Fluoride metabolism: its significance in water fluoridation

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The purpose of this report is the review of the present knowledge of the metabolism of fluorides, particularly in the human body, and the use of this knowledge in estimating the factors of safety in water fluoridation. In this discussion, many of the biological effects of fluorides (purported or well-established) will receive no mention. On the other hand, there are a few important biological effects of fluorides so well studied that there is an established relation between the effect and the intake of fluoride responsible, specifically, acute fluoride poisoning, crippling fluorosis, osteosclerosis and mottled enamel. The facts of fluoride metabolism give an insight into the nature and in some instances the mechanism of these effects. This report will include a discussion of the following: (1) blood fluoride levels; (2) the rates and mechanisms of urinary excretion of fluoride and (3) the magnitude and mechanisms of bone deposition. In each instance an attempt will be made to estimate the magnitude of the safety factors between these toxic fluoride effects and the fluoride exposure that will accompany the ingestion of fluoridated water. It is concluded from present information that the factors of safety are adequate to justify the practice of community water supply fluoridation.

BLOOD

Circulating human blood normally contains a trace of fluoride. When the drinking water has only negligible levels of fluoride (<0.1 ppm), on the average, the blood level is about 1 microgram per hundred milliliters of blood.[1] There is a considerable range of variation from individual to individual, and values as high as 10 micrograms per hundred milliliters of blood or higher have been obtained.

Presumably the blood level reflects in some measure the daily intake. Persons living in Rochester, N. Y., prior to water fluoridation ingested mostly by food 1 to 2 mg. of fluoride per day. The drinking water supply in Rochester, N. Y. prior to water fluoridation contained about 0.06 ppm of fluoride (F). When the daily fluoride intake is increased by fluoridating the water supply, the blood level of fluoride increases slightly. For example, in Newburgh, N. Y., where the water supply contains about 1.1 ppm of fluoride (F), the average blood level was 4 micrograms per hundred milliliters of blood. Thus, when Rochester and Newburgh are compared, it is seen that an increase of 20 times in the fluoride water concentration was accompanied by an in-

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1. Smith, F. A.; Gardner, D. E., and Hodge, H. C. Investigations on the metabolism of fluoride. II. Fluoride content of blood and urine as a function of the fluorine in drinking water. J. D. Res. 29:596 Oct. 1950.

crease of only four times in the blood fluoride level. Blood does not tend to accumulate fluoride.

When a large oral dose of fluoride is given to an experimental animal, the blood level rises very rapidly to reach a peak in a half hour to an hour. Thus, in a rat given a near lethal dose of fluoride orally, the blood level in 30 to 60 minutes rose to values of 1,000 to 1,200 micrograms per hundred milliliters of blood.[2] The blood concentrations thereafter fell almost as rapidly so that after two to three hours, only 200 to 300 micrograms of fluoride per hundred milliliters of blood remained. In 24 hours the values were essentially normal, that is, below 20 micrograms per hundred milliliters of blood. The shape of this curve looked like the familiar sugar tolerance curve (except that there were no subnormal levels terminally). When fluorides enter the body, blood fluoride rises to peak concentrations and falls again with extraordinary rapidity.

The body has powerful mechanisms for disposing of the fluoride ion: (1) excretion in the urine and (2) deposition in the skeleton.

URINARY EXCRETION

Human urine normally contains small amounts of fluoride. In Rochester, N. Y., in the prefluoridation days, urinary levels ranged from less than 0.1 ppm to a little over 1.0 ppm fluoride.[1] The average was approximately the same as the concentration in the drinking water supply, that is, 0.06 ppm. The exact urinary level reflected the amount of fluoride taken in the food, and consequently varied significantly from day to day. Daily excretions of 0.5 or even 1.5 mg. were regarded as normal. In Newburgh, N. Y., the average urinary excretion was about 1.1 ppm, which is numerically nearly identical to the concentration in the drinking water.

When a human being ingests small amounts of fluoride, a significant fraction is promptly excreted in the urine. For example, when normal young adults drank a half a glass of water containing 1.5 mg. of fluoride, a smooth curve of excretion was found in which elevated values were apparent in one hour, and a quarter of the total fluoride had been excreted in three hours.[2] This curve reveals how prompt and effective the mechanism is for removing fluoride from the body.

Further ideas on the effectiveness of fluoride excretion in the urine are gained by consideration of the magnitude of the total halogen pool, mostly, of course, the chlorides of the body. The "standard" 70 kg. man has in his body about 150 Gm. of chloride. When 1.5 mg. of fluoride are added, assuming that the fluoride is completely distributed through the halogen pool, the fluoride must constitute approximately 10 ppm of the chloride-fluoride total (150.0015 Gm.). The normal sodium chloride excretion is about 10 Gm. a day or about 6 Gm. of chloride per day. On an hourly basis, about 250 mg. of chloride are excreted or 750 mg. in three hours. Thus, when approximately 0.5 mg. of fluoride are excreted in three hours, the excreted halide has 700 ppm of fluoride of the chloride-fluoride total. Compared to a body concentration, the urine is highly concentrated with respect to fluoride.

The question arose whether this specific faculty of ridding the body of fluoride involves some special mechanism. Philip Chen[3] studied the removal of fluoride from the blood of adult dogs and its urinary excretion and found that there is no special mechanism for the fluoride excretion in the urine. The rapid excretion reflects the fact that fluoride is resorbed from the urine in the kidney tubule somewhat less efficiently than is

2. Smith, F. A., and Gardner, D. E. Unpublished data.

3. Chen, Philip S., and others. Renal clearance of fluoride. Technical report U.R. 420. Rochester, N. Y., University of Rochester Atomic Energy Project, 1955.

chloride. It is well known that of the chloride filtered through the glomerulus and entering the renal tubule over 99 per cent is resorbed, that is, taken back into the venous blood and returned to the circulation. In comparison, the fraction of fluoride resorbed is about 90 per cent. This may seem to be a highly effective operation in both instances, but so much blood passes through the kidney that this difference in the resorptions of fluoride and chloride accounts for the high rate of elimination of fluoride.

The percentage of the ingested fluoride that appears in the urine is somewhat variable but probably amounts to a half to two-thirds of the daily intake. Reliable data of this sort on humans exposed over protracted periods are not available. Largent,[4] however, carried on a study which lasted over many months in which he systematically increased his daily oral intake of fluorides beginning with about a milligram a day for a month followed by 2 mg. daily, then 5 or 6 mg. daily, then 12 mg. daily, and finally, for a period of one month, nearly 20 mg. of fluoride were ingested daily. During this entire period he analyzed his total urinary (and fecal) excretion day by day and was able to show that the urinary excretion of fluoride was a simple straight line function of the intake. Specifically, approximately half of the fluoride absorbed each day was excreted in the urine. It is probable that when humans ingest smaller amounts of fluoride, such as 1 ppm, over a period of years, the daily urinary excretion is a greater fraction of the intake.

The extraordinarily rapid and efficient urinary excretion of fluoride is attributable to a somewhat lower resorption in the kidney tubule than is characteristic of chloride.

BONE DEPOSITION

Bone and tooth substance normally contain small amounts of fluoride. The amount present in the hard tissues probably depends directly on the amounts of fluoride that have been taken into the body day after day; certainly the amount increases in a regular fashion with age. For example, in persons who were lifelong residents of Rochester, the average fluoride content of selected bones, such as rib or vertebra, increased in a nearly linear fashion from about 200 ppm of fluoride in the bone ash of 10 to 20 year olds, to about 1,200 ppm at ages 80 to 100.[5] These people had drunk water containing probably about 0.06 ppm of fluoride in the prefluoridation days in Rochester. There are no systematic data on the concentrations of fluoride in the skeletons of persons who have been lifelong residents of regions where the drinking water contains elevated amounts of fluoride. Isolated data are available, however, on the bone fluoride contents in industrial fluoride exposures; values as high as 10,000 ppm of fluoride have been recorded.

The mechanism of the deposition of fluoride in bone when the fluoride is given at low concentrations such as would occur from drinking fluoridated water has been elucidated. Fluoride deposits by a simple ionic exchange in which fluoride from the extracellular fluid exchanges with hydroxyl groups of the surface of the bone crystals.[6] Bone crystals have a hydroxyapatite crystal lattice in which calcium, phosphate and hydroxyl groups occupy well-defined positions. The hydroxyl ion and the fluoride ion are of the same size, have the same negative charge and can substitute one for the other. The hydroxyl ion is a more stable occupant of the site, but if sufficient

4. Largent, E. J., and Heyroth, F. F. Absorption and excretion of fluorides; further observations on metabolism of fluorides at high levels of intake. J. Indust. Hyg. & Toxicol. 31:134 May 1949.

5. Smith, F. A.; Gardner, D. E., and Hodge, H. C. Age increase and fluoride content in human bone. (Abst.) Federation Proc. 12:368 March 1953.

6. Neuman, W. F., and others. Surface chemistry of bone; fluoride deposition. J. Biol. Chem. 187:655 Dec. 1950.

fluoride ions are present, fluoride replaces hydroxyl. In effect, the surface of the crystal is converted into the fluorapatite lattice instead of the hydroxyapatite lattice. These two lattices, however, are nearly identical, and there is no indication that bone mineral with the fluorapatite lattice has any notable biological disadvantages.

Fluoride is not deposited irreversibly in the bone. It is true that the removal from bone is slow, and it is probable that the removal involves reworking and remodeling of bone carried on by the haversian systems and involving osteoblastic and osteoplastic activity. Of the available quantitative data, the best are those of Largent. In the experiment previously described,[4] he ingested fluorides systematically over a period of many months and kept track of how much fluoride entered his body and how much was excreted. It is therefore possible to calculate that at the end of the experimental period he had stored in his skeleton 1.7 Gm. of fluoride. In the months following, the fluoride excretion was analyzed day after day. In the first month, more of the stored fluoride was excreted than appeared during the third to fourth month. Subsequent examinations after a year and again after two years showed that the excretion of fluoride decreased in a simple linear fashion when plotted on the basis of the logarithm of the percentage stored. This relation permits the calculation of what might be called a "biological half-time," that is, the period required to mobilize and remove from the body half of the skeletal fluoride. This "biological half-time" is longer than a year and perhaps as long as two years. The removal, therefore, is slow but predictable and presumably is related to normal physiological processes in the skeleton.

In summary, it can be stated that skeletal deposition of fluoride is a continuing process in which a considerable portion of the ingested fluoride, perhaps a quarter or as much as a half, is deposited in the skeleton. Stored fluoride is mobilized only slowly.

ACUTE FLUORIDE POISONING

Accidental or homicidal poisonings by fluoride are well known. Following a certainly lethal dose of fluoride (probably 5 to 10 Gm. of sodium fluoride), signs of violent gastrointestinal irritation, such as nausea, vomiting and diarrhea, are promptly seen. A shocklike state develops, and the victims usually die between two and four hours after ingesting the fluoride. Survivors after four hours usually live. The means of excretion of fluorides from the body by the kidney or by deposition in the bone are so effective and so prompt that if the concentration does not overwhelm the cellular processes, excretion thereafter reduces fluoride concentration to a level that is no longer lethal. Since 5 to 10 Gm. of sodium fluoride contain 2.5 to 5 Gm. of fluoride (2,500 to 5,000 mg.), and since by drinking a quart of fluoridated water at 1 ppm daily involves the ingestion of 1 mg. of fluoride, there is at least a 2,500-fold factor of safety against acute fluoride poisoning.[7]

Sometimes the question is raised, What would happen if there were a mechanical breakdown at the fluoridation plant and all of one day's supply of sodium fluoride or sodium silicofluoride were suddenly dumped into the water. If this large weight of fluoride could be dissolved, mixed and distributed within an hour, there would still be a factor of safety sufficient to predict that the water could be drunk for ten years or more without serious toxic consequences. For Rochester, N. Y., to add enough fluoride to the water supply so that a quart would contain a deadly amount, 400 tons of fluoride

7. Hodge, H. C., and Smith, F. A. Some public health aspects of water fluoridation. In Fluoridation as a public health measure, Shaw, J. H., editor. Washington, D. C., American Association for the Advancement of Science, 1954.

would have to be dissolved in the volume of water distributed each day. The machine used in Rochester has a hopper that contains only a half a ton; it is clearly impossible to produce acute fluoride poisoning by water fluoridation.

CRIPPLING FLUOROSIS

First described as an industrial disease, crippling fluorosis, as the name implies, so hinders the function of a workman that he is unable to carry on his daily work. Crippling fluorosis is characterized by a "poker back," a stiffening of the back, traced to the calcification of the broad ligaments of the back. The workman is crippled because he can no longer bend over to pick up tools or to do simple manual jobs. Crippling fluorosis occurs when men ingest or inhale 20 to 80 mg. of fluoride or more daily for a period of 10 to 20 years. Since 5 gallons of fluoridated water (at 1 ppm) contain 20 mg., it is obvious that crippling fluorosis can never be produced by drinking fluoridated water.

When teeth are treated topically using a solution of sodium fluoride, that is, at 2 per cent, the total amount of fluoride applied to the teeth (which under extraordinary circumstances might be ingested) could be as large as 20 mg. If this fluoride were absorbed, it would mostly be excreted in the urine during the succeeding 24 hours. There would be no detectable effects from such a dose. It would be necessary to apply this amount or more to the teeth and to ingest it daily for 10 to 20 years to evoke crippling fluorosis. It is obvious that there is no danger from ingesting fluoride applied topically to the teeth.

OSTEOSCLEROSIS

The condition of osteosclerosis, a hypercalcification detectable by roentgenographic examination, has been repeatedly described in persons with excessive fluoride intakes. This hypercalcification has not been associated necessarily with any loss of function or other ill effects. In the population of Bartlett, Texas, for example, where drinking water contained 8 ppm of fluoride (F), 13 of 114 lifelong residents drinking this water showed some osteosclerosis.[8] In industrial populations, Irwin[9] has come to the conclusion that if the urine contains less than 5 mg. per liter (presumably indicating a fluoride intake of less than 5 to 10 mg. per day), osteosclerosis never develops. On this basis, it can be predicted that persons drinking fluoridated water and excreting approximately 1 mg. of fluoride per day will never develop demonstrable osteosclerosis.

MOTTLED ENAMEL

Enamel hypoplasia appears with graded severity when the drinking water contains 2 to 5 ppm of fluoride (F) or more. The degree of mottling is not a uniform one from child to child, but has a statistical distribution such that an occasional child will show this effect at 2 ppm and an increasing percentage of the children will show mottling as the fluoride content increases. It should be recalled that enamel hypoplasia (dental fluorosis) can only be produced during the first eight years of life when the enamel-forming cells are functioning.

Predictions of the factor of safety against mottling involve to some extent a knowledge of the variation in water drinking of children up to eight years of age. Very little is known about the water drinking habits of children. The guarantee of safety comes from communities where water supplies naturally bear fluorides. In these communities presumably may be found all of the possible

8. Leone, N. C., and others. Roentgenologic study of a human population exposed to high-fluoride domestic water. Am. J. Roentgenol. 74:874 Nov. 1955.

9. Irwin, Dudley. Personal communication.

variability in water drinking habits. The demonstration that in 10 to 12 year old children of these communities, the severity of mottling has a predictable dependence on the fluoride content of the drinking water constitutes an extraordinary basis for the prediction that when water is fluoridated artificially there will be the same incidence of enamel hypoplasia for a given fluoride level in the drinking water. Enamel hypoplasia has been shown to be minimal when drinking water contains 1 ppm of fluoride. It is therefore judged that there is a twofold to fivefold factor of safety against mottled enamel when populations drink artificially fluoridated water (1 ppm).

HEART DISEASE

In certain statistics gathered by the Department of Public Health of the State of Illinois[10] are given the best evaluation to date of the general health of populations taking in small amounts of fluoride in the drinking water. The conclusion was reached that "there is no significant difference in the risk of death from specific diseases such as heart, cancer, nephritis and diabetes." Bishop, Richardson and Muhler[11] recently described a depressor effect on the blood pressure of normal dogs when a milligram of fluoride was administered intravenously. The intravenous administration to human beings of a comparable dose on a body weight basis would mean that a blood level of perhaps 100 micrograms per hundred milliliters of blood would be obtained. Such a value is about 25 times as high as the blood levels actually found in persons drinking fluoridated water containing 1 ppm of fluoride. There seems to be, therefore, an adequate factor of safety against such vasomotor effects.

THYROID

From time to time reports appear of fluoride influences on the thyroid gland. These reports gain plausibility from the selective concentration of iodine in the thyroid gland. The study of small animals (rats) given doses of radioactive fluorine has revealed that small amounts of fluoride go to the thyroid gland. In one study, for example, 90 minutes after the administration of the radioactive fluoride, a total of 213 counts per minute were found in the thyroid gland.[12] This activity may be contrasted with the total of 385 counts found in the submaxillary and sublingual salivary glands or the 155 counts in the adrenal glands. Evidently, although the thyroid gland takes up some fluoride, there is no such concentrating ability as with iodine. Other organs in the same rat contained much more radioactive fluoride; the kidney contained 34,075 counts, the liver, 9,500, and the bone, 5,175 counts per minute. Histological thyroid changes have been produced, but always as a result of large doses of fluoride.

KIDNEY DISEASE

Because the kidney is important in excreting fluoride, the question has repeatedly been asked whether kidney disease might impair fluoride excretion and thereby constitute a health hazard to the individual. Large doses of fluoride (near the acute toxic dose) produce a specific kidney injury of the columnar tubule cells. Small doses have no detectable kidney effect. For persons drinking fluoridated water, there is no evidence of adverse kidney effects of the fluoride thus consumed. The Department of Health of the State of Illinois specifically found no increase in risk of death by nephritis.

10. Health statistics bulletin, special release no. 20, 1952. Springfield, Ill., Bureau of Statistics, Illinois State Department of Health, 1952.

11. Bishop, J. G.; Richardson, A. W., and Muhler, J. C. Effect of different fluorides on vascular tone and alteration in the rate of blood flow. J. D. Res. 34:478 Aug. 1955.

12. Hein, J. W.; Smith, F. A., and Brudevold, F. Distribution of 1 ppm fluoride as radioactively tagged NaF in soft tissues of adult female albino rats. (Abst.) J. D. Res. 33:709 Oct. 1954.

In an animal experiment by Smith, Gardner and Hodge,[13] rabbits were given doses of uranium sufficient to cause severe kidney injury, almost enough to be fatal. This injury develops almost solely in the renal tubule cells. These rabbits and an equal group of control rabbits were given a drinking water supply containing 15 ppm of fluoride for a period of 42 days. The daily intake and excretion were measured for each rabbit individually. At the end of the test, it was shown that the control rabbits and the rabbits poisoned by uranium had excreted almost identical fractions of the fluoride ingested, that is, 45 to 48 per cent, respectively. No difference in the renal handling of fluoride was found in the rabbits tested, even in the presence of severe chemical nephritis.

Additional observations have been made on two groups each comprising about a dozen elderly patients of a county hospital, one with normal kidney function which served as a control group and the other an equal group of patients with long-standing kidney disease.[13] Urine samples were analyzed before water fluoridation and again after water fluoridation was begun. There was no difference in the range of concentrations of fluoride in the urine of the normal patients and the urine of the nephritic patients. After water fluoridation, more fluoride was found in the urine of both groups; again the values showed considerable variation and again the ranges overlapped.

With the limited amount of evidence at hand, it can be said that there is no known evidence that kidney disease is worsened or makes water fluoridation any more of a problem to the individual. Even if kidneys did not excrete any fluoride whatsoever and a person drank fluoridated water for a period of 70 years, all the fluoride thus ingested would only convert a quarter of the total mineral of the skeleton into fluorapatite. Such conversions have been seen in experimental animals without any evidence of loss of function or ill health.

CANCER

Recurrent statements about fluorides in cancer perhaps deserve a word of comment. First, the statistics of the Department of Public Health of the State of Illinois should be referred to. No evidence was found of a difference in the risk of death from cancer when the drinking water of the community contained small amounts of fluoride. The reports by Alfred Taylor, a biochemist at the University of Texas, on the increased incidence of cancer in mice drinking fluoride-treated water have been shown to be unfounded since the food that he was giving the mice had many times the fluoride content of the drinking water and the food was supplied both to the control and experimental groups.[14] Subsequent tests did not confirm the differences. An additional piece of Public Health data may be cited.[7] In New England where water supplies contain little or no fluoride, the average incidence of breast cancer is 17 per hundred thousand. This rate can be contrasted with the incidence in Texas where many water supplies contain 3 or more ppm of fluoride; the average rate is only seven per hundred thousand. There is no indication that the risk of death by cancer is increased by drinking fluoridated water.

SUMMARY

Studies of the metabolism of fluoride help in understanding the rapid disappearance of fluoride from the body after ingestion and the appearance of fluoride in the

13. Smith, F. A.; Gardner, D. E., and Hodge, H. C. Investigations on the metabolism of fluoride. III. Effect of acute renal tubular injury on urinary excretion of fluoride by the rabbit. A.M.A. Arch. Indust. Health 11:2 Jan. 1955.

14. Taylor, E. Facts relative to rumors that fluoridation is harmful. Texas D. J. 69:381 Sept. 1951.

bones and teeth. When all the evidence is put together, it may be concluded that in water fluoridation adequate factors of safety exist against the known toxic effects of fluoride. Additional studies are needed of population groups that have been for many years drinking fluoridated water. At present, the evidence does not justify the postponement of water fluoridation.

Newburgh-Kingston caries-fluorine study XIV. Combined clinical and roentgenographic dental findings after ten years of fluoride experience

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Among the important questions which have to be answered when a new public health practice is considered are (1) the need for this new practice, (2) its safety, (3) its practicability and (4) its effectiveness. The literature during the past two decades has reported numerous surveys which have demonstrated the magnitude of dental caries prevalence and the yearly incidence rates.[1] The inadequate means which are available to cope with this problem have also been reported.[2] The previous authors have discussed the practicability and safety of community water fluoridation as a prophylactic program for the partial control of new dental carious lesions. I shall try to demonstrate the degree to which a community water fluoridation program has contributed to the control of this disease.

Between June 1944 and February 1946, clinical dental examinations were made for all of the elementary grade school children aged 6 to 12 in both the public and parochial schools in Newburgh and Kingston, N. Y. All the examinations at that time were made by one staff dentist using the classic mouth mirror and explorer technic. The recording was made according to an established classification which provided for caries-free teeth, untreated caries, filled, missing and unerupted teeth. Each tooth on the chart had some notation to indicate its status (Fig. 1).

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1. National Academy of Sciences—National Research Council. Survey of the literature of dental caries. Publication 225. Washington, D. C., National Academy of Sciences, 1952.

2. Klein, H., and Palmer, C. E. Disparity between dental need and dental care in school children of Hagerstown, Md., and environs. J.A.D.A. 28:1489 Sept. 1941.