The Pharmacology of Fluoride

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The dental profession and the public at large have been made conscious of the potentially important role of fluoride in the control of dental caries.

While the reports coming from such sources as the United States Public Health Service are encouraging, the lay press has unfortunately printed a picture that would at times seem to be much too optimistic. At this time there are two distinct methods for the use of fluoride as a prophylaxis against dental caries. The topical application of soluble fluoride to tooth surfaces has had a moderate amount of practical success; however, not content with the recommendations of the originators of this method, many commercial firms have modified and adjusted the simple procedure of applying 2% sodium fluoride to the teeth so that now the dentist may, if he wishes, practice a therapeutic ritual which, while impressive to the patient, cannot be any more effective, optimistic advertising notwithstanding.

The second method of fluoride treatment, which consists of adding the drug to communal waters, is based on the premise that adding sodium fluoride to ordinary domestic water produces the same aqueous environment for teeth as is found in the endemic fluoride areas in the country. The validity for this premise is still highly questionable and is to be touched upon later in the paper.

While most of the interest in fluoride as a drug has centered upon its activity on oral structures there are many other parts of the human body that feel the effects of the presence of fluoride. This paper has as its object a review and evaluation of data concerning the pharmacology of fluoride with special emphasis upon those aspects that might be of practical interest to the dental profession.

Sources of Fluorides

We are so used to thinking of the water supply as *the* source of fluoride that we consume, that we are apt to forget the numerous

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other sources in our daily life. A review of the literature indicates that many of the common foods in the American diet contain fluoride concentrations in the same order of magnitude as the soil or water in the environment in which they grow. *Table I* gives examples of some of these foods.

It will be noted that even though an individual were to drink fluoride-free water he could virtually not escape ingesting some fluoride in the course of a normal meal. In addition to these which might be considered natural sources for fluoride, there are others with which we are apt to come in contact and which, as an inspection of *Table II* will indicate, are potentially great sources of fluoride intake.

TABLE I

THE CONCENTRATIONS OF FLUORIDE IN SOME COMMON FOODS

Food	Fluoride, Parts Per million	Food	Fluoride, Parts Per Million
Milks	0.05-0.23	Whole wheat	1.3
Eggs	0.04-2.0	White bread	1.0
Butter	1.5	Gelatin	0.0
Cheese	1.6	Dextrose	0.5
Liver	1.5-1-6	Honey	1.0
Chicken	1.4	Tea (dry)	30.0-60.0
Pork	0.2	Tomatoes	0.6-0.9
Oysters	1.5	Apples	0.8

The chief observation that should be made at this point of the discussion is that the daily intake of fluoride must be considered from several sources and not from water alone. This becomes important in such areas as are now adding or contemplating adding soluble fluoride to their water supply.

Absorption and Retention of Fluoride

The absorption of fluoride into the body can be brought about in a number of ways. It has been noted, for instance, that workers in cryolite plants achieve a rather high body fluoride content because of its absorption from inhaled cryolite dust. To be sure, this pathway of absorption is unusual, but it points to the fact that we must take many sources of fluoride into consideration when we discuss the matter of fluorosis. By far the most important pathway for the absorption of fluoride is the alimentary tract.

Let us first discuss some factors which influence the rate and the amount of fluoride absorption. The solubility of the fluoride source is one of the most important. This can be seen from *Table III.* Since the solubility of fluoride sources is related to the acidity or alkalinity of the medium in which they exist and since in general a low pH is conducive to solubilizing fluoride sources, the mere fact that a salt like calcium fluoride is insoluble in water does not necessarily mean that it is not a good source of available fluoride. This is so because the

TABLE II

Fluoride Sources of Industrial Origin

Uses	Fluoride Compounds
Binder for emery wheels	CaF_2
Laundry bleach	Na_2SiF_6
Coagulating rubber	Na_2SiF_6; $MgSiF_6$
Disinfection of hides and skins	H_2SiF_6
Fixer in dye works	SbF_3
Flux	Na_3AlF_6; CaF_2
Glass etching	HF; NH_4F
Insect powders	NaF
Optical paste	CaF_2
Wood stain	CrF_3

high acidity of the stomach can dissolve a good portion of the ingested calcium fluoride which might then be absorbed by the gastro-intestinal tract. There is a secondary mitigating influence in the human gastrointestinal tract and that is the high alkalinity of the intestinal juices in the small intestine. In contradistinction to the solubilizing effect of the gastric juice, the intestinal juices change many soluble fluorides into insoluble ones.

A second factor influencing absorption is concentration of fluoride in the source. The absorption of fluoride is a strictly physical phenomenon. As such it depends entirely upon the relative concentration of the drug on either side of a membrane. The laws of physical absorption state that the higher the concentration the greater will be the rate and amount of material absorbed.

A third factor influencing absorption is the amount of substance available. This is such an obvious limitation that no further discussion is necessary.

A fourth factor and indeed an important one is the pH of the medium from which absorption is to take place. While at first glance this may seem to be a duplicate of the first criterion discussed, the implications are far different. Studies have indicated that the absorption of fluoride takes place largely from the undissociated hydrogen fluoride molecule. From any source, the amount of undissociated hydrogen fluoride is a direct function of the pH. *Table IV* indicates data obtained when the absorption of fluoride from an intact intestinal loop of a dog is measured. These experiments illustrate quite clearly that there is a very close relationship between the acidity of the medium and the absorption of fluoride from it.

TABLE III

Solubility of Some Fluoride Salts

Compound	Solubility in Grams Per 100 CC.
NaF	4.0
Na_2SiF_6	0.65
AgF	182.0
CaF_2	0.0016
PbF_2	0.064
LiF	0.27
MgF_2	0.0087
$MgSiF_6$	65.0

The fifth factor influencing the absorption of fluoride is the presence or absence of fluoride-insolubilizing substances. It is obvious, from a consideration of the first factor discussed above, that under conditions when the available fluoride is rendered insoluble by the presence, say, of excess calcium ions, the amount absorbed materially diminishes. This statement is borne out by the experiments which are summarized in *Table V*. In this experiment rats were fed fluoride in food or in water at a 20 ppm level. Control groups received only the fluorided food or water whereas the experimental groups received calcium hydroxide in addition to the fluorided food or water. The amount of fluoride ingested and excreted was measured from the food consumption and from the fluoride concentration in the excreta. From these data we can calculate the amount of fluoride retained by the animal. Since the retention in the body is a mirror of the amount absorbed, as will be explained in a subsequent section, we can assume that a high fluoride excretion under the conditions of this experiment indicates a low absorption.

In addition to the factor which influences absorption we must also consider the factor which influences fluoride retention. One of these factors is the amount of fluoride being ingested. In general, the

TABLE IV

FLUORIDE ABSORPTION FROM A 0.01% SODIUM FLUORIDE SOLUTION PLACED INTO AN INTACT DOG'S INTESTINAL LOOP

pH	% Absorbed
8.0	18
7.0	22
6.0	39
5.0	46
4.0	52
3.0	67

TABLE V

EFFECT OF AN INSOLUBILIZER ON FLUORIDE ABSORPTION

Group	Av. Amt. F Ingested	Av. Amt. F Excreted
Fluoride in Water	17.5 mg.	8.4 mg.
Fluoride in Food	23.2 mg.	12.7 mg.
Fluoride in Water plus $Ca(OH)_2$	18.7 mg.	17.5 mg.
Fluoride in Food plus $Ca(OH)_2$	21.5 mg.	19.7 mg.

greater the amount being ingested, the greater the amount will be retained. This follows from the law of mass-action. It is important to remember in this connection that more fluoride will be retained if it is given in small multiple doses than when a similar quantity is given in a smaller number of larger doses.

A second factor which influences fluoride retention is the activity of the calcifying tissues. Since in general the only so-called storage depot in the body is the calcified structure and since the method of storage is to build the fluoride ion into the crystallin structure of the bones and teeth, it shows that those animals which are in an act of calcification will retain more fluoride in their body than those in whom the calcification process is virtually finished. The phenomenon can be recognized by inspecting *Table VI.* It will be seen as the animals grow older they retain less of the ingested fluoride than when they were young.

TABLE VI

THE RELATION BETWEEN THE AMOUNT OF FLUORIDE RETAINED AND THE AGE OF THE ANIMAL, FROM TIME OF WEANING

Days on Experiment	% of F Intake Excreted
1	52
40	58
80	63
120	68
160	72
200	79
220	83

Distribution of Fluoride in the Body

We normally think of fluorides as being accumulated in the hard structures of the body such as the bones and the teeth. However, since the fluoride ion is so small and so diffusible it may be found distributed throughout the entire body. It is true, of course, that we find a high concentration in the hard tissues and that, as has been indicated, is due to the fixing of fluoride as an integral part of those structures. *Table VII* illustrates the distribution of fluoride throughout the body tissue of normal adult humans. If we compare these values with those illustrated in *Table VIII* it is little short of astonishing to find only small differences. For the values found in *Table VIII* were obtained from individuals who had died of fluoride poison and these figures have been interpreted as being the lethal fluoride concentrations of internal organs. From a comparison of these two tables it would appear that while the concentration of fluoride in the normal and fluorosed individual is small, the activity of fluoride may be vastly different and possibly accounts for the physiologic differences between these two groups.

This problem of fluoride activity rather than fluoride concentration appears to be an important one and will be referred to again in a later portion of the paper.

Table IX indicates at rather interesting distribution of fluoride in male and female rats. There can be no doubt that the female rats retain a greater portion of fluoride than do the males. This difference

TABLE VII

Distribution of Fluoride in Normal Body Tissues

Tissue	Fluoride in Parts Per Million
Blood	3.5
Brain	0.6
Liver	2.1
Kidney	4.5
Heart	1.6
Spleen	2.7
Muscles	1.6
Femur	2.9

possibly has as its basis the higher metabolic rate in the females. This contention is strengthened somewhat by a report of an investigation in which the metabolic rate of male rats was artificially increased. Under these circumstances the male rats had a fluoride retention more comparable to that found in the females.

Table X illustrates the high specific distribution of fluoride in teeth. Again the most physiologically active portions seem to contain the greater amount of fluoride. This highly selective concentration of fluoride in teeth is of course the basis of systemic therapy for caries prevention.

It is interesting to note that the fluoride ion passes the placental barrier. The importance of this is that the fetus has already accumulated fluoride during its development. This also accounts for the fact that the decidous teeth of youngsters living in endemic fluoride areas show a greater resistance to caries than those living in non-fluoride areas.

The Excretion of Fluorides

Because of its water solubility the fluoride ion is excreted through all pathways which have water as the vehicle. We find fluoride in urine, feces, sweat, saliva, and tears. The fluoride concentration of urine in subjects living on fluoride-free water ranges from 0.3 to 1 ppm. If the fluoride content of the ingested water rises to as little as ½ to 1 ppm the urinary fluoride concentration may rise to as high as 3 ppm.

TABLE VIII

LETHAL FLUORIDE CONCENTRATION IN BODY TISSUES

Tissue	Fluoride in Parts Per Million
Blood	3.6
Brain	1.6
Liver	4.0
Kidney	4.6
Heart	2.1
Spleen	3.9
Muscles	2.6

Workers in a magnesium foundry where fluoride-bearing dust is inhaled have been found with a urinary fluoride as high as 10 ppm.

From a practical point of view the dentist should be interested in fluoride excretion through the saliva. Since saliva bathes the teeth more or less constantly it would seem that the salivary fluoride should act as additional protection against tooth decay. Unfortunately the data which relate salivary fluoride to blood fluoride indicate that only about one-tenth the blood fluoride concentration is found in the saliva. This points to a selective retention of fluoride in the blood or perhaps a barrier to fluoride excretion through the saliva, since a similar study on blood and salivary chloride indicates that there is a saliva to plasma chloride ratio of approximately 0.4 to 1.

The sweat serves as a surprisingly good pathway of fluoride excretion. Subjects living in a fluoride water area excrete sweat containing from

0.3 to 2.0 ppm of fluoride. When these same individuals are placed on non-fluoride water their excretion in the sweat drops to approximately 0.2 to 0.3 ppm after two weeks.

When an experimental animal is first placed on a fluoride-containing diet he retains virtually one-half of the absorbed fluoride. As the concentration in the diet is increased there is a progressively greater output through the excretory organs and above a given level virtually all of the additional fluoride in the food is apparently excreted. These data point toward a saturation phenomenon. In humans it has been found that a total daily fluoride intake of from 4 to 5 milligrams

TABLE IX

TOTAL AMOUNT OF FLUORIDE IN RAT CARCAS AFTER FEEDING 4 PPM FLUORIDE

	Rat	Weight	PPM Fluoride
	1	230.2 Gm.	13.0
Male	2	271.2	10.9
	3	346.2	11.6
	4	271.2	11.3
Average		279.7	11.7
	5	172.7	13.7
Female	6	187.9	14.1
	7	177.3	13.9
	8	175.4	14.7
	9	173.3	13.9
Average		177.3	14.1

produces saturation. Below this figure some of the ingested fluoride is retained but above this figure there is no further retention.

Pharmacologic Effects of Fluorides

In the human body, the physiologic systems that are affected by fluorides are the bones, teeth, skin, hair, viscera, circulatory system, and genito-urinary system. The manner in which each of these systems is affected varies with the concentration of the drug, the length of time it is allowed to remain in contact, and the individual susceptibility of the system to fluorides.

This problem of fluoride susceptibility seems at first glance to be a rather unpredictable one. However, when one considers the basic mode of action of fluorides, most of the symptomatic phenomena can be understood.

In general, fluorides seem to exert their effects upon enzymes, cells, and calcifying tissues. In the case of the effect upon enzymes, there is a selective activity demonstrated in its effect. Since enzymes can be considered to be complexes consisting of proteins, vitamins, and a metallic component, and since the metal portion of each enzyme is not identical with that in another enzyme, it follows that only those

TABLE X

The Accumulation of Fluoride in Human Teeth

Treatment	Incisors Enamel	Incisors Dentin	Molars Enamel	Molars Dentin
Distilled Water	36 ppm	46 ppm	34 ppm	89 ppm
10 ppm Fluoride in water	160 ppm	495 ppm	130 ppm	415 ppm

Table XI

An Effect of Fluoride on Carbohydrate Metabolism

Group	Blood Glucose	Blood Lactic Acid	Liver Glycogen	Muscle Glycogen
Control	118 mg%	17 mg%	3.6%	0.78%
20 ppm F in Water	223 mg%	198 mg%	0.64%	0.17%

enzymes which have metallic components capable of being rendered insoluble, or non-available, will be affected by the presence of fluorides.

One of the most important systems of enzymes that are susceptible to fluorides are those involved with phosphate transport. The effect on phosphatases and phosphorylases becomes important from several points of view. In the first place, phosphate transporting enzymes are important in the absorption of carbohydrates from the small intestine. When these enzymes are absent or poisoned in any manner, sugar absorption takes place only slowly. Secondly, these enzymes are also important in the utilization of carbohydrates in the body. Indirectly they are also concerned with the metabolisms of fats and proteins. In the presence of an adequate amount of fluorides, these enzymes are poisoned and, as will be seen from *Table XI,* the normal sugar metabolism is disturbed. Compare the blood sugar, muscle and liver glycogen, and blood lactic acid concentrations under the influence of fluorides. A more than casual glance at this table will indicate that the effects are very similar to those obtained in a diabetic animal. This does not mean at all that fluorides can cause diabetes! It merely means that the presence of fluorides seems to interfere with metabolic systems similar to those affected by an insufficiency of insulin.

A recent study has pointed to the importance of these same phosphate transporting enzymes for renal reabsorption of glucose. In the presence of an adequate amount of fluorides, a normal animal such as a dog or rabbit can be made to have glycosuria. This glycosuria can be produced even in the animal with normal blood sugar levels, indicating quite clearly that the fault lies with a deficiency of renal reabsorption.

Much speculation has been raised about the effect of fluorides on the blood clotting mechanism, since this depends in part on the availability of calcium ions. Calcium ions have a high affinity for fluorides and can conceivably remove these from solution. As a corollary, fluoride ions can remove essential calcium ions from solution. In the test tube we can demonstrate an interference with the blood clotting mechanisms by adding fluorides. In the intact animal no such interference has ever been demonstrated unless impractically high concentrations were used. This difference between the *in vitro* and *in vivo* behavior of the drug towards the clotting mechanisms is not easily explained.

The effect of fluorides on cells is of importance. All cells are affected by fluoride to a greater or lesser degree. The extent of effect on a cell seems to be directly related to the cell's dependence on carbohydrate metabolism. While tissue cells are affected to some degree, of more importance is the fact that fluorides in the proper concentrations can affect bacterial cells. It can be shown that microorganisms inhabiting the oral cavity can be materially inhibited by fluorides. It is interesting, however, that the concentrations must be many times those required to inhibit enzymes. For example, the concentration which inhibits acid production is 1 ppm, while lactobacilli are not inhibited until a concentration of 250 ppm is used.

The effects of fluorides on the calcified structures of the body are striking. Fluorosed tooth enamel, for example, is denser, harder, and more resistant to acid decalcification than is a corresponding normal enamel. These effects have been ascribed to the fact that fluoride becomes part of the crystal lattice of the calcified structures. It differs physically from the hydroxyl-containing crystal only in its denseness of packing.

Sometimes the effect of fluoride-fixation by the calified structures results in a visible change in the normal structure. The dental profession is very familiar with the mottled enamel of fluorosed teeth. While the exact nature of this malfomed tooth substance is not known, it seems likely that the presence of a certain critical amount of fluoride during the formative stage of the enamel so affects some enzymes concerned with the formation of this material that an abnormal structure results.

The well known practical effects of fluoride affecting the tooth enamel are on the one hand desirable and on the other hand lamentable. When fluorides are present in the environment of calcifying tooth enamel below a certain critical level, the fluoride is simply built into the crystal lattice and hard, dense, resistant enamel is formed which clinically has the ability to resist the carious process. Such a building of fluoride into the enamel, at least on its surface, seems also to be achieved by topical application of a concentrated solution of soluble fluoride (2% sodium fluoride). The exact manner in which this method of fluorosing the enamel exerts its beneficial effect is not yet determined. However, the practical result seems to be a reduction in the caries experience of individuals thus treated. Recent evidence indicates that adults as well as children can benefit from such a treatment, when it is carried out correctly.

On the other side of the picture is the fact that when the critical level of fluoride in the environment from which the tooth is calcifying is overstepped, unsightly mottling can result. It appears to be simply a matter of concentration control in order to achieve either of the two results mentioned. Unfortunately the line between mottling and no mottling is an elusive one and the degree of control to be exercised seems to be very fine.

The experimental addition of soluble fluorides to domestic water supplies in concentrations resembling those found in natural fluoride waters is interesting and bears very close watching. While there seems to be no doubt that it is, in fact, the fluoride content of the natural water that is responsible for the beneficial effects from such waters there are still some very important questions that need answering. What is the response of the body to fluoride that is not accompanied by the other mineral substances invariably found in natural fluoride waters? Do these other substances augment or limit the effective *activity* of fluoride even though they do not affect its concentration? What relation exists between the *concentration* of fluoride and its *activity* in media of various mineral compositions? What is the relation between the intake of fluoride from food and/or water and its activity with respect to its concentration associated with calcifying tissues?

When these questions have been answered, together with those other questions which continued research on fluoride and its effect on living systems will propose, then only can we say that fluoride therapy is out of the experimental stage. Until that time we must be wary not to draw hasty, unwarranted, and perhaps regrettable conclusions.

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