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THREE YEARS' EXPERIENCE WITH SODIUM-FLUORIDE THERAPY OF OSTEOPOROSIS

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The importance that has been attributed to osteoporosis in recent times is demonstrated by figures given by Lutwak & Whedon (1969). In the U. S. more than 4 million people were found to suffer from osteoporosis. Smith & Rizek (1966) even estimated that 14 million women in the U. S. show a significant vertebral atrophy, and about 1.6 million have dorsolumbar vertebral fractures without symptoms. The incidence of advanced osteoporosis in the male population is much lower with advanced age (e. g. 5 to 10 per cent over 50 years of age).

In spite of the above-mentioned importance of osteoporosis the success of previous therapy methods was not encouraging.

As we have seen massive osteosclerosis (Franke 1968 a, b, 1972 a, b, d, Runge et al. 1972) in many patients with industrial fluorosis, and encouraged by the good results with the treatment of the osteoporosis with sodium fluoride reported in the literature (Rich. et al. 1961, 1964, 1966, Bernstein et al. 1963, 1967, Cohen & Rubini 1965, Adams & Jowsey 1965, Reutter & Siebenmann 1965, Cass et al. 1966, Luckert et al. 1967, Reutter 1967, 1970, Jowsey et al. 1968 a, b, 1971, Cohen et al. 1969, Kuhlencordt et al. 1969, 1970, Schenk et al. 1970, Merz et al. 1970, Thiébaud et al. 1970 a, b, Dalderup 1970, Beickert 1971) as well as by reports of lower incidence of osteoporosis in high fluoride areas in Texas and North Dakota (Leone et al. 1955, Leone 1960, Bernstein et al. 1966), we started sodium fluoride therapy in January 1969. A report on our first results of this treatment was given by Mattner & Franke at the Congress of the Orthopaedic Society of the GDR in

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1971. The purpose of this paper is to demonstrate our experiences, successes and failures with the NaF-therapy of osteoporosis.

MATERIAL AND METHODS

Since that time we have treated 46 patients with sodium fluoride. In the present paper 33 patients between 31 and 69 years of age with ideopathic osteoporosis are evaluated, and one patient with steroid osteoporosis. These patients were treated for a period 13 to 42 months with sodium fluoride. The time of treatment of the 12 missing patients was too short (under 12 months).

Osteoporosis was diagnosed clinically (diffuse bone pains, loss of height, indirect and direct compression-pain of the spine), roentgenologically (diminution of the mineral content, ballooned disks, compression vertebral fractures, determination of the corticalis-index according to Barnett & Nordin (1960), histologically by means of iliac crest biopsy (diminution of the bone mass, exclusion of other bone diseases) and biochemically (failure of specific abnormalities).

The patients were given 20 to 60 mg sodium fluoride per day in three portions, either as 10 or 20 mg powder or as tablets ("Fluoretten forte"). After the onset of the effect of fluoride (approximately after 1.5 to 2 years) we reduced the daily doses to 10 to 20 mg sodium fluoride or we passed over to the interval therapy with a 4 to 8 weeks' pause.

Once a year we carried out an accurate clinical examination, such as measuring the body height, the indirect and direct compression-pain of the spine and the chest and the sensitivity to tapping of the spine. Patients came to our clinic at intervals of 6 to 8 weeks, in order to have the serum calcium and phosphorus levels, alkaline and acid phosphatase determined.

Each year we carried out a radiological control (thoracic and lumbal spinal column in 2 planes and pelvis). As the usual x-ray picture shows only changes of the bone density of 20 to 40 per cent mineral-loss (von Leitner 1969, Heuck 1970), we used a method of comparative radiological densitometry. We took an x-ray picture of the thoracolumbal transition with an aluminium wedge (9 steps), that lay in an 18 cm high water-column beside the patient lying on his side. In a vertebral body the relative radiological change of the density was measured with the photometer (Schnellphotometer des VEB Carl Zeiss Jena) before the beginning of the treatment and then once a year under equal conditions. With our method it is not possible to determine the absolute concentration of hydroxyapatite in the vertebral body.

In 10 patients we carried out a second iliac crest biopsy after 14 to 27 months of fluoride therapy. The bone material was decalcified with nitric acid and stained with azan, hematoxylin-eosin, PAS, alcian-blue. In addition, we examined these preparations histomorphometrically. With the eyepiecemicrometer (VEB Carl Zeiss Jena) we determined the average thickness of the trabeculae in the biopsy cylinders before and after treatment with NaF. We measured about 20 trabeculae per patient. Simultaneously, we determined the volumetric density of the bone with an integration eyepiece on the basis of the point-counting-volumetry. We counted on the average 10 visual fields per biopsy cylinder. The measurings were compared before and after treatment and secured statistically by means of Student's t-test.

Table 1. Subjective results of 34 patients with osteoporosis after 13 to 42 months treatment with sodium fluoride.

Time of the treatment	Group 1 painless or distinctly improved	Group 2 improved	Group 3 unchanged	Group 4 deteriorated	Total numbers
13–42 months	19	4	5	6	34
27–42 months	15	3	4	4	26

We examined the 24-h-urinary excretion of fluorine and the conditions of the gastric juice in order to find causes for the failure of our treatment in a few patients. The 24-h excretion of fluorine was controlled twice a year during the NaF-treatment. We determined the normal acidity, hyper- and hypoacidity with the indicator tablets (Acidotest of Chinoin-Budapest Hungary).

RESULTS

Subjective:

Table 1 shows the subjective results of the treatment. Group 1 involves painless patients and persons with intermittent slight back pains. Group 2 involves patients with distinctly diminished complaints, which temporarily disappear, and with stronger load capacity of the skeleton. Both groups comprise 23 patients, i. e. that more than two-thirds of the patients felt better after the fluoride therapy. An isolated evaluation of the patients, treated for 27 to 42 months and having received much reduced doses in the last half to one year (upper part of Table 1) yielded similar results (18 of 26 patients show an improvement).

Clinical:

Table 2 shows the behaviour of the clinical symptoms: direct and indirect compression-pain of the spine, compression-pain of the chest, sensitivity to tapping of the spine and body height in relation to the subjective disorders. There is a good correlation and a distinct improvement of these findings in more than half of the patients.

Radiological:

In the normal usual x-ray picture we could demonstrate a distinct increase of the density of the vertebral bone and an enlargement of the

Table 2. Clinical results of 34 patients with osteoporosis after 14 to 42 months of treatment with sodium fluoride.

Time of treatment	Group 1 – clinical			Group 2 – clinical			Group 3 – clinical			Group 4 – clinical			total numbers clin.		
	improved	unchanged	deteriorated	improved	unchanged	deteriorated	improved	unchanged	deteriorated	improved	unchanged	deteriorated	improved	unchanged	deteriorated
13–42 months	12	7	–	3	1	–	3	1	1	–	2	4	18	11	5
27–42 months	10	5	–	2	1	–	3	1	–	–	1	3	15	8	3

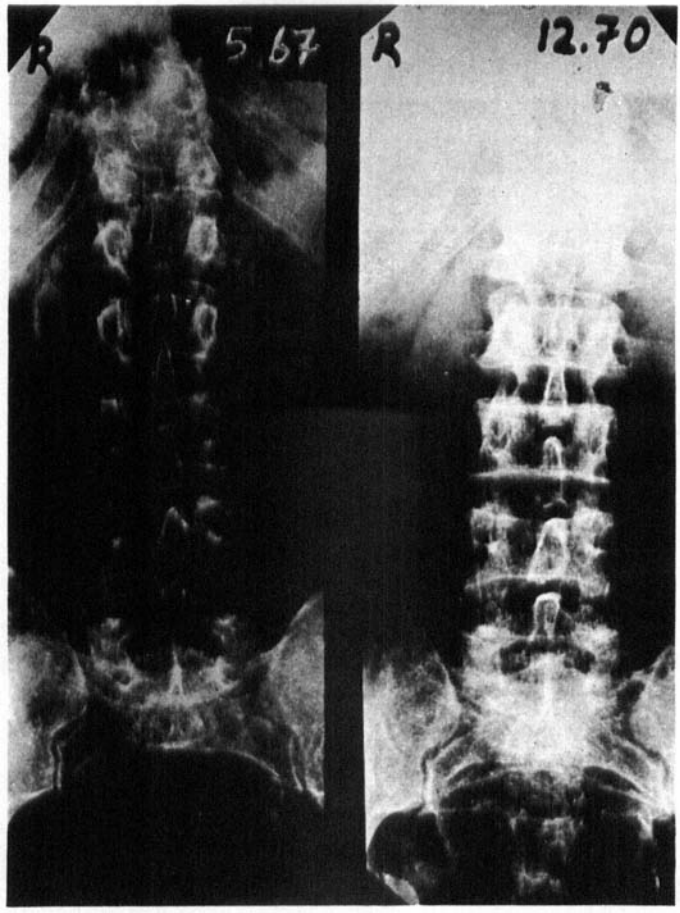

Figure 1. Pat. K. K.: The skeleton shows a clear remineralization after 2 years of treatment with 40 to 60 mg sodium fluoride per day.

bone trabeculae in 6 patients (only males) with a dosage of 30 to 60 mg/sodium fluoride per day after 18 to 33 months (Figure 1).

In groups 3 and 4 three patients showed an impairment of the radiological findings in the form of a fracture of the femur and two fractures of vertebral bodies. By means of our densitometry method we examined 23 patients after 1 to 2 years of treatment. Table 3 shows: an increase of the bone density in 18 persons, an unchanged density in one person and a decrease in 4 patients. The control of the densitometry revealed the same trend after two to three years of fluoride

Table 3. Results of the comparative radiological densitometry in 23 patients with osteoporosis after 1 to 2 years of treatment with sodium fluoride in relation to the subjective success of this therapy.

Group 1 13 patients with distinct improvement or painless				Group 2 3 patients with improvement				Group 3 5 patients with unchanged complaints				Group 4 2 patients with deterioration			
++	+	=	—	++	+	=	—	++	+	=	—	++	+	=	—
4	8	0	1	2	1	0	0	0	2	1	2	0	1	0	1

++ = distinctly improved e.g.: increase of the density of the vertebral body of 4 or more steps in the aluminium wedge = 6 patients

\+ = improved e.g.: increase of the density of the vertebral body of 1 to 3 steps in the aluminium wedge = 12 patients

= = unchanged e.g.: no increase of the density = 1 patient

— = deteriorated e.g.: decrease of the density of the vertebral body of 1 to 2 steps in the aluminium wedge = 4 patients

therapy. An accurate statement was not possible at this time because of changed technical conditions (installation of a new x-ray-apparatus).

Biochemical:

Blood phosphate levels, the plasma alkaline and acid phosphatase levels did not show any distinct changes. The blood calcium levels, however, showed a significant increase (Student's t-test) in the course of the treatment (Figure 2).

The urinary excretion of fluoride did not show any positive trend resulting from therapy. However, we found a surprising result in the evaluation of the gastric acid. Of the 11 patients of groups 3 and 4 seven patients showed a reduction or a complete lack of gastric acid. But in groups 1 and 2, 4 patients only out of 21 had a reduction of gastric acid. The difference was significant in the x^2-test with 1 per cent likelihood of error.

Histological:

In our histological investigations we found a distinct increase in the bone mass in spite of the small dose we had applied (Figure 3).

Histomorphometrically we found in 8 patients in measuring the average thickness of the trabeculae before and after the NaF-treatment

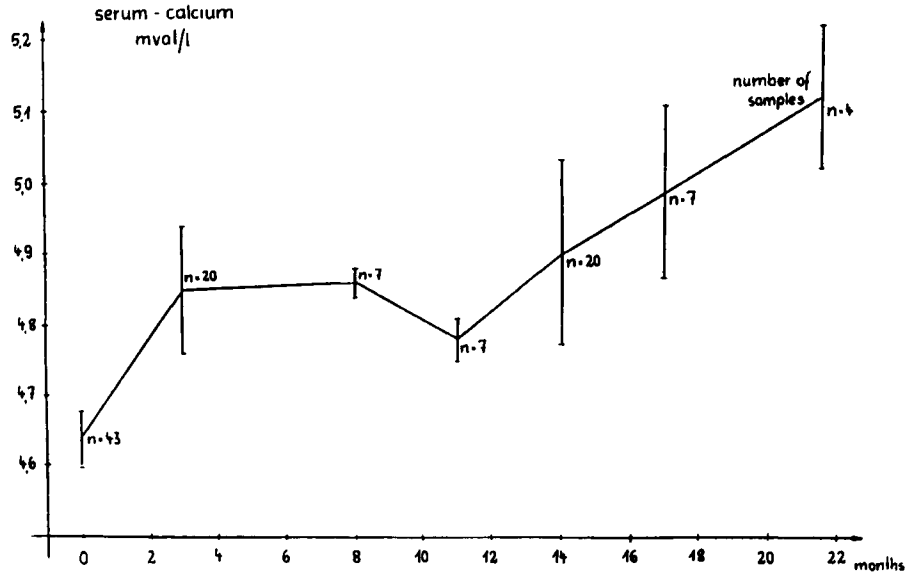

Figure 2. The average levels of the serum calcium before and during the NaF-therapy. (The levels for the months 1–6 and 13–18 differ significantly from the starting levels according to Student's t-test).

a significant increase to 70 μm and in determining the volumetric bone density by means of point counting volumetry an increase of the bone mass to 16 per cent (Table 4). The results were made sure by means of the Student t-test.

The new bone formation developed subperiostally in the form of fibrous bone formation with beginning transformation in lamellar bone (Figure 4) and on previously existing trabeculae (Figure 5).

The newly formed bone is in particular irregular and atypical in the compacta. Figure 6 shows a strongly trickened compacta with irregularly arranged osteons and enlarged cavities of osteocytes, with osteoid between them. Spread osteoid seams and the so-called "mottled bone" according to Johnson (1965) were found only rarely. In one instance we could identify a so-called "spongiosation of corticalis", which we (Franke et al. 1971, 1972 a, c) and other authors (Weinmann & Sicher 1955) had established in human and experimental animal bone fluorosis (Figure 7).

In the microradiogram, for which we are indebted to Prof. Dr. Kuhlencordt, Hamburg, the newly formed bone shows enlarged osteocytes lacunae, but almost normal mineralization (Figure 8).

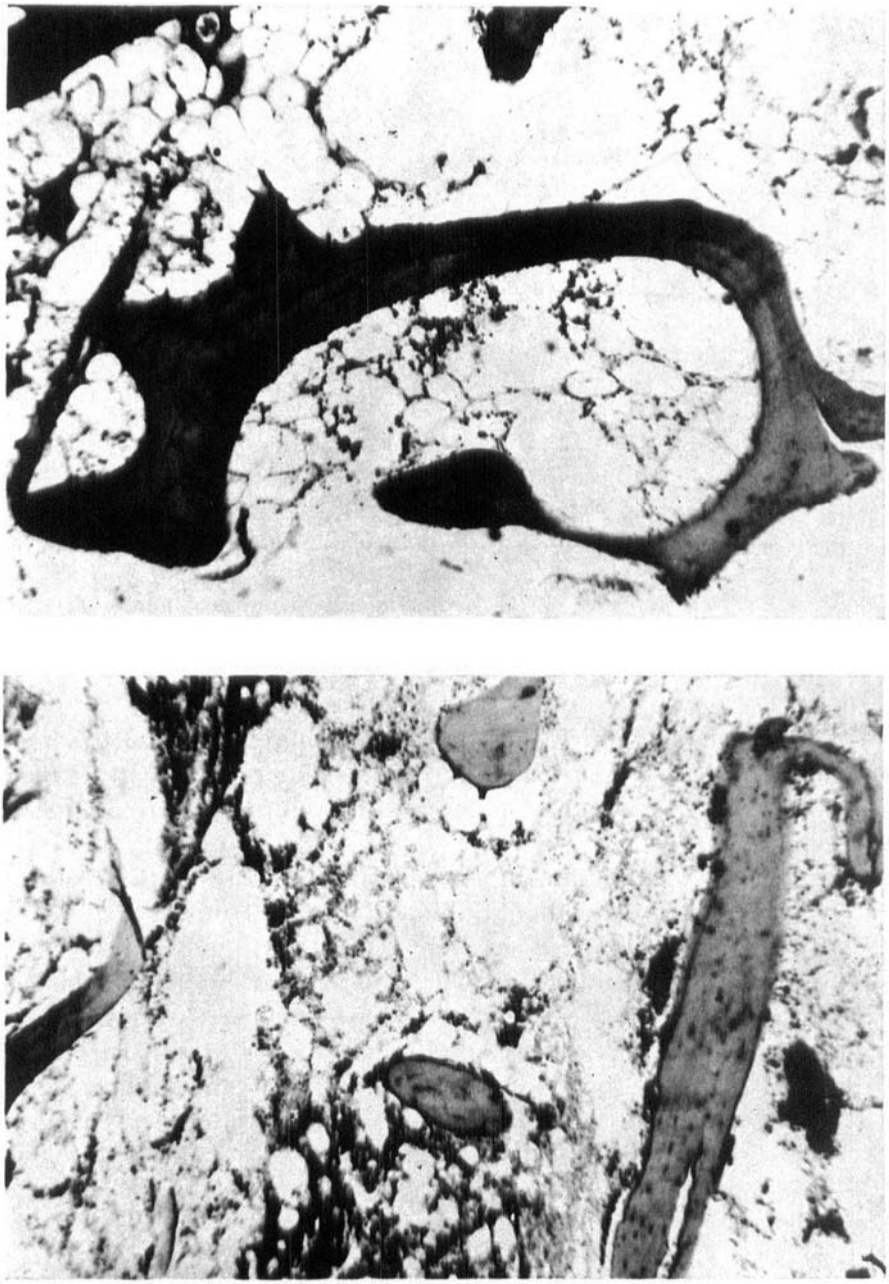

Figure 3. The increase of the bone mass in the NaF-therapy in 2 patients:
left side—before the treatment H.E. 1:50
right side—after the theatment H.E. 1:50

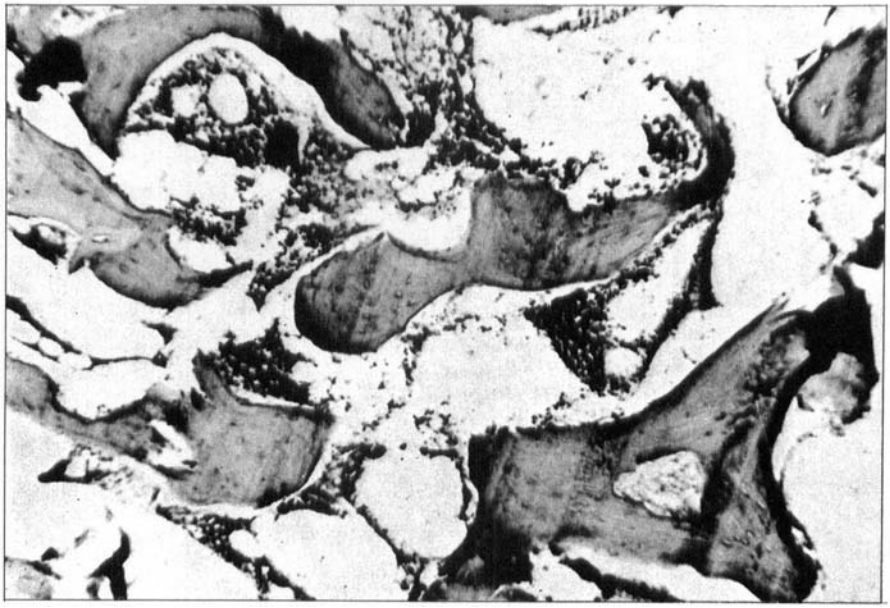

Table 4. Histomorphometric results of the iliac crest biopsies of 10 patients with osteoporosis before and after treatment with sodium fluoride.

Patient	Dose in mg NaF per day	Time of treatment in months	Result group	Average thickness of the trabeculae in μm			Volumetric bone density		
				before treatment	after treatment	increase significant	before treatment	treatment after	increase significant
1. K. K.	40–60	24	1	98.0	168.5	yes	30.4	38.9	yes
2. F. E.	40	18	2	115.4	115.6	no	21.6	29.5	yes
3. E. B.	35–40	18	3	90.4	113.9	yes	15.1	25.0	yes
3. J. J.	20–60	14	2	119.0	179.5	yes	26.2	30.6	no
5. K. Kh.	20–40	18	1	109.3	120.2	no	27.1	34.3	no
6. M. H.	30–40	19	4	98.6	98.9	no	25.8	21.7	no
7. G. R.	40–53	14	2	125.0	171.7	yes	26.1	32.5	yes
8. H. H.	20–30	18	1	89.8	135.7	yes	23.5	36.8	yes
9. H. P.	30–40	14	1	–	168.0	–	–	36.6	–
10. B. L.	20–30	27	1	110.9	158.5	yes	20.5	36.5	yes

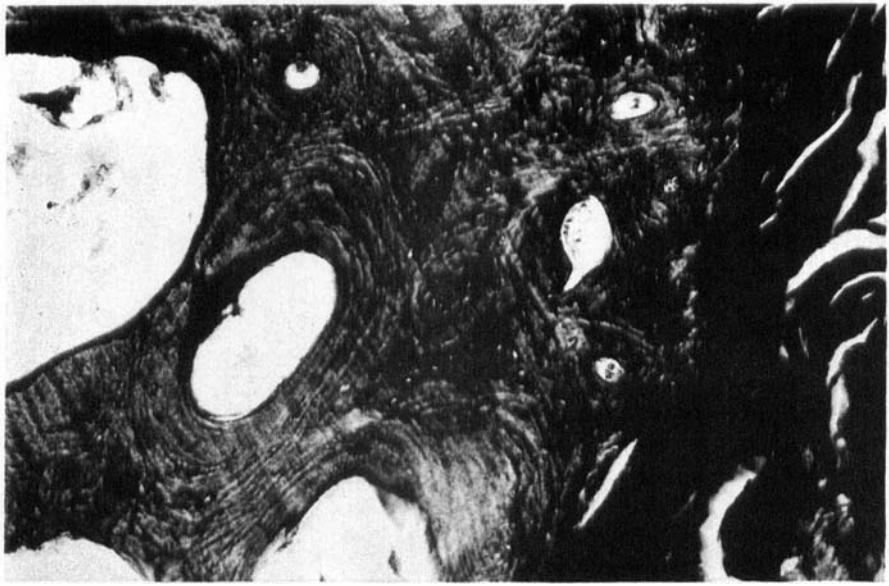

Figure 4. Subperiostal new formation of fibrous bone with transformation in lamellar bone. (Azan 1:80)

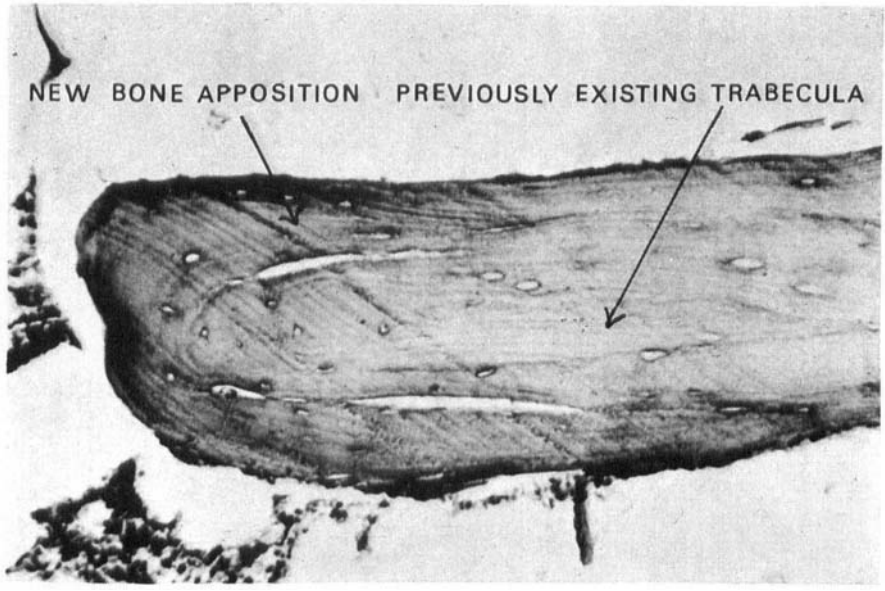

Figure 5. Distinct apposition of new bone on previously existing trabecula. (H.E. 1:130)

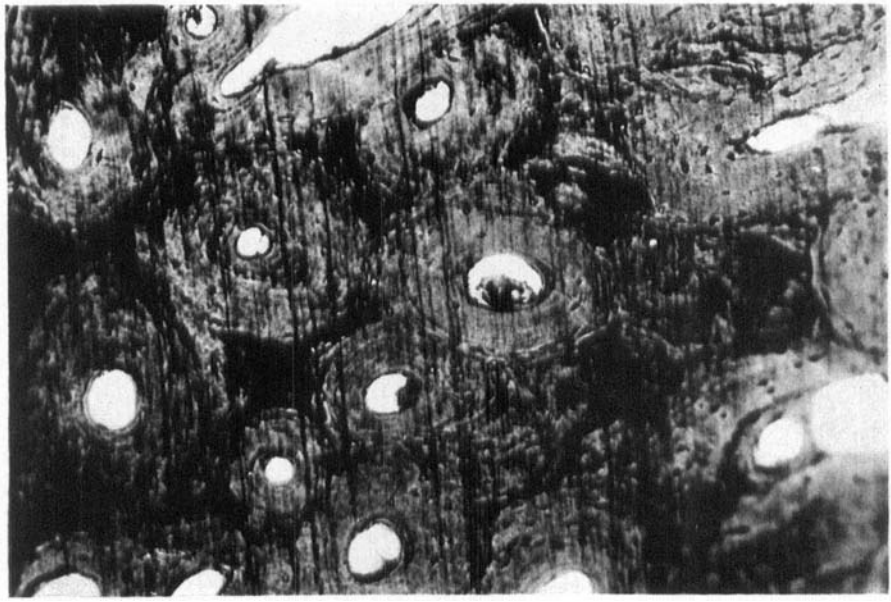

Figure 6. Strong thickened compacta with enlarged cavities of osteocytes, between the oesteons is osteoid. (Azan 1:80)

Figure 7. Spongiosation of the corticalis. (H.E. 1:50)

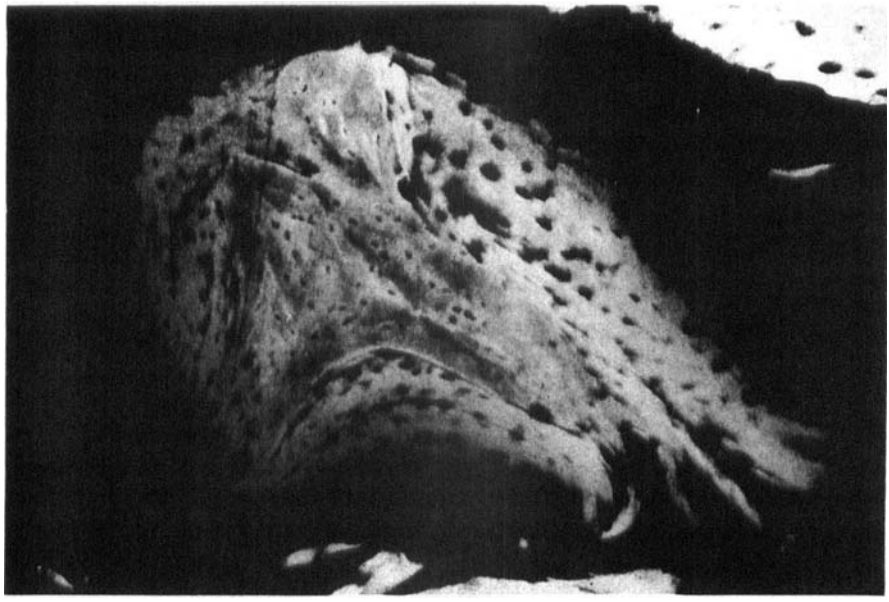

Figure 8. Microradiogram. Distinct bone apposition around previously existing trabeculae is to be seen. The new formed bone shows enlarged cavities for osteocytes, but good mineralization. (1:50)

Side effects:

In the beginning of the therapy we observed the following side effects: nausea, sensation of repletion, gastric disorders, anorexia, vomitus and diarrhea. The patients with vegetative and pre-existing gastrointestinal disorders suffered from these complaints more violently. Since there were no "enteric coated tablets" available, these gastrointestinal complaints appeared in particular in doses over 40 to 60 mg NaF per day. The highest dose which was tolerated by a patient was 80 mg NaF per day. Patients with known hyperacidity could not take in more than 20 mg NaF per day.

Powder and tablets were tolerated differently. In most patients these disturbances diminished spontaneously after a certain time or through application of sodium fluoride with much liquid after the meals.

In 8 patients we observed a very unpleasant side effect, also described by other authors (Rich et al. 1964, Lukert et al. 1967, Bernstein & Cohen 1967, Thiebaud et al. 1970 a). These patients complained of severe pain in the feet, knee or hip joints. Some of them had earlier

suffered from similar complaints. After temporary reduction of the dose these pains disappeared and did not appear again later.

In a woman we observed the following alarming side effect: for a period of 14 months she received 30 to 40 mg, then, for a period of 12 months 20 mg sodium fluoride per day. After these 2 years she developed a distinct hypaesthesia in both legs to the navel and in both arms to the elbows. Apart from a slight peripheral ataxia, the reflex status was normal. The neurologist diagnosed a sensible neuritis. A toxical neuro-myelopathia could not be excluded. The complaints, however, disappeared completely. Whether the damage was due to the application of fluorine could not be discerned.

DISCUSSION

The results of treatment of osteoporosis have not been satisfactory so far. The therapy with sex hormones, introduced by Albright et al. (1948), gave subjective alleviation of pain and positive nitrogen and calcium balances. New bone formation, however, was found neither roentgenologically nor histologically (Jesserer 1953, Lafferty et al. 1964, Reutter 1967, Rose 1967). With estrogens it is possible to reduce bone resorption only. Similar results were obtained in the treatment with anabolic hormones (Wagner 1965, Rose 1967, Saville 1968, Kuhlencordt et al. 1969, Jesserer 1970).

The administration of high doses of calcium propagated by Nordin (1962) was not sufficiently successful either, since an increase of the bone mass was not found (Lafferty et al. 1964, Rose 1967, Reutter 1967, Kuhlencordt et al. 1969, Jesserer 1970). Likewise, the therapy with vitamin D was disappointing (Jesserer 1953, Rose 1967, Reutter 1967).

The application of calcitonin (Milhaud et al. 1969, Baud et al. 1969) also only resulted in a reduced effect of bone resorption, whereas Jowsey et al. (1971) and Bellwinkel et al. (1971) observed even a negative effect. The phosphonate-treatment proposed by Fleisch et al. (1969) also seems to be unsuccessful (increase of the osteoid mass) according to Jowsey et al. (1970).

By the NaF-therapy of osteoporosis it was possible to demonstrate new bone formation roentgenologically as well as histologically for the first time.

As has been previously shown, there were many cases with partly enthusiastic success, but nevertheless also a few therapeutical failures. Therefore we studied intensively the causes of failure of fluoride thera-

py in these patients. Among the 6 cases with complete therapeutical failures there were 2 patients who had taken sodium fluoride irregularly and had thus received too small doses. This explanation, however, fails in the rest of the patients. Obviously there exists a distinctly different response of the individual to fluoride. This fact is known in the chronical industrial human fluorosis. We observed two aluminium-smelters who had worked at the same place for 15 years; one of them suffered from fluorosis of stage III, the other from just beginning changes. Which factors play a role in this process are not yet fully known, but Pandit et al. (1940) found an increase in the fluoride effect in vitamin C deficiency and in malnutrition. Kidney insufficiency also leads to an increased storage of fluorine in the body (Linsman & McMurray 1943, Havelka 1970). However, the ability of resorption of the gastrointestinal tract and the height of the kidney threshold for fluorine have a distinct influence on the intake of fluorine in bone. The finding that there was frequently a reduction of the gastric acid in groups 3 and 4 leads to the conclusion that there is obviously a bad resorption of fluorine in a gastric acid deficiency. In these cases a therapy of substitution with pepsin acid is perhaps indicated.

There are three further problems:

1. The combination therapy with calcium or anabolic steroids. We combined the fluoride intake with calcium or anabolic steroids in a few patients. A comparison of these groups, which were very small, with the patient groups which received NaF alone, showed no clear differences. On the strength of our investigations we must reject the simultaneous intake of fluoride and calcium (Cohen et al. 1969, Jowsey et al. 1971), because insoluble calcium fluoride develops in the intestine which is absorbed with difficulty. Ericsson (1971) therefore recommended a combination of sodium monofluorphosphate with complex-fixed calcium. A combination therapy with anabolic steroids seems to be recommendable.
2. Since the publications of Larget (1952, 1960) it has been known that the storage of fluorine in the skeleton is reversible. Roholm (1938) and Fritz (1958) found a regression of sclerosis in industrial fluorosis after the fluoride influence had stopped. New investigations are necessary to find out whether one must go on giving continuous small doses of 5 to 10 mg/NaF per day after the success of the treatment or if an interval therapy with pauses of 4 to 12 weeks should be preferred.

3. The slight increase of the serum calcium level could indicate an increased activity of parathyroid during the fluoride therapy. In animal experiments (Faccini 1969, Franke 1971) there were also signs of a stimulation of parathyroid. Cohen & Bernstein (1967) and Reutter et al. (1970) demonstrated signs of hyperplasia of these glands during fluoride therapy. However, we could not find radiological and biochemical signs of hyperparathyroidism in workers with industrial fluorosis, even in serious cases.

Opponents of the fluoride treatment maintain, however, that newly formed bone is of poor quality. The following reasons speak against that argument:

1. As we have shown above, pathological changes of the newly formed bone are limitated with our small doses of 20 to 60 mg per day—a finding that was also made by Schenk et al. (1970) in a patient after the reduction of the fluoride dose.
2. In investigations on the breaking load on a fluorosis skeleton we (Franke et al. 1972 b, Runge et al. 1972) found a small diminution of the resistance to pressure in the isolated cylinders of the corticalis of femur in comparison to the normal bone. However, the total lumbar vertebral body showed a resistance to pressure, which was three times higher.
3. The determination of the absolute content of hydroxapatite showed in the femur neck in a patient with serious industrial fluorosis (stage III of Roholm) approximately a higher amount by three times: 683 mg hydroxy-apatite/ml bone in comparison to a normal content of 320 mg hydroxy-apatite/ml bone (Rempel 1972).

Fluoride treatment does not necessarily result in replacement bone. Some patients recorded that the complete load capacity of their skeleton was recovered after fluoride treatment. Furthermore, we believe that any new formation of bone, even of inferior quality, is better than no formation at all.

Nevertheless, each fluoride treatment of osteoporosis should be carried out under strict control of a specialist.

SUMMARY

Since the end of 1969 we have treated 46 patients suffering from idiopathic osteoporosis with sodium fluoride. The duration of the treat-

ment was 12 to 42 months. In spite of the relatively small doses of 20 to 60 mg sodium fluoride/d—as compared to those given in the literature—we obtained significant alleviation of pain or freedom from pain in ⅔ of the patients. In the normal x-ray-picture some patients showed obvious remineralization. In 18 out of 23 patients we were able to detect a strong increase of bone density by means of comparative densitometry of the thoraco-lumbal transition, a method we developed. In 10 patients we performed repeated biopsies of the iliac crest. Histologically there was clear evidence of an increase in bone mass. We found a new formation of subperiostal fibrous bone and a formation of new bone on previously existing trabeculae. The bone structure was only partly irregular: spread osteoid seams were found by us only rarely. We attribute the relatively rare atypical bone changes—in comparison to those given in the literature—to our small doses. Employing histomorphometric methods (measuring of the average thickness of the trabeculae and determination of the volumetric bone density by means of point-counting volumetry) we could show an increase in thickness of the trabeculae from 50 to 70 μm and an increase in density of 16 per cent. Furthermore, attention is given to the side effects and possible causes of complete failure of the sodium fluoride therapy in a number of patients (reduction in gastric acid).

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