

# Reversibility of skeletal fluorosis

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**ABSTRACT** At two x ray examinations in 1957 and 1967, 17 cases of skeletal fluorosis were identified among long term cryolite workers in Copenhagen. In 1982 four of these patients were alive, eight to 15 years after exposure had ended. Radiographs were obtained, and the urinary fluoride excretion was measured. A similar picture emerged in all four cases: extensive fading of the sclerosis of trabecular bone in ribs, vertebral bodies, and pelvis, whereas cortical bone thickening and calcification of muscle insertions and ligaments remained virtually unchanged. The fluoride excretion was increased in three cases (with the shortest exposure free period). These findings indicate that with continuous remodelling of bone tissue trabecular sclerosis is slowly reversible and the excess fluoride is excreted in the urine.

Skeletal fluorosis was first recognised 50 years ago by Møller and Gudjonsson.<sup>1</sup> After long term heavy fluoride exposures, the bone density increases, subperiosteal bone tissue is formed, and ligaments are calcified. This disease was studied in detail at the Copenhagen cryolite factory by Roholm.<sup>2</sup> More recently, cases of skeletal fluorosis have been identified, mainly from aluminium production plants, magnesium foundries, and superphosphate and hydrofluoric acid manufacturing industries.<sup>3</sup> Skeletal fluorosis is now widely accepted as an occupational disease eligible, in some countries, for possible compensation.

In his original study Roholm observed that the skeletal fluorosis was less pronounced than expected in retired cryolite workers,<sup>2</sup> and suggested that the osteosclerosis might be reversible. This possibility has been supported by a few case reports.<sup>4</sup> We have traced all Danish cryolite workers who had acquired skeletal fluorosis and have re-examined all patients still alive.

## Study population

### FLUORIDE EXPOSURE LEVELS

Roholm measured dust levels in the grinding room where exposures were supposedly constant and of average value.<sup>2</sup> Total dust was between 32 and 48

mg/m<sup>3</sup>. Later, Brun *et al* recorded (preshift?) urinary fluoride excretion results averaging about 15–20 mg/l in 24 male cryolite workers.<sup>5</sup> In 1955 a small number of dust measurements performed by the Labour Inspectorate suggested that average fluoride exposures might reach 28 mg/m<sup>3</sup> and that certain work processes caused much higher dust levels. At about that time urine analyses in 15 male workers showed (preshift?) concentrations below 20 mg/l with a median of 7.6 mg/l. Ventilation and enclosure of dusty processes were continuously improved. More importantly, perhaps, in the late 1950s production was gradually switched to separation by the flotation method. By mid-1961, all cryolite was produced by flotation. This “wet” technique considerably improved the hygiene conditions. With further refinements of ventilation and encapsulation, exposure levels now appear to comply with the limit of 2.5 mg/m<sup>3</sup>. Although this information is insufficient for estimating the dose response relationships, a significant overexposure until the early 1960s has been documented.

### OCCURRENCE OF SKELETAL FLUOROSIS

In 1957, 154 long term cryolite workers were examined at Rigshospitalet and 14 cases of skeletal fluorosis were identified. Three of the patients had been employed at the time of Roholm's examinations in 1934 and may have been diagnosed at that time. At least 11 new cases, however, had occurred as a result of more recent exposure. Ten years later, in 1967, 59 workers of the same group who were still employed with the cryolite factory were re-examined. Three new cases of skeletal fluorosis were

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Received 4 August 1982

Accepted 30 September 1982

found. One of the patients diagnosed in 1957, however, showed some apparent improvement of his condition. All radiographs obtained at these two studies were examined and evaluated by one of us (GT).

The 17 patients with fluorosis have been followed up. By the end of 1981, five had died from myocardial infarction, four from cancer, and four from various other causes; the average age at death was 68. Four of the 17 patients with skeletal fluorosis were alive by 1982. Each has been re-examined and the case histories are given below.

### Case histories

#### CASE 1

A man, born in 1900, started working with the cryolite factory in 1929. Employment continued during 1940–5, despite the shut down of production. He retired in 1967. A third grade fluorosis (according to Roholm's criteria) was diagnosed in 1957 (fig 1); and a note in the records indicates that fluorosis had been diagnosed previously. This patient may have participated in Roholm's examinations, but the original records have now been lost. The fluorosis was found to be unchanged in 1967, shortly before retirement. No results of urine analysis during the employment are available. In 1982 the diffuse osteosclerosis of spine and pelvis had almost disappeared (fig 2). The ribs were normal, except for calcified muscle insertions at the lower border. The lumbar vertebrae still showed osteosclerosis of the

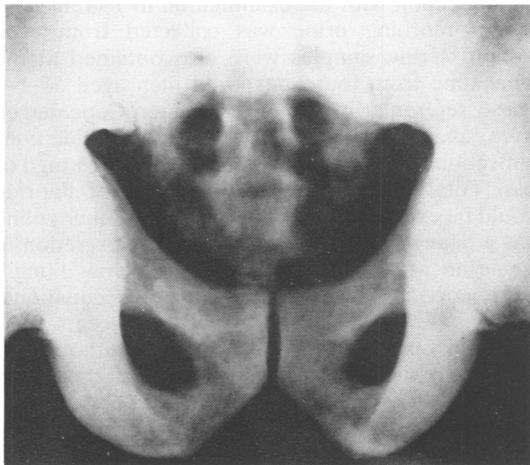


Fig 1 Case 1. Pelvis in 1957 after 28 years of fluoride exposure. Bone density in this stage three fluorosis is greatly increased, trabeculation appears accentuated, and bone edges are woolly due to irregular periosteal bone formation. No appreciable ligamentous calcification has developed.



Fig 2 Case 1. Pelvis in 1982, 15 years after retirement. Diffuse osteosclerosis has decreased, but cortical bone still appears thickened. Trabeculation has become blurred and the bone appears rather structureless. Considerable arteriosclerosis has developed.

end plates and of the vertebral arch, but the trabecular bone appeared almost normal. The pelvic bones and the femora showed osteosclerosis of the cortical tissue. The pelvis had a diffuse trabeculation. Thus the osteosclerosis of the trabecular bone tissue had decreased appreciably, while thickened cortical bone and calcified muscle insertions showed no improvement. This 81 year old patient is now confined to bed most of the time owing to muscular weakness.

#### CASE 2

A man, born in 1920, was hired in 1947. From the late 1960s, he often worked temporarily as a foreman in the office. In 1970 his right crus was broken in a traffic accident. Healing was delayed, partly because nails could not be used in the fluorotic bone; he was away from work for a year. Shortly after his return he was promoted to foreman and worked in an office until his retirement in 1981. A stage three fluorosis (Roholm's criteria) was found in 1957 (fig 3) and again in 1967; urine analysis in 1969 showed a fluoride excretion of 8.4 mg/l. The bone structure has changed considerably since 1967, particularly the trabecular bone tissue which has become more translucent (fig 3). The osteosclerosis of vertebral end plates and cortical tissue of the pel-

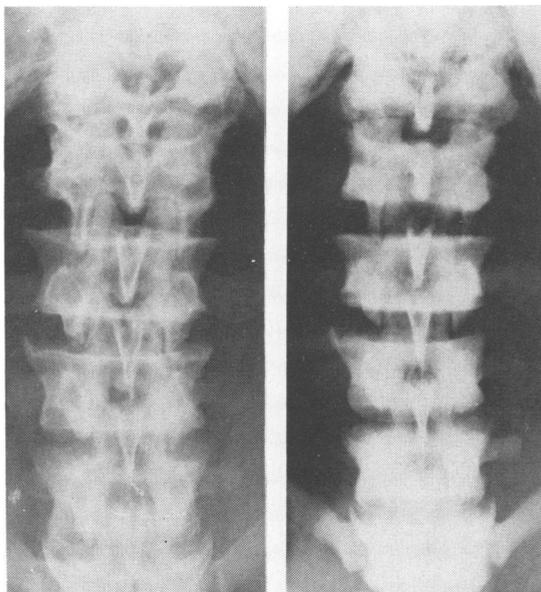


Fig 3 Case 2. Frontal view of lumbar spine in 1957 (left) and 1982 (right). After 10 years of exposure, a stage three fluorosis was diagnosed in 1957, and increased density and blurred structure of the spine is apparent. Twelve years after exposure ended, the spongy part of the vertebrae appears almost normal, though somewhat blurred, but the cortical bone, especially of the end plates and the vertebral arch, is still sclerotic. Also, osteophytes have developed.

vis, however, remains almost unchanged. Some osteophytosis of the lumbar spine has developed. This 61 year old man now suffers pain and restricted movement of his right knee and ankle, possible sequelae of the accident and the long immobilisation of the leg. In addition, rheumatic pain of his left knee is more frequent.

#### CASE 3

A man, born in 1917, started working at the plant in 1939. After one year he was laid off because no cryolite ore reached Copenhagen during the war. In 1946 he was rehired when production started again. From 1973 he has been employed as a door keeper. Skeletal fluorosis was not present in 1957, but radiographs in 1967 clearly showed a second grade fluorosis (Roholm's criteria) (fig 4). One urine sample from 1969 showed 18.5 mg/l, indicating an unusually high exposure. The chest radiograph in 1982 shows that ribs and vertebrae were almost normal with little osteosclerosis left (fig 4). The lumbar vertebrae exhibited sclerosis of the end plates and the vertebral arch, and the trabeculation was somewhat diffuse. In addition, osteophytes had

formed since 1967. In the pelvis the osteosclerosis had partly disappeared, but the trabeculation was still irregular and diffuse. The sclerosis of cortical bone, subperiosteal growths, and calcified ligaments appeared unchanged. Thus only the sclerosis of trabecular bone had ceased somewhat. This 64 year old man now has frequent lower back pain, constant pain in the hips, restriction of movements of the back, and difficulty rising from a low chair. His rheumatic pains were a main cause for his transfer in 1973 to the job as door keeper.

#### CASE 4

A man, born in 1918, was hired in 1948 and continued to work until 1974 when he retired because of a cerebral haemorrhage that caused a hemiparesis of the left side. A second stage fluorosis (Roholm's criteria) was found in 1957 (fig 5), and radiographs from 1967 showed no changes in the condition. A urine test result of 8.6 mg/l in 1969 indicated continued high exposures. In 1982 the sclerosis of ribs and vertebrae had almost ceased but the end plates and arches of the vertebrae still appeared sclerotic (fig 5). In addition, osteophyte development of the lumbar spine had continued. The pelvic trabecular bone was less sclerotic but more diffuse than in 1967, and the cortical bone was unchanged. Decrease of the trabecular osteosclerosis was thus apparent. This 63 year old man has sequelae from the stroke and a left side arthrosis of the hip.

#### FLUORIDE EXCRETION

In connection with the examination in 1982 a sample of morning urine was collected from each patient. Urine samples were also obtained at the same time from four unexposed men aged 55–64. These referents lived in the Greater Copenhagen Area, as did the patients, where the fluoride concentration in the drinking-water is about 0.5 mg/l or less. Total daily intakes below 1 mg of fluoride would be expected in all individuals examined; none was a heavy tea drinker. Thus fluoride excretion in the urine would be expected to be below 1 mg/l. Experience at the National Institute of Occupational Health indicates that urinary fluoride concentrations are usually below 1 mg/l in individuals without considerable exposures to fluorides at work or from drinking water. Measurements of EDTA-treated urine samples are carried out by fluoride sensitive electrode.<sup>6</sup> All referents had urinary fluoride concentrations below 1 mg/l. Case 1, who retired 15 years ago, had by now a fluoride excretion comparable with the level expected in non-exposed individuals. The three other patients had increased fluoride concentrations in the urine (table). Adjust-

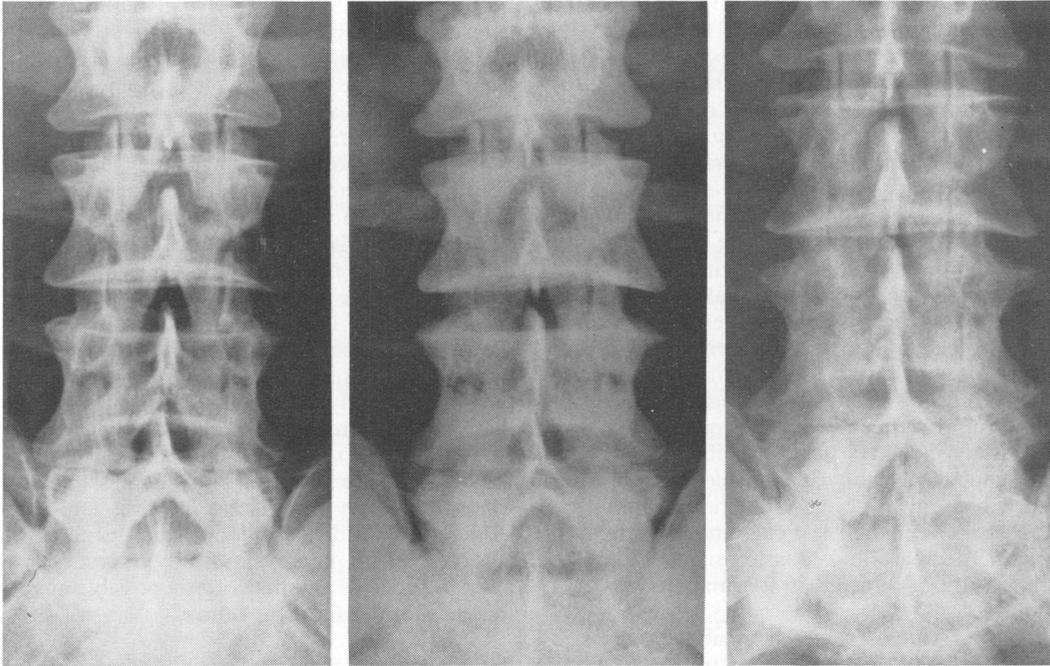


Fig 4 Case 3. Frontal view of lumbar spine in 1957 (left), 1967 (centre), and 1982 (right). No fluorosis was seen in 1957 after 12 years of employment. Ten years later, however, increased exposure levels had caused a stage two fluorosis. In 1982, nine years after cessation of exposure, bone density has decreased but trabeculation is blurred, and sclerosis of cortical bone persists.

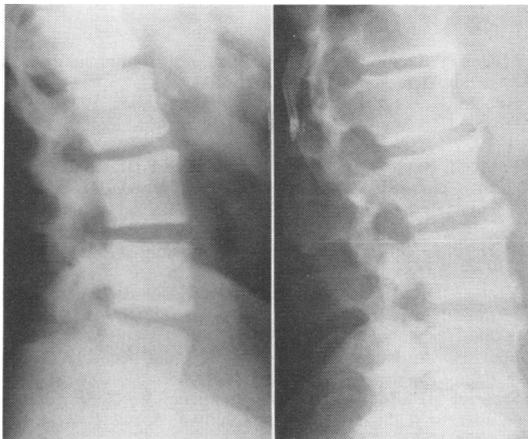


Fig 5 Case 4. Lateral view of lumbar spine in 1957 (left) and 1982 (right). A stage two fluorosis was diagnosed in 1957 after nine years of exposure. The vertebrae exhibit increased density which in 1982, eight years after retirement, has decreased. The bone structure is still blurred, however, and the cortical bone shows no decreased density.

#### Fluoride excretion in urine

Case No	Fluorosis stage in 1967	Year exposure ceased	Fluoride in urine		
			1969 (mg/l)	1982* (mg/l)	(mg/g Creat)
1	III	1967	—	0.7	0.8
2	III	1970	8.4	3.4	3.1
3	II	1973	18.5	2.6	2.1
4	II	1974	8.6	2.6	1.7

\*Four male referents aged 55–64 without occupational fluoride exposure showed the following results: 0.6, 0.6, 0.6, and 0.8 mg/l or 0.3, 0.3, 0.7, and 0.7 mg/g creatinine.

ment according to the creatinine excretion levels did not significantly change the results.

#### Discussion

The reversibility of skeletal fluorosis suggested by Roholm<sup>2</sup> has been studied in more detail by Fritz.<sup>7</sup> Seven of 42 German patients with skeletal fluorosis showed a decreased degree of osteosclerosis 13–19 years after exposure ceased. Three cases were described in detail, but little information was given

on other cases of fluorosis known to Fritz. Thus the evidence presented suggests that reversibility of osteosclerosis occurred in at least seven cases. Schlegel mentioned five patients who, two to three years after retirement, experienced both a decrease in fluoride content of bone tissue and a decreased bone density on the radiographs.<sup>8</sup> Franke *et al* noted that in two patients osteosclerosis faded within two to five years, though in nine other patients, no appreciable improvement could be seen after five years without occupational exposure to fluoride.<sup>4</sup> These studies support the notion that reversibility of osteosclerosis is possible. In patients with slight degrees of skeletal fluorosis any improvement of the condition after a few years of retirement may be difficult to recognise. Thus over longer periods considerable improvement would be more likely. The present study indicates that reversibility may be a normal course of trabecular osteosclerosis after exposure has ended. Thus all patients who were alive 15 years after their last examination showed a remarkable decrease in osteosclerosis, although the resulting diffuse, blurred trabeculation was not normal.

The earlier studies referred to above suggest a characteristic pattern: decrease of trabecular bone density but unchanged cortical sclerosis, subperiosteal growths, and calcification of ligaments. These observations are entirely in agreement with the present study. One particular form of possible fluorosis followed a different pattern, however. In the 1950s several patients in Spain suffered a "periostitis deformans," apparently related to adulteration of wine with large amounts of fluoride.<sup>9</sup> The patients initially developed some osteosclerosis that later reverted into a definite osteoporosis. Further, the subperiosteal nodules tended to disappear spontaneously.<sup>9</sup> Thus the wine related bone disease seems to differ from occupational fluorosis.

The reversibility of the osteosclerosis may be related to the continued excretion of fluoride accumulated in the body. Brun *et al* found increased fluoride concentrations in the urine of cryolite workers several years after retirement.<sup>5</sup> After defluoridation of the drinking water in a Texas community, local residents continued to excrete excess fluoride in the urine for at least 113 weeks.<sup>10</sup> These observations are in agreement with the present study. More than 99% of the body burden of fluoride is retained in the calcified tissues, and the continued excretion must be related to a slow release from the bones. After a period of high fluoride exposure, experimental subjects excrete fluoride in amounts that decrease exponentially with time.<sup>11</sup> Calculations based on these data suggest that half of the fluoride accumulated in the body would

be excreted in about eight years.<sup>12</sup> Other data indicate that the annual turnover, or remodelling, rate of bone tissue is 2.5% and 10% for cortical and trabecular bone, respectively.<sup>13</sup> Spine and pelvis appear to have average turnover rates of 7–8%,<sup>13</sup> which would correspond to a half life of about nine years. The information available indicates that fluoride, after incorporation into skeletal tissues, is later released in relation to the normal remodelling of the bones. If high fluoride exposures are no longer present normal bone tissue is then formed.

Other "bone seekers," such as lead, may be released slowly from the skeletal stores and may then prevent blood concentrations from returning to normal even several years after exposure has ended.<sup>14</sup> Similarly, continued release of accumulated fluoride could prevent blood fluoride concentrations from returning to normal and could cause a continued exposure of other body tissues to fluoride. The reversibility of skeletal fluorosis and skeletal storage of fluoride could then, theoretically, lead to chronic effects. A mortality study of cryolite workers is in progress and may offer a possible answer to this question in the near future.

Patients records from past examinations were kindly made available by Dr F Gyntelberg, department of occupational medicine, Rigshospitalet. Fluoride and creatinine determinations were performed by Jytte Molin Christensen of the Danish National Institute of Occupational Health.

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- <sup>1</sup> International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;1:532-5.
- <sup>2</sup> Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
- <sup>3</sup> Weinstein L, Swartz MN. Pathogenic properties of invading micro-organisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.