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Health and Biology

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SUMMARY OF RESEARCH AND SERVICE PROGRAMS

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Submitted by: Henry A. Blair,
Director

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PROGRAM F.

FLUORIDE

Problem Code: F.4 (Fate)

Section Code: 3210, 3220

To supply evidence useful in the litigation arising from an alleged loss of a fruit crop several years ago, a number of problems have been opened. Since excessive blood fluoride levels were reported in human residents of the same area, our principal effort has been devoted to describing the relationship of blood fluorides to toxic effects.

The principal defect in undertaking this study originally was the lack of a method for determining the fluoride content of blood.

Determination of Fluoride in Blood:

A reproducible, accurate method suitable for routine work was developed which depended upon a preliminary separation of the fluoride from the organic components of the blood by distillation from concentrated sulfuric acid at 134-137° C, evaporation and ashing of the distillate in platinum in the presence of lime, and a final redistillation of the fluoride from concentrated perchloric acid. The fluoride content of a suitable aliquot of the distillate is done by a modification of the thorium nitrate -- alizarin red titration.

It is necessary in the absence of information to determine first the content of fluoride in normal human and animal blood to serve as a base line for the toxicity studies.

Fluoride Content of Normal Human Blood: Application of this method to the determination of the fluoride content of 20 specimens of nonfasting blood of donors whose water supply contained 0.06 ppm fluoride showed a range of from 0-9 micrograms of fluoride per 100 ml of blood; 45 per cent of these bloods contained no fluoride. In contrast to these observations, the analysis of 12 bloods from donors whose community water supply contained 1.36 ppm fluoride showed only 8 per cent of the samples to contain no fluoride; 42 per cent of the samples contained 3-6 micrograms of fluoride per 100 ml. However, the range of values found for the group was no different from the range of 0-9 μg F/100 ml found for the previous group of samples. These data may indicate that the mean blood fluoride level is related to the fluoride content of the community water supply; the data are being extended to include samples from localities whose drinking water contains still greater amounts of fluoride.

Fluoride Content of Normal Dog and Rabbit Blood: In the course of experimental work, 75 analyses were obtained on 30 normal dogs and 20 analyses were obtained for 13 normal rabbits. Food analyses showed the diet of the dogs to contain 13.1 ppm of fluoride; that of the rabbits contained 3.4 ppm. Drinking

water contained 0.06 ppm of fluoride. Approximately 80 per cent of the bloods from both species were found to contain less than 10 μg F/ml. An additional 13 per cent of the dog bloods and 20 per cent of the rabbit bloods contained 10-20 μg F/100 ml. A small number of dog samples contained relatively large quantities of fluoride, ranging up to 70 μg/100 ml.

Routes of Fluoride Administration: Two routes of administration of fluorides have been used: (1) Rats have been given large doses of sodium fluoride intraperitoneally; (2) Rabbits and dogs have been placed in atmosphere of hydrogen fluoride so that inhalation exposures were made.

Blood Fluoride Levels in Rats Following the Intraperitoneal Injection of NaF: Groups of 20 female rats weighing approximately 134 g were injected intraperitoneally with 37.8 mg NaF/kg, the approximate LD50 for rats of this sex and weight. At regular time intervals following the injection, the survivors in different groups were sacrificed and the fluoride content of the pooled blood sample determined. It was found that the fluoride content reached a peak of approximately 900 μg F/100 ml within 30 minutes following the injection; the level then decreased again. Twenty-four hours after the injection, the blood content was again at a normal level of 0-3 μg F/100 ml. In spite of the fact that the maximum blood level is reached within a half hour after injection, significant numbers of fatalities did not begin to occur until 4-5 hours after the injection, by which time the blood fluoride level was reduced to approximately one-tenth of its maximum value.

Blood Fluoride Content Following Exposure to Hydrogen Fluoride: The complete absence of reliable data on blood fluoride levels in previously reported studies of toxic effects of hydrogen fluoride leaves an undesirable gap in the information available regarding the metabolism of fluorides. In order to obtain data of this nature, two 5-day exposures of animals to hydrogen fluoride were completed with blood fluoride analyses being made at regular intervals throughout the exposure period.

The exposure of rabbits to approximately 29 mg HF/m³ for intervals of 1 to 5 days resulted in a five-fold increase in the blood fluoride level. The blood level reached a plateau after 1 day of exposure and did not increase with continued exposure. The fluoride content decreased immediately following termination of the exposure, but was still significantly above the normal for at least 3 days after the animals were removed from the hydrogen fluoride atmosphere.

When dogs were exposed for intervals of 1 to 5 days to approximately 20 mg HF/m³, however, the blood fluoride content showed a progressive increase through the 4th day; to a maximal value of 291 μg F/100 ml at the conclusion of the 5th day of exposure, the blood level showed a precipitous drop to 103 μg F/100 ml. The plateau effect so striking in the rabbits was not noted with the dogs; moreover, the maximal level occurring in the dog was approximately 2.5 times as great as was the highest level seen in the rabbit. Five days after termination of the exposure the blood levels were still 3-5 times greater than the pre-exposure levels.

Urinary Excretion of Fluoride:

Work by various investigators has shown that under usual conditions of exposure to fluoride, as in cryolite factories, magnesium foundries or in communities whose water supplies contain appreciable quantities of fluoride, the greater portion of the ingested or inhaled fluoride is excreted by the kidneys. However, these investigations have ignored the relation, if any, between the functional status of the kidney and the corresponding urinary fluoride excretion.

The Effect of Renal Dysfunction on the Urinary Excretion of Fluoride in the Rabbit: The effect of uranium-produced nephritis on the urinary excretion of fluoride has been studied in rabbits receiving: (1) a subcutaneous injection of 0.3 mg U/kg as uranyl nitrate; (2) the same dosage of uranium in addition to 15 ppm fluoride in the drinking water; and (3) 15 ppm fluoride in the water supply. Control urinary fluoride excretion was also determined.

Within 3 to 4 days after injection of the nitrate, the uranium excretion of fluoride in those rabbits receiving only the injected nitrate dropped from a pre-injection level of 0.35 mg F/total daily urine sample to a level of 0.05 mg U/total daily urine sample (a sever-fold decrease). In those rabbits receiving both uranium and fluoride the urinary excretion dropped from a pre-injection level of 1.9 mg F/total daily sample to a level of 0.25 mg F/total daily sample, which again is approximately a seven-fold decrease. The urinary excretion returned to the pre-injection level in both groups approximately 12 days after the injection.

Fluoride content of the tooth and bone indicated that the presence of uranium in the kidney may inhibit the deposition of ingested fluoride in the bone and thus offer a degree of protection against fluorosis. The fluoride contents of the tooth root, femoral epiphysis and jaw alveolar bone for rabbits receiving only added fluoride were singificantly higher than in comparable tissues from rabbits treated with both uranium and fluoride, despite the greater quantity of fluoride consumed by these latter animals. Other supporting evidence for the protective effect of added fluoride on uranium poisoning was: (1) a two and one-half-fold lower blood urea nitrogen; and (2) lowered mortality in those rabbits receiving both agents, as compared to the results obtained in rabbits receiving only the uranium injection.

The Determination of Urinary Fluoride Excretion as a Possible Test for Renal Dysfunction: The determination of the urinary excretion of small doses of ingested fluoride has been measured in two individuals with normal renal function, and in two patients with known abnormal kidney function. One patient with chronic glomerulonephritis was only able to excrete 20 per cent of the ingested fluoride; the second patient with chronic pyelonephritis with hypertension could excrete none of the fluoride. The two control individuals excreted 45 and 51 per cent of the dose of ingested fluroide.

These preliminary data indicate that the measurement of the urinary excretion of a test dose of fluoride may prove of value in detecting certain types of renal disorders.

Fluoride in Bone:

The problem of the mechanism of deposition of fluoride in bone has never been settled. This problem is doubly important: It is basic to an understanding of fluoride toxicology and also to the use of fluoride in the prevention of dental caries. A program of investigation was designed to test whether fluoride ion underwent ionic exchange with some grouping in the bone mineral substance. It was found that, for the most part, fluoride exchanges for hydroxyl ion in the apatite lattice of bone. This process is analogous to that observed for uranium.