set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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IV

This book is dedicated to Wallace D. Armstrong, Yngve Ericsson, Harold C. Hodge, Leon Singer, Frank A. Smith and Donald R. Taves, esteemed teachers who became my colleagues and friends.

Contents

Foreword to the Second Edition .. IX
Acknowledgments .. X
Introduction .. XI

1. Overview of Fluoride Metabolism and Intake ..1
   Fluoride Metabolism ..1
   Fluoride Intake ..3
   Fluoride Intake and Dental Fluorosis ..5

II. Absorption and Plasma Concentrations of Fluoride ..10
   Oral Absorption ..10
   Gastrointestinal Absorption ..10
General Features ..10
Interfering Substances ..12
Enhancement by Dietary Fat? ..14
Monofluorophosphate ..14
Effect of Gastric Acidity and Solution pH ..15
Secretion into the Gastrointestinal Tract ..18
Fluoride in Plasma ..21
Some Characteristics of Fluoride Analysis with the Electrode 24
Limit of Sensitivity ..24
Hexamethyldisiloxane Diffusion ..26
Precautions ..27
Contamination from Anticoagulants ..29

III. Soft Tissue Distribution of Fluoride ..30
Inaccuracy of Early Data ..30
General Features ..30
Calculating Intracellular Concentrations ..31
Atypical Distribution ..34
Mechanism of the Soft Tissue Distribution of Fluoride ..36
Normal Asymmetric Transmembrane Distribution ..36
Theoretical Considerations ..38
Experimental Evidence for the Diffusion Equilibrium of HF ..40
Fluoride in Specialized Body Fluids ..44

IV. Renal Handling of Fluoride ..46
Physiological Principles ..46
Normal Human Clearance Values ..47
Urinary Flow, pH and Chloride ..48
Mechanism of the Renal Tubular Reabsorption of Fluoride ..56
Fluoride Absorption from the Urinary Bladder ..57

VII

V. Factors That Modify the Metabolism or Effects of Fluoride 59
Chronic Acid-Base Disturbances ..59
Acute Acid-Base Disturbances ..64
High Altitude ..68
Hematocrit ..78
Exercise ..80
Circadian Rhythm and Hormones ..83
Site of Blood Drawing ..86
Stage of Skeletal Development ..90
Since the publication of The Metabolism and Toxicity of Fluoride in 1989, a considerable amount of new information has been published. The second edition has been updated to include much of this material. The section dealing with fluoride absorption
from the gastrointestinal tract has been revised to include discussions of the absorption of monofluorophosphate, the effects of the composition of the diet, especially dietary calcium, and endogenous fluoride concentrations, two variables that can markedly reduce fluoride absorption or even promote net secretion resulting in a negative fluoride balance. Recently published data on the urinary excretion of fluoride by infants suggest that the renal clearance is affected by the magnitude of plasma fluoride concentrations, a relationship that has not been noted in adults. Possible explanations for this finding are presented. Results from recent studies showing the fluorosis-like effects of acid-base disturbances, especially acidosis, and hypobaric hypoxia on enamel mineralization are presented. The effects of hypoxia caused by simulated high altitude on the metabolism of fluoride, which include increased soft and hard tissue fluoride concentrations, are described in light of new information concerning changes in urinary pH. Contrary to the urinary alkalinization which occurs in the short term, chronic hypoxia causes urinary pH to decline which reduces the excretion of fluoride. This finding clarifies the increased tissue fluoride concentrations which were previously unexplained. The effects of sharp changes in fluoride intake on the absorption and retention of the ion indicate that fluoride balance may be strongly positive or negative and provide additional evidence for the dynamic relationship between fluoride in blood and bone. New findings from both acute and chronic studies indicate that the `skeletal steady-state hypothesis' has little validity. The results of several experiments indicate that the ingestion of coffee or caffeine has little, if any, effect on the pharmacokinetics of fluoride. The effects of fluoride on the structure and function of the gastric mucosa are presented in terms of fluoride concentration, the time course of recovery, solution pH, PGE2 and the relative effects of monofluorophosphate and sodium fluoride. The final section presents an overview of the effects of long-term excessive fluoride intake with particular attention given to the influence on bone strength in both humans and laboratory animals.

G.M. Whitford

IX

Acknowledgments

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X
Introduction

Fluoride is the ionic form of fluorine, a halogen and the most electronegative of the elements of the periodic table. It is a natural component of the biosphere and the 13th most abundant element in the crust of the earth. As such, it is not surprising that it has been found in a wide range of concentrations in virtually all inanimate and living things.

Among the halogens, fluoride is unusual in several ways including the fact that it reversibly combines with hydrogen ions to form the weak acid, hydrogen fluoride or hydrofluoric acid (HF; pKa approx. 3.4). Indeed, much of the physiological behavior of fluoride can be explained in terms of the diffusibility of HF. Fluoride is a potent inhibitor of many enzymes and was used as an important tool to define certain steps in the glycolytic pathway. Unlike iodide, fluoride does not accumulate in the thyroid. Its elimination from the body by the kidneys is many times greater than that of the other halogens. It is an avid calcified tissue seeker and its ability to stimulate new bone formation is unique among the osteoactive drugs. Its ability to inhibit, and even reverse, the formation of dental caries is also unique.

Our knowledge of the dental effects of fluoride began to emerge about 90 years ago with the search for the etiologic factor responsible for mottled enamel, a condition which was endemic in several regions of the southwestern USA [Murray, 1973; Sognnaes, 1979]. Some 60 years ago, that factor was identified as water-borne fluoride. At the same time, the epidemiologists recognized that the regular consumption of drinking water containing naturally occurring fluoride was associated, in a dose-related manner, with reductions in the incidence of dental caries. Several studies involving the controlled addition of fluoride to drinking water supplies were then conducted which yielded similar findings. Currently, more than 50% of the US population consumes drinking water with controlled fluoride concentrations. Shortly after the early studies of water fluoridation, salt was tested as a vehicle for the delivery of fluoride to populations living in rural areas or regions without central water supplies. Salt fluoridation is now an important public health measure in several countries including Switzerland, France, Hungary, Mexico and Cuba.

The studies of methods to provide fluoride systemically were followed by others to test the efficacy of fluoride-containing preparations designed primarily for topical application to the teeth. Today, various fluoride compounds are added to dentrifices, mouthrinses, topical gels, lacquers and other products. The remarkable decline in dental caries that is now occurring throughout much of the world can be largely attributed to the use of the ingested and topical forms of fluoride. Indeed, fluoride is now widely regarded as the cornerstone of modern preventive dentistry.

After years of extensive research, it is now generally agreed that the cariostatic effect of fluoride is due in large part to its ability to promote enamel remineralization and to inhibit acid production by plaque bacteria. The mechanisms underlying the development of dental fluorosis are less well understood. There is evidence, however,
that they probably involve effects on the ameloblasts, the developing enamel matrix and proteolytic activity in the maturing enamel [DenBesten and Thariani, 1992]. Further, it has become increasingly clear that the late secretory or early maturation stage is the most sensitive to the development of enamel fluorosis [Ishii and Suckling, 1986; Angmar-Mnsson and Whitford, 1987; Evans and Stamm, 1991].

The beneficial effects of fluoride may not be limited to the oral environment. Either alone or in combination with estrogen, calcium and/or vitamin D, high fluoride doses are administered daily for the treatment of osteoporosis [Courvoisier et al., 1978; Jowsey et al., 1979; Riggs et al., 1982, 1990, 1994; Baylink et al., 1983; Farley et al., 1987; Kleerekoper and Mendlovic, 1993]. It is clear that fluoride stimulates the production of osteoid, some of which subsequently calcifies, but whether this increases bone strength is a matter of current investigation. There is some evidence that the long-term consumption of water-borne fluoride may reduce the incidence and severity of osteoporosis [Leone et al., 1955, 1960; Bernstein et al., 1966] although this too is a controversial matter [Sowers et al., 1986, 1991]. More information is needed on these important subjects for it is estimated that 16,000,000 US citizens, mainly postmenopausal women, are afflicted to some degree with this debilitating skeletal disorder.

One of the most striking developments in recent public health history is the sharp decline in the standardized death rate due to cardiovascular disease, particularly ischemic heart disease, in the USA [Gordon and Thom, 1975; Taves, 1978] and several other countries [Guberan, 1979]. The decline first became apparent in the early 1960s, some 20 years after controlled water fluoridation had been started in the USA and, while the phenomenon continues, its cause has yet to be determined. The decline is not attributable to population changes in any of the major risk factors. There are both epidemiological [Bernstein et al., 1966; Taves, 1978; Luoma, 1980] and laboratory data [Taves and Neuman, 1964; Zipkin et al., 1970], however, which suggest the involvement of fluoride through its ability, at relatively low levels, to inhibit soft tissue calcification. There is a clear need for in-depth research in this important area.

In addition to its established cariostatic effect and its possible preventive or therapeutic roles in other major diseases, fluoride is a hazardous substance when large doses are taken acutely or when lower doses are taken chronically. Its effects range from dental fluorosis [Fejerskov et al., 1977; DenBesten and Thariani, 1992], reversible gastric disturbances [Jowsey et al., 1979] and transient reductions in urinary concentrating ability [Goldemberg, 1931; Whitford and Taves, 1973] to skeletal fluorosis [Singh and Jolly, 1970] and death [Hodge and Smith, 1965; Church, 1976; Dukes, 1980; Eichler et al., 1982; Gessner et al., 1994].

It is noteworthy that crippling skeletal fluorosis has bever been a clinically important problem in the USA [Leone et al., 1954; Stevenson and Watson, 1957; USPHS Ad Hoc Committee on Fluoride, 1991; NRC Subcommittee on Health Effects of Ingested
This is true even though, for many generations, there were numerous communities whose drinking water contained fluoride at levels which could have produced this disorder as judged by experience in other countries [Singh and Jolly, 1970]. The puzzling geographic distribution of this disorder has usually been ascribed to unidentified dietary factors which render the skeleton more or less susceptible. There is now evidence to support an equally plausible explanation, namely that there have been differences among the populations with respect to fluoride metabolism so that fluoride balance was significantly affected. The most potent variable in this regard now appears to be acid-base status and the concomitant changes in urinary pH. More research is needed to evaluate the impact of acid-base status and other physiological variables on fluoride metabolism in humans. The results of such efforts could shed light not only on skeletal fluorosis but also on dental fluorosis, cariostasis and other matters of importance.

In view of the diverse effects that fluoride can produce in biological systems, it is not surprising that it has been the subject of thousands of scientific reports. It is clear that the beneficial as well as the adverse effects of fluoride can be attributed to the magnitude and duration of the concentrations of the ion at specific tissue or cellular sites. In addition to the level of prior fluoride exposure, these concentrations are determined by the characteristics of the general metabolism of fluoride within given populations or individuals. Therefore, the purposes of this monograph are:

(1) to provide a critical review of the scientific literature upon which our understanding of fluoride metabolism is based and

(2) to identify areas of importance which are incompletely understood and thus are in need of additional res