Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage 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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Contents

Dedication VII
Acknowledgments VIII
Introduction IX
I. Overview of Fluoride Metabolism 1
Fluoride Intake 3
Fluoride Intake and Dental Fluorosis 6
Absorption of Fluoride 11
Oral Absorption 11
Gastrointestinal Absorption 13
Fluoride in Plasma 21
Some Characteristics of Fluoride Analysis with the Electrode 23
Limit of Sensitivity 23
HMDS Diffusion 26
II. Soft Tissue Distribution of Fluoride 31
Questionable Reliability of Early Data 31
Short-Term Distribution 31
Calculating Intracellular Concentrations 32
Atypical Distribution 36
Mechanism of the Soft Tissue Distribution of Fluoride 39
Normal Asymmetric Transmembrane Distribution 39
This book is dedicated with love to Nancy
and to Gary, Jr., Matthew and Jennifer
with the hope that they will find as much
joy in their work as I have found in mine.

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Introduction

Fluoride is the ionic form of fluorine, a halogen and the most electronegative
of the elements of the periodic table. It is unusual among the
halogens 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 ca 3.4). 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.

Our knowledge of the dental effects of fluoride began to emerge about 80
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 40 years ago that factor was
identified as water-borne fluoride.

The epidemiologists who unraveled these relationships 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, about 50% of the population of the USA consumes
drinking water with controlled water 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 Switzerland, Hungary and France and it is soon likely to become
so in several South American countries, Mexico, Cuba and Spain.
These studies of methods to provide fluoride systematically were followed by others to test the efficacy of fluoride-containing preparations primarily designed for topical application to the teeth. Today, various fluoride compounds are added to dentifrices, 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 remarkable 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 mechanism underlying the development of dental fluorosis, however, is less well understood. It is not clear whether it involves the secretory products of the ameloblasts or the mineral phase or which stage of amelogenesis is most sensitive. These unresolved matters are being actively investigated in several laboratories so that our understanding of the pathogenesis of dental fluorosis should rapidly improve.

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, it is used in high daily doses for the treatment of osteoporosis and other bone disorders [Jowsey et al., 1979; Courvoisier et al., 1978; Riggs et al., 1982; Baylink et al., 1983; Farley et al., 1987]. 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 is a controversial matter [Sowers et al., 1986]. More information is needed on this important subject 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 was 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], 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],

It is noteworthy that crippling skeletal fluorosis has never been a clinically important problem in the USA [Leone et al., 1954; Stevenson and Watson, 1957]. This is true even though, for many generations, there were many 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 physiologic 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 biologic 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 research.