3. Franke, J., Rath, F., Range, H., Fengler, F., Auermann, E., and Lennart, C.: Industrial Fluorosis. Fluoride, 8:61, 1975.
4. Cooperation Group of Metallurgical System for Fluoride Protection: Temporary Diagnosis Criteria for Industrial Fluorosis. J. Metallurgical Labor Hyg., China, 7:2, 1981.
5. Huo Daijei: X-ray Analysis of 34 Cases of Foodborne Skeletal Fluorosis. Fluoride, 14:51, 1981.
6. Guiyang Medical College: Endemic Foodborne Fluorosis in Guizhou.Chinese Journal of Preventive Medicine, 13:148, 1979.
7. Brudevold, F., McCann, H.G., and Gron, P.: An Enamel Biopsy Method for Determination of Fluoride in Human Teeth. Arch. Oral Biol., 13: 877, 1968.
8. Editorial: Fluoride and the Heart, Fluoride, 8:38, 1975.
9. Waldbott, G.L.: Symposium on the Nonskeletal Phase of Chronic Fluorosis. The Arteries. Fluoride, 9:24, 1976.
10. Cooperation Group of Metallurgical System for Fluoride Protection: Fluoride Effects on Workers' Health in Metallurgical Enterprise. J. Metallurgical Labor Hyg., China, 8:193, 1982.

****

EFFECT OF FLUORIDE ON SOFT TISSUES IN VERTEBRATES (A REVIEW)

by

P.A. Monsour and B.J. Kruger
Brisbane, Australia

Detectable traces of fluoride occur in almost every substance, and animals everywhere consume measurable amounts of fluoride. At sub-lethal doses, the concentration of fluoride in blood will approach a steady state, proportional to the rate of fluoride infusion (1). However the total amount of fluoride in sera of different species given the same dose of fluoride varies considerably, and the peak concentration of fluoride in sera of these different species occurs at different times and varies in duration (2).

Signs of acute high dose fluoride poisoning in mammals are nausea, vomiting and diarrhea, followed by cramping, collapse, coma, and death. In humans, death from an oral dose usually occurs within 4 hours. The signs of chronic (low dose) fluoride poisoning are, however, less well defined.

The purpose of this paper is to summarize data concerning the effects of fluoride on various soft tissue systems in vertebrates after oral, subcutaneous, or intraperitoneal administration.

From the Department of Oral Biology and Oral Surgery, Physiology Building, University of Queensland, St. Lucia, Queensland.

Endocrine System

Adrenals: Several authors have reported an increase in weight of adrenals after fluoride intoxication, allegedly due to an increased content of protein (3,4). McGown and Suttie (5) reported a four-to five-fold increase in plasma epinephrine and suggested that the hyperglycemia induced by the fluoride was mediated by epinephrine, secreted by the adrenal medulla. It is possible that these phenomena represent a general stress response, secondary to metabolic poisoning by fluoride, and mediated through the sympathetic nervous system.

Thyroid: In high enough concentrations , fluoride will interfere with the functions of the thyroid directly or indirectly (6-8), but this effect will be minimized when the supply of iodine is adequate (6). Fluoride may interfere with the normal functioning of follicular cells, for example, by inhibiting the proteinases responsible for spliting thyroglobulin molecules into thyroxine and triiodothyronine (9, 10). There could possibly be an effect of fluoride on the feedback mechanism mediated through the hypothalamus and adenohypophysis which regulate thyroid secretions through thyrotropin (TSH).

Parathyroid: Studies on humans and animals indicate that, in high enough concentrations, fluoride affects the function of the parathyroids indirectly by altering serum calcium and phosphate (11-17). Evidence for secondary hyperparathyroidism in fluoride-treated animals and man is structural and ultrastructural appearance (12, 14,15, 17-19). It is also based on changes in bone resorption (20) and direct measurements of parathormone concentrations in blood by radioimmunological assay methods (12, 21). In sheep, treated with 100 mg of fluoride ion per day for four weeks, circulating parathormone increased five-fold (12). In humans, four out of nine patients suffering from skeletal fluorosis had elevated levels of immunoreactive parathormone (21). However, in studies with rats, no changes were found in the parathyroid glands, bone resorption and circulating levels of parathormone (22-25).

Fluoride has caused a drop in the circulating calcium in man and in several experimental animals (26-28). It has been suggested that the reduction in circulating calcium is due to fluorapatite formation and, because of its decreased crystal solubility, inhibition of osteoclastic bone resorption. Any situation which causes decreased levels of circulating calcium would induce parathormone release and, if prolonged, would lead to secondary hyperparathyroidism. Due to species variability (29-31) and the dose-dependent effect of fluoride, it is reasonable to assume that rats, which are known to be more resistant to fluoride than sheep and rabbits, would exhibit fewer toxic changes, particularly if the fluoride dose is not excessive, as in the recent studies of Rosenquist et al. (25).

Urinary System

Nephropathy is a major manifestation of fluoride toxicity in its early stages. Large doses of fluoride induce necrosis of the convoluted tubules and inflammation of glomeruli, changes which result in impaired kid-

ney function such as polyuria, polydipsia, and increased non-protein nitrogen (33). In rats, at low levels (for example 1 to 10 ppm NaF), alterations to kidney structure and function are reported to be minimal(34-37).

Renal function studies on rats exposed to constant IV infusion of fluoride have produced, in dose-dependent responses, an increase in urine flow rate, urinary osmolality, inner medullary sodium and chloride concentrations, and glomerular filtration rate, and a decrease in the excretion of sodium, chloride, and potassium (38).

All published data reflect the dose-dependent effect of fluoride on kidney tissues. Tissue destruction increasing with the dose, and the toxic effects are seemingly related to altered activity of enzyme systems, some stimulated (37,39-40) and some inhibited (39, 41-42). As kidney damage increases, clearance of fluoride is reduced (43). The toxic effects of fluoride are also exacerbated by the altered renal clearance of other electrolytes, metabolites, and waste.

Digestive System

Gastrointestinal tract: Waldbott et al. (44) have designated stomach and bowel disorders as cardinal features of fluoride intolerance in humans. Formation of hydrofluoric acid in the gut appears to account for the symptoms of nausea, vomiting, abdominal pain, and diarrhea associated with fluoride poisoning (44,45). Data on the effect of fluoride on absorption of calcium from the gastrointestinal tract are equivocal (46-48). On theoretical grounds, it might be expected that simultaneous administration of fluoride and calcium would result in reduced calcium absorption due to precipitation of the relatively insoluble fluoride salts of calcium. It is not known whether fluoride interferes with the absorption of calcium by the epithelial cells of the duodenum and jejunum. The possibility that fluoride interferes with the active transport mechanism or with calcium-binding proteins has not been explored.

Oral Mucosa: Branemark (49) cautioned dentists about the potential toxicity of topical fluoride to gingiva, particularly when the tissue is inflamed. Gabler (50) showed that fluoride ions can be absorbed through the oral mucosa of rats, even if at a relatively slow rate.

The gingival crevice is a natural sink for the retention of fluoride long after topical application has been completed. Patients with extensive supra and/or infra-bony gingival pockets would be predisposed to prolonged retention of fluoride against tissues.

In rabbits, Hume et al. (51) found that exposure to gingival explants to levels of fluoride up to 10,000 ppm reduced incorporation of H^3 proline and H^3 thymidine, and that the degree of depression varied directly with the concentration and exposure time. Comparison of their data with that of previously reported studies showed that gingival tissue metabolism was profoundly depressed by fluoride applications at or near the *in vitro* threshold for preventing growth of suspected periodontal pathogens. However, if gingival epithelium were intact, fluoride toxicity

from topical application was considered to be negligible. Different cellular responses to NaF in vitro, namely genotoxic transformations, have been reported with other cells (52).

Liver: Fluoride interferes with the normal functioning of the liver and causes disruption of hepatocytes (53,54). The route of fluoride administration is important. Pathological changes in the liver of rats ensued following use of a gastric tube to administer chronic doses of the sodium fluoride and to ensure that each animal received a constant daily dose (55). On the other hand, deCamargo and Merzel (37) who simply added the fluoride to the water supply, found no changes in the liver. In the latter experiments, if the animals ate first and then drank, the fluoride would have entered a full stomach which might have resulted in decreased absorption of fluoride.

Cardiovascular System

Branemark (49) applied 0.05, 0.2, 1.0 and 2.0 per cent solutions of sodium fluoride to the cheek pouch of hamsters. The resulting disturbances varied in degree and severity according to the concentration of fluoride and the state of the tissue. Vascular changes, characterized by microvascular injury, perivascular disintegration of tissue cells, and vascular proliferation, predominated. Another indication of the vulnerability of vessels to fluoride is the microscopic appearance of the bruise-like skin lesions, Chizzola maculae which have been emphasized by Waldbott (44). (See "Skin" for additional details).

Large doses of NaF (12 mg/kg) fed to rats (56) have induced chronic myocarditis and dystrophic changes in heart muscle fibres. Massive doses of fluoride can cause severe heart damage resulting in cardiac irregularities and low blood pressure in experimental animals (57). Changes in ECGs of humans and dogs due to massive doses of fluoride have been cited by Baltazar et al. (58). It is not clear whether these cardiac changes are secondary to fluoride poisoning or a direct effect of fluoride on cardiovascular tissue. Most authors agree that calcification of arteries is an integral feature of skeletal fluorosis.

Central Nervous System

In humans, the partial and complete paralysis of arms and legs in advanced fluorosis is usually considered to be related to pressure upon the spinal cord by newly formed bone protruding into the spinal canal, and upon nerves at the point of their exit from the spine. However, it has been suggested that the spinal cord lesions and muscular damage in patients suffering occupational fluorosis are also the result of a direct action of the fluoride ion on the ganglion and muscle cells (59).

Due to a lack of precise experimental data, it is difficult to draw conclusions concerning the effects of fluoride on the central nervous system. It seems likely that chronic ingestion of low doses of fluoride stimulates enzymes systems (60), and that this effect may be mediated through fluoride activated adenylate cyclase (61,62).

Eyes: Large doses of NaF are toxic to the retina in varying degrees. Waldbott (44) observed in his patients, that fluoride could cause a widening of retinal vessels leading to retinitis and involvement in cataract formation.

Rabbits and mice show dystrophy of retinal pigment cells with subsequent damage to the photoreceptors by fluoride doses exceeding 25 mg/kg body weight (55). In the ganglion cells of the retina, the content of rRNA was reduced in mice when the dose of fluoride was 12 mg NaF/kg body weight. This inhibition of RNA synthesis was more pronounced in the ganglion cells, and a decrease in protein synthesis was detected in the perikaryons of the photoreceptors. It has been proposed that this retinopathy is correlated with a disturbance of ascorbic acid metabolism, namely in the transport of its oxidized form (4). The retina is basically composed of modified neurons (rods, cones). As such, it is susceptible to fluoride toxicity. Furthermore, the production of rhodopsin (visual purple) is dependent upon several enzyme-catalyzed reactions, which may be inhibited by fluoride.

Respiratory System

Gaseous fluoride above 3 ppm for more than 10 minutes (63) is toxic to respiratory tissues. Whitford et al. (64) however, found no evidence of fluoride binding in the lung of rats following a single intravenous injection of ^{18}F, 9.1 μCi/rat. Detailed histological investigations as well as studies on the effects of ingested fluoride on respiratory tissues seem to be lacking.

Some Selective Tissues

Muscle: The signs and symptoms of muscle involvement in acute fluoride toxicity, namely hyperactive reflexes, painful muscle spasms, weakness and tetanic contractions have been related to fluoride-induced hypocalcemia. Studies are lacking on the direct effect of an acute dose of fluoride on muscle. In chronic fluoride intoxication, fluoride seems to alter muscle function and to damage muscle cells (44, 65.66) but, if the dose is not excessive (4), muscle is able to adapt to the insult.

Skin: From clinical observations, Steinegger (67) and Waldbott (68) described a characteristic sign of chronic fluoride poisoning which occurs mainly in children and women, namely, pinkish to bluish-brown skin lesions called Chizzola maculae (inflammation around capillary blood vessels). These lesions can be distinguished from traumatic bruises, mainly because they are always round or oval, about 1 to 2.5 cm in diameter, and are usually asymptomatic. They fade after 5 to 7 days but do not turn yellow as do bruishes, which can be any size or shape. There is little doubt that fluoride is involved in the production of these lesions. However the lesions were not reproduced experimentally; their high prevalence among children and women suggest that other factors as well as fluoride may be involved (68,69).

Collagen: Fluoride influences the metabolism of bones and teeth. It

has been proposed, but not proven, that it is essential for normal calcification (70,71). Excessive fluoride intake can interfere with bone metabolism, particularly through its effect on collagen formation: 2 mg F/kg body weight given to young rabbits (72) interfered with the normal hydroxylation of proline, producing inadequately hydroxylated collagen; fluoride reduced the synthesis of tropocollagen molecules with reduced numbers of aldehydes resulting in inadequate cross-linked collagen fibres; reduced lysine residues which caused inadequate cross links in collagen; and the collagen laid down during excessive exposure to fluoride was more rapidly catabolized. Fluoride has also been shown to decrease the amount of soluble and insoluble collagen in skin and lungs (73). Joseph and Tydd (74), however, found that 10 and 150 ppm sodium fluoride in the drinking water of rabbits accelerated tissue regeneration during the first three or four weeks following removal of the whole thickness of 1 cm^2 of the rabbit's ear.

The mechanism of the effect of fluoride on collagen metabolism is still unknown. At high concentrations, fluoride may inhibit proline uptake into collagen and its conversion into hydroxyproline but at the same time stimulate enzyme systems involved in collagen formation. It is difficult to compare the work of Susheela and Sharma (71) and that of Drozdz et al. (73), with that of Joseph and Tydd (74) because their research protocols differed; tissues and animals studied were different; the fluoride was administered differently and the fluoride doses differed. Nevertheless, fluoride administration seems to lead to production of abnormal collagen (75).

Retention of fluoride in soft tissues: Under normal conditions soft tissue organs contain little or no fluoride (68,76). However, with impaired kidney function or prolonged fluoride exposure, relatively large amounts of fluoride can accumulate in soft tissues (44). Based on data from a survey by Call et al. (77) on humans, the order of magnitude of storage is as follows: aorta, thyroid, lung, kidney, heart, pancreas, brain, spleen and liver. Levels as high as 8400 (78) ppm in the aorta have been recorded in a fluoridated area; 290 ppm in skin (79), 186 in nails (79), 185 in bladder (79), and 181 (79) in kidneys in an area with little or no fluoride in water.

Accumulation of fluoride may be involved in many disease processes and it may induce a wide variety of signs and symptoms. Fluoride is one of the most reactive ions in nature. To what extent it affects the function of vital organs remains an enigma. Further work on this and on certain idiopathic clinical phenomena are warranted.

References

1. Knaus, R.M., Dost, F.N., Johnson, D.E., and Wang, C.H.: Fluoride Distribution in Rats During and After Continuous Infusion of $Na^{18}F$. Toxicology and Applied Pharmacology, 38:335-343, 1976.
2. Patterson, C.M., Kruger, B.J., and Daley, T.J.: Differences in Fluoride Levels in the Blood Between Sheep, Rabbit and Rat. Arch. Oral Biol., 22:419-423, 1977.
3. Rao, K., and Susheela, A.K.: Effect of Sodium Fluoride on Adrenal Gland of Rabbit I. Studies on Ascorbic Acid and Delta 5-3 Beta Hydroxysteroid Dehydrogenase Activity. Fluoride, 12:65-71, 1979.
4. Zhavoronkov, A.A., and Strochkova, L.S.: Fluorosis: Geographical Pathology and Some Experimental Findings. Fluoride, 14:182-191, 1981.
5. McCown, E.L., and Suttie, J.W.: Mechanism of Fluoride-Induced Hyperglycemia in the Rat. Toxicol. and Appl. Pharmacol., 40:83-90, 1977.

6. Hodge, H.C.: Fluoride Toxicology. Fluorides and Dental Caries, 2nd edition. Ed. E. Newburn, Thomas, Springfield, Ill., Chapter 7, 1975, pp. 138-146.
7. Ogilvie, A.L.: Histologic Findings in the Kidney, Liver, Pancreas, Adrenal and Thyroid Glands of the Rats Following Sodium Fluoride Administration. J. Dent. Res., 32:386-397, 1953.
8. Hillman, D., Bolenbaugh, D., and Convey, E.M.: Hypothyroidism and Anemia Related to Fluoride in Dairy Cattle. J. Dairy Science, 62:416-423, 1979.
9. Willems, C., Berberofvan Sande, J., and Dumont, J.E.: Inhibition of Thyroid Secretion by Sodium Fluoride in vitro. Biochim. Biophys. Acta, 264:197-204, 1972.
10. Bobek, S., Kahl, S., and Ewy, Z.: Effect of Long-Term Fluoride Administration on Thyroid Hormones Level in Blood in Rats. Endocrinol. Exp., 10:289-295, 1976.
11. Faccini, J.M., and Teotia, S.P.S.: Histopathological Assessment of Endemic Skeletal Fluorosis. Calcif. Tissue Res., 16:45-57, 1974.
12. Faccini, J.M., and Care, A.D.: Effect of Sodium Fluoride on the Ultrastructure of the Parathyroid Glands of Sheep. Nature, 207:1399-1401, 1965.
13. Teotia, S.P.S., and Teotia, M.: Secondary Hyperparathyroidism in Patients with Endemic Skeletal Fluorosis. Brit. Med. J., 1:637-640, 1973.
14. Ream, L.J., and Principato, R.: Fluoride Stimulation of the Rat Parathyroid Gland: An Ultrastructural Study. Am. J. Anatomy, 162:233-241, 1981.
15. Ream, L.J.: Ultrastructural Observations on the Effects of Fluoride Ingestion on the Parathyroid Gland of the Rat. Fluoride, 15:208-214, 1982.
16. Faccini, J.M.: Fluoride and Bone. Calcif. Tissue Res., 3:1-16, 1969.
17. Makhni, S.S., Sidhu, S.S., Singh, P., and Singh, G.: The Parathyroid in Human Fluorotic Syndrome. Fluoride, 13:17-19, 1980.
18. Makhni, S.S., Sidhu, S.S., Singh, P., and Grover, A.S.: Long-Term Effects of Fluoride Administration in Rabbits - An Experimental Study: Histological Changes in the Parathyroid and Correlation with Changes in the Bone. Fluoride, 12:124-128, 1979.
19. Rich, C., and Feist, E.: The Action of Fluoride on Bone. In: Fluoride in Medicine. T.L. Vischer, Ed. Hans Huber, Bern, 1970, pp. 70-87.
20. Yates, C., Doty, S., and Talmage, R.V.: Effects of ium Fluoride on Calcium Homeostasis. Proc. Soc. Exp. Biol. Med., 115:1103-1108, 1964.
21. Teotia, S.P.S., Teotia, M., Singh, R.K., et al.: Plasma Fluoride, 25-Hydroxycholecalciferol, Immunoreactive Parathyroid Hormone and Calcitonin in Patients with Endemic Skeletal Fluorosis. Fluoride, 11:115-119, 1978.
22. Raisz, L.G., and Taves, D.R.: The Effect of Fluoride on Parathyroid Function and Responsivess in the Rat. Calcif. Tissue Res., 1:219-228, 1967.
23. Hac, L.R., Freeman, S., and Nock, W.B.: Effects of Fluoride and Parathyroid Extract on Citrate and Bone Metabolism. Am. J. Physiol., 212:213-216, 1967.
24. Kraintz, L.: The Effect of Fluoride Ingestion on the Response of the Rat to Parathormone and Calcitonin. Can. J. Physiol. Pharmacol., 47:477-481, 1969.
25. Rosenquist, J.B., Lorentzon, P.R., and Boquist, L.L.V.: Effect of Fluoride on Parathyroid Activity of Normal and Calcium-Deficient Rats. Calcif. Tissue Internat., 35:533-537, 1983.
26. Baker, K.L.: Fluoride and Tetracycline-Induced Changes in Rat Serum Calcium and Phosphate Levels. Arch. Oral Biol., 19:717-723, 1974.
27. Larsen, M.J., Fejerskov, O., Josephsen, K., and Hammarstrom, L.: The Action of Acute Doses of Fluoride on Serum Calcium Level in Relation to Dental Hard Tissue Formation in Rats. Calcif. Tissue Res., Suppl. 22:454-457, 1977.
28. Larsen, M.J., Melsen, F., Mosekilde, L., and Christensen, M.S.: Effects of a Single Dose of Fluoride on Calcium Metabolism. Calcif. Tissue Res., 26:199-202, 1978.
29. Shupe, J.L., Miner, M.L., Harris, L.E., and Greenwood, D.A.: Relative Effects of Feeding Hay Atmospherically Contaminated by Fluoride Residue, Normal Hay Plus Calcium Fluoride, and Normal Hay Plus Sodium Fluoride to Dairy Heifers. Am. J. Vet. Res., 23:777-787, 1962.
30. Shearer, T.R.: Comparative Metabolic Responses of Rat Kidney and Liver to Acute Doses of Fluoride. Proc. Soc. Exp. Biol. Med., 146:209-212, 1974.
31. Kruger, B.J., Patterson, C.M., and Masters, C.J.: Species Differences in Uptake and Distribution of ^{18}F. Aust. J. Exp. Biol. Med. Sci., 56:427-431, 1978.

32. Whitford, G.M., and Taves, D.R.: Fluoride Induced Diuresis; Plasma Concentrations in the Rat. Proc. Soc. Exp. Biol. Med., 137:458, 1971.
33. Jankauskas, J.: Effects of Fluoride on the Kidney (A Review). Fluoride, 7:93-105, 1974.
34. Pindborg, J.J.: The Effect of 0.025 and 0.0125 % Dietary Sodium Fluoride on the Rat Kidney. Odontologisk Revy., 8:177-180, 1957.
35. Ramseyer, W.F., Smith, C.A.H., and McCay, C.M.: Effect of Sodium Fluoride Administration on Body Changes in Old Rats. J. Gerontol., 12:14019, 1957. Bosworth, E., and McCay, C.M.: Pathologic Studies of Rat Kidneys; Absence of Effects Ascribed to Fluoride Following Long-Term Ingestion of Drinking Water Containing Fluoride. J. Dent. Res., 4:949-960, 1962.
36. Shearer, T.R.: Comparative Metabolic Responses of Rat Kidney and Liver to Acute Doses of Fluoride. Proc. Soc. Exp. Biol. Med., 146:209-212, 1974.
37. deCamargo, A.M., and Merzel, J.: Histological and Histochemical Appearance of Livers and Kidneys of Rats After Long-Term Treatment with Different Concentrations of Sodium Fluoride in Drinking Water. Acta Anat. 108:288-294, 1980.
38. Whitford, G.M., and Stringer, G.: Duration of the Fluoride-Induced Urinary Concentrating Defect in Rats. Proc. Soc. Exp. Biol. Med., 157:44-49, 1978.
39. Singh, M., and Kanwar, K.S.: Effect of Fluoride on Tissue Enzyme Activities in Rat: Biochemical and Histochemical Studies. Fluoride, 14:132-141, 1981.
40. Singh, M.: Biochemical and Cytochemical Alterations in Liver and Kidney Following Experimental Fluorosis. Fluoride, 17:81-93, 1984.
41. Suketa, Y., Ohtami, K., and Yamamoto, T.: Changes in Glucose-6-Phosphatase Activities in Kidney and Liver of Rats after Administration of a Single Dose of Fluoride. Fluoride, 12:84-91, 1979.
42. Takagi, M., and Shiraki, S.: Acute Sodium Fluoride Toxicity in the Rat Kidney. Bull. Tokyo Med. Dent. Univ. 29:123-130, 1982.
43. Koichi Kono, Yasuhisa Yoshida, Misuzu Watanabe, et al.: Urinary Fluoride Excretion in Fluoride Exposed Workers with Diminished Renal Function. Industrial Health, 22:33-40, 1984.
44. Waldbott, G.L., Burgstahler, A.W., and McKinney, H.L.: Fluoridation: The Great Dilemma. Coronado Press, Inc., Lawrence, Kansas, 1978, pp. 148-174.
45. Duxburg, A.J., Leach, F.N., and Duxburg, J.T.: Acute Fluoride Toxicity. Br. Dent. J., 153:64-66, 1982.
46. Spencer, H., Lewin, I., Fowler, J., and Samachson, J.: Effect of Sodium Fluoride on Calcium Absorption and Balances in Man. Am. J. Clin. Nutr., 22:381-390, 1969.
47. Ramberg, C.F., Phang, J.M., Mayer, G.P., et al.: Inhibition of Calcium Absorption and Elevation of Calcium Removal Rate from Bone in Fluoride-Treated Calves. J. Nutr., 100:981, 1980.
48. Change, Y.O., Pan, M., and Varnell, T.: The Effect of Fluoride on Calcium Absorption in Rats. Nutrition Reports International, 16:539-547, 1977.
49. Branemark, P.I.: Local Tissue Effects of Sodium Fluoride. Odont. Revy. 18: 273-294, 1967.
50. Gabler, W.L.: Absorption of Fluoride Through the Oral Mucosa of Rats. Arch. Oral Biol., 13:619-623, 1968.
51. Hume, W.R., Yoon, N.A., and Matsunaga, M.L.: Comparison of Fluoride Toxicity Between Periodontal Pathogenic Bacteria and Rabbit Gingiva. Arch. Oral Biol, 26: 467-472, 1981.
52. Takeki Tsutsui, Nobuko Suzuki, and Manabu Ohmori: Sodium Fluoride-Induced Morphological and Neoplastic Transformation, Chromosome Aberrations, Sister Chromatid Exchanges, and Unscheduled DNA Synthesis in Cultured Syrian Hamster Embryo Cells. Cancer Research, 44:938-941, 1984.
53. Kour, K., Koul, M.L., and Koul, R.I.: Histological Changes in Liver Following Sodium Fluoride Ingestion. Fluoride, 14:119-123, 1981.
54. Lee, J.: Gilbert's Disease and Fluoride Intake. Fluoride, 16:139-145, 1983.
55. Laurushenko, L.F., Trunov, V.I., and Okunev, V.N.: Morphofunctional Characterization of Certain Ultrastructures of Rat Liver Hepatocytes Under the Prolonged Influence of Sodium Fluoride. Tsilogiia I Genetika, 14:19-20, 1980.
56. Zhavoronkov, A.A.: Nonskeletal Forms of Fluorosis. Arch. Pathol., 39:83-91,1977.

57. Leone, N.C., Geever, E.F., and Moran, N.C.: Acute and Subacute Toxicity Studies of Sodium Fluoride in Animals. Public Health Report, 71:459-467, 1956. (Reprinted in McClure, F.J.: Fluoride Drinking Waters, Public Health Service Publication #825, 1962, pp. 539-544.
58. Baltazar, R.F., Mower, M.M., Reider, R., et al.: Acute Fluoride Poisoning Leading to Fatal Hyperkalemia. Chest, 78:660-663, 1980.
59. Franke, J., Rath, F., Runge, H., et al.: Industrial Fluorosis. Fluoride, 8:61-85, 1975.
60. Czechowicz, K., Osada, A., and Slesak, B.: Histochemical Studies on the Effect of Sodium Fluoride on Metabolism in Purkinje's Cells. Folia Histochem. Cytochem. 12:37-44, 1974.
61. Susheela, A.K., and Singh, M.: Adenyl Cyclase Activity Following Fluoride Ingestion. Toxicol. Letters, 10:209-212, 1982.
62. Strochkova, L.S., and Zhavoronkov, A.A.: Fluoride as an Activator of Enzymatic Systems. Fluoride, 16:181-186, 1983.
63. Hodge, H.C., and Smith, F.A.: Occupational Fluoride Exposure. J. Occupational Med., 19:12-39, 1977.
64. Whitford, G.M., Callan, R.S., and Pearson, D.E.: Radiofluoride Distribution in Rat Lung, Colon and Heart. J. Dent. Res., 59:1171, 1980.
65. Kaul, R.D., and Susheela, A.K.: Evidence of Muscle Fibre Degeneration in Rabbits Treated with Sodium Fluoride. Fluoride, 17:177-181, 1974.
66. Kaul, R.D., Keswane, N.H., and Susheela, A.K.: Histoenzymic and Ultrastructural Effects of Fluoride Toxicity. Proceedings of the Symposium of Fluorosis. Geological Society of India, 1977, p. 457.
67. Steinegger, S.: Endemic Skin Lesions Near an Aluminum Factory. Fluoride, 2:37-39, 1969.
68. Waldbott, G.L., and Cecilioni, V.A.: Chizzola Maculae. Cutis, 6:331-334, 337, 1970. Waldbott, G.L., and Steinegger, S.: New Observations on Chizzola Maculae. In: Proceedings of the Third International Clean Air Congress, Düsseldorf, Federal Republic of Germany, Oct. 8-12, 1973, Verlag des Vereins Deutscher Ingenieure, Düsseldorf, 1973, pp. A63-A67.
69. Cavanga, G., Locati, G., and Ambrosi, L.: Experimental Studies in Newborn Rats and Mice on the Supposed Capillary-Damaging Effect of Fluorine-Containing Industrial Pollutants. Fluoride, 2:214, 1969.
70. Purves, M.J.: Some Effects of Administering Sodium Fluoride to Patients with Paget's Disease. Lancet, 2:1188-1189, 1962.
71. Jowsey, J., Riggs, B.C., Kelly, P.J., and Hoffman, D.L.: Effect of Combined Therapy with Sodium Fluoride, Vitamin D and Calcium in Osteoporosis. Am. J. Med., 53:43-49, 1972.
72. Susheela, A.K., and Sharma, Y.D.: Certain Facets of F^- Action on Collagen Protein in Osseous and Non-Osseous Tissues. Fluoride, 15:177-190, 1982.
73. Drozdz, M., Kucharz, E., and Grucka-Mamczar, E.: Effects of Sodium Fluoride on Collagen Content in Skin and Lungs of Growing Rats. Acta Biol. Med. Ger., 39: 287-293, 1980.
74. Joseph, J., and Tydd, M.: Effect of Sodium Fluoride on Regeneration in the Rabbit Ear. Nature, 246:165-166, 1973.
75. Uslu, B.: Effect of Fluoride on Collagen Synthesis in the Rat. Res. Exp. Med., 182:7-12, 1983.
76. Van Rensburg, B.G.J.: Metabolism of Fluorides. J. Dent. Assoc. S. Africa, 34: 163-166, 1973.
77. Call, R.A., Greenwood, D.A., LeCheminant, W.H., Shupe, J.L., et al.: Histological and Chemical Studies in Man on Effects of Fluoride. Public Health Reports, 80:529-538, 1965.
78. Geever, E.F., McCann, H.G., McClure, F.J., et al.: Fluoridated Water, Skeletal Structure and Chemistry. Health Serv. Mental Health Admin. Health Rep., 86: 820-828, 1971.
79. Herman, J.R., Mason, B., and Light, F.: Fluorine in Urinary Tract Calculi. J. Urol., 80:263-267, 1958.

****