FLUORIDES AND MAN[1,2]

By Harold C. Hodge and Frank A. Smith
Departments of Pharmacology, and of Radiation Biology and Biophysics, School of Medicine and Dentistry, University of Rochester, Rochester, New York

Introduction

Brief mention will be made of the principal and most important application of fluoride to the health of man—water fluoridation. In recent months, this public health measure has been adopted by state legislatures in Connecticut, Minnesota, and Illinois. No serious scientific question remains about the efficacy of water fluoridation in reducing the incidence of dental caries. Some view this as remedying a fluoride deficiency. As to safety, no injurious effect has been detected in individuals living in communities with natural or added fluoride at the optimal concentrations in the water supplies. No specific large scale epidemiological studies are available comparing the health of the populations of fluoridated communities with that of communities where the water contains only traces of fluoride. Clinicians, however, hold the opinion that there is no difference in the incidence nor the severity of morbidity dependent on the presence or absence of recommended levels of fluoride in the community drinking water.

The bulk of this review is devoted to the possibility that fluoride can be used in the prevention or treatment of osteoporosis. Finally, some comments are added on other properties of fluoride as they affect man.

Dental Caries

Water fluoridation ranks as one of the important public health measures of our time. Optimal concentrations of fluoride in community water supplies are associated with fewer carious teeth; cavities tend to be smaller, and to progress more slowly (13). Time-cost studies show a reduction to about one-half in the cost of providing dental care (6). The beneficial effect of fluoride on tooth health is established (*a*) by evidence drawn from communities in which water supplies are naturally fluoridated, where populations for generations have consumed concentrations of up to several parts per million; (*b*) by studies of communities in which fluoride has been added to the drinking water supply to achieve optimal concentrations; and (*c*) from a large number of studies on experimental animals. About 72 million citizens of the United States now are benefited by this measure, approximately 10 million of whom

[1] The survey of literature pertaining to this review was concluded in August, 1967.

[2] This paper is based on work performed in part under contract with the U. S. Atomic Energy Commision at the University of Rochester Atomic Energy Project and is Report No. UR-49-842.

consume naturally fluoridated community water supplies. Under control conditions enamel mottling has not been a problem. No disfiguring brown stain has been found; on the contrary, the teeth are described as esthetically satisfying. Malocclusion does not differ markedly regardless of whether water supplies are fluoridated (13). Dental decay can also be reduced by dietary control, e.g. by breast feeding compared to formula-feeding, by limiting dietary sugar and refined carbohydrates, and especially by reduction in total food intake as occurred in war-time Europe. In each case, however, data are available to show that fluoride exerts an additional protective influence (36, 77, 83). Fluoride presented a possible hazard, enamel mottling, in the proposed use of fish flour to combat protein malnutrition in infants in many parts of the world. The 169 ppm of fluoride in fish flour (43), due almost entirely to fish bone, would contribute 1.7 to 8.4 mg F per day to the diets of children consuming 10 to 50 g of fish flour. Vehicles other than public water supplies are being investigated in various countries, e.g. tablets, fluoridated milk, fluoridated salt, topical applications, and fluoride dentrifices (31). In most cases, these measures have been shown to be less effective than water fluoridation.

Placental transfer.—The question of whether prenatally administered fluoride has a beneficial effect on the health of the deciduous teeth is unresolved. A number of facts about placental transfer of fluoride are reasonably well established. (*a*) Fetal blood fluoride concentration is approximately equal to that of the maternal blood (39). Most analyses give values of 0.1 to 0.2 ppm for the fetal or maternal blood levels. Whether the value should be approximately 1/10 this concentration is the subject of active research on analytical methods (71, 78). (*b*) The placenta contains fluoride, normally around 1 ppm. Calcified loci have higher fluoride concentrations, presumably reflecting the fact that calcifications anywhere in the body tend to fix fluoride. (*c*) The placenta is permeable to the fluoride ion, but the passage appears to be impeded. Studies with radiofluoride administered intravenously to women in labor showed that the fetal blood concentrations of ^{18}F never reached more than one-third the maternal blood concentrations (32). Placental concentrations were intermediate. (*d*) Fluoride not only crosses the placenta but deposits in fetal bones and teeth; the concentration is increased with the age of the human fetus (15) and with higher fluoride intake by the mother, human (38) or guinea pig (47). Percentages of calcium and calcium: phosphorus ratios in fetal bones and teeth were significantly higher when the maternal drinking water contained 0.5 to 1 ppm F than when the drinking water contained only 0.1 ppm F (40). An increase of calcium: phosphorus ratio is important because the presence of a more stable molecular form of the crystalline mineral is implied, i.e. greater resistance to carious attack.

Evidence is divided on the question of whether prenatally deposited fluoride in the deciduous tooth is able to reduce the incidence of dental caries. Blanyey & Hill in the Evanston fluoridation study (13, 14), and Arnold et al. (5) in the Grand Rapids study found that children who had

received fluoride both prenatally and postnatally had less caries at the ages of 6, 7 or 8 than children who had received fluoride postnatally only. Contradictory evidence was provided by Carlos in the Newburgh study (19), and most recently by Horowitz in the incomplete Minneapolis study (46); no benefit accrued to the teeth of the offspring whose mothers drank fluoridated water during pregnancy. Since the surface enamel, which is important in the initiation of caries, is laid down in the deciduous teeth after birth, in our judgment it is improbable that prenatal fluoride decreases caries incidence in deciduous teeth.

Osteoporosis

Skeletal effects of fluoride.—The first identification of human skeletal fluorosis by Møller & Gudjonsson in 1932 (54) focused attention on the injury to bone produced by excess fluoride. Only a year previously, mottled enamel, an injury to the teeth, had been attributed to fluoride. Skeletal fluorosis from consuming drinking waters containing excess fluoride has in the meantime been reported from widely separated geographical areas, most recently in the United States by Morris (55) and abroad by Azar (7) and Latham (50). A peculiar deformation of bones ascribed to the habitual drinking of wine containing fluoride has been reported from Spain (74). The adverse effects of fluoride on the skeleton, crippling fluorosis, characterized in Roholm's monograph, captured the scientific mind to such an extent that when the beneficial effects of fluoride on tooth health became apparent in 1938, the possibility that water-borne fluoride even at 1 ppm or less might injure the skeleton was still held to be an important consideration. The upper fluoride concentration which could be consumed in drinking water without bone injury, therefore, served as one of the fixed points in setting the margin of safety for water fluoridation.

One of the early suggestions that fluoride might benefit the skeleton followed the finding by Leone et al. in 1955 (51) that eight new cases of osteoporosis developed during a ten-year period in a group of 121 residents of Cameron, Texas, where the water contained 0.4 ppm F, compared to a single new case among 116 residents in the nearby community of Bartlett, Texas, in which the drinking water contained 8 ppm F. Leone et al. were impressed by the history of one woman, who had shown in the initial examination in 1943, increased bone density and coarsened trabeculation and who ten years later had a lessened bone density to a point more closely resembling normal. They commented that fluoride " . . . may, on occasion, have a beneficial effect on adult bone, as in counteracting the osteoporotic changes of the aged." Some years later, Leone et al. (52) found "an unusual incidence of severe osteoporosis (77 out of 556) . . . in . . . Framingham," Massachusetts where the drinking water contained only traces of fluoride. This was in marked contrast to the radiographic findings of lesser incidence in thousands of residents of Texas where many communities have naturally fluoridated water. Leone et al. suggested that "disadvantageous effects on the bone structure of the

adult population may be associated with the prolonged use of drinking water that contains an insufficient concentration of fluoride (52)."

In the past two years, three investigations have been directed at the hypothesis that fluoride in the skeleton may reduce or offset osteoporotic changes. Goggin et al., (41), found no difference in the femoral fracture frequency in a group of 420 women, 60 years of age or older, during the five-year periods preceding and immediately following fluoridation of the community water supply. Only a few patients were diagnosed as suffering from osteoporosis either before or after water fluoridation. In contrast to this negative finding, Ansell & Lawrence (3) reported that the incidence of osteoporosis in the hand and the cervical spine (but not in the lumbar spine) was significantly less than expected in residents of an English village in which the water supply had been fluoridated beginning five years previously.

Bernstein et al (10) found little difference in the incidence of collapsed vertebrae in male subjects over 45 years of age who had been life-time residents of an area in North Dakota of high fluoride concentration in the drinking water (3 to 5.8 ppm) and of an area in the same state where the fluoride concentration was low (0.15 to 0.3 ppm). The strongest support for the hypothesis that fluoride offsets osteoporotic change came from the radiographic examinations of the women. In women residents of the high fluoride area, the incidence of collapsed vertebrae was notably reduced and increased much less rapidly with age. The authors infer that the higher fluoride concentration " . . . materially and significantly lessens the prevalence of osteoporosis and collapsed vertebrae. . . . "

Each of these studies involved relatively small population groups. More extensive data in confirmation or denial are urgently needed. If fluoride is indeed an "important etiological factor in osteoporosis" [Hegsted (44)], the fact should be established without delay and the suffering of future millions of prospective victims of osteoporosis mitigated or prevented.

Fluoride treatment of osteoporosis.—Osteoporosis must be accepted as one of the commonest diseases of the aged; an estimated 14,000,000 women in the United States show a significant vertebral atrophy, and about 1.6 million have dorsolumbar vertebral fractures without symptoms (73). The male population ordinarily has a much lower incidence of advanced osteoporosis with age (e.g. 5 to 10 per cent over 50 years old). Smith & Rizek found that 20 per cent of 2063 women residents of Michigan between the ages of 45 and 50 years exhibited reduced bone density in radiographs. Frequency increased with age: more than 80 per cent of the women over 70 years of age had significant osteoporosis.

Osteoporosis has been defined "as a reduction in total bone mass" [Bernstein & Guri (9)], but the nature of the metabolic disturbance(s) has not been identified. Osteoporosis in women commonly is post-menopausal; however, osteoporosis is seen in hyperthyroidism, Paget's disease, Cushing's syndrome, eunuchoidism, hyperparathyroidism, urticaria pigmentosa, and diabetes [Bernstein & Guri (9)].

No specific therapy is available for osteoporosis. The objectives of therapy are the elimination of bone pain, the prevention of fractures, especially of the vertebra, and ultimately the recalcification of the skeleton. A certainly adequate daily calcium dose (1 g of calcium salt or more) is prescribed; sometimes hormonal therapy, e.g. androgens and estrogens, is added together with adequate but not excessive amounts of vitamin D. In almost a score of recent investigations, large daily doses of sodium fluoride given over extended periods of time have shown effects of sufficient promise to warrant further study. A summary of some of the observations is presented in Table I. Most of these patients suffered from osteoporosis, though a few exhibited other bone disorders, such as multiple myeloma, rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease.

Fluoride dose-duration.—The highest doses were about 100 mg of fluoride ion a day; the lowest for extended periods, about 30 mg a day, although lesser amounts have been tried in a few instances. Fluoride is usually administered in divided doses to avoid epigastric distress. The periods of study ranged from 34 months to about one month. One subject, on his own initiative, took about 100 mg fluoride daily for a period of six years as a prophylactic measure against dental caries; his skeleton, presumably normal initially, became fluorosed.

Criteria.—In Table I, five frequently used criteria have been selected from the many employed at least once and a sixth column records "other" observations. Fourteen investigators have recorded the development of *osteosclerosis.* In the six studies in which patients developed osteosclerosis the fluoride doses were 0.6 mg/kg/day or more. Of the 39 patients included in these six studies, seven were not osteoporotics, but suffered from other bone disorders, e.g. multiple myeloma, rheumatoid arthritis, osteogenesis imperfecta. The most rapid development of osteosclerosis required 14 to 15 months of fluoride therapy [Cohen & Gardner (26)]. These investigators found increased bone density radiographically in three months in two patients in their 40's with normal skeletons. Radiographic densitometry in one patient (66) showed an increase in mass of 11 per cent in the mid-phalanx, 27 per cent in the distal phalanx, and 21 per cent in the os calcis. No new lytic lesions appeared in a patient suffering from multiple myeloma during a protracted period of F treatment (27).

The reduction of bone pain reported by ten investigators occurred only in patients receiving 0.5 mg/kg/day or more for periods of two months or longer. The relief of the "agonizing bone pain" in multiple myeloma is a major factor in the treatment [Cohen & Gardner (27)] because "The pain alone often causes the patient's condition to deteriorate at a time when the other three major complications (anemia, susceptibility to infections, and renal failure) are under control."

Fluoride administration frequently (in six of eight studies) produced a decrease in urinary calcium concentration and daily excretion; 0.4 mg/kg/day or more are required to obtain this effect. Fecal calcium was unaltered;

TABLE I

SUMMARY OF REPORTED USES OF FLUORIDE IN THE TREATMENT OF BONE DISORDERS

Daily Dose[1,2] (mgF/kg)	Duration, mos.	Reference	Number of Patients	Disorder[3]	Osteosclerosis	Decreased bone pain	Decreased urinary Ca	Decreased ^{47}Ca retention	Positive Ca balance or lessened negative Ca balance	Other
1.0	4.5	(65)	7	6 osteoporosis, 1 Paget's disease	−		+		+	
1.0	1–3.75	(64)	7	osteoporosis, Paget's disease	−		+		+	
1.0	3.5–10	(68)	4	osteoporosis					sl. less neg. in 1 of 4	Marginal clinical improvement
1.0	14	(21)	1	osteoporosis	−	+	+		+	"Mottled bone"; decreased or abnormal collagen; new bone formation; much uncalcified osteoid
0.8–1.0	30	(66)	1	osteoporosis	+	+			+	Increased bone density coefficient in radiographs
0.8–1.0	73	(17)	1		+					On his own initiative, took daily 4–5 drops of soln. of 1 part HF and 2 parts water as a dental prophylaxis
0.7–1.4	2–19	(67)	6	5 osteoporosis, 1 Paget's disease	−				positive balance in 4	Urinary hydroxyproline decreased in 1 of 6 Blood F concns. reported (cf. Armstrong et al. (4)). Balance data for P. N. F.
0.6–1.0	4	(25)	3	osteoporosis	−	+ (transient)	+ in 1 of 3	+	+ in 2 of 3	Decreased accretion and resorption rates
0.2–1.0	≤12	(8)	30	osteoporosis	+ in 4	+ in 18 of 20	+		+ in 18 of 20	Larger bone crystals, uncalcified osteoid

[1] Estimated from the total daily dose and body weight. When body weights were not reported, weights of 50 to 70 kg were assumed.
[2] 1 mgF = 2.2 mgNaF.
[3] + means effect of F demonstrated; − means absence of effect demonstrated; no mark means the criterion was not applied.

TABLE I—(*Continued*)

Daily Dose[1,2] (mgF/kg)	Duration, mos.	Reference	Number of Patients	Disorder[2]	Osteosclerosis	Decreased bone pain	Decreased urinary Ca	Decreased ^{47}Ca retention	Positive Ca balance or lessened negative Ca balance	Other
0.8	14–15	(26)	2	1 rheumatoid arthritis 1 osteoporosis	+	+				
0.3–0.8	12	(1)	1	osteogenesis imperfecta congenita (infant)	+		+		+	Relative retention of P
0.6	3–34	(27)	4	multiple myeloma	+	+			+ in 1 of 4	No new osteolytic lesions in 1 patient in 34 mos.
0.6	1.5	(37)	1	osteoporosis	−	−				
0.2–0.6	1	(2)	1	osteoporosis					−	
0.5	3–8	(28)	4	Paget's disease	−	+ in 1 of 4		−		Urinary hydroxyproline increased in 1 of 4
0.5	1–4	(45)	3	Paget's disease	−	+ in 2 of 3	−		−	
0.5	2	(35)	1	Paget's disease	−	+	+			Urinary hydroxyproline and serum alk. phosphatase decreased
0.2–0.5	up to 12	(62)	16	Paget's disease		+		+	+	
0.4	13	(56)	1	multiple myeloma and osteoporosis	−		+	+	+	Transient increase in alk. phosphatase, decrease in labile Ca pool, decrease in stable Ca entering labile pool. High retention of F
0.2–0.7	12 or more	(57)	3	osteoporosis	−					Low incorporation of proline into collagen. In 1 subject lactate production and collagen uptake of proline returned to normal from elevated values; proline retention in bone cells increased
0.2	2	(70)	"few"							Fading "in some" of intensity of Schwartze sign in otosclerosis

thus, the decreased urinary excretion presumably reflected an increasing skeletal deposition.

Purves (62) reported a decrease in ^{47}Ca deposition in osteoporotic bone after fluoride treatment. Two other investigators confirmed this observation; one could not. The doses of fluoride were 0.4 mg/kg/day or more. Osteoporotic bone presumably has a greater amount of the mineral available to the circulation than normal, so that if F induced new bone formation, the availability of bone mineral and, therefore, the retention of ^{47}Ca should be reduced.

Ten investigators reported positive calcium balances or lessened negative calcium balances when doses of 0.5 mg/kg/day or more were administered for protracted periods. Two investigators failed to find any such change. In only one study reporting favorable calcium balances were osteosclerotic changes absent after treatment periods of ten months or longer.

Several miscellaneous criteria deserve comment. The urinary excretion of hydroxyproline may serve as an index of new bone formation. Two investigators (28, 67) reported increases in some patients; decreases also were found (35, 67). Certain balance studies included phosphorus, nitrogen (1, 45, 66, 67) and fluoride (1, 28, 56, 66–68). Limited data on plasma fluoride concentrations indicate that in some patients a marked increase occurred, whereas in others no large increase was maintained (4). No change occurred in the serum alkaline phosphatase (1, 8, 17, 28, 45, 67).

A number of function studies, for example renal, hepatic, and hematopoetic, failed to show significant changes during fluoride therapy (8, 17, 28, 65, 67, 68). No change occurred in the fat balance nor in the absorption of fat (67). One investigator reported no change in the ocular fundi (28). Serum or plasma samples analyzed for calcium, phosphorus, and other biochemical indices have not revealed significant changes during fluoride therapy (1, 8, 17, 27, 28, 35, 45, 65, 67).

Adverse reactions.—Large but tolerated doses of fluoride (11) produce nausea, epigastric distress, and occasionally diarrhea; smaller doses produce some of these effects in some patients, as almost every investigator since Woakes (84) has reported. A few patients developed severe bone or joint pain; in each instance, these patients had previously experienced severe pain and fluoride caused an exacerbation. One patient developed optic neuritis and macular edema after daily doses of 30 mg of fluoride for six weeks. This patient had a long history of illness, had been to surgery for a partial gastrectomy and for a parathyroidectomy within the preceding 18 months and took several drugs daily. No other investigator has seen such changes in patients. Waldbott (81) attributed a retinopathy in one patient and incipient changes in the retina of another patient to the fluoridated water which they were drinking. de Deuxchaisnes & Krane (28) found no abnormality in the ocular fundi and visual fields of their patients.

Can fluoride be regarded as a therapeutic agent for treating osteoporosis? Evidence at present is by no means conclusive. Some patients certainly ap-

pear to have been benefited. The disappearance of bone pain alone when it occurs would justify further study. On the other hand, some patients give well documented support of the absence of any improvement in calcium balance or in radiographic status. The benign nature of early skeletal fluorosis and the mild nature of the adverse reactions (excepting the possible instance of optic neuritis) from fluoride doses in the range of 30 to 100 mg daily make the risks of F treatment acceptable. Further investigation of this promising procedure is warranted by the severe and debilitating consequences of progressive osteoporosis and by its widespread and common occurrence.

Mechanism.—If the mechanisms of the fluoride effects on bone were understood, a more rational approach to fluoride therapy could be made. Unfortunately, the mechanisms are almost complete mysteries. Nevertheless, a summary of the present evidence and hypotheses may bear some fruit, perhaps in the form of suggested experiments.

The primary effect of small doses of fluoride is the stimulation of the osteocyte (or of the ameloblast). Larger doses impair the function of the osteocyte and of the ameloblast; e.g. Johnson (48) has described mottled bone which is analogous to mottled enamel. Fluoride in sufficient doses induces new bone formation with more osteoblasts characteristically in these areas than in normal bone. Osteoclastic activity continues—whether at an unchanged rate is not clear. With excess fluoride, the new bone both woven and osteonal is abnormal as shown (*a*) by its mottling, i.e. by the pigment it contains; (*b*) by the abnormal staining properties in undecalcified sections; and (*c*) by its abnormal appearance in polarized light revealing abnormal collagen, at least in alignment. In bone that is severely osteoporotic, the additional new bone, endosteal and periosteal, induced by F, imperfect as it may be, probably has a splinting and, therefore, a strengthening action. The new bone, appearing as exostoses on normal bone and in crippling fluorosis, does not alter the breaking strength of the bone. There is some apparently contradictory evidence that initially fluoride may induce some loss of bone. Excessive doses of fluoride stimulate osteoclasts giving a "moth-eaten" appearance.

(*a*) *F depresses collagen formation.*—In part at least the abnormalities in bone and collagen can be traced to abnormalities in matrix formation. Rats given drinking water containing 50 ppm F exhibited a decreased rate of collagen formation and a decreased total amount of collagen (60). These observations supported the earlier demonstration that F concentrations exceeding 20 ppm in the media of bone culture fluids reduced the incorporation of ^{14}C-proline into protein (61). Samples of human osteoporotic bone generally showed normal or lower rates of incorporation of proline into collagen and accumulation of proline in bone cells. In two osteoporotic patients treated for a year with F, low rates of collagen formation were found, and in one patient, for whom data were available initially and again after F therapy for a year, the proline incorporation into collagen had decreased (57). The accumulation of

proline in the cells was normal for the two patients following a year's treatment, and in the other patient, proline had accumulated to a greater than normal extent suggesting a block either in collagen formation within the cell or in transporting collagen to its extracellular location. In general, the responses of the osteoporotic patients agree reasonably well with data from experimental animals.

(*b*) *F decreases resorption and increases bone crystal size.*—A decreased resorption has been established by Neer et al. from ^{47}Ca distribution studies in man (56). Using a kinetic analysis, they proposed not only a decreased resorption rate, but a decreased labile pool of calcium, and a decrease in the rate of transfer of Ca from the stable to the labile pool. Some suggestion of the physical basis for a decreased resportion rate can be gained from the X-ray diffraction studies of bone of fluoride-treated patients which showed that the crystal size was increased (8). Larger crystals have proportionately smaller total surfaces; the mineral would thus tend to dissolve more slowly than do smaller crystals normally involved in osteoclastic removal. The smaller surface would provide a reasonable basis for the decrease in the size of the labile pool and for the decrease in the rate of transfer of calcium from the stable to the labile pool. On the other hand, rats given about 80 ppm of fluoride in the drinking water for three weeks showed no interference with calcium removal from bone into a peritoneal lavage fluid [Talmage & Doty (76)]. Decreased resorption in F-treated individuals may be sufficient to account for the improvement in osteoporotic patients when it occurs, and perhaps for the excessive accumulation of new bone in normal individuals.

(*c*) *Parathyroid gland participation in F effects?*—Singh and colleagues (72) found no evidence of stimulated parathyroid function, e.g. serum calcium, inorganic phosphorus, phosphate clearance, and calcium deprivation tests were within normal ranges, in a group of patients 30 to 76 years of age with "radiologically proved skeletal fluorosis." Serum alkaline phosphatase levels were significantly elevated, a finding also reported by Srikantia & Siddiqui (75).

Patients suffering from multiple myeloma exhibit elevated bone cell metabolism whether fluoride-treated or not (57). Bone from one osteoporotic patient exhibited elevated cellular lactate production (also typically a parathormone effect); F therapy during one year reduced lactate production to normal (57).

Studies in experimental animals show marked species variations. Young sheep were found by direct immunological assay to develop sharply elevated levels of circulating parathyroid hormone when maintained on drinking water containing 100 ppm F [Faccini & Care (34)]. Under somewhat similar conditions, the parathyroid glands of rabbits "...revealed the changes indicative of hyperactivity . . . " (33). Rats, in contrast, given 125 ppm F in the drinking water for nine weeks responded normally to parathormone administration (42). Fluoride treatment did not alter the response of fetal rat bone to parathormone, and no evidence was found of parathormone participation in fluoride effects in rats given about 200 ppm F for eight weeks (63).

Thus, the status is uncertain of the hypothesis (58, 76, 85) that F depresses bone mineral solubility, and tends to reduce serum calcium levels sufficient to stimulate the parathyroid gland to secrete parathyroid hormone and re-establish the normal serum calcium level. Nichols, Flanagan & Woods (58) added a further hypothesis based on evidence that the inhibition of proline incorporation into the collagen of rat bone produced by parathormone extract is followed by a stimulation of collagen biosynthesis. They suggest that " . . . fluoride induces a special kind of secondary hyperparathyroidism in which the increased bone resorption is blocked and only the stimulation of new bone formation is manifest. The idea, implicit in this hypothesis, that intact normally responsive parathyroid glands are a prerequisite for the development of fluorosis is presently being tested. Just where this hypothesis will lead us is difficult to predict."

Other Sites of Calcification

Bone scanning.—^{18}F rapidly accumulates in the skeleton in substantial amounts. Abnormal bone or bone in the process of dynamic change fixes more fluoride than normal bone. ^{18}F decays with a .65 MeV positron in a half-time of about 1.87 hours; the annililation radiation, a .51 MeV photon, permits external scanning. ^{18}F is prepared from the neutron bombardment either of $^{6}Li_2CO_3$ (12) or of oxygen 18 (59). The short half-life of ^{18}F reduces the hazard from radiation but limits the use to patients within one to two half-lives of a neutron source. Whole body radiation is estimated to be 0.03 rad/mc, and radiation to the bone to be 0.12 to 0.23 rad/mc (12, 29, 30, 59). Following an intravenous dose of 200 μc in man, the bladder dose (or the stomach dose if given by mouth) is probably 0.5 to 1 rad; the average whole body dose is less than 0.02 rad and of bone less than 1 rad (80). Photographs with a positron camera visualized the ^{18}F concentrated in fracture sites or in the pathological bone in Paget's disease (80). Dworkin & Filmanowicz (29) found a specific and perhaps unique use for ^{18}F in the location of lesions in reticulum cell sarcomas not revealed by ^{85}Sr scanning.

Skeletal blood flow can be estimated using ^{18}F (80). Assuming that bone clears 100 per cent of the ^{18}F in one passage, and that the rate of blood flow is uniform, Van Dyke et al. (80) calculated that the skeleton cleared ten times the plasma volume in one hour, or 17 per cent of the plasma volume per minute. Skeletal blood flow accounted for at least 4.3 per cent of the cardiac output. Previous attempts to estimate skeletal blood flow in rats and dogs have given roughly comparable figures.

Aortic calcification.—The tendency for calcification in the aorta and in other arteries to increase with age roughly parallels the tendency for osteoporosis to increase with age. Bernstein and colleagues (10) surveyed the increase of osteoporosis with age: collapsed vertebral bodies shown in lateral radiographs became the basis of selecting the study groups. Not only the degree of osteoporosis, but also the presence and the amount of aortic calcification was recorded. A decreased incidence of aortic calcification was found in both men and women residents of communities with high fluoride

concentrations. The mechanism is unknown. Animal experiments from Phillips' laboratory are of interest in this connection. Puppies made acutely magnesium-deficient developed aortic califications which could be prevented by the addition of F to the diets. No such calcinosis, however, was observed in magnesium-deficient rats (16, 24).

One additional point deserves mention. Fluoride concentrations of human aortas are directly correlated with the calcium contents reflecting th ability of calcium phosphate mineral (apatite) anywhere in the body to take up and hold fluoride (18).

Fluoride and deafness.—In a few cases of otosclerosis, the administration of 30 mg of fluoride daily for two months changed the appearance of the structures suggesting that the otosclerotic focus had become more mature and avascular (70). Audiometer tests were made on children living in counties in Illinois where the water "does not contain fluorine"; 4.9 per cent of 109,869 children had defective hearing (53). In contrast, in 4 counties near Chicago where the drinking water contained fluoride (not over 1.4 ppm), 2.8 per cent of 20,408 children had defective hearing (53). Further study seems indicated.

Bone fluoride as related to kidney disease.—Fluoride accumulates slowly but steadily in the human skeleton during most of the lifetime, ultimately reaching a maximal concentration at about the sixth decade. This level depends quantitatively on the intake. While the kidney has a large factor of safety in its ability to excrete fluoride, kidney failure is associated with a reduced excretion rate and a concomitant tendency for increased storage. Two recent case histories bear on this point. The first is that of a 43-year-old female with longstanding high-grade kidney disease (49, 79) and the second a 64-year-old man with kidney disease less clearly characterized (69). In both cases, skeletal fluoride concentration was notably increased, being 5500 ppm F (ash weight basis) in the first instance and 6100 ppm (dry weight) in the second.

Bone fluoride concentrations of persons who had lived in industrial areas of Utah and sustained fluoride exposures from atmospheric contamination ranged from 82 to 1800 ppm (18); " . . . most of the higher levels were found in patients with an advanced chronic renal disease." These levels still were within the normal range ". . . and no disease associated with fluorides was evident."

The rapidity of the urinary excretion of fluoride has been accounted for in the dog by a less efficient tubular resorption (23). Studies of renal fluoride excretion in the human (20) using ^{18}F showed high values for the renal concentrating ratio of fluoride and for ^{18}F clearances (average = 75 and 312, respectively, for two individuals; range 45 to over 1000 times the chloride clearance). Recent data by Walser & Rahill (82), on the dog, indicated that fluoride and chloride resorption occur passively, but that the tubular permeability to fluoride is less, perhaps 1/6 that of chloride. Thus, a retention of fluoride will occur when kidney function is impaired to such an extent that passive resorption is enhanced.

LITERATURE CITED

1. Aeschlimann, M. I., Grunt, J. A., Crigler, J. F., Jr., *Metab. Clin. Exptl.*, **15**, 905–14 (1966)
2. Albright, F., Reifenstein, E. C., Jr., Forbes, A. P., *Josiah Macy Foundation Trans. Conf. Metabolic Aspects of Convalescence including Bone and Wound Healing*, **8**, 20–25 (1944)
3. Ansell, B. M., Lawrence, J. S., *Ann. Rheumat. Diseases*, **25**, 67–75 (1966)
4. Armstrong, W. D., Singer, L., Ensinck, J., Rich, C., *J. Clin. Invest.*, **43**, 555–56 (1964)
5. Arnold, F. A., Jr., Dean, H. T., Jay, P., Knutson, J. W., *U. S. Publ. Health Repts.*, **71**, 652–58 (1956)
6. Ast, D. B., Cons, N. C., Carlos, J. P., Maiwald, A., *Am. J. Publ. Health*, **55**, 811–20 (1965)
7. Azar, H. A., Nucho, C. K., Bayyuk, S. I., Bayyuk, W. B., *Ann. Internal Med.*, **55**, 193–200 (1961)
8. Bernstein, D. S., Cohen, P., *J. Clin. Endocrinol. Metab.*, **27**, 197–210 (1967)
9. Bernstein, D. S., Guri, C. D., *Postgrad. Med.*, **34**, 407–9 (1963)
10. Bernstein, D. S., Sadowsky, N., Hegsted, D. M., Guri, C. D., Stare, F. J., *J. Am. Med. Assoc.*, **198**, 499–504 (1966)
11. Black, M. M., Kleiner, I. S., Bolker, H., *N. Y. State J. Med.*, **49**, 1187–88 (1949)
12. Blau, M., Nagler, W., Bender, M. A., *J. Nucl. Med.*, **3**, 332–34 (1962)
13. Blayney, J. R., Hill, I. D., *J. Am. Dental Assoc.*, **74**, No. 2 (Special issue, Jan. 1967)
14. Blayney, J. R., Hill, I. D., *J. Am. Dental Assoc.*, **69**, 291–94 (1964)
15. Brzezinski, A., Bercovici, B., Gedalia, I., *Obstet. Gynecol.*, **15**, 329–31 (1960)
16. Bunce, G. E., Chiemchaisri, Y., Phillips, P. H., *J. Nutr.*, **76**, 23–29 (1962)
17. Calenoff, L., *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, **87**, 1112–15 (1962)
18. Call, R. A., Greenwood, D. A., LeCheminant, W. H., Shupe, J. L., Nielsen, H. M., Olson, L. E., Lamborn, R. E., Mangelson, F. L., Davis, R. V., *U S. Publ. Health Repts.*, **80**, 529–38 (1965)
19. Carlos, J. P., Gittelsohn, A. M., Haddon, W. Jr., *U. S. Publ. Health Repts.*, **77**, 658–60 (1962)
20. Carlson, C. H., Armstrong, W. D., Singer, L., *Proc. Soc. Exptl. Biol. Med.*, **104**, 235–39 (1960)
21. Cass, R. M., Croft, J. D., Jr., Perkins, P., Nye, W., Waterhouse, C., Terry, R., *Arch. Internal Med.*, **118**, 111–16 (1966)
22. Charkes, N. D., Sklaroff, D. M., *J. Nucl. Med.*, **5**, 168–79 (1964)
23. Chen, P. S., Jr., Smith, F. A., Gardner, D. E., O'Brien, J. A., Hodge, H. C., *Proc. Soc. Exptl. Biol. Med.*, **92**, 879–83 (1956)
24. Chiemchaisri, Y., Phillips, P. H., *J. Nutr.*, **81**, 307–11 (1963)
25. Cohen, M. B., Rubini, M. E., *Clin. Orthopaed.*, **40**, 147–52 (1965)
26. Cohen, P., Gardner, F. H., *J. Am. Med. Assoc.*, **195**, 962–63 (1966)
27. Cohen, P., Gardner, F. H., *New Engl. J. Med.*, **271**, 1129–33 (1964)
28. de Deuxchaisnes, C. N., Krane, S. M., *Medicine*, **43**, 233–66 (1964)
29. Dworkin, H. J., Filmanowicz, E. V., *J. Am. Med. Assoc.*, **198**, 985–88 (1966)
30. Dworkin, H. J., Moon, N. F., Lessard, R. J., La Fleur, P., *J. Nucl. Med.*, **7**, 510–20 (1966)
31. Ericsson, Y., in *Nutrition and Caries Prevention*, 112–22 (Blix, G., Ed., Swedish Nutrition Foundation, Upsala, Sweden, 1965)
32. Ericsson, Y., Malmnäs, Cl., *Acta Obstet. Gynecol. Scand.*, **41**, 144–58 (1962)
33. Faccini, J. M., *Nature*, **214**, 1269–71 (1967)
34. Faccini, J. M., Care, A. D., *Nature*, **207**, 1399–1401 (1965)
35. Faglia, G., Norbiato, G., *Metabolismo*, **1**, 399–409 (1965)
36. Feltman, R., Kosel, G., *J. Dental Med.*, **16**, 1998 (1961)
37. Geall, M. G., Beilin, L. J., *Brit. Med. J.*, **2**, 355–56 (1964)
38. Gedalia, I., Brzezinski, A., Portuguese, N., Bercovici, B., *Arch. Oral Biol.*, **9**, 331–40 (1964)
39. Gedalia, I., Brzezinski, A., Zukerman, H., Mayersdorf, A., *J. Dental Res.*, **43**, 669–71 (1964)
40. Gedalia, I., Menczel, J., Antebi, S., Zuckerman, H., Pinchevski, Z., *Proc. Soc. Exptl. Biol. Med.*, **119**, 694–97 (1965)
41. Goggin, J. E., Haddon, W. Jr., Hambly, G. S., Hoveland, J. R., *U. S. Publ. Health Repts.*, **80**, 1005–12 (1965)
42. Hac, L. R., Freeman, S., Nock, W. B., *Am. J. Physiol.*, **212**, 213–16 (1967)

43. Hadjimarkos, D. M., *J. Pediat.*, **65,** 782–84 (1964)
44. Hegsted, D. M., *Postgrad. Med.*, **41,** A49–A53 (1967)
45. Higgins, B. A., Nassim, J. R., Alexander, R., Hilb, A., *Brit. Med. J.*, **1,** 1159–61 (1965)
46. Horowitz, H. (Quoted by W. L. Babeaux, I. Zipkin) *J. Oral Therap. Pharmacol.*, **3,** 124–35 (1966)
47. Hudson, J. T., Stookey, G. K., Muhler, J. C., *Arch. Oral Biol.*, **12,** 237–46 (1967)
48. Johnson, L. C., in Hodge, H. C., Smith, F. A., *Fluorine Chemistry*, **IV,** 424–39 (Simons, J. H., Ed., Academic Press, New York, 1965)
49. Kretchmar, L. H., Greene, W. M., Waterhouse, C. W., Parry, W. L., *J. Am. Med. Assoc.*, **184,** 1030–31 (1963)
50. Latham, M. C., *Lancet*, **1,** 131–32 (1966)
51. Leone, N. C., Stevenson, C. A., Hilbish, T. F., Sosman, M. C., *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, **74,** 874–85 (1955)
52. Leone, N. C., Stevenson, C. A., Besse, B., Hawes, L. E., Dawber, T. A., Claffey, W. J., *Arch. Indust. Health*, **21,** 326–27 (1960)
53. Lewy, A., *Arch. Otolaryngol.*, **39,** 152–54 (1944)
54. Møller, P. F., Gudjonsson, S. V., *Acta Radiol.*, **13,** 269–94 (1932)
55. Morris, J. W., *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, **94,** 608–15 (1965)
56. Neer, R. M., Zipkin, I., Carbone, P. P., Rosenberg, L. E., *J. Clin. Endocrinol. Metab.*, **26,** 1059–68 (1966)
57. Nichols, G., Jr., Flanagan, B., *Federation Proc.*, **25,** 922–27 (1966)
58. Nichols, G., Jr., Flanagan, B., Woods, J. F., in *The Parathyroid Glands, Ultrastructure, Secretion and Function*, 243–60 (Gaillard, P. J., Talmage R. V., Budy A. M., Eds., Univ. Chicago Press, Chicago, 1965)
59. Nusynowitz, M. L., Feldman, M. H., Maier, J. G., *J. Nucl. Med.*, **6,** 473–80 (1965)
60. Peck, W. A., Zipkin, I., Whedon, G. D., *Clin. Res.*, **13,** 330 (1965)
61. Proffit, W. R., Ackerman, J. L., *Science*, **145,** 932–34 (1964)
62. Purves, M. J., *Lancet*, **2,** 1188–89 (1962)
63. Raisz, L. G., Taves, D. R., *Calcified Tissue Res.* (In press)
64. Rich, C., Ensinck, J., *Clin. Res.*, **10,** 118 (1962)
65. Rich, C., Ensinck, J., *Nature*, **191,** 184–85 (1961)
66. Rich, C., Ivanovich, P., *Ann. Internal Med.*, **63,** 1069–74 (1965)
67. Rich, C., Ensinck, J., Ivanovich, P., *J. Clin. Invest.*, **43,** 545–56 (1964)
68. Rose, G. A., *Proc. Roy. Soc. Med.*, **58,** 436–40 (1965)
69. Sauerbrunn, B. J. L., Ryan, C. M., Shaw, J. F., *Ann. Internal Med.*, **63,** 1074–78 (1965)
70. Shambaugh, G. E., Jr., Scott, A., *Arch. Otolaryngol.*, **80,** 263–70 (1964)
71. Singer, L., Armstrong, W. D., *J. Appl. Physiol.*, **15,** 508–10 (1960)
72. Singh, A., Singh, B. M., Singh, I. D., Jolly, S. S., Malhotra, K. C., *Indian J. Med. Res.*, **54,** 591–96 (1966)
73. Smith, R. W., Rizek, J., *Clin. Orthopaed.*, **45,** 31–48 (1966)
74. Soriano, M., Manchon, F., *Radiology*, **87,** 1089–94 (1966)
75. Srikantia, S. G., Siddiqui, A. H., *Clin. Sci.*, **28,** 477–85 (1965)
76. Talmage, R. V., Doty, S. B., *Gen. Comp. Endocrinol.*, **2,** 473–79 (1962)
77. Tank, G., Storvick, C. A., *J. Am. Dental Assoc.*, **70,** 394–403 (1965)
78. Taves, D. R., *Nature*, **211,** 192–93 (1966)
79. Taves, D. R., Terry, R., Smith, F. A., Gardner, D. E., *Arch. Internal Med.*, **115,** 167–72 (1965)
80. Van Dyke, D., Anger, H. O., Yano, Y., Bozzini, C., *Am. J. Physiol.*, **209,** 65–70 (1965)
81. Waldbott, G. L., *Brit. Med. J.*, **2,** 945 (1964)
82. Walser, M., Rahill, W. J., *Am. J. Physiol.*, **210,** 1290–92 (1966)
83. Weaver, R., *Brit. Dental J.*, **88,** 231–39 (1950)
84. Woakes, E., *Lancet*, **1,** 448–50, 497–98, 537–38 (1881)
85. Yates, C., Doty, S., Talmage, R. V., *Proc. Soc. Exptl. Biol. Med.*, **115,** 1103–8 (1964)

CONTENTS