crippling fluorosis cases were observed, whereas not a single similar case was detected in Rajthal. This wide discrepancy clearly points to the existence of factors in addition to the F concentration in water.

2. **Duration of Fluoride Exposure:** The duration of F consumption influences the development of endemic fluorosis. In villages with a similar F concentration the incidence was found to increase with age. In those with a lower F concentration, skeletal fluorosis is detected in the higher age group whereas where high F water is imbibed it is encountered at a younger age.
### Table 6: Relationship of Fluoride Levels to Other Constituents of Water (ppm)

<table>
<thead>
<tr>
<th>Village</th>
<th>Fluoride (Mean)</th>
<th>Total Hardness</th>
<th>Ca Hardness</th>
<th>Mg Hardness</th>
<th>Alkalinity</th>
<th>Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.28</td>
<td>287</td>
<td>96</td>
<td>13</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td>Gharachon</td>
<td>1.4</td>
<td>235</td>
<td>71</td>
<td>191</td>
<td>588</td>
<td>129</td>
</tr>
<tr>
<td>Laluwala</td>
<td>2.4</td>
<td>116</td>
<td>48</td>
<td>708</td>
<td>798</td>
<td>143</td>
</tr>
<tr>
<td>Dhapai</td>
<td>3</td>
<td>357</td>
<td>108</td>
<td>260</td>
<td>755</td>
<td>265</td>
</tr>
<tr>
<td>Bhodipura</td>
<td>3</td>
<td>287</td>
<td>73</td>
<td>205</td>
<td>488</td>
<td>27</td>
</tr>
<tr>
<td>Rajthal</td>
<td>3.3</td>
<td>601</td>
<td>358</td>
<td>344</td>
<td>519</td>
<td>409</td>
</tr>
<tr>
<td>Bikhil</td>
<td>3.3</td>
<td>136</td>
<td>56</td>
<td>80</td>
<td>300</td>
<td>87</td>
</tr>
<tr>
<td>Sangher</td>
<td>3.6</td>
<td>237</td>
<td>81</td>
<td>185</td>
<td>460</td>
<td>107</td>
</tr>
<tr>
<td>Ramuwal</td>
<td>5.0</td>
<td>101</td>
<td>27</td>
<td>62</td>
<td>869</td>
<td>54</td>
</tr>
<tr>
<td>Genjigulab/</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singh</td>
<td>8.5</td>
<td>30</td>
<td>14</td>
<td>17</td>
<td>851</td>
<td>53</td>
</tr>
<tr>
<td>Khara</td>
<td>8.5</td>
<td>30</td>
<td>14</td>
<td>17</td>
<td>851</td>
<td>53</td>
</tr>
</tbody>
</table>

3. **Sex and Occupation:** These factors also influence the development of endemic fluorosis, particularly in relationship to severe complications of neurological and crippling fluorosis. There were only 5 females compared to 57 males with neurological fluorosis in the hospitalized cases. The disease is far more common in laborers and farmers who have to do hard manual work and carry heavy loads on the head. This factor may account for the higher incidence of neurological (Table 5) and crippling fluorosis in men than in women.

Another contributory factor could be the fact that women migrate to another village after their marriage where the F content of the water supply is different.

4. **Chemical Composition of the Water:** Besides F in water a number of other constituents are also important especially calcium and magnesium hardness and alkalinity. We showed that F concentration bears an inverse relationship to total hardness and calcium hardness (8). In areas with little F in water, we found high hardness values. That the incidence of endemic fluorosis is dependent to a great extent upon the hardness of water is illustrated by comparing the analyses of water constituents from the village of Bikhil and Rajthal (Table 6).

These two villages with the same mean F content show a wide variation in incidence of endemic fluorosis. Other variants such as the nutritional status, climate, duration of fluoride exposure, sex, profession etc. were identical in the two villages. Hardness of water was the only difference. In the U.S.A. most water containing fluoride is hard water and the fluoride/hardness ratio is greater than 1 in 500. In our study the fluoride/hardness ratio was much less as shown in Table 7.
FLUOROSIS PUNJAB

TABLE 7

Relation Between Fluoride and Other Constituents of Water

<table>
<thead>
<tr>
<th>Name of Localities</th>
<th>F: Total Hardness</th>
<th>F: Ca Hardness</th>
<th>F: Alkalinity</th>
<th>Ca: Alkalinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1:125</td>
<td>1:340</td>
<td>1:97</td>
<td>1:2.8</td>
</tr>
<tr>
<td>Gharachaon</td>
<td>1:167.8</td>
<td>1:51</td>
<td>1:420</td>
<td>1:8.2</td>
</tr>
<tr>
<td>Laluwal</td>
<td>1:48</td>
<td>1:20</td>
<td>1:332</td>
<td>1:16.6</td>
</tr>
<tr>
<td>Dhampai</td>
<td>1:125</td>
<td>1:36</td>
<td>1:251</td>
<td>1:6.9</td>
</tr>
<tr>
<td>Bhodipura</td>
<td>1:96</td>
<td>1:24</td>
<td>1:162</td>
<td>1:6.6</td>
</tr>
<tr>
<td>Reithal</td>
<td>1:182</td>
<td>1:108</td>
<td>1:159</td>
<td>1:1.4</td>
</tr>
<tr>
<td>Bhikki</td>
<td>1:41</td>
<td>1:17</td>
<td>1:91</td>
<td>1:6.4</td>
</tr>
<tr>
<td>Sanghera</td>
<td>1:66</td>
<td>1:22</td>
<td>1:128</td>
<td>1:5.6</td>
</tr>
<tr>
<td>Ranauana</td>
<td>1:20</td>
<td>1:5</td>
<td>1:194</td>
<td>1:32.1</td>
</tr>
<tr>
<td>Gangigulab/Singh</td>
<td>1:4</td>
<td>1:2</td>
<td>1:101</td>
<td>1:60.7</td>
</tr>
<tr>
<td>Khara</td>
<td>1:10</td>
<td>1:3</td>
<td>1:40</td>
<td>1:11.5</td>
</tr>
</tbody>
</table>

Both Calcium and magnesium content of water have a protective influence regarding the absorption of F and its subsequent deposition in the skeleton (9). In India, lower toxic levels of F may therefore be related to lesser hardness of water as shown in the analysis of water constituents in some of the endemic areas.

5. Nutritional Factors: Some believe that the high incidence of endemic fluorosis in India is partly related to malnutrition. Our studies in Punjab did not bear out this theory. Punjab is one of the best nourished states in India and yet this very state shows the highest incidence of fluorosis. It has recently been shown by calcium balance studies (10) that the cases of fluorosis retain greater amounts of calcium and that increased retention is due to lower excretion in urine and faeces.

6. Climatic and Geographical Factors: Endemic fluorosis has been observed only in those areas where the soil is sandy and the climate is hot and dry. The average temperature during the summer is above 100°F. Rainfall is rather scanty. Moreover fluorosis occurred only in villages with superficial subsoil water. The deep wells showed less F in water. This observation has been utilized in the prevention of the disease.

7. Fluoride from Food and Beverages: Besides F imbibed in drinking water considerable quantities of F may be ingested with food grown in F rich soil and with tea and wines (11). Recently high levels of fluoride have been shown to be present in the Punjab cooking salt and in turmeric which is used as an adjuvant in cooking throughout India. We have not as yet precisely evaluated these factors in our endemic area. They may be significant since the Punjab villager consumes much tea and alcoholic drinks.
JOLLY

Bibliography

SKELETAL FLUOROSIS IN NALGONDA DISTRICT, A.P., INDIA

by

A. H. Siddiqui
Hyderabad, India

Endemic fluorosis occurs with varying intensity in Andhra Pradesh, Madras, Mysore, Punjab and Kerala (1-10). The pioneer work on fluorosis was done by Shortt and his collaborators in 1937 (7,8).

Extensive surveys carried out in India covered endemic areas in Andhra Pradesh, Madras and Punjab. Singh et al. (11) calculated that at least one quarter of the Punjab contains a belt in which the F content of drinking water is unusually high. According to this estimate roughly five million people are liable to experience the toxic effects of this ion. An even larger population is exposed to the risk of fluorine intoxication in Andhra Pradesh and Madras. According to Singh et al. (11) drinking water in the Punjab contains 16.2 ppm F, the highest figure reported from India.

This paper deals mainly with endemic fluorosis in Nalgonda District of Andhra Pradesh, a small backward area. The climate of this region is hot. In summer, the temperature touches 115° F (46.1°C) in the shade. The average annual rainfall is 25 inches (63.5 cm). The soil is sandy. It consists of granite containing fluoride. Work on tobacco plantations is the main occupation of the people.

The population of the endemic area under review is 4,000. Drinking water which is obtained from wells varies in fluorine concentration from 2.5 to 11.8 ppm. The concentration of fluorine in the mud samples obtained from the wells is shown in Table 1. The general standard of living is low, the hygienic conditions and nutritional status of the people is poor, the diet is deficient in animal proteins, fats, calcium and vitamins A and C, as seen from average figures in Table 2.

TABLE 1

<table>
<thead>
<tr>
<th>Place of Sampling</th>
<th>Fluorine Content of Mud Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamaguda</td>
<td>0.15%</td>
</tr>
<tr>
<td>Yedewelli</td>
<td>0.11%</td>
</tr>
<tr>
<td>Yellareddyguda</td>
<td>0.09%</td>
</tr>
</tbody>
</table>

From the Osmania General Hospital, Hyderabad, India.

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TABLE 2

Composition of Daily Diet Consumed in Villages

<table>
<thead>
<tr>
<th>Protein (g)</th>
<th>Calcium (g)</th>
<th>Carotene (i.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td>5.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Vegetable</td>
<td>73.1</td>
<td>1048</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fats (g)</th>
<th>Iron (mg)</th>
<th>Vitamin A (i.u.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal</td>
<td>8.9</td>
<td>176</td>
</tr>
<tr>
<td>Vegetable</td>
<td>19.9</td>
<td>2</td>
</tr>
</tbody>
</table>

Vitamins

<table>
<thead>
<tr>
<th>Vitamin B₁ (mg)</th>
<th>Vitamin C (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>23</td>
</tr>
</tbody>
</table>

Carbohydrates (g) 494.9
Total Cals. 2618

Clinical Data

Children - Apart from dental changes, children do not appear to suffer from other ill-effects of F in drinking water. Probably the growing tissues are somehow able to cope with the ingestion of F.

Adults - Prolonged intake of water with high F content causes skeletal fluorosis in adults. There is an extraordinary uniformity of symptoms and signs of intoxication. In the cases under review the initial symptom was paresthesia in the limbs or all over the body followed by pain and stiffness in the spine, especially in the lumbar region. Extension was more painful than flexion. Later, stiffness of the various joints due to the calcification of periosteal tissues, tendonous insertions of muscles and interosseous fasciae occurred causing difficulty in getting up from a squatting position. Diminished expansion of the chest and dyspnea on exertion due to calcification of costo-verte-
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bony ligaments and a "polker-back" appearance were seen in the later stages. Bony exostoses were either seen or felt in advanced cases (Fig. 1 and 2). Full-fledged skeletal fluorosis was seen in individuals between the ages of 30 and 40 years.

The patients exhibited cachexia, loss of appetite and signs of spinal root and cord compression with loss of sphincter control. They were finally bed-ridden. Their mental faculties remained unimpaired.

Involvement of the nervous system in skeletal fluorosis has been reported mainly from India. In the series reported here 53 advanced cases of the disease with neurological manifestations were investigated. Patchy type of anaesthesia, muscular wasting, spastic paraplegia, absence of vibration sense and loss of sphincter control were the usual manifestations. The neurological signs were due to pressure on the spinal roots and the cord by bony growths into the spinal canal which in the cervical region resembled the clinical picture of cervical spondylosis. The pathogenic mechanism of root and cord compression is similar. However, the manifestations of cord compression are a more integral part of fluorosis whereas root compression is much more common in cervical spondylosis.

Fig. 3 is a preoperative myelogram of a case of skeletal fluorosis with signs of cord compression in the cervical region. Decompression relieved the patient of his symptoms and signs.

An interesting case of syringomyelia with neuropathic joints (Charcot's Joints) complicating fluorosis was seen (Fig. 4).

Rao and Siddiqui (12) noted that cases exhibiting radiological changes in the skull suffered from perceptive type of deafness. Hearing loss commenced at 3000 c.p.s. and was marked (up to 60 db) at 8000 c.p.s. Bone conduction seemed to be affected more than air conduction. Hearing loss which affected

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the higher frequencies (Fig. 5), was probably the result of pressure on the eighth nerve during its passage through the narrowed and sclerosed internal auditory meatus.

**Radiological findings** - Sclerosis of bones was observed throughout the skeleton, similar to that described by Roholm (13) and Shortt et al. (7). Reference will be made in this paper only to the findings which were not described by previous workers. Lipping of the bodies of the vertebrae, especially in the lumbar region, was common. The beaking exostoses were mostly from the lower margins (Fig. 6). Sclerosis around the suture lines was often observed in the vault of the skull. In advanced cases marked thickening was noted in the vault and the base. The air cells were narrowed in four cases. The clival processes were thick and dense in another four cases.

The degree of osteosclerosis was found to be related to the duration of intoxication and the concentration of F in water. Physical strain was also found responsible; the greater the strain, the more pronounced were the changes. The skull and the cervical spine were frequently affected contrary to observations by Roholm and others. These changes could likewise be ascribed to the phenomenon of strain. All patients investigated were manual laborers who carried heavy loads on their heads. This is not a common practice in countries where previous observations on fluorosis have been made.

**Laboratory findings** - Besides routine blood counts, urine and stool examinations and the blood Wassermann reaction, the following investigations were made in each case: serum calcium, serum inorganic phosphorus, serum alkaline phosphatase, blood urea, glucose tolerance test, fluorine estimation of blood and of urine, fractional test meal, cerebro-spinal fluid routine, including the Wassermann reaction and the colloidal gold curve. Only the abnormal findings need be mentioned.
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The concentration of serum calcium and inorganic phosphorus were within normal limits (vide infra). Serum alkaline phosphatase values were above normal in all cases. The average was 29 K.A. units.

Fasting test meals were done in every case, since in many patients an extensor plantar response was elicited with absent or impaired vibration sense. These findings suggested the possibility of subacute combined degeneration of the cord. In no instance was achlorhydria encountered.

With the use of the thorium nitrate titration method the mean values for blood and urinary F were 0.32 and 5.2 ppm respectively. Excretion of previously stored F in urine was seen in case No. 29 who resided in the endemic area until age 30 and then migrated to the city of Hyderabad, where the water is practically fluoride free. The urinary F content was 3.4 ppm 10 years after he had left the endemic area.

F assays of stools were carried out in 3 cases with negative results. Estimation of F loss in the sweat, which is considerable, could not be made.

Calcium balance in skeletal fluorosis - Thirty-one male adults between the ages of 18 and 40 years with various degrees of skeletal fluorosis formed the subjects of this study. The water from four wells which they consumed contained between 6.8 and 8.2 ppm of F.

All subjects were hospitalized and 24 hour collection of urine was made on three consecutive days for the determination of Ca and F. Samples of blood under fasting conditions were drawn for the determination of calcium, inorganic phosphorus, alkaline phosphatase and fluoride. Urine was preserved at -40°C in polyethylene containers, with 0.5 ml chloroform as preservative until taken for analysis.

On 6 of these subjects Ca balance studies were carried out at an intake level of 800 mg/day. After an adjustment period of 7 days, urine and faeces were collected for three consecutive days for determination of Ca. To obtain duplicate values and to establish the validity of the results of the balance study, a second collection period of three days was carried out after an interval of ten days. Samples of diets consumed were analyzed for calcium on seven occasions during the balance period.

On 10 apparently normal subjects, all biochemical studies were made as a control. Calcium balance studies were done on 4 subjects on diets identical with those of the fluorosis patients.

Concentrations of serum Ca and inorganic P were within normal limits. Alkaline phosphatase activity, however, was elevated with a mean of 16.86 ± 2.724 Bodansky units/100 ml as compared with 3.95 ± 0.318 units/100 ml in the controls (Table 3).
TABLE 3

Serum Biochemistry in Subjects with Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Serum Calcium (mg/100 ml)</th>
<th>Serum Inorganic Phosphorus (mg/100 ml)</th>
<th>Serum Alkaline Phosphatase Activity (Bodansky units/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals (10)</td>
<td>9.90 ± 0.251</td>
<td>3.77 ± 0.242</td>
<td>3.95 ± 0.318</td>
</tr>
<tr>
<td>Fluorosis (31)</td>
<td>10.05 ± 0.164</td>
<td>3.57 ± 0.247</td>
<td>16.86*</td>
</tr>
</tbody>
</table>

All values are means with Standard Error.

*Significant difference, P < 0.02.

TABLE 4

Urinary Calcium in Subjects with Skeletal Fluorosis

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Calcium (mg/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normals (10)</td>
<td>117.72 ± 13.161</td>
</tr>
<tr>
<td>Fluorosis (31)</td>
<td>69.32* ± 10.964</td>
</tr>
</tbody>
</table>

All values are means with Standard Error. *Differences between controls and fluorosis cases are significant, P < 0.001.

The mean values for the urinary calcium were 69.32 ± 10.964 mg/24 hr in fluorosis subjects and 117.72 ± 13.161 mg/24 hr in the controls. The difference is significant (Table 4 and Fig. 7). Fourteen of the 31 subjects with fluorosis excreted less than 50 mg/day and 23 less than 100 mg/day. In contrast, only two of ten normals excreted between 75 and 100 mg/day and the rest above 100 mg/day.
FLUOROSIS NALGONDA

The mean retention of calcium in 6 fluorosis subjects on balance was 405 mg/day (range 278 to 512) as against only 139 mg in 4 normal ones (range 39 to 203). Both urinary and faecal calcium were lower in the fluorosis subjects than in the normal ones (Table 5) (18). Further studies obviously are needed to elucidate the mechanism by which fluorides influence calcium absorption.

TABLE 5

Calcium Balance in Six Subjects with Skeletal Fluorosis on an Intake of 800 mg Daily

<table>
<thead>
<tr>
<th>Subject</th>
<th>Period</th>
<th>Urine Calcium (mg/day)</th>
<th>Faecal Calcium (mg/day)</th>
<th>Total Excretion (mg/day)</th>
<th>Retention (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.H.R.</td>
<td>1</td>
<td>42</td>
<td>480</td>
<td>522</td>
<td>278</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>59</td>
<td>329</td>
<td>388</td>
<td>412</td>
</tr>
<tr>
<td>V.R.</td>
<td>1</td>
<td>60</td>
<td>270</td>
<td>330</td>
<td>470</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>54</td>
<td>390</td>
<td>444</td>
<td>356</td>
</tr>
<tr>
<td>C.H.L.</td>
<td>1</td>
<td>185</td>
<td>248</td>
<td>433</td>
<td>367</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>189</td>
<td>250</td>
<td>439</td>
<td>361</td>
</tr>
<tr>
<td>C.H.N.</td>
<td>1</td>
<td>61</td>
<td>378</td>
<td>439</td>
<td>361</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>81</td>
<td>418</td>
<td>499</td>
<td>301</td>
</tr>
<tr>
<td>C.H.M.</td>
<td>1</td>
<td>108</td>
<td>184</td>
<td>292</td>
<td>508</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>107</td>
<td>181</td>
<td>288</td>
<td>512</td>
</tr>
<tr>
<td>K.L.</td>
<td>1</td>
<td>19</td>
<td>298</td>
<td>317</td>
<td>483</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>25</td>
<td>324</td>
<td>349</td>
<td>451</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>83</td>
<td>312</td>
<td>395</td>
<td>405</td>
</tr>
<tr>
<td>Mean of four normal subjects</td>
<td>130</td>
<td>531</td>
<td>661</td>
<td>139</td>
<td></td>
</tr>
</tbody>
</table>

To assess more precisely the significance of the increased retention of calcium, the kinetics of bone formation was studied in 3 adult male subjects with skeletal fluorosis by the use of radioactive Ca. The radioactivity was measured in blood, urine and stools for a period of ten days.

The cumulative excretion of radioactivity in urine and stools over a period of ten days when expressed as percentage of the injected dose was quite small when compared to the response of normal subjects. This observation confirms the results of chemical balance studies.
SIDDQUI

An analysis of the specific radioactivity curve of the serum indicates that the exchangeable calcium in all fluorosis subjects was much higher than in normal subjects. However, the fractional turnover rate appeared to be different.

Earlier studies of Ranganathan (14) have indicated that supplement of dietary calcium can prolong the survival period of rats exposed to F. Since most clinical manifestations of fluorosis are secondary to excessive bone formation, calcium supplementation over long periods may be undesirable.

Factors Influencing the Severity of Fluorosis - The severity of the disease is definitely related to the F concentration in water, to the length of time of ingestion, to meteorological factors (for example temperature), to the economic and nutritional status of the population and to the physical strain to which they are exposed.

In the series under review the degree of disability and the time of onset of the symptoms of the disease were related to the F concentration in water and to the duration of its ingestion. In Kamaguda village (one of the three villages reported here) the F concentration in water was 11.8 ppm. Symptoms of intoxication appeared in immigrants into this area within one to four years after their arrival. At the time of the present investigation the new arrivals in the endemic area were free from symptoms of intoxication. whereas those who had migrated one to four years earlier showed marked skeletal symptoms. This observation is at variance with that of Shortt et al. (7) who concluded that a 30 to 40 year residence in an endemic area was required for skeletal fluorosis to develop. An exceptionally high F content of water, excessive heat and a poor state of nutrition are probably factors responsible for the early development of skeletal fluorosis in Kamaguda village. The presence of signs of fluorosis in poultry, which is very resistant to fluorine also points to the intensity of intoxication. In the other two villages, where the fluorine content of water is relatively low, a much longer period, similar to that described by Shortt et al. (7) was necessary before signs of intoxication appeared. The poultry was unaffected in these villages.

The severity of disease has a definite relation to meteorological factors and to the economic and nutritional status of the people. Hot weather not only increases the water intake but also increases the concentration of fluorine (Table 6) and ingestion of an abnormal amount of sediment. The protective action of calcium and vitamin C has been noted in experimental animals. The state of nutrition in the villages under review was poor. The diet was deficient in calcium and vitamin C. These factors might have been responsible to a certain extent for the severity of bony changes in these cases.

The degree of disability was also related to the physical strain. Disability was most prominent in manual laborers. Subjects pursuing sedentary occupations, such as the local village administration officials and school teachers, had less severe symptoms although they were utilizing the same sources of water supply. Pain and stiffness were more severe in joints most frequently used by the individual as for example, the wrists and shoulders in the females, who were mainly engaged in household work, the lumbar spine and joints of the
FLUOROSIS NALGONDA

TABLE 6

<table>
<thead>
<tr>
<th>Place of Sampling</th>
<th>Temperature at Time of Sampling</th>
<th>Fluorine Content of Water (ppm)*</th>
<th>Well No. 1**</th>
<th>Well No. 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamaguda</td>
<td>90° F (32.2° C)</td>
<td>9.2</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115° F (46.1° C)</td>
<td>9.6</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Yedvilli</td>
<td>108° F (42.2° C)</td>
<td>5.5</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>115° F (46.1° C)</td>
<td>5.8</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Yellareddyguda</td>
<td>115° F (46.1° C)</td>
<td>5.2</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated by thorium nitrate titration method.
**Well Nos. 1 and 2 are situated hardly 100 yards apart.

Lower limbs in males working in the fields. Most of the cases reported in this series were manual laborers who were accustomed to carrying heavy loads on their heads. This is not a common practice in Europe and in the United States.

Summary

Details of investigation of 53 adults with neurological manifestations of skeletal fluorosis are described. In addition to the radiological features described by others we noted serum alkaline phosphatase was consistently high. Serum calcium and phosphorus levels were within normal limits. The mean urinary fluoride was 5.2 ppm. In one of the patients excretion of previously stored fluoride continued in the urine at a high level 10 years after the subject had left the endemic area.

Balance studies showed a significant increase in calcium retention in cases of skeletal fluorosis. The limitations of short-term balance studies are emphasized.

Factors responsible for early skeletal changes in one of the villages are discussed.

Bibliography

ENDEMIC FLUOROSIS IN THE SAHARA

by

A. Pinet and F. Pinet
Lyon, France

In the Sahara, fluorosis is different from that encountered in other parts of North Africa, where it has been associated with natural phosphate deposits. In the Sahara where there are no phosphate deposits, fluoric intoxication is specifically attributable to drinking-water containing up to 4 mg F per liter. This level may not seem especially high in relation to concentrations reported from other countries. However, in desert regions high water intake suffices to induce widespread lesions among the inhabitants.

Water-borne F in the Sahara originates from soil composed of ancient volcanic deposits. This is probably an "in depth" phenomenon, because vegetables grown in regions of endemic fluorosis contain only a minimal amount of F, i.e., 0.1 ppm. We are thus dealing with intoxication induced almost exclusively by F in solution.

In terms of geography, the endemic area is situated in the eastern region of the Sahara. To localize it, we have obtained complete chemical analyses of the waters of the different regions including their F content. The F content increases in a South-to-North and West-to-East trend, corresponding to the existence of an extensive subterranean water reservoir which broadens in the lower Sahara "Chott" region of the North-East.

By means of systematic inquiries in regions with diverse F concentrations in drinking-water, we have attempted to correlate F distribution with the health of the population.

Dental Effects

The most striking observation is the incidence of dental abnormalities. To establish the extent of the dental lesions as a function of F in drinking-water, 3,000 children between the ages of 6 and 14 were examined. We have noticed that:

(a) Where the drinking-water contained 0.5 ppm F, 25% of the children had dental lesions.

(b) Where the fluoride content of the children's drinking water was 1.0 ppm, 100% had dental lesions.

(c) The severity of the dental lesions was indisputably related to F levels of the drinking water. "Brown stain" mottling is frequently seen when the water attains a concentration of 1.0 ppm F. Gingivitis is rarely observed below the level of 2.5 ppm.

From the Hôpital de l'Antiguel, Lyon, France
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(d) Without exception, the deciduous teeth were not affected.

(e) The lesions predominate in the upper teeth.

Analysis of teeth in 29 cases for fluoride content was performed by Prof. Truhaut, Paris. It revealed the following:

(i) The F content of deciduous teeth increases progressively, despite the apparent normal appearance.

(ii) The F content of permanent teeth increases gradually with the age of the individual, and with the fluoride content of the drinking water.

Skeletal Effects

The second phase of our studies was concerned with the distribution of waterborne F in relation to the skeletal system. X-ray examination provided a ready means to assess bone alterations. A total of 148 patients with osteosclerosis were X-rayed.

In summary:

(a) There were no detectable bone changes where the water content was less than 1.5 ppm F.

(b) The skeletal changes were most frequent and severe in the El Oued region, where the water contains up to 4.0 ppm F.

The pelvic bone was most frequently affected. The most common pattern was osteosclerosis with calcification of ligaments. The foramen obturatum showed ragged excrescences. Periosteal deposits were noted on the iliac and ischium bones (Fig. 1). These changes occur even in youthful subjects.

In 30% of our cases, we noted a generalized increased radio-density of the skeleton in which two features appear to be unique:

(1) Increased density in the sacrum, a feature present in all cases.

(2) Calcification of the articular capsule of the hip joint, a fairly specific sign of fluorosis, especially in the young adult.

In the spinal column, we noted a fairly advanced form of osteophytosis, an increased radio-opacity of the vertebrae without structural alteration and a peculiar form of lesion in which increased skeletal density is associated with a decreased height of the vertebrae (Fig. 2).

The spinal and cervical columns, ribs and shoulder bones are affected much later than the pelvis. Noteworthy is the fact that the cranium is rarely affected. Only two of our 148 cases showed signs of discrete cranial density.
(A) Trabeculated vertebrae due to heterogenous Ca deposition. (B) "Ivory" vertebra; uniform Ca deposition. (C) Osteomalacia of sclerotic vertebrae. (D) Sclerosis with osteophyte formation. (E) Sclerosis with marginal syndesmosis.
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Fig. 3
M. 66, Kouinine (3 ppm F). Osteoporosis of pelvis; calcifications of ligaments; ragged outline of foramen obturatum; calcified capsule of hip joint.

Fig. 4

Fig. 5

Fig. 6
M. 65, Telga (2.5 ppm F). Diffuse osteopetrosis of pelvis and spine.

F. 18, from Touggourt (3 ppm F). Calcification of capsule of hip joint.
FLUOROSIS IN SAHARA

**Fig. 7**

Tomographic aspect of sclerotic vertebrae. Sclerosis originates at the vertebral plates.

**Fig. 8**

F. 44, Tiksept (3 ppm F) Osteoporosis of spine (iliac crest biopsy 6280 ppm ashed).

**Fig. 9**

M. 65, Togla (2.5 ppm F). Periostosis of radius and complete calcification of interosseous membrane.

Generally, we do not observe osteosclerosis in the upper arm. In advanced cases, there can be slightly increased radio-density in the proximal region of the humerus. Periostitis at the humeral site of the shoulder-muscle attachment is not uncommon.
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An important observation in the forearm is periostitis of the radius, which can proliferate in advanced cases with calcification of the intra-osseous membrane. In the early stages it can be localized as a small lump. This consistent feature, which appears early, is of great value in the diagnosis of fluorosis, especially when the skeletal density is not pronounced. Involvement of the cubital area is much rarer. The lesions are of the same type in the leg regions. Only one case of paraplegia was associated with osteosclerosis in a 79-year-old man.

There was no evidence that livestock exposed to the highest levels of waterborne fluoride showed any sign of skeletal fluorosis. X-ray examinations revealed no changes in the skeletons of 2-year-old sheep.

**Laboratory Data**

Despite the definite diagnosis of osteosclerosis and narrowing of the marrow spaces of long bones, blood composition was not significantly affected. Twelve patients with increased skeletal radio-density had normal blood counts and leucocyte concentrations. No cellular abnormalities were observed in the cerebro-spinal fluid of 2 patients.

Six examinations of splenic biopsy material failed to reveal any disturbance related to hematoctisis. The same was true of three liver biopsies.

In all cases, analysis of transaminase activity gave essentially normal values. In one patient a level of 58 units was found. However, it did not seem to have pathological significance.

Serum calcium in 15 cases ranged between 9.1 and 11.3 mg%. In 4 of these cases, the blood calcium was below 10 mg%, in 7 cases above 10.5 mg%.

Serum phosphorus was consistently elevated, ranging between 3.8 and 8.0 mg%. In 6 cases, it was below 5.0 mg%, whereas in 9 patients the concentrations were above this level.

Alkaline phosphatase in 14 subjects varied between 2.7 and 9.2 units. However, 11 of these values were below 5 units. It was therefore impossible to claim a significant increase in the alkaline phosphatase level.

**Fluoride Assays**

The F concentration in blood and urine was surveyed in 139 patients namely:

- Blood and urine analyses: 94 patients
- Blood analysis only: 45
- Urine analysis only: 6

Evaluation of the data led to the following conclusions concerning urinary F excretion in fluorosis:
FLUOROSIS IN SAHARA

(a) There is a great variation among individuals. Urinary F concentrations varied between 0.5 to 12 ppm with an average of 3 ppm.

(b) There is no correlation between urinary F elimination and F content of drinking water, at least not when the water contained up to 1.0 ppm F.

(c) Urinary F elimination does not correlate significantly with the age of the patient. F essays in children and adolescents revealed essentially the same concentrations and the same variability as in adults and in the elderly.

(d) The irregularities persist whether we use 24-hour urine collections or individual samples of urine from each patient.

Serum F analyses gave values between 0.1 and 2.0 ppm with an average of 0.9 ppm. Only two cases showed higher values, namely 3.5 and 4.0 ppm. There was no consistent parallelism between F levels in blood and in the urine.

Appropriate therapy can markedly influence the F concentration in both blood and urine. Two of our patients were treated with an EDTA chelating agent (one 50,000 unit ampule per day). On the second day of this treatment, we observed a striking increase in the F concentration of both blood and urine. However, no detectable radiological improvement could be seen in these patients.

Analysis of F concentration in bone (performed by Prof. Truhaut) was possible in 14 cases, ranging in age from 32 to 79 years, all of whom exhibited various stages of skeletal fluorosis. In 12 of the 14 individuals the iliac crest served as test material. Bone F content varied between 1800 and 6280 ppm (on a dry, fat-free basis). Contrary to expectations, there was no absolute correlation between F content of bones and the degree of bone density, as indicated by X-ray.

Histology of Bones

In 10 cases, anatomical-pathological studies were conducted by Prof. Laffargue. Thickening of the osteoid seams was the most striking and most consistent feature. Cancellous bone was mainly involved. It was rarely observed in cortical bone. Morphologically, there were indications of a very active osteogenesis, often accompanied by large osteoblasts at the periphery of the bone lamellae and of the osteoid seams. The defense mechanism of direct osteolysis seems of little importance. However, the number of resorption sites, and their irregularity, are suggestive of the "mosaic pattern" often seen in bone disease, and attest to an activity that combines osteogenesis and osteolysis. The appearance of the bone marrow was either normal or adipose, but never fibrous.

In an attempt to relate the above clinical and radiological observations to the F content of water, we noted that the F concentration was not the only factor involved in fluorosis, particularly in the manifestation of skeletal lesions.
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Water Analysis

An examination of the log-scale diagrams relating to chemical composition of the waters reveals that the regions of endemic osteosclerosis present a consistent pattern.

The waters in these districts have a high calcium content and are relatively low in magnesium, thus yielding a high Ca/Mg ratio; they are also high in sulfate and low in alkaline components. In contrast, the waters with inverse characteristics typify regions in which osteosclerosis is extremely rare.

It would therefore seem that such factors as alkalinity, sulfate, and Ca/Mg ratio are important in determining the toxicity of waterborne fluoride. In the Sahara, the high level of calcium and sulfate in the "osteosclerosis" regions strikes us as being of prime importance.

Summary

In a fluorosis belt in the Eastern region of the Sahara, where drinking water contains between 1.5 and 4.0 ppm of fluoride and constitutes the predominant source of ingested fluoride, the authors report 148 cases of skeletal fluorosis.

Unlike in India, the authors encountered only one case of paraplegia associated with osteosclerosis. Only two individuals showed signs of increased cranial density. Calcification of the interosseous membrane was an early sign of the disease. Serum Phosphates were consistently elevated. There was no correlation between bone fluoride content and radiologically detectable increases in density. No significant increase in serum alkaline phosphatase was noted. Urinary fluoride ranged from 0.5 to 12 ppm.

Clinical and radiological findings were not solely dependent on F concentration of water. Thus, the "toxic" waters had a low Mg/Ca ratio, were low in alkaline components and high in sulfate. The reverse pattern was observed in non-toxic drinking waters.

Bibliography


HYDROFLUOROSIS IN THE U.S.A.

by

G. L. Waldcott, M.D.
Detroit, Michigan

The term hydrofluorosis or chronic fluoride intoxication from drinking water was conceived by Frada (1) who reported a series of 63 cases from a volcanic area in Sicily where fluoride occurs naturally in water at concentrations of 3 to 6 ppm. In addition to the typical dental and skeletal changes he reported chronic gastroduodenitis, spastic colitis, arthritis and disturbances in kidney and liver function.

The principal areas in the U.S.A. where fluoride occurs naturally in water at concentrations above 1 ppm are located in Western Texas, Arizona, New Mexico, Colorado, the panhandle of Oklahoma and in North and South Dakota. In the U.S.A., skeletal fluorosis was first described by Linsman and McMurray (2) in a Texas soldier; dental fluorosis by McKay (3) in Colorado, by H. V. and M. C. Smith (4) in Arizona and Texas, by Churchill (5) in Bauxite, Arkansas and by Blue (6) in Oklahoma.

In 1934, Hodges et al. (7) examined X-ray films of 117 inhabitants with dental fluorosis in two Illinois cities, Kepton and Bureen, with fluoride naturally in water at 1.2 and 3 ppm respectively. They found no skeletal abnormalities. Upon reviewing X-rays on 170,000 cases at the Scott and White Clinic in Western Texas, Stevenson and Watson (8) detected 23 cases of skeletal fluorosis; the youngest was 44 years of age. Leone et al. (9) identified practically the same number, namely 21 cases, among 257 individuals in a Western Texas survey of Bartlett and Cameron. The discrepancy in the two surveys may be explained on the basis that the clinic from which Stevenson's data were procured, although located in the same endemic fluoride belt, treats patients from many areas of the world, not necessarily from Western Texas.

Four fatalities are recorded in the U.S. medical literature in which fluoride water is strongly implicated as the primary cause of death, namely two from fluoride naturally in water and two from artificially fluoridated water.

The first case was reported by Linsman and McMurray (2) in a Texas soldier, age 22, who died with advanced bone changes characteristic of fluoride poisoning, with extensive bilateral pyelonephritis and a terminal sepsisemia. For 19 years he had been drinking water which naturally contained fluoride at a concentration ranging from 1.2 to 5.7 ppm. The kidney disease to which the patient succumbed had been attributed, by some, to a minor injury to one kidney sustained at age 15. This explanation is difficult to accept because a minor injury to one kidney does not induce pathologic changes in both (Fig. 1).
The second fatality concerns a 63-year-old Texas male (10) with a kidney disease, marked skeletal fluorosis and paraplegia. His drinking water for 43 years contained fluoride at a concentration of 2.2 to 3.5 ppm. For 20 years, polydipsia caused him to consume 1 to 2½ gallons of that water daily. The patient succumbed to a terminal pneumonia. Polydipsia and polyuria are manifestations of acute and chronic fluoride poisoning and must be considered a part of the clinical picture in this case rather than a coincidence as interpreted by the author.

In both fatalities the fluoride concentration in water was only slightly higher (Table I) than the so-called safe (1 ppm) concentration. Because of the lack of knowledge among physicians regarding fluorosis and its slow, insidious onset, it is impossible to estimate how many fatal cases of chronic pyelitis and paraplegia due to fluoride in water have remained unrelated to their cause.

![Osteosclerosis of lower ribs, lumbar vertebrae and pelvis. Obliteration of trabecular pattern.](Fig. 1)

Courtesy, Dr. J. F. Linsman, Beverly Hills, California.

**TABLE I**

<table>
<thead>
<tr>
<th>Case</th>
<th>At Age</th>
<th>He Lived in</th>
<th>With PPM of F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linsman-McMurray</td>
<td>1 – 7</td>
<td>Spur, Texas</td>
<td>1.2</td>
</tr>
<tr>
<td>Texan Soldier,</td>
<td>7 – 9</td>
<td>Post, Texas</td>
<td>5.7</td>
</tr>
<tr>
<td>Age 22</td>
<td>9 – 16</td>
<td>Lubbock, Texas</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>16 – 18</td>
<td>Washington, D.C.</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>18 – 21</td>
<td>Lubbock, Texas</td>
<td>4.4</td>
</tr>
<tr>
<td>Sauerbrunn et al.</td>
<td>0 – 7</td>
<td>Calhoun, Ga.</td>
<td></td>
</tr>
<tr>
<td>Male Texan</td>
<td>8 – 50</td>
<td>Ellis and Dallas Co.</td>
<td>2.4 – 3.5</td>
</tr>
<tr>
<td>Age 65</td>
<td>50 – 64</td>
<td>Grapevine Area</td>
<td>2.2 – 2.4</td>
</tr>
</tbody>
</table>

The third fatality was from artificially fluoridated water at 1 ppm. It concerned a 43-year-old Rochester, N.Y. nurse, with an advanced kidney disease and marked osteosclerosis. The patient expired shortly after her 14th hemodialysis with fluoridated water. A vertebral bone contained 5500 ppm fluoride. In their report of this case, the authors warned physicians to refrain from using fluoridated water for hemodialysis. The account of the case appeared in one journal (11), the laboratory data in another (12).
In a fourth fatality (13), fluoridated water must be considered at least a contributing, if not the sole cause of death. A premature male infant expired 18 hours after birth with extensive calcifications of the entire aorta and arteries of the pelvis and the extremities. The cause of this unusually rare disease was not established by the authors. The parents had resided for 4 years in artificially fluoridated Ames, Iowa. Subsequent inquiry revealed
WALDBOTT

Fig. 5

(Courtesy Prof. M. Soriano, Barcelona).

the fact that neither parent had drunk an excessive amount of water or had
ate an unusual amount of food high in fluoride. Since a significant inci-
dence of arterial calcification has been well documented (1, 14, 15) as a
manifestation of fluorosis (Fig. 2-5) and in view of the absence of any other
known cause of death in this thus far insufficiently explored illness, a causal
relation of this child's illness with the mother's consumption of fluoride in
drinking water during her pregnancy must be considered. This interpretation is
supported by the unusually high fluoride content of the baby's aorta analyzed
at my request, namely 59.3 ppm (normal values in children with healthy kidneys
are near zero). *

This case illustrates another significant point, namely that fluoride
can, under certain conditions, pass the placental barrier at unpredictable
magnitudes.

In 1965, Morris (17) reported 20 cases of skeletal fluorosis from an
Indian reservation in Arizona where the water contained between 1.0 to 9.0
parts per million of fluoride. In the Papago Reservation, where 16 of the
20 cases were encountered, about 75% of the wells sampled yielded water of
less than 1.5 ppm. Morris limited his report to a description of the radio-
graphic data and to fluoride levels in bone specimens. They ranged from 1260
to 6990 ppm. He noted that "every single patient had associated infirmities"
(18), but offered no data on which he based his seemingly contradictory con-
clusion that the "skeletal fluorosis produced no physiological adversities".
In two cases in which he presented only fragmentary information, advanced
kidney disease was also present.

* Other fluoride levels in this patient's soft tissues were: Lungs, 5.85 ppm;
Thymus, 2.86; Kidney, 0.85; Heart, 0.81; Liver, 0.

FLUORIDE
HYDROFLUOROSIS U.S.A.

The case of a 73 year old S. Dakota farmer was reported by Gilbaugh and Thompson (16) with typical skeletal fluorosis, chronic osteoarthritis and urinary incontinence. It had presented a "diagnostic riddle" because it simulated carcinoma of the prostate with bony metastases. It was eventually attributed to the "high" fluoride content of the patient's drinking water.

In contrast to reports based on the conspicuous dental and skeletal changes, I have described soft tissue effects of the kind reported by Freda due to fluoridated water in a detailed case report in 1955 (19). Subsequently I observed more than 100 cases. At least 20 of them had extensive tests and consultations with other specialists (20, 21). The patients sought medical care in physicians' offices for what, at first glance, appeared to be vague symptoms. Some had been hospitalized repeatedly for diagnostic studies. Their physicians, unaware of ill-effect from fluoridated water, failed to identify the ailment with any known disease. In several instances the patients were suspected of being neurotic. Psychiatric consultation did not bear out this view. Medication was without benefit. Usually the patients themselves recognized water as the source of their ailment because, upon visiting a non-fluoridated city, their condition improved. They had not been aware at the time that their municipal water supply was fluoridated nor of the fact that water in the city they visited contained little or no fluoride.

Case 1: Mrs. C.M.K., a 30 year old ragweed, hayfever patient, under my care since March 1963, had allergic reactions to many drugs including codeine, iodine, penicillin and xylocaine. On 1/15/65 shortly after the Windsor, Ontario water supply, unbeknown to her, had become fluoridated, she had extensive laboratory studies in a Windsor hospital because of periorbital edema, a tendency to generalized fluid retention associated with headaches, scintillating scotomata and spastic bowels. The EEG had suggested a tendency to "convulsive disorders", but otherwise no diagnosis had been made.

On May 20, 1966 she was hospitalized at Harper Hospital by Dr. J.P.G. In addition to the above complaints, she stated that she had frequent episodes of abdominal pains, dysuria and urinary tenesmus, muscular weakness with a tendency to fall down without warning and without losing consciousness. She had noted slurred speech, pains, paresthesias in arms and legs, general malaise, marked mental sluggishness and a gradual deterioration of the eyesight which was not corrected by glasses.

On examination she showed fibrillation of the facial muscles and grayish-blue suffusions on arms and legs, 2 to 3 cm in diameter, which she stated came on frequently without trauma. The neurological examination (Dr. J.E.G.) showed slightly increased tendon reflexes. Electromyographic tests (Dr. F.S. S.) were indicative of hypocalcemic tetany. Retinoscopy (Dr. O.A.B.) showed slight edema of the discs bilaterally. Cystoscopic examination (Dr. H.V.M.) revealed evidence of mild urethritis and cystitis.

A test dose of 6.8 mg of fluoride (15 cc NaF) 24 hours prior to admission resulted in marked aggravation of her condition and precipitated an episode of urticaria which persisted for 2 days. Throughout the hospital stay, while on low fluoride water (0.1 ppm) she improved progressively. Upon discharge, June 6, 1966, she was free of symptoms. Serum calcium levels ranged from 8.2 to 9.2 mg% shortly after admission, urinary calcium from 86 to 150 mg. Otherwise the laboratory tests were unremarkable.

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On June 9, 1966 she was given a double-blind test under supervision of Dr. J.P.G. She was able to identify the bottle which contained the fluoride in water because of the gradual return of her previous illness, particularly the general edema and the abdominal symptoms. Since avoiding tea, seafood and fluoridated water, she has remained well except for minor recurrences which have been due to inadvertently imbining Windsor fluoridated water. On 5/20/66, after she was given the above test dose the 24 hour urinary F excretion was 2.8 mg; on 6/6/66, the day she was discharged from the hospital, 0.27 mg.

Case 2: Miss G. L., 27 years old, had been under my care since July, 1966, because of allergic nasal and sinus disease of about six years' duration. She complained also of frontal and occipital headaches, of paresthesias and pains in arms and hands, of backache and of arthritis in the interphalangeal joints, of persistent gastralgia and spastic constipation, of frequent episodes of ulcers in the mouth and of pyelocystitis for which she was being treated by other specialists. Desensitization for ragweed, grass pollen and fungi to which she was sensitive cleared up the nasal allergy but failed to affect any of the other symptoms.

The urinary tract disturbances and the marked generalized weakness progressed to such an extent that they interfered with her employment as a teacher and necessitated hospitalization at Hutzel Hospital on 2/1/67.

Laboratory tests, including kidney function studies were unremarkable. A cystoscopy and pyelography revealed an ectopic left kidney, which failed to excrete the indigo carmine dye. The urologist (Dr. F.S.B.) considered this kidney without function and advised its removal. There was also a congenital fusion of the lumbar vertebrae, congenital absence of two lumbar segments and disc spaces; the right leg had been amputated at age 8 because of a congenital abnormality.

Because the patient's condition failed to respond to therapy and because of the similarity of the clinical picture with that encountered in other individuals intolerant to fluoride — without being aware of it she had been drinking fluoridated water for 17 years in Highland Park, Michigan — she was placed on distilled water for cooking and drinking and instructed to avoid "high fluoride" food (tea and seafood). The gastrointestinal symptoms and headaches began to clear up immediately. Arthritis, neuromuscular and urinary symptoms disappeared completely within 10 days. On June 12, 1967, pyelography and cystoscopy revealed that the function of the left kidney had returned to normal. No blind or double-blind tests were carried out in this case because of the risk involved, particularly with respect to the kidneys.

The patient has had no further urinary disturbances and has remained symptom-free. 24 hour urinary fluoride determinations prior to the hospitalization December 9, 1966, was 1.3 mg. On 6/14/67 no fluoride was detected in the urine.

**Diagnosis**

The disease fits a clear-cut clinical pattern which agrees with that encountered from large doses of F both in acute intoxication (22) and in industrial and "neighborhood" fluorosis due to fluoride emitting factories (23).
There are mainly two groups of symptoms: The principal neuromuscular features are arthritis in the spine and peripheral joints, paresthesias and pains in arms and legs, muscular fibrillation and migraine-like headaches. The gastro-intestinal symptoms are nausea, epigastric pain, vomiting, spastic pains in the bowels, spastic constipation alternating with diarrhea. Episodes of pyelocystitis, polyuria and polydipsia and ulcers in the mouth occur less frequently.

The most striking feature of the disease is extreme progressive exhaustion with increasing loss of mental acuity, deterioration of memory and ability to concentrate. Eventually the patient becomes completely disabled. Some patients manifest episodes of dryness in the mouth, swelling of salivary glands in conjunction with polydipsia, a tendency to chronic tonsillitis and pharyngitis similar to that seen in sensitivity to iodine. The condition is reversible in the early stage.

Objective findings are: Limitation of motion in the cervical and lumbar spine, decrease of muscular power of arms and legs, fasciculation of muscles, hyperhidrosis, abdominal distention and tenderness upon palpation of the abdomen. Changes in the retina, especially dilatation of retinal vessels and evidence of retinitis occur in a limited number of cases.

Laboratory data are generally unremarkable. Serum calcium, phosphorus and magnesium levels show slight deviations from normal in either direction. Serum alkaline phosphatase is frequently elevated.

In the hospitalized cases the following procedure was followed in establishing the diagnosis:

1. The patients were examined by consulting specialists in order to determine whether or not illness other than fluoride intoxication could account for the disease. Hyperparathyroidism was mainly considered in differential diagnosis.

2. After the patients had been taken off fluoridated water and food high in fluoride (tea, seafood) and had completely recovered without medication, the diagnosis of chronic fluoride intoxication was confirmed by a double-blind test. Fluoride was administered in distilled water in the following manner:

Three identical bottles labeled #1, 2 and 3 are prepared by the pharmacist: Two contain plain distilled water, the third 1 mg of fluoride (2.2 mg NaF) per tablespoon of water, the daily dose recommended for prevention of tooth decay. Neither the patient nor the physician knows which bottle contains fluoride. The patient is instructed to take 1/2 a tablespoon twice a day in 1 pint of water (before breakfast and before dinner) from bottle #1 for one week, from bottle #2 the second week and from bottle #3 the third week. Usually the fluoride water causes the symptoms to recur within 1 to 3 days. During the test, urinary fluoride determinations are made.

Blind and double-blind tests have been repeated with varying doses and varying concentrations of fluoride in water which had no adverse effect on normal individuals. The disease was thus reproduced in the patients. Upon withdrawal of fluoridated water, the patients recovered without medication.
In relating ill-effect from F water to its cause certain difficulties arise because of the slow insidious onset, the wide variety of symptoms and the fact that these symptoms do occur in many other diseases. Therefore, it is essential to rule out other diseases in differential diagnosis.

Smith and Hodge (24) have set up guidelines for the diagnosis of chronic F poisoning based on what some consider "normal" or innocuous F values in bones, urine and blood. These criteria have not been borne out by others. For instance, Singh et al. (25) and, more recently, Pinet (26) reported advanced crippling "in many persons" with daily urinary F excretion of less than "5 mg/l". Singh et al. (27) described skeletal fluorosis in individuals with F levels in bones in the 700 to 1600 ppm range.

This F level in bones is far below that at which many claim fluorosis cannot occur. Data published by Cell (28) demonstrated that F content of bones does not parallel the F content in soft tissue organs. Therefore the presence or absence of ill-effect due to fluoride cannot be established on the basis of the F content of bones.

Some of the data reported here point to kidney damage in hydrofluorosis and/or to enhanced susceptibility to fluorosis in persons with kidney disease. The kidneys are known to contain substantial amounts of fluoride in individuals with nephrolithiasis (29). Individuals with renal dysfunction eliminate considerably less F in their urine than normal persons when they drink fluoridated water (1 ppm) (30). Bones of patients with pyelonephrosis contain elevated amounts of fluoride (31). In chronic skeletal fluorosis kidney function is impaired (32, 25).

On the other hand, urine examinations of 100 boys in fluoridated Newburgh, N.Y., revealed no evidence of kidney damage after 10 years of fluoridation (33). However, in this survey all children "with a history of clinical illness no matter how mild during the previous two weeks" were excluded. Thus, cases of intermittent pyelocystitis due to fluoride in water could not have been detected.

Smith et al. (34) reported no appreciable differences in urinary F excretion in nephritic patients prior to and following the initiation of fluoridation. In this study, however, persons aged 74 to 98 were used as "normal" controls. At such an advanced age kidney function cannot be considered normal.

Summary

Skeletal fluorosis has been reported in the U.S.A. where water contains fluoride in concentrations from 1.0 to 9.2 ppm. In two fatal cases with fluoride osteosclerosis who died of terminal septicemia and pneumonia, respectively, water consumed during their lifetime contained 1.2 to 5.7 ppm fluoride.

Two cases of chronic fluoride intoxication are reported prior to the development of skeletal changes. As described in previous publications, the nonskeletal manifestations involve mainly the neuromuscular system, the gastro-intestinal and urinary tracts. In one case the diagnosis was supported by a double-blind test; in the other, the function of an ectopic
kidney, which had ceased to eliminate indigo carmine, was promptly restored and the patient’s symptoms subsided completely upon avoidance of fluoridated water.

Evidence presented here indicates that patients with lower urinary tract disease are particularly susceptible to fluorosis.

Bibliography

FOUR CASES OF ACUTE SILICOFLUORIDE INTOXICATION

CLINICAL AND PATHOLOGICAL FINDINGS

by

O. Pribilla
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Acute poisoning with hydrofluosilicic acid or its salts is a relatively rare condition. In 1954 Garcho and Pribilla (1) reported a case of accidental poisoning in a 67 year old man who drank a 13% solution of hydrofluosilicic acid. Since then we have encountered three additional cases in which the acid was used for suicidal purposes.

In 1959 Fasske (2) described a case in which the victim survived for 12 days after the intake of a F compound. He noted massive myocardial necrosis limited to paranchymatous cells of the heart muscle. He attributed the cardiac changes to inhibition of the carbohydrate metabolism by fluoride in the muscular tissue of the heart. He confirmed his concept by experiments on rabbits poisoned by fluoride and by histochemical analysis of the inhibiting enzyme in the heart muscle. Fasske was unable to determine whether or not calcium deprivation by fluoride i.e., hypocalcemia constituted the cause of death.

The following is a report of four cases of acute intoxication with silico-
fluoride:

Case I (autopsy No. 14/54): A 42 year old woman was found lying on the ground in the woods complaining of extreme weakness, groaning and writhing in pain. She became gradually less agitated, visibly cyanotic and died on the way to the hospital. She had had suicidal intentions. Among her belongings was a 0.33 liter bottle labelled "Na-Fluosilicate Insulating Agent - Poison" of which half the content was missing. The time between ingestion of the poison and death was less than 2 hours.

At autopsy the color of the lips was strikingly dark blueish-red alternating with some light blueish-red marks. The hands were in a claw-like position; the feet pointed upwards. Eyelids and conjunctiva exhibited ecchymoses; the pupils were wide. The mouth and the esophagus were completely free of corrosive changes. The lungs showed pulmonary congestion, partial emphysema and subepicardial hemorrhages. Liquid blood was present in the heart cavity. The myocardium had a fresh-brown color and showed no macroscopic changes. The stomach contained 150 ml black-red liquid. The gastric mucosa was moderately loose and covered with a black, mucoid substance. The folds of the gastric mucosa showed white and dark-red corroded areas (Fig. 1). There was no corrosion in the duodenum. The liver showed very severe congestion and edema. The brain was somewhat congested. The kidneys exhibited edema and cloudy swelling.

From the Institute of Forensic Medicine - University of Kiel, West Germany
(Dir.: Prof. Dr. M.C.W. Hallermann)
ACUTE INTOXICATION

Histologically the myocardium showed isolated fibrillolysis, beginning fibrous necrosis and dissolution of nuclei. In the interstitial spaces a fibrinous, edematous fluid, an abundance of minute hemorrhages and infiltration by histiocytes, lymphocytes and granulocytes were noted. Most other organs were markedly congested and edematous. In the liver there was isolated central necrosis with round cell infiltration.

The serum calcium was 13.25 mg%. The liquid in the bottle contained 37.6\% Mg Silico-fluoride. The fatal dose was approximately 60 g Mg SiF₆.

Case 2 (autopsy No. 181/58): A 28 year old man who had taken an unknown amount of "Olatrin" (zinc-aluminum-magnesium-lead-fluosilicate) was found lying on the street, vomiting profusely and having involuntary defecation and urination. He appeared to be in severe pain. He was carried into a house, stood up and tried to walk out. He sank to the ground, vomited and remained lying on the ground. On his way to the hospital more vomiting, defecation and urination occurred. He expired about two hours later.

The postmortem showed an unusually intense, blue-greyish discoloration of the lips and marked rigor mortis, especially in the lower extremities. The heart contained dark-red liquid blood. The color of the heart muscle was brown-red, the left ventricle was contracted. The stomach contained about 200 ml dark-red, viscous, slimy substance, without a characteristic odor. The mucosa of the stomach was extremely flaccid, warped, corroded and dark-red in color. There was marked autolysis of the mucosa. The lungs, liver, kidneys and spleen were severely congested and there was moderate cerebral edema.

Histologically the myocardium showed changes similar to those of case 1, namely interstitial edema, fibrillolysis and fibrous necrosis (Fig. 2). The other
organs were congested and edematous, the liver showed diffuse cellular necrosis. The blood vessels of the gastric submucosa were markedly congested. Otherwise there was no unusual cellular reaction. Postmortem autolysis interfered with evaluation of the kidney pathology. The serum contained 6.61% of calcium.

Fig. 3

Heart muscle. Edema of muscle fibers; necrosis without cellular reaction. Interstitial edema. Formation of vacuoles (Case 3).

Case 3 (autopsy No. 341/64): A 37-year-old man took seriously ill with abdominal pains. One hour and 15 minutes later the attending physician found him highly agitated and apprehensive with severe abdominal cramps, vomiting and involuntary defecation. His face was pale, the lips cyanotic, the pulse rate about 120. Upon admission at the hospital he stated that shortly after luncheon he was overcome by abdominal pains, vomiting and diarrhea. He believed that his wife had poisoned him.

On examination he appeared to be in constant severe pain. The skin was very pale and moist, the pupils wide. They failed to react to light. The tongue was moist and coated; the heart sounds clear and regular, blood pressure 145/95; the respiratory rate 20–22.

The lungs showed few scattered vesicular rales. The abdomen was tender throughout. Liver and spleen were not palpable. Reflexes were equal bilaterally, ankle and patellar reflexes exaggerated, abdominal reflex strongly positive, Babinski negative. The patient was treated with gastric lavage, activated charcoal, Methylprednisolone, atropin and applications of moist heat to the abdomen.

The pulse rate slowed down at first but soon increased to 140–160/min. The abdominal pains seemed to have lessened. A cardiac stimulant (Cardalin) was of no avail. He expired in what appeared to be heart failure, 3 hours later.

Postmortem revealed again the unusual blue-grey or dark-violet discoloration of the lips as noted in the previous cases. There were hemorrhages in the conjunctivae. The wrists and toes were over-extended and the big toe had spread away from the others. The heart showed moderate coronary sclerosis. The right auricle was greatly enlarged. There was also congestion of the esophageal and tracheal mucosa. The lungs were extremely congested and edematous. The stomach contained 100 ml dark-brown-red, viscous material. The gastric mucosa and the entire small intestines were congested and exhibited isolated petechial hemorrhages. Congestive changes were also present in the pancreas, kidneys, liver and brain.
ACUTE INTOXICATION

Histologically the heart and liver were most remarkable: The myocardium showed interstitial edema, toxic damage of the parenchyma associated with fibrous necrosis (Fig. 3-4).

Fig. 4

The liver cells were separated from each other; they appeared honeycombed with marginal cytoplasmin. In certain areas the spaces which had been occupied by liver cells appeared empty. There was little cellular reaction. Between the plates of the liver cells and the liver cells a greasy, protein-rich, edematous substance and fatty droplets of different sizes were noted in the cytoplasm.

The serum cholinesterase was 0.62 delta pH in 2 hours. The condition of the other organs was similar to that in the above cases, except for the liver which showed extreme edema and toxic parenchymal damage.

Case 4 (published in 1954); concerns a 67 year old man, who drank a gulp of 15% hydrofluosilic acid accidentally. Death occurred within 15 minutes after extensive vomiting of a dark fluid, profuse sweating and extreme weakness. The autopsy was performed on an already putrefied corpse and no histological examination was possible. In the stomach and in the small intestines silicofluoride was found. Table I shows the fluorine content in organs. The analysis was made by means of a distillation method in a closed system, with subsequent titration with Thorium-nitrate (3,4).

Discussion

All cases experienced severe abdominal pains and rigidity. They were unable to walk but remained conscious. They vomited profusely and had diarrhea shortly after intake of the poison. All showed circulatory changes with cyanosis and tachycardia. Hyperreflexia, as found in case 3, could be interpreted as a sign of involvement of the central nervous system. The unusual position of the hands and feet noted at autopsy points to a tetanic condition prior to death. There was extensive corrosion of the gastric mucosa.

It is questionable whether or not the calciprivic effect of fluorine plays a decisive part in acute poisoning. In a case described by Müller and Bock (5) there was a steady decline of the serum calcium from 4.2 m/equivalent at the beginning of intoxication to 2.2 m/equivalent shortly before death. Leone et al. (6), observed a decrease of the serum calcium level in some of their dogs poisoned by F infusion. In our case 2, serum calcium was also decreased. The
## TABLE 1

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Drug/Dose</th>
<th>Time until Exitus</th>
<th>Serum Ca/MgF</th>
<th>Stomach</th>
<th>Vomitus</th>
<th>Small Intestines</th>
<th>Liver</th>
<th>Brain</th>
<th>Muscle</th>
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<td>42</td>
<td>37,6 F</td>
<td>Ca 2h</td>
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<td>-</td>
<td>4,97</td>
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<td>F</td>
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<td>28</td>
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<td>Ca 2h</td>
<td>6,6 118,15 - 28,25 2,39</td>
<td>0,27</td>
<td>1,5</td>
<td>2,7 Urin 1,1</td>
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<td>- 1,25 800,0 1,89</td>
<td>0,76</td>
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<td>M</td>
<td>H₂SiF₆ 13%</td>
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### Normal Values (E. Artken, same Method)

<table>
<thead>
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<th>Value</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>0,02</td>
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<td>8,2</td>
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above authors noted a steady fall of blood pressure with increasing doses of F, cardiac failure, depression of the central nervous system followed by respiratory failure, a change in the atrio-ventricular condition and the ventricular rhythm in EKG which led to myocardial fibrillation or asystole. The effect of hydrofluosilicic acid is evidently determined by the toxic action of the fluoride ion because the clinical picture is the same as that in intoxication with other F compounds.

Fluoride poisoning has been reported (7-9) without corrosion of the gastric and duodenal mucosa. On the other hand, the majority of the recorded cases exhibited gastro-intestinal changes, gastric corrosion and hemorrhages, especially when free hydrofluosilicic acid was involved.
ACUTE INTOXICATION

Histologically, the changes in the myocardium, extreme interstitial edema, beginning fibrillolysis and fibrous necrosis are significant. These findings were present in every case. They should be considered the initial pathology which precedes what Fasske described as "bland myocardial necrosis". Twelve days following poisoning by hydro-fluoric acid, he found damage to the syncytial structure of the myocardium. Whereas in some areas, the capillaries showed no pathology, far the largest portions of the muscle cells exhibited what is called the "Conheimische Felderung" i.e. the replacement of delicate sarcolemma by fibrous structures.

The fibrillolysis and the beginning fibrous necrosis observed here are similar to the changes described by Fasske (10). However, in two of our cases, there were also small hemorrhages and irregularly distributed infiltrating histiocytes in the interstitial areas. Such changes were described by Takamori (11) in rats. He observed a regressive degeneration of muscle fibers, cloudy swelling with vacuolar degeneration, round-cell infiltration and minute hemorrhages after intravenous injections of sodium fluoride. Our results suggest that F interferes with the metabolism of the myocardium, a condition observed by Hashimoto (12) who noted cardiac changes on the bullfrog due to the glycolysis by exposing the perfused heart to fluorine. In the case described by Muller and Back (5) edema of the myocardium with diapedesis of erythrocytes and leucocytes and acute right dilation of the heart were found in addition to a general venous hyperemia.

In case 3, the liver changes could be interpreted as the result of the overall circulatory damage. On the other hand, they could also be due to interference of fluoride with the cell-metabolism of the liver. As soon as one hour after injecting rabbits intravenously with hydrofluoric acid, Fasske (2) observed changes in the enzyme-system of both heart and liver.

The findings in our cases support Fasske's theory that the toxic effect of fluoride lies in the destruction of enzymes, especially of organs rich in glycogen. Fluorine suppresses selectively glycolytic enzymes and phosphatase. Following the clinical progress and assessing the pathology in our cases, it appears that the calciprivic effect of fluoride may be relatively unimportant in acute intoxication by hydrofluosilicic acid. The cause of death is likely to be circulatory failure due to the toxic action of the fluorine ion i.e. its interference with enzymes in the myocardium.

Summary

Four cases of acute intoxication with hydrofluosilicic acid are presented. The principal pathology was noted in the heart, namely fibrous necrosis, dissolution of nuclei, fibrillolysis and interstitial edema.

The pathology indicated that the cause of death was the action of the poison upon the heart muscle followed by cardiac failure.

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Bibliography

CHEMICAL-TOXICOLOGICAL INVESTIGATION ON THE FLUORINE CONTENT
IN HUMAN VISCERA

by

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W. Krakowie, Poland

At the Institute of Forensic Research in Krakow several cases of fatal poisoning from fluorine compounds have been recorded during the period 1960 - 1966. Four cases on which chemical-toxicological studies were performed seem to be of special interest. A study on fluorine levels in human organs has been carried out simultaneously in order to evaluate the results of the toxicological findings. Viscera from persons whose death did not result from fluorine poisoning were used for analysis.

Method of Analysis

The organs were ashed in an electric oven at 450° C with addition of F-free calcium oxide. The ashes were distilled by the well-known Willard-Winter method. A special apparatus according to Pietzka-Ehrlich (1) was used. In case 1, fluoride was determined in the distillate with the thorium-alizarin method of Somachson (2), in the other cases with Spadna-Zr-Reagent (3, 4). The spectrophotometric determinations were done by means of the Spectrophotometer Speko manufactured by Zeiss. In the control cases, the F content was determined in a similar manner. Tables 1 and 2 present the results of the F analyses per 100 grams of fresh tissue.

Case Reports

Case 1: A healthy 70 year old man (E.W.) died suddenly. Coronary thrombosis was suspected as the cause of death. Twenty days later, the prosecuting attorney ordered the body exhumed. Post-mortem examination failed to reveal the cause of death. However, chemical-toxicological analysis of tissues proved definitely that E.W. was poisoned with sodium fluorosilicate by his 50-year-old wife. This compound was used extensively in the factory where he had worked. Frequently workers took small amounts of the poison home with them in order to exterminate rats. The symptoms in this case were not known.

Case 2: At about 9:00 a.m., a 21-year-old man (T.I.) took several swallows of a fluid which he believed was whiskey. He immediately noted severe burning in the oral cavity, followed by abdominal pains and cramps in the legs. He took two glasses of milk as an antidote and rode on his bicycle to a Red Cross station whence he was taken to the nearest hospital in a moribund condition. Although conscious, he was very agitated and apprehensive. He had severe cramp-like pains in the extremities. From time to time he vomited. His face was pale, his lips livid blue. The heart rate was 80 per minute, the pulse was weak, blood pressure 70 to 60. He received oxygen, coramin with caffeine, intravenous glucose and vitamin C. In spite of these measures, he expired in circulatory failure at 10:25 a.m.

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(Dir.: Jan Markiewicz, Ph.D.)

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### TABLE 1

**F Content of Viscera in Persons Poisoned by F Compounds**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Kind of Poisoning</th>
<th>F Compound</th>
<th>F in Mg per 100g (Fresh)</th>
<th>Intestines</th>
<th>Liver</th>
<th>Spleen</th>
<th>Kidney</th>
<th>Urine</th>
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<td>70</td>
<td>Homicide</td>
<td>Sodium</td>
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<td>20.0</td>
<td>22.7</td>
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<tr>
<td>2</td>
<td>Male</td>
<td>41</td>
<td>Accident</td>
<td>Fluorosilicate</td>
<td>10.0</td>
<td>3.17</td>
<td>4.17</td>
<td>4.59</td>
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<tr>
<td>3</td>
<td>Male</td>
<td>40</td>
<td>Accident</td>
<td>Halothane * during Anaesthesia</td>
<td>-</td>
<td>2.70</td>
<td>-</td>
<td>1.20</td>
<td>-</td>
<td>-</td>
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<tr>
<td>4</td>
<td>Female</td>
<td>28</td>
<td>Suicide</td>
<td>Sodium</td>
<td>Fluorosilicate</td>
<td>1.86</td>
<td>0.70</td>
<td>1.09</td>
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*2-Bromo-2-Chloro-1, 1, 1-Trifluoroethane
**205.0 mg% or 2050 ppm.

### TABLE 2

**F Content of Viscera in Persons Not Poisoned by F in µg% (Microgram %)**

<table>
<thead>
<tr>
<th></th>
<th>Intestines</th>
<th>Liver</th>
<th>Spleen</th>
<th>Kidney</th>
<th>F Content in Water-Supply in Krakow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>159.7 (7)*</td>
<td>189.9 (14)</td>
<td>234.1 (16)</td>
<td>224.6 (20)</td>
<td>25.0 µg%</td>
</tr>
<tr>
<td>Range</td>
<td>102-188</td>
<td>50-390</td>
<td>76-400</td>
<td>81-452</td>
<td>(or 0.25 ppm)</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>38</td>
<td>106</td>
<td>146</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

Number of cases in brackets.
*159.7 µg% or 1.59 ppm
All assays made on fresh material.
The post-mortem showed edema and brownish discoloration of the esophageal mucous membranes, hemorrhages of the gastric mucosa, capillary congestion, cerebral edema. Histologically, the gastric mucosa showed superficial necrosis. Chemical analysis revealed high concentrations of F in organs and in the urine. The fluid which he had imbibed was a 4% watery solution of fluorosilicic acid.

Case 3: An otherwise healthy 43-year-old man (W.W.) died suddenly during surgery with "Halothan" ("Fluothan") narcosis. The body was exhumed shortly thereafter in order to establish the cause of death. The tissues contained excess fluoride. In evaluating the results of F analysis in this case, the high volatility of the compound must be taken into account.

Case 4: A 28-year-old female had taken an unknown quantity of sodium-fluorosilicate for suicidal purposes. Ten minutes later she vomited and became unconscious. She died 3½ hours later in spite of extensive therapeutic measures.

The autopsy showed marked congestive changes of all internal organs, hyperemia of the gastric and duodenal mucosa, hemorrhages and necrosis in the stomach.

Bibliography

ABSTRACTS

RESEARCH ON ENDEMIC FLUOROSIS

by

G. Fracà, G. Montesana and G. Nalbone
Istituto di Medicina del Lavoro, Università di Palermo, Italy

(Abstracted from Minerva Medica 54:45-59, 1963)

The authors investigated numerous areas in Sicily where fluorosis is endemic. Some of these regions had been studied by Tempestini and others. They concentrated their studies upon Acquaviva Platani, a city of 2500 population located in a somewhat economically depressed area. The occupation of the inhabitants was limited to agriculture and mining of rock salt. The dwellings had earthen floors; many consisted of only one room. The diet was lacking in protein and vitamins and consisted mainly of starches and vegetables. The fluoride content of the city water was 5.2 ppm.

Three hundred persons (190 male, 110 female) were examined at ages ranging from 7 to 71 years.

Teeth: Nearly all had severe mottling, many extensive pyorrhea. The deciduous teeth were not affected by mottling (Fig. 1a, b, c).

General Health: In children, there were signs of somatic underdevelopment, of rickets and of mental retardation. Adults showed evidence of premature senescence and signs of hypoadrenal activity including melanotic spots on the mucosa of lips and gums. Many were afflicted with degenerative joint disease and what they called "rheumatism". The digestive system was involved in 70%. The patients complained of dyspepsia. Gastritis, chronic catarrhal gastro-duodenitis, spastic colitis and signs of liver disorders were common. Gastric ulcers were rare. The authors noted prevalence of intestinal parasites, mostly oxyuriasis and ascariasis, a common affliction in the rural population of Sicily. Bronchitis and chronic respiratory disease were frequently encountered. They were attributed to the extreme humidity. There was a high incidence of rheumatic heart disease and of early arteriosclerosis with tortuous and hardened temporal and radial arteries. This, however, was not accompanied by arterial hypertension.

Infantile morbidity and mortality did not differ from those of other areas in central Sicily. There were no disturbances of the menstrual cycle, of fertility and of the course of pregnancy, nor was there evidence of an increased incidence of kidney stones, diabetes and other metabolic diseases. Goiter was rare and the frequency of fractures was insignificant.

Adults who had moved into the area from a low F region showed no dental lesions. They developed digestive disturbances shortly after their arrival.

Skeletal Changes: Sixty-three persons, namely 43 males and 20 females were selected for a special study: 39.6% showed no radiological changes. In 30.2%, the bone changes were moderate with small osteophytes at elbows, knees and vertebrae and partial ossification of tendons at their insertions on the
Mottled teeth from endemic area in Sicily; 3 to 6 ppm of F in water. Courtesy Prof. Frada, University of Palermo, Italy.
Marginal Osteophytosis of Vertebral Bodies. Ossification of Vertebral Ligaments.

Ossification of Tendon at Insertion of Anterior Tuberosity of Tibia. Osteoporosis in Epiphysis of Tibia.

Interosseus Membrane Ossified; Osteosclerosis of Diaphysis.

Osteosclerosis of Skull and Cervical Spine.

All cases from Sicily with F in water between 3 and 6 ppm. (Courtesy of Prof. Fradé).
ABSTRACTS

bones. There was no change in bone density. Many in this group of cases, not yet advanced in age, had evidence of arthritis usually with limitation of movement.

More extensive evidence of osteosclerosis was noted in another 30.2% of cases. In 10 patients advanced bone changes were seen with diffuse or localized increase in bone density, thickening and irregularity of trabeculae, peristosis and endostosis accompanied by ossification of tendons and ligaments and at times by marked constrictions of the spinal canal. In the aged there was often a considerable diffuse porosis, especially of the spongiosa.

In many patients the bone changes were difficult to differentiate from the usual forms of arthrosis deformans. With advancing age (after 40) the skeletal changes were more pronounced. They were practically always present in the aged, especially in males.

Laboratory Data: Red cell counts and hemoglobin were somewhat decreased. There was usually a shift to the left with microcythemia. The cellular diameter and red blood volumes remained usually within normal limits; there was no poikilocytosis. Sternal puncture showed a deficiency of erythropoiesis. The resistance of red cells, white cells, the differential counts and platelet counts were normal. There was a slight increase in sedimentation rate. Proteins were within normal limits but in 80% there was a slight decrease of the gamma globulin fraction of the serum.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of Laboratory Data</td>
</tr>
<tr>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>Calcium (serum)</td>
</tr>
<tr>
<td>Calcium (urine)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>Cholesterol Esters</td>
</tr>
<tr>
<td>17 Ketosteroids (urine)</td>
</tr>
</tbody>
</table>

The authors concluded that gastric disturbances were caused by the action of fluoride on the gastric mucosa. They questioned whether the evidence of hypoadrenalism should be attributed to nutritional deficiencies or to fluorosis. In children, some of the abnormalities could have been associated with rickets. With respect to the hematological findings, the authors' observations differed somewhat from those of Takamori in 1955 in Japan, who observed macrocytosis and shift to the left of the lymph formula. He also had noted increased reticuloocytes. The authors emphasized the multiplicity of changes observed in their cases in addition to the involvement of teeth and skeleton.
ENDEMIC FLUOROSIS WITH NEUROLOGICAL COMPLICATIONS IN A HAMPSHIRE MAN

by

M. M. Webb-Peploe and W. G. Bradley
Royal South Hants Hospital, Southampton, England

(Abstracted from J. of Neurology, Neurosurgery and Psychiatry,
29:577-585, 1966)

A 57-year-old carpenter was admitted in 1964 to the Royal South Hants Hospital with progressive weakness of the legs. This condition originated in 1956, following a 12-foot fall from a ladder. He had recovered within 2 weeks from other effects of the fall.

In 1959, the pelvis and lumbar vertebrae showed osteosclerosis which led to the diagnosis of Paget's disease and osteoarthritis. In 1963, the skeletal condition was diagnosed as fluorosis. It corresponded to the changes described by Roholm in 1937.

Examination revealed marked lumbar sclerosis, restriction of movements in the spine, hips and elbows, wasting of the gluteal muscles, coarse fasciculation of the leg muscles, spastic bilateral footdrop and a sensory loss of pain in some areas of the lower vertebral. Laboratory findings were unremarkable.

Pelvis and lumbar spine showed radiographic evidence of increased bone density, bone spurs at the site of the tendon insertions in the iliac and pubic regions and vertebral lipping. A myelogram demonstrated obstruction of the fluid flow in the spinal canal. Upon surgery, the spinal cord showed a compression due to thickening (up to 2 cm) of the laminae at levels T 10, 11 and 12. A dorsal laminectomy produced decompression of the cord and improved the patient's condition to such an extent that he became employable.

The compact and spongy bone removed at surgery revealed normal hemopoietic marrow, prominent osteoid seams and other signs of osteoblastic activity. Some disc fibrocartilage attached to one specimen showed calcification. It contained 2530 ppm F, which the authors consider "twice the normal level" (Singh et al. reported skeletal fluorosis in the 1000 ppm range). The F levels in blood and urine were "normal" i.e., less than 0.2 ppm. The diagnosis of skeletal fluorosis was confirmed on the basis of the x-rays, the histological findings and the F content of the bone.

This is the first case of non-industrial fluorosis with neurological involvement reported from Britain and the first one to be treated surgically with benefit.

With respect to the source of the F intake, the patient was a heavy tea drinker. There was no history of occupational exposure to F nor to unusually high F levels in water. Up to 1940 (age 33) his drinking water had come from
the rivers Avon (at Christchurch) and Tamar, both with low F content, namely 0.1 and 0.04 ppm respectively. For the next 5 years (up to age 38), he had used water from his own well from which no samples could be obtained for F analysis. No F was found in a surface sample from 1 of the 2 boreholes (now closed) from which he took his tea water while at work until 1961.

The authors considered the possibility that the water from the well which could not be analyzed was high in F. This, however, is unlikely because in Hampshire, the highest F level in water is 1 to 1.25 ppm in a small area supplied by the Thames Valley Water Board. Furthermore, a well one mile distant from the well in question showed no F. The patient developed his first symptoms of fluorosis at age 49. The first radiographic evidence of osteosclerosis was detected at age 51.

The authors failed to consider fluoride in tea, an important source of F intake in Great Britain, as the cause of fluorosis.
FURTHER OBSERVATIONS ON THE KENHARDT BONE DISEASE AND ITS
RELATION TO FLUOROSIS

by

W. P. U. Jackson
Groote Schuur Hospital, Capetown, South Africa

(Abstracted from Gordenoff, T. The Toxicology of Fluorine 58-69
Schwabe and Co. Publ. Basel 1964)

In 1960 the author in conjunction with Dodd, N.F., Levy, D.W. and Traut,
M.L., in the South African Medical Journal 1960, published the study of a
certain bone deformity which occurred among school children from Rooiblok,
near Kenhardt in N. E. Karoo, a colored settlement. They were unable to identify its cause. Subsequent studies established that the disease was related to
high fluoride content of drinking water. The problem was subsequently studied
by a team from Pretoria University Medical School headed by Prof. Douw Steyn

The disease did not represent true skeletal fluorosis since it occurred
at an early age and began with rarefaction and softening of bones instead of
sclerosis. Fluoride analyses by three different independent laboratories
showed the values given in Table 1.

| TABLE 1 |
|-----------------|-----------------|
|                  | Fluorine (ppm)  |
| February 1960    |                 |
| Kenhardt town (top) | 2.6            |
| Rooiblok North    | 6.0             |
| Rooiblok South    | 7.4             |
| Rooiblok South (September well) | 11.6 |
| Kenhardt town (various) | 2.6-3.2        |
| Rooiberg dam (dry bed) | 1.8           |
| Rooiberkgkema     | 4.0             |
| Rooiblok (North, various) | 3.6-8.0    |
| Rooiblok (South, various) | 7.5-13.0     |
| March 1960 (before the recent floods) |           |
| Kenhardt town (borehole) | 4.2           |
| Rooiblok South (September's well "most evil") | 4.8        |
| Rooiblok Central  | 3.7             |

One bone biopsy showed 8,500 ppm of fluoride in bone ash; a goat horn
from Rooiblok 2,200 ppm; a sheep bone 145 ppm.
ABSTRACTS

All 7 to 10 year old pupils of the colored school of Kenhardt were examined, about one-third of whom came from Rooiblok. A similar group of European children and some colored and white adults were studied. Table 2 shows the degree of dental fluorosis in Kenhardt and Lokasie. Deciduous as well as permanent teeth were affected. The youngest child with at least a 2+ dental fluorosis was only 10 months old.

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>+</th>
<th>++</th>
<th>+++</th>
<th>++++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always lived in Kenhardt (25)</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>From Outlying Areas (25)</td>
<td>10</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Colored</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From Lokasie</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(town water) (32)</td>
<td>3</td>
<td>5</td>
<td>16</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Rooiblok (37)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

Forty-seven out of 98 colored children from Rooiblok had bone pains in the shins. Only 3 out of 60 white and 3 out of 124 colored children from Lokasie complained of leg pain, mostly in the knees. None had pain in the lower spine, the usual early sign of skeletal fluorosis.

The deformity observed in the colored children of Rooiblok was lateral bowing of the femora, anterior bowing of the tibiae, with variable knock-knee or bow-legs.

In 22 of 40 Rooiblok children x-rays of the legs showed abnormalities in the form of expansion of the shafts, thinning of cortices and forward bowing of the tibiae with anterior thickening of the cortex. The demarcation between cortex and medulla was obliterated. The bones of the hands showed evidence of demineralized and coarsened trabeculations. The vertebrae showed transverse lines.

In six children who had moved to Rooiblok some 5 or 6 years previously bone pain started after 3 or 4 years of residence. There was no evidence of anemia. Although the three children with the most severe dental fluorosis had the bone disease, there was no correlation of bone changes with dental fluorosis.

![Fig. 1](Mildly Affected Tibiae from Rooiblok. Slight Cortical Thickening and Forward Bowing. (Courtesy of Dr. Jackson)).
fluorosis. There was correlation between pains in the shin and x-ray changes. Five of 34 Lokasie children with doubtful x-ray changes were symptom-free. The colored children did not appear to be undernourished. Several elderly colored people who had been using the most "evil" well had no complaints of back pain and no impairment of motion in the spine, although some showed marked osteosclerosis on x-ray. Two children who had always lived in the worst affected plot were completely free of bone symptoms.

The author did not consider the bone disease in the Rooiblok area congenital, inherited or attributable to rickets, syphilis or anemia. He established that the disease was related to the high F content of drinking water. However, some other still undiagnosed environmental factor had entered into the picture. In Rooiblok itself the calcium content of the water was not particularly low, but the levels of lead, boron and aluminum were higher than in the town water.
FLUORIDE OSTEOSCLEROSIS SIMULATING CARCINOMA OF THE PROSTATE
WITH WIDESPREAD BONY METASTASIS: A CASE REPORT

by

J. H. Gilbaugh, Jr. and G. L. Thompson
Rochester, Minnesota

(Abstracted from Journal of Urology 96:944-946, 1966)

The illness of a 73 year old retired farmer from a farming community in South Dakota had constituted a "diagnostic riddle" for many years.

The patient had frequency of urination, nocturia (7 to 10 times) and urinary incontinence. For more than 10 years he had a chronic osteoarthritis of the right hip. The fluoride content of his community's drinking water was known to be high. During his lifetime, he had drunk "more than the usual amount of water".*

In 1958 he had a transurethral prostatic resection at the Mayo Clinic. In 1962 a traumatic right subdural hematoma was evacuated surgically.

Examination revealed a long-standing osteoarthritis with moderate limitation of motion in the right hip. Laboratory tests including acid phosphatase and liver function studies were normal. X-rays showed markedly increased density of the ribs. The skull exhibited osteosclerosis and calcification of the falx cerebri. Widespread bony involvement of the lumbar spine and the pelvis, which had been noted as early as in 1952, suggested at first extensive bony metastasis. There was also bilateral calcification of the sacrospinous ligaments. The urogram showed a solitary right kidney with moderate pyelocaliectasis. The left kidney was absent.

The obstructive prostate was removed surgically. It showed adenofibromatous hyperplasia. Subsequent x-rays revealed increased trabeculation in most bones but no bony destruction or areas of smudging as seen in osteoblastic metastasis.

The final diagnosis was fluoride osteosclerosis. The authors emphasized the similarity of the bone changes to those associated with carcinoma of the prostate.

(*Polydipsia is a symptom of fluorosis and of renal insufficiency.)

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MASS INTOXICATION WITH FLUORIDE IN SODA WATER

by

L. Horvath, J. Palicska and I. Hanny
Szolnok, Hungary

(Abstracted from Orvosi Hetilop 108:306-7, February 13, 1967.)

On April 29, 1965, 15 to 20 customers of a restaurant became violently ill after drinking soda water. Simultaneously, 55 children and 5 adults in a kindergarten vomited profusely within minutes after drinking an orangeade made from orange syrup and soda water. They improved within a short time. None required hospitalization. Eight adults and 2 children who had not consumed any of this beverage were not affected.

Specimens of vomitus, orangeade, soda water and of water at the soda-water plant were tested in the laboratories of the health department for fluoride and for microorganisms. There was no bacterial contamination. Two samples of the soda water contained 900 ppm of fluoride, three samples of the orangeade 300 to 650 ppm and two samples of the vomitus 45 to 10 ppm. Uncontaminated soda water manufactured on the same day contained only 0.2 to 0.3 ppm of fluoride.

It was learned that water was supplied by a direct pipe to the soda-water plant from the neighboring municipal waterworks. The public water supply was fluoridated to 1 ppm F by an automatic feeder. The pipe connecting the soda-water plant, however, was located well above the point where fluoride was added to the water, so that the soda-water plant was not supplied with fluoridated water.

In April 1965, the waterworks closed off the pipe leading to the soda-water plant because of maintenance work scheduled for the 27th. During the time of the shutoff, the soda-water plant used a different source of water. On April 29, the soda-water plant was notified that repairs were completed and water was available again. It reverted to its initial source without first flushing out the connecting water pipe. Investigation disclosed that F containing water had accumulated in blind pipe sections and had gotten into the soda-water plant and into the bottles after the valves were reopened. A worker at the plant who had drunk water used for filling of bottles also became sick with the symptoms encountered in the above groups.