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Serum Phosphatase Activity in Generalized Osteosclerosis Due to Chronic Fluorine Intoxication in Man.

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Flemming Møller and Gudjonsson[1] called attention to a peculiar form of generalized osteosclerosis, hitherto unknown, occurring in Danish workers exposed to dust of cryolite, a fluorine compound (Na_3AlF_6). The condition is characterized[1-5] by a diffuse increase in density of the bones, particularly of the spine, pelvis and ribs, and by calcification of ligaments and tendinous muscle attachments. Because of marked periosteal proliferation and the calcification of contiguous fibrous tissues, the sclerotic bones are often irregular in contour. There may be considerable impingement also upon the medullary cavity. The spine and thoracic cage ultimately become rigid, resulting in loss of mobility and vague "rheumatic" pains; but clinical signs and symptoms are otherwise remarkably few, even in advanced cases. At necropsy,[2, 6] the sclerosed bones are found to be heavy (up to 3 times the normal weight) with rough surface and relatively brittle texture. Histologically, the peculiar if not pathognomonic osseous structure is characterized by the partial deposition of lime salts in the form of irregular granules. The fluorine content of the bone ash[2, 5] is increased to about 10 times the normal values.

While distinctly less common than abnormalities of dentition, ("mottled enamel"),[19] skeletal changes due to chronic fluorine intoxication probably occur more widely in man than is generally appreciated. A number of cases of osteosclerosis have been reported from North Africa[7] and from India.[8] In the United States, Bishop[5] recently described typical skeletal changes in a man who for 18

1 Møller, P. F., and Gudjonsson, S. V., *Acta radiol.*, 1932, **13**, 269.

2 Roholm, K., *Fluorine Intoxication*, Lewis & Co., London, 1937.

3 Roholm, K., *Arch. F. Gewerbepath.*, 1936, **7**, 255.

4 Roholm, K., *J. Ind. Hygiene*, 1937, **19**, 126.

5 Bishop, P. A., *Am. J. Roent.*, 1936, **35**, 577.

6 Bauer, J. T., Bishop, P. A., and Wolff, W. A., *Bull. Ayer Clin. Lab.*, 1937, **3**, 67.

19 Smith, M. C., Lantz, E. M., and Smith, H. V., *J. Am. Dent. Assn.*, 1935, **22**, 817.

7 Spéder, E., *Bull. Mém. Soc. Radiol. Méd. France*, 1936, **24**, 200.

8 Shortt, H. E., Pandit, C. G., and Raghavachari, T. N. S., *Indian Med. Gaz.*, 1937, **72**, 396.

years had handled finely ground rock phosphate (a complex calcium-fluorphosphate) in a "superphosphate" fertilizer factory.

In the literature on chronic fluorine intoxication in man, no values could be found for serum phosphatase, an enzyme to which is ascribed an important rôle in bone formation. Marked increases in serum phosphatase activity are known to occur in other diseases presenting widespread osteosclerosis, notably in Paget's disease,[9] carcinoma with osteoplastic metastases,[9] and in some cases of Albers-Schönberg disease.[10] In chronic fluorine intoxication produced experimentally in animals, Phillips[11] reported mean plasma phosphatase values approximately twice those of control animals whereas Smith and Lantz[12] found no difference between their treated and control groups and De Eds[13] obtained inconclusive results.

We have determined the phosphatase activity of the serum in 20 cases of chronic fluorine intoxication (Table I) representing various stages of bone involvement, from advanced osteosclerosis to roentgenographically negative cases. The subjects, 16 men and 4 women employed 8-34 years in the Copenhagen cryolite factory, were selected from the group originally studied roentgenographically by Flemming Møller and Gudjonsson[1] and later *in extenso* by Roholm.[2] Blood samples were obtained 2-3 hours after a light breakfast. Serum phosphatase activity was determined by the Bodansky method within a few hours after collection, inorganic phosphorus by the Kuttner-Lichtenstein method, calcium by the Clark-Collip modification of the Kramer-Tisdall method.

Despite the presence of extensive osteosclerosis in many subjects, the serum phosphatase activity was found to be within the normal range (1.0-4.0 Bodansky units per 100 cc. serum) in 14 of 20 cases. In 6 instances the serum phosphatase activity was slightly increased, 7.0 Bodansky units being the highest value observed. There was no proportionality between the level of serum phosphatase activity and the degree of osteosclerosis. The inorganic phosphorus values were within normal limits and the serum calcium, in confirmation of Roholm[2] and Bishop,[5] was normal or slightly increased.

The absence of appreciable increases in serum phosphatase activity in our cases may, of course, be due simply to the extremely slow development of osteosclerosis. The average period of exposure to

[9] Gutman, A. B., Tyson, T. L., and Gutman, E. B., *Arch. Int. Med.*, 1936, **57**, 379.

[10] Bodansky, A., and Jaffe, H. L., *Arch. Int. Med.*, 1934, **54**, 88.

[11] Phillips, P. H., *Science*, 1932, **76**, 239.

[12] Smith, M. C., and Lantz, E. M., *J. Biol. Chem.*, 1935, **112**, 303.

[13] DeEds, F., *J. Am. Dent. Assn.*, 1936, **23**, 568.

TABLE I.
Serum Phosphatase Activity, Inorganic Phosphorus and Calcium in 20 Cases of Chronic Fluorine Intoxication in Man.

No.*	Sex	Age	Years of exposure	Serum: Phosphatase (Bodansky units per 100 cc.)	Serum: Inorg. P (mg. %)	Serum: Calcium (mg. %)
Group without osteosclerosis roentgenographically.						
17	M	37	12	3.5	2.7	—
39	M	31	9	4.1	3.1	—
43	M	33	8	1.8	3.4	10.1
Group with osteosclerosis of 1st phase.†						
52	F	58	22	3.3	3.1	9.9
4	M	38	11	3.3	2.8	11.3
30	M	41	8	4.4	3.2	—
45	M	35	14	1.8	2.7	—
62	F	59	22	3.3	3.4	11.2
65	M	45	13	3.3	2.8	11.2
Group with osteosclerosis of 2nd phase.†						
2	M	42	15	2.8	2.6	12.0
6	M	38	14	7.0	2.6	11.4
19	M	35	13	2.6	2.7	—
20	M	38	18	1.6	2.8	—
23	F	31	9	2.7	4.0	—
32	M	33	9	6.2	2.9	11.1
41	F	61	34	5.3	3.4	10.5
50	M	59	14	3.8	2.8	—
Group with osteosclerosis of 3rd phase.†						
15	M	62	21	2.7	3.2	10.9
34	M	48	18	4.3	2.8	11.6
51	M	66	15	3.6	3.6	11.2

*The numbers correspond with those in Roholm's monograph,[2], which see for further details regarding these subjects.

†1st phase: just recognizable roentgenographic changes, slightly increased density. 3rd phase: marble-like density, pronounced periosteal proliferation and calcification of ligaments.

fluorine for the group with early bone changes (1st phase) was 9.3 years, for the group with advanced osteosclerosis (3rd phase) 21.1 years.[2] This is probably not the only factor involved, however, since Paget's disease is often equally slow in development, yet the serum phosphatase activity may exceed 100 Bodansky units per 100 cc. A likely further possibility is that the mechanism of bone formation in chronic fluorine intoxication differs in some significant though as yet obscure manner from that operating in other osteosclerotic conditions. This difference in mechanism of bone formation is suggested also by the unusually pronounced periosteal activity, by the presence of granules, and by the few active osteoblasts and the narrow osteoid borders seen in bone sections.

We think it improbable that the normal serum phosphatase activity found in most of our cases is due to direct inhibition of serum phos-

phatase by fluorides. When serum of a case of chronic fluorine intoxication was mixed with a very active blood sample obtained from a case of metastatic osteoplastic carcinoma (64.6 Bodansky units per 100 cc.) the resulting serum phosphatase activity was not lower than calculated. Fluoride in concentrations as high as 0.01 molar does not significantly inhibit the phosphatase activity of normal or Paget serum[14] *in vitro*. "Alkaline" bone phosphatase activity is similarly not appreciably inhibited by fluorides *in vitro*, according to most investigators.[12, 15, 16, 17] Fluorides do inhibit "acid" phosphatases, which may play a rôle in bone formation,[15, 17, 18] but how this affects the level of "alkaline" serum phosphatase activity is not now clear.

A practical point worth emphasizing is that chronic fluorine intoxication should be considered as a possible cause of obscure generalized osteosclerosis, particularly if associated with normal serum phosphatase activity.

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Excretion of Inulin, Creatinine, Xylose and Urea in the Sheep.

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We are presenting a summary of observations on the renal excretion of inulin, creatinine, xylose, and urea in a single normal sheep. These observations were made in 1934 and since the results were concordant with similar observations on the dog,[1] further investiga-

TABLE I.
Summary of Observations on Sheep (Weight, 30.0 kg.).

	Experiments	No. of Observations	Mean
Inulin clearance	3	10	58.5 cc./min.
Creatinine/inulin clearance ratio	3	10	1.03
Xylose/inulin clearance ratio	1	2	.73
Urea/inulin clearance ratio	2	6	.52

14 Gutman, A. B., and Gutman, E. B., unpublished data.

15 Robison, R., and Rosenheim, A. H., *Biochem. J.*, 1934, **28**, 684.

16 Folley, S. J., and Kay, H. D., *Erg. Enzymforsch.*, 1936, **5**, 159.

17 Gutman, E. B., Sproul, E. E., and Gutman, A. B., *Am. J. Cancer*, 1936, **28**, 485. For contrary opinion, see 13 and 16.

18 Phillips, P. H., and Hart, E. B., *J. Biol. Chem.*, 1935, **109**, 657.

1 Shannon, James A., *Am. J. Physiol.*, 1935, **112**, 405.