Part II

EXPERIMENTAL STUDIES ON THE EFFECTS OF SODIUM FLUORIDE UPON THE HEART MUSCLE OF RABBITS

by

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Fluoride is abundant in the mineral as well as in the plant and animal worlds. It is present in water in varying amounts. In the earth's crust it is found as the 20th element in abundance occurring as the minerals fluospar (CaF_2), cryolite (Na_3ALF_6), and sedimentary phosphate rock ($Ca_3(PO_4)_2$ CaF_2.

In the past, the toxicity hazard of fluoride compounds has been encountered in the smelting of cryolite. In 1932 Møller and Gudjonsson (1) detected toxic effects in 30 workers who had been employed for a long time at a factory crushing cryolite in Denmark. About the same time, Roholm described "Eine neue Krankheit" (2, 3) after conducting several detailed experiments on fluoride poisoning. Toxicity by fluoride, as severe as that from working in a cryolite factory, can be caused by a high content of fluoride in drinking water as shown by Smith (4), Smith, Lantz and Smith (5) in 1931, by Churchill (6) and others (7 to 13).

In Part I of this study (14) the author reported a higher incidence of myocardial damage electrocardiographically and cardiac dilatation roentgenographically, in inhabitants of a high-fluoride zone than where water contained little or no fluoride. The myocardial damage was related to the high content of fluoride in drinking water.

In this study, Part II, rabbits were given sodium fluoride orally to supplement our previous observations.

Experimental Material and Methods

Healthy mature white rabbits weighing about 2kg were divided into four groups according to the dosage of sodium fluoride:

A Group:	11 individuals		
	received	orally	10 mg/kg NaF daily
B Group:	10	"	30 mg/kg NaF
C Group:	13	"	50 mg/kg NaF
D Group:	3	"	100 mg/kg NaF
E Group:	16	"	Control

Nutritious food such as the "Tofukara" (the residue of bean-curd) and grass (standard diet) were given to rabbits, and their health was given constant attention.

Electrocardiography was performed in limb leads. Each limb was fixed on an insulated table. Since the rabbit heart had a tendency to move with the change of the body position in the photography, great care was taken to avoid an error due to this factor. Normal limits of PQ and QT interval were employed in accordance with Shimizu's (24) expression as follows:

$$QT = 2.83 \sqrt{RR} \pm 0.025$$
$$PQ = 2.32 \sqrt{RR} \pm 0.025$$

Rabbits were killed at various intervals and every heart was studied macroscopically and histologically.

Discussion

The author had previously described a rise in myocardial damage electrocardiographically and cardiac dilatation in the X-rays in residents of high-fluoride areas. These changes which appear to be due to the high content of fluoride in drinking water, were fully confirmed by the current laboratory experiments.

The degree of myocardial damage was proportionate to the dosage of sodium fluoride and the length of time of its administration. The pathological changes appeared to be more prominent in the papillary muscles and on the inside wall of the myocardium than at the exterior cardiac wall.

Patterns of myocardial damage such as depressed ST, inverted T, prolonged QT interval, bundle branch block, and pulmonary P, were observed in these laboratory experiments as well as in our field work (14).

In autopsied cows in Nango village, Kumamoto Prefecture, Kono and the author found hypertrophy of the myocardium associated with dental fluorosis and fluoride bone changes. In the heart muscle, we observed numerous small hemorrhages, slight infiltration of round cells, and marked regressive degeneration similar to that produced in the current laboratory experiment (Fig. 1 to 7). We also observed the same changes in rats recently (15). Takamori and Kawahara (16) noted marked cloudy swelling of the skeletal muscle of frogs suspended in a 25 mg% of NaF solution.

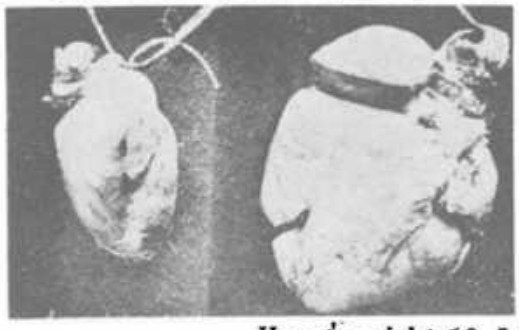
Among the available studies, Friedenthal (17) assumed that calcium precipitation is the principal cause of poisoning by sodium fluoride. Meyerhof (18) reported that a n/500 NaF solution completely inhibited fermentation. Lipine (19) noted that fluoride inhibited glycolysis in muscle.

Embden drew attention to the fact that fluoride decreased the amount

Fig. 1

Heart Size in Fluorodic Rabbit No. 301

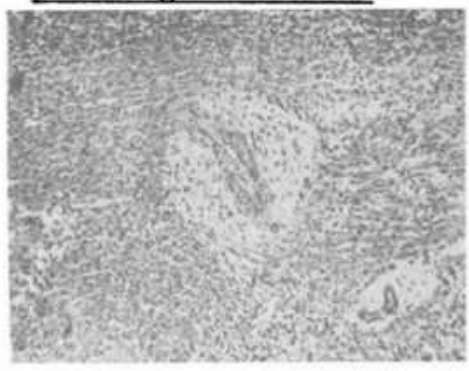
Control NaF 30 mg/kg (51 Days)



Heart weight 10.5 gr.

Fig. 2

Infiltration with Round Cells, Thickening of Adventitia



Rabbit No. 101. NaF 10 mg/kg (132 days)
Left ventricle (x 170)

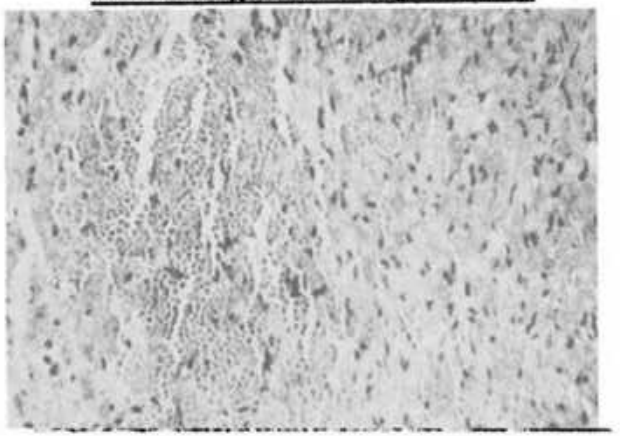
Fig. 3

Diffuse Hemorrhages, Infiltration of Round Cells and Cloudy Swelling

Rabbit No. 304. NaF 30 mg/kg (19 days).
Papillary muscle (x 130).

Fig. 4

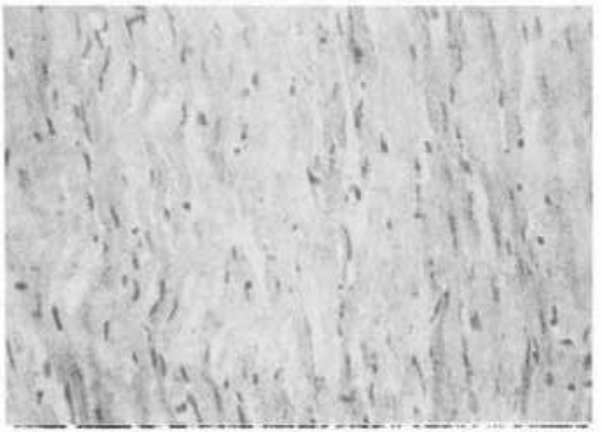
Hemorrhage and Cloudy Swelling



Rabbit No. 310. NaF 30 mg/kg (51 days)
Right ventricle (x 400).

Fig. 5

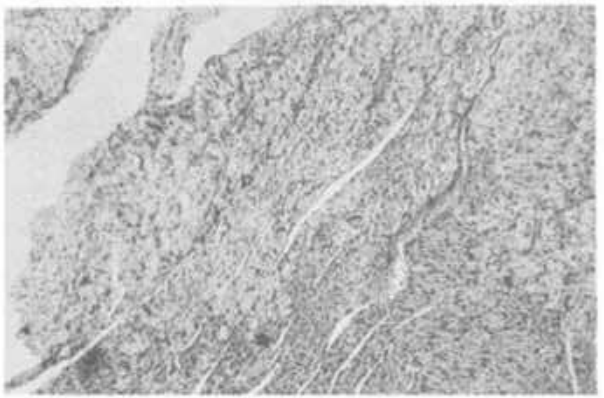
Cloudy Swelling



Rabbit No. 503. NaF 50 mg/kg (59 days).
Left ventricle (x 400).

Fig. 6

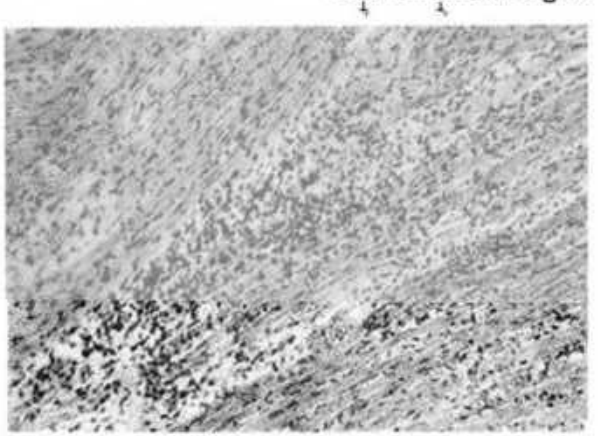
Cloudy Swelling, Vacuolar and Colloid Degeneration



Rabbit No. 502. NaF 50 mg/kg (60 days)
Left ventricle (x 130)

Fig. 7

Infiltration with Round Cells and Small Hemorrhages



Rabbit No. 507. 50 mg/kg (31 days)
Right auricle (x 170)

of free phosphoric acid formed in muscle suspended in butyric solutions. Extensive studies concerned with the action of fluoride on glycolysis and the influence of fluoride ions upon the chemical changes associated with muscle metabolism have been carried out by Embden and his school (20-23). Their experiments indicated that tartrate and fluoride inhibit or even reverse the glycogen breakdown in muscle. It is concluded that fluoride affects the muscular metabolism by depressing the enzymatic reaction and the intermediary metabolism (24).

Summary

In the electrocardiogram of rabbits given sodium fluoride orally, a pattern of myocardial damage was observed, namely depressed ST, inverted T, prolonged QT interval, multifocal ventricular premature contraction, bundle branch block, and pulmonary P. Histologically, regressive degeneration, cellular infiltration, hyperemia, hemorrhages and thickening of vessel wall were noted in the heart muscle.

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ELECTROCARDIOGRAPHIC STUDIES OF THE INHABITANTS IN HIGH FLUORIDE DISTRICTS

by

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In the Aso volcano districts of Kumamoto Prefecture, Japan, a dental disease occurs which is known locally as "Yonaba", meaning "teeth affected by volcano ash". Undoubtedly, this condition is identical with mottled teeth, irrespective of the cause.

Since the reports of Smith, Lantz and Smith (1) and Churchill (2), we know that mottled enamel is usually caused by drinking water which contains fluoride in excess of 1 ppm.

No systematic studies on how fluoride affects the cardiovascular system had appeared previous to Okushi's report (3) from our department in 1954.

The authors examined the inhabitants of a high fluoride area where a high incidence of mottled enamel was encountered. In 1953, electrocardiographic and X-ray examinations in Shionoe, Kagawa Prefecture, and in Odani, Okayama Prefecture, revealed many instances of myocardial damage, cardiac hypertrophy and dilatation. In 1954 Okushi (4) published experimental data concerned with the effect of sodium fluoride upon the heart muscle of rabbits. This communication presents EKG observations on subjects residing in the Mt. Aso fluoride area.

Method and Procedure

In 1954 electrocardiograms were taken on 102 inhabitants (90 children and 12 adults) of the Aso volcano district and 59 children in Beppu city. The examina-

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