Fluoride Protection of Bones and Teeth

Some changing concepts of dosage and application are shedding new light on fluoridation.

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There is current evidence of a new interest in the extent to which tissue tolerates fluoride and in the potential benefits of ingested fluoride in the management of various general illnesses, notably metabolic bone diseases. The fluoride dosages tolerated in tissue culture (5 to 10 parts of fluoride ion per million) and used in recent medical applications (20 to 100 mg of fluoride ion per day) suggest that ingestion of water containing fluoride at a concentration of 1 part per million (0.5 to 1 mg of fluoride ion per day), as recommended for the prevention of dental caries, provides a higher margin of systemic safety than is generally believed.

This contrast between potential medical and conventional dental applications of fluorides struck me as particularly significant when I recently served as a U.S. representative before a World Health Organization conference in Geneva, Switzerland. Here representatives from many countries were convened to consider the worldwide incidence of dental disease, with particular reference to the need for and potential impact of expanded dental research. A paradox appeared in observations indicating continued widespread concern about the presumed "poisoning" effects of supplementation of the fluoride content of drinking water to the level recommended for the prevention of dental caries and in data showing a worldwide spread of dental disease, both in the developing countries (in some of which there is only one dentist for each 1 million people) and in the affluent societies, where one dentist for each 1500 to 3000 people is the ratio considered necessary to meet the public demand—though not the total need—for dental treatment.

The purpose of this article is to provide a summary of very recent references to an emerging field of research which may shed new light on the questions of safety and potential usefulness of fluorides both in medicine and in dentistry.

Fluoride Levels in Cell and Organ Culture

Insofar as I can interpret recent observations on the effects of fluoride on cell cultures, the weight of evidence now indicates that cellular reproductivity goes on in the presence of an amount of fluoride greater than the amount which can be brought into the body's circulating tissue fluids through oral ingestion. Albright (*1*), in a study at Yale University Medical School, used cultures of murine leukemic lymphoblasts and found no inhibition of cell multiplication in a medium containing fluoride at a concentration of 5.7 parts per million (3×10^{-4} *M*).

Two British workers, Berry and Trillwood (*2*), using cultures of HeLa cells and a strain of mouse fibroblasts, found no significant reduction in the cellular reproductive capacity at sodium fluoride concentrations up to 10 parts per million (10 mg/liter). They contended, however, that the *growth* of these cell lines was depressed by fluoride at concentrations much lower than these. But Armstrong and his co-workers (*3*) made similar experiments at the University of Minnesota Medical School and failed to find any depression either of protein synthesis or of cell multiplication when fluoride at concentrations up to 10 parts per million was added to cultures of HeLa cells or of esophageal epithelial cells.

Berry and Trillwood (*4*) in a rejoinder, responding to a "flurry of press and scientific comment upon [their] work," suggested that the discrepancy between the British and American findings was caused by variations in technique and in the base-line growth rate of the control cultures (also, they disclaimed any inference that they may have wanted to interpret their results in terms of the merits of fluoridation). Promptly thereafter, Armstrong's group (*5*) conducted additional experiments in conformity with the experimental conditions of the British investigations. The results of these latest experiments are regarded as having confirmed the results of their previous study (*3*). Simultaneously, an additional British study (*6*) demonstrated that the growth of HeLa cells in culture is reduced by fluoride only at concentrations considerably higher than those reported by Berry and Trillwood (*2*). Though these are not mammalian cells, it is noteworthy, according to Armstrong's group, that it might take fluoride concentrations of the order of 30 to 50 times the concentration ordinarily found in human body fluids to affect the HeLa cell cultures.

The specialized cells (ameloblasts) that form the dental enamel in *children* appear to be more sensitive to fluoride than the HeLa cells, but possibly the enamel organ possesses a mechanism for local concentration of salt.

In organ cultures, Proffit and Ackerman (*7*) subjected bones of the forepaws of young rats to varying concentrations of fluoride. The formation of DNA and protein synthesis were appraised by the uptake of tritiated thymidine and C^{14}-labeled proline. Fluoride concentrations as high as 10 to 20 parts per million had no demonstrable effect on these basic parameters of skeletal growth.

Fluoride Levels in Tissue Fluid

One of the remarkable aspects of fluoride ingestion and metabolism is the curious fact that it is almost impossible to raise markedly the fluoride level in blood plasma in logical relation to oral ingestion of fluoride at extremely high concentration. This mechanism of fluoride homeostasis has been studied recently both in animals and in man by Armstrong and his colleagues (*8–11*).

Animals given fluoride, in a wide range of concentrations, by mouth, have been shown to have unexpectedly

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constant plasma levels of fluoride (*9*). Even the administration of parathyroid extract (to induce excessive bone resorption) caused no significant increase in the amount of fluoride retained in the blood plasma, though the blood calcium was increased, as had been expected, because of the dissolution of bone mineral in this extreme metabolic state.

In man, Singer and Armstrong (*10*) have shown a similarly constant level of fluoride in blood plasma in populations of individuals who used communal water supplies that varied widely in fluoride concentration.

In Table 1 are given some specific data (*8, 10*) on fluoride levels in blood plasma, as observed in U.S. communities with domestic water supplies containing from 0.15 part to 5.4 parts of fluoride per million.

It appears that there is no marked increase in the fluoride levels in plasma even at intakes twice the 1 part per million recommended for the prevention of dental caries. The body has an effective means of maintaining a constant concentration of fluoride in body fluids, even when there are large variations in fluoride intake. This homeostasis is effected in part by the kidney, which operates as an efficient organ of fluoride excretion, and in part by the skeleton. Using radiofluoride as a tracer, Carlson *et al.* (*11*) showed that renal fluoride clearance was always many times as high as renal chloride clearance and increased with urine flow, and that soft tissues lost nearly all fluoride within 4 hours after ingestion. It was calculated that in man only about 10 percent of an oral dose of fluoride is retained in the body's plasma 1 hour after ingestion.

In patients deliberately given enormous dosages of fluoride in the treatment of bone disease, as described below, the fluoride concentration in plasma was investigated by Armstrong *et al.* (*12*), who found surprisingly low concentrations. Even though the intake of fluoride was from 50 to 100 times normal intake, the plasma concentration was increased by a factor of no more than 4 or 5. Even with extremely high oral dosages of fluoride, the kidneys rapidly excrete half or more of the ingested fluoride, and a lesser portion is deposited on the bone crystals, a biophysical process which it may be possible to exploit to protect human beings against pathological bone destruction.

Fluoride Dosages Administered to Human Subjects

High fluoride levels and the pertinent biological effects in man have been studied in subjects who have ingested large amounts of naturally occurring fluoride and in patients who have been given high dosages in the treatment of disease.

Among the first to explore the potential benefits of such treatment were the endocrinologist Fuller Albright and his associates (*13*), working at the Massachusetts General Hospital, when, 20 years ago, they made an effort to protect the skeleton of patients with idiopathic osteoporosis by means of what then was an unprecedentedly high fluoride intake (the equivalent of 30 parts or more per million). It appears from later studies, discussed below, that the dosages were not high enough for the purpose or were administered for too short a time.

A thorough roentgenological study of a human population ingesting relatively large amounts of naturally occurring fluoride from domestic water supplies (fluoride concentration, up to 8 parts per million) was made 10 years ago by some of the foremost authorities in this field (*14*). The population was given a clean bill of skeletal health. Furthermore these workers noted some indication that the ingestion of excessive amounts of fluoride may indeed have had "a beneficial effect in adult bone, as in counteracting the osteoporotic changes of the aged."

More than a decade ago, in an effort to help patients beyond hope of cure by any known medication, Black and his co-workers at the New York Medical College (*15*) resorted to treatment with enormous dosages of fluoride. In 70 persons suffering from incurable illnesses, mostly cancer, fluoride doses of 80 to 400 milligrams a day were administered for 4 to 6 months (about 320 times the amount recommended for water fluoridation). This extraordinarily high intake produced no observable toxicity. I mention this study because it permitted histopathological examination of internal organs, following death from the incurable illness; despite these high dosages of fluoride, no microscopically demonstrable damage of organs, tissues, or cells was apparent.

More recent studies (*16–20*) relate to people with disturbances in calcium metabolism generally and with various destructive diseases of the skeleton for which no conventional treatment has proved satisfactory. These conditions include postmenopausal bone defects, osteoporosis in general, Paget's disease, osteogenesis imperfecta, multiple myeloma, and metastatic carcinoma spreading to bone.

One of the first recent reports along these lines was that of Purves (*16*) on the fluoride treatment of Paget's disease, an extreme disturbance of the normal remodeling capacity of the skeleton. Sixteen patients were given 60 milligrams of sodium fluoride a day in divided daily doses of 20 milligrams each for 2 to 3 months and then a total daily dose of 20 milligrams for up to a year. Within 4 to 6 weeks after the beginning of the treatment, 14 of the patients gained substantial relief from their bone pain and concomitant disability. Six of the patients showed an improvement in calcium balance; four of these had formerly shown a negative balance.

This approach to bone protection has been followed up by more elaborate observations on general metabolic effects, biochemical changes, calcium balance, and so on. The most extensive reports published to date are those by Rich and his co-workers (*17*). In one detailed study of six patients they made 13 balance studies of 5 to 75 weeks' duration. To the adult patient weighing about 60 kilograms they administered orally, in the form of sodium fluoride, the equivalent of from 42 to 88 milligrams of fluoride (that is, 0.7 to 1.4 mg of fluoride per kilogram of body weight per day). Detailed biochemical studies were conducted before and during the treatment. One of the subjects with Paget's disease and others with osteoporosis retained calcium during the treatment. Urinary excretion of calcium fell to very low values in several subjects, and excretion of fecal calcium was also usually reduced. There were no clinical symptoms or biochemical evidences of toxic effect in any patient.

In discussing these findings Rich and his co-workers suggested that fluoride causes bone-destroying cells to be exposed to greater concentration of fluoride than cells of other tissues. The possibility that fluoride may offer protection both in osteoporosis and in Paget's disease suggests that fluoride exerts a general effect on bone rather than producing a specific interference with the metabolic abnormality caused by a given disease process. Rich and his associates not only believe that fluoride causes a significant retention of calcium but look upon fluoride as "the only known agent suitable for prolonged administration to humans for the purpose of increasing the density of the skeleton."

Bernstein *et al.* (*19*), working at Harvard and its affiliated Peter Bent Brigham Hospital, administered from 50 to 200 milligrams of sodium fluoride per day to patients with Paget's disease and with different types of osteoporosis—postmenopausal, idiopathic, and the type that accompanies urticaria pigmentosa. The clinical findings indicated that all patients experienced relief from bone pain after administration of fluoride. Biochemical studies showed that fluoride initiated calcium retention. Serial bone biopsies indicated an increase in mineralization after administration of fluoride. Concomitant studies with calcium-47 showed an increase in rate of bone accretion after administration of fluoride. Bernstein and his associates concluded that sodium fluoride may be an important "bone nutrient" in diseases where there is abnormally high resorption or defective mineralization of bone.

In three patients suffering from Paget's disease, Higgins *et al.* (*20*) found that short-term fluoride therapy had no effect on the balance of calcium, phosphorus, and nitrogen. According to these observers, the relief of bone pain experienced by two of their three patients "was probably a placebo effect." However, Purves (*21*) and Rich and Ensinck (*22*) hastened to point out that their own previously published and far more extensive studies (*16, 17*) had already made it clear that positive effects of such fluoride treatment were manifested only after periods longer than the periods of administration in the studies of Higgins *et al.*

The British investigator Purves (*21*) sums up the currently available information with the conclusion that prolonged intake of high dosages of sodium fluoride, "besides being associated with the relief of pain of Paget's disease and osteoporosis, causes retention of calcium with negligible toxic effects."

Meanwhile, Bernstein *et al.* (*23*) had greatly extended their own studies. At a recent national nutrition conference held at the Massachusetts Institute of Technology they reported on very comprehensive findings (*24*). They found

Table 1. Data on fluoride levels in blood plasma, as observed in U.S. communities with water supplies containing fluoride at various concentrations. [After Armstrong (*8*) and Singer and Armstrong (*10*)]

Community	Fluoride (parts per million)	
	In water supply	In plasma
Rochester, Minn.	0.15	0.14 ± 0.0050
Minneapolis–St. Paul, Minn.	1.1	.15 ± 0.0044
Grand Rapids, Mich.	1.1	.19 ± 0.0085
Gettysburg, S.D.	2.5	.16 ± 0.0073
Lake Preston, S.D.	5.4	.26 ± 0.0124

that following clinical administration of high dosages of fluoride, the serum calcium was slightly decreased, but still within normal limits, and both the phosphate balance and the calcium balance were mildly positive. On the other hand, the urinary excretion of calcium was reduced by about one-fourth relative to the level before treatment. They checked the neurological, cardiac, renal, gastrointestinal, and hepatic functions and found no toxic systemic effects from ingestion of fluoride dosages of from 40 to 75 milligrams per day. The treated patients showed an increase in bone density and a reduction in bone fractures. In addition, these investigators obtained bone biopsies from the iliac crest of patients before fluoride treatment and after a year of therapy at these massive dosages. They demonstrated by means of x-ray diffraction that the fluoride therapy had resulted in the formation of bone exhibiting larger inorganic crystals, of more perfect structure, than were observed in bone of these patients before treatment.

Thus, very detailed data—metabolic, biochemical, microscopic, and crystallographic—suggest surprisingly few, if any, adverse effects of fluoride at these dosages, high as they are relative to the dosages previously used for prevention or therapy.

As noted above, there has been concern for a long time regarding dosage and administration of fluoride. More than 80 years ago a British physician, Edward Woakes (*25*), made a brief note regarding favorable results from treatment of "bronchocele and goitre" by means of daily doses of from ½ to 2 "drachms of a half percent solution of fluoric acid."

There is now, as there was then, healthy skepticism regarding such high dosages. Thus this summary would be incomplete without mention of three very recent but less favorable views. In reviewing Paget's disease of bone, deDeuxchaisnes and Krane (*26*) recognized that, in Paget's disease, the skeleton does retain more fluoride; but they were not satisfied by the effects of fluoride on the disease per se. In commenting on osteoporosis, Whedon (*27*) concluded that the beneficial effects of fluoride salts (as compared to the effects of other, more or less empirical medicaments now in use) have not as yet been demonstrated to be sufficiently significant to warrant widespread use of such salts. Taylor and Taylor, who explored the effects on soft tissues of administering sodium salts of bromine, fluorine, and iodine, have reported (*28*) that all these salts appear to stimulate cell multiplication in experimental tumors. But they found a curious lack of response when fluoride, in a wide range of dosages, was added to the drinking water of tumor-bearing mice. They give no data on the fluoride content of the rodents' diet; this content is generally very high to begin with.

The results of most current research on fluoride treatment are encouraging, but much additional study is needed, not only regarding the effect of fluorides on body fluids, hard tissues, and soft tissues but also on the basic and seemingly complex causes of our widespread skeletal and dental demineralization syndromes (*29*).

At this time it is prudent to take a somewhat conservative approach to the subject of fluoride therapy at high and prolonged dosages. Indeed, today much more is known about the effects of fluoride salts on the teeth than on the skeleton in human beings of various ages. Better protection and stabilization of the human skeleton than has been achieved to date may well be attainable through further studies of optimum timing, dosage, and duration of treatment with fluorides.

Concluding Comments and Summary

Contrary to earlier views it now seems possible that cells, tissues, organs, and organisms may tolerate somewhat higher levels of fluoride than can readily be introduced into circulating tissue fluids through oral administration of fluoride (Fig. 1).

The mean fluoride content of the plasma of persons whose drinking water contains more than twice the amount of fluoride recommended for the prevention of caries has been found to lie below 0.20 part per million; even in persons whose drinking water contained five times that amount of fluoride the fluoride content of plasma was no more than 0.26 part per million.

Furthermore, in patients deliberately given 50 to 100 milligrams of fluoride a day, by mouth, for periods of up to 34 weeks (in the management of metabolic bone disease), the highest concentration of fluoride in the plasma was less than 2 parts per million after 2 weeks of treatment; after continued treatment for nearly a year the fluoride content of the plasma dropped to less than 0.5 part per million (see *12*).

It seems important to make further studies which can confirm or refute the validity of (i) findings in basic studies, which suggest that cells, tissues, and organs can tolerate fluoride concentrations above those hitherto attainable in the body fluids through oral ingestion, and (ii) clinical observations which suggest that fluorides ingested in dosages 100 times the highest dosage hitherto recommended for the prevention of caries may have significant preventive and curative effects in regard to other mechanisms of hard-tissue destruction (*29*).

Validation of these findings would imply that additional applications of fluoride therapy should be explored, pertaining to various hard-tissue disorders about the cause, control, and cure of which very little is known at this time.

In addition to the generalized metabolic bone diseases discussed above, we are, in dentistry, faced with severe localized alveolar jawbone destruction, which, in the adult population, is now leading to greater loss of teeth than is caused by dental caries. Against these processes of bone resorption we have very little to offer in the way of prophylactic and therapeutic medication. The possibility that bones and teeth can be protected through systemic administration of fluoride, or even through vascular and topical injection of higher concentrations of fluoride than those used in the prevention of dental caries, merits intensive investigations.

Furthermore, it has been well established through radioisotope studies (*30*) that the enamel of the teeth is much more reactive to ionic exchange mechanisms *before* the teeth emerge into the mouth than afterwards. Hence, it is entirely possible that "topical application" of fluoride at a high dosage through injection into the submucosal area adjacent to the enamel of the unerupted teeth may result in incorporation of high concentrations of fluoride and thus enhance the resistance of enamel to decay after eruption. The mechanism of this fluoride protection, discussed in detail elsewhere (*31*), is thought to be related in part to the resulting increased crystallinity of the tooth mineral. Similarly, a series of studies by Zipkin and his associates (*32*) on human and animal bone suggest that fluoride produces a more stable bone apatite and larger crystals (hence smaller surface exposure per mass unit) by isomorphous substitutions, which apparently reduce the concentrations of two solubilizing anions, carbonate and citrate, on the crystal surfaces. The indirect effects of fluoride at high concentrations within the bone and tooth substance on the adjacent environments merit further study.

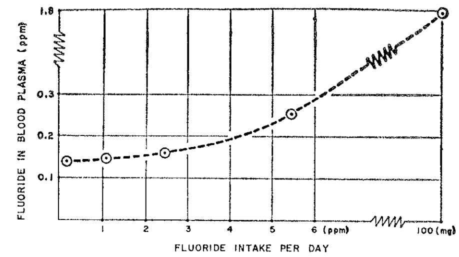

Fig. 1. Diagram summarizing data from studies by Armstrong and his co-workers (see *8*, *10*, and *12*) on fluoride ingestion and plasma levels.

Lastly, it seems fitting to anticipate the potential need for some special protection of skeletal tissues during the periods of immobilization and weightlessness of prolonged space travel (*33*). Hitherto, space flights have been too short to present definitive problems of this nature, though mention has been made (*34*), in a preliminary way, of problems related to bone loss and elevated concentrations of calcium in urine and blood. In hibernating animals, which are both immobile and undergoing nutritional and other metabolic changes, extensive bone loss has been observed in the skeleton generally as well as in the alveolar jawbone surrounding the teeth (*35*).

In conclusion, then, it would appear of interest to establish more conclusively (i) the maximum fluoride levels that can be tolerated by human tissue; (ii) the potential applications of direct administration of fluoride at high concentrations, through the circulatory system or through topical injection, so as to attain optimum concentrations in tissue fluids in immediate contact with bone and tooth surfaces; and (iii) the possibilities of protecting the skeleton by medication with fluoride in anticipation of bone loss accompanying incipient or predictable changes in the internal metabolism (as at menopause) or in the external environment (as during space travel).

Meanwhile, the newer concepts reviewed above may be summarized as follows. Tissue cultures can tolerate concentrations of fluoride higher than those that can reach the body's circulating tissue fluids through oral ingestion. Blood plasma levels remain remarkably low despite very high fluoride intake. Dosages of fluoride above the 1-part-per-million level may have new preventive and therapeutic applications for *adult* individuals suffering from common skeletal and dento-alveolar jawbone disorders of obscure etiology (*36*).

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National Planning of Science and Technology in France

France develops a national science policy through cooperation of government, industry, and scientists.

James Brian Quinn

France is in the midst of an imaginative and dynamic experiment in the planning of civil science and technology (S&T) on a national scale. France has the most formalized structure for national planning in the Western world, and many countries expect her to lead in developing useful new concepts and techniques for integrating science and technology into national plans. French efforts and progress in this regard deserve the attention of thoughtful scientists and national policymakers throughout the world.

Planning: An Orderly Technique

What France is attempting to develop is an orderly technique for making essential decisions about science and technology. Increasingly the nation has realized that there is no major sphere of national policy which is unaffected by science and technology. Economic and fiscal policies must be tailored to the country's capacity to compete internationally and to provide ever higher domestic living standards. Defense and foreign policies depend on the country's technological and economic strength. And rational policies for agriculture, health, welfare, and education must reflect the present and future potential of modern science and technology. Recognizing this, the French are trying to develop organized ways to include "science in national policy" and to establish "national policies for science" (*1*). On the one hand they are attempting to analyze the potential effects of science and technology on various national affairs and to provide for scientific advice at proper levels throughout their policy-formulation structure. On the other, they are trying: (i) to allocate their limited scientific and technical resources to achieve maximum support for France's entire complex of national goals, and (ii) to advance the health of their scientific and technical communities by providing sufficient resources both for adequate academic training and for active pursuit of research and development in areas of vital national interest.

The alternative to planning scientific and technical commitments is not, as many initially believe, to leave S&T in a wondrously free state, uninvolved in political or economic affairs, for government and the economic community must make decisions which are affected by—or which actively influence—science and technology. In France, the government must build and staff educational and research institutions. It must maintain a viable military establishment to support international goals. Through its nationalized industries, the government must also determine what technologies will be used for transportation, energy conversion, and communications. In most other fields private decisions determine the nation's technology, that is, the nature of its producing units, the sophistication of its industrial processes, the variety of its products, and the raw materials and human skills

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