Effects of Fluorides in Animals

NATIONAL ACADEMY OF SCIENCES

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Subcommittee on Fluorosis
Committee on Animal Nutrition
Board on Agriculture and Renewable Resources
National Research Council

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Preface

This report reviews and evaluates information on the effects of fluorides in animals. It emphasizes the adverse effects of excessive ingested amounts of fluorides as related to structural and functional responses. Charts are included as aids in diagnosing fluoride toxicosis in animals, and methods of toxicosis prevention and control are presented.

The authoring subcommittee wishes to express its appreciation to all who have assisted them in preparing this report.

Contents

Introduction

FLUORINE, THE MOST ELECTRONEGATIVE OF ALL elements, is ubiquitous. It rarely occurs free in nature, but combines chemically to form fluorides that are widely distributed in nature and occur in various amounts in soils, water, the atmosphere, vegetation, and body tissues. Inorganic fluoride compounds are the most important sources so far as fluoride toxicosis in animals is concerned. Organic fluorides, i.e., compounds in which fluorine is bound to carbon, occur in nature and in certain commercial products, but have not to date been implicated as causing fluoride problems in livestock.

Animals normally ingest some fluoride without adverse effect. Indeed, fluoride in small amounts may be beneficial, but it is harmful when ingested in excess. The most common sources of excessive fluoride intake by animals are (1) forages that have been subjected to airborne contamination from nearby industrial operations, (2) feed supplements and mineral mixtures containing too much fluoride, (3) water that is excessively high in fluoride, and (4) forages contaminated with soils high in fluoride.

HISTORY

Fluoride toxicosis in sheep was apparently noted as many as 1,000 years ago in Iceland, where its occurrence was correlated with volcanic eruptions (Roholm, 1937). In many areas along the coastal plains of North Africa, animals and man have been troubled for centuries by a serious, often painful, deterioration of the teeth called darmous (McClure, 1970) that is caused by excessive fluoride ingestion (Velu, 1932).

In the 1920's the use of feed supplements containing excessive fluoride increased the incidence of toxicosis in animals. Cases of tox-

icosis have been reported in many countries, often in the vicinity of industrial operations where processing methods have permitted emissions to contaminate vegetation. With the expansion of certain industries into agricultural areas, especially during and shortly after World War II, fluoride toxicosis in livestock and wildlife became an important issue. More recently, preventive measures have eliminated contamination in certain areas. It is anticipated that enforcement of additional regulatory measures will further alleviate the problem.

Extensive epidemiological and experimental work has established the relationship of the biologic responses of animals to fluoride dosage and to other factors that influence physiologic and anatomic response.

DEFINITIONS

In the pertinent literature the terms "fluorine" and "fluoride" are often used interchangeably in referring to fluoride compounds or to the element fluorine (F). In this report the term "fluoride" will be used except when referring to the actual amounts of fluorine as expressed in parts per million (ppm). The term "fluorine" will also be used in referring to the element per se (i.e., "a fluorine-containing organic compound") or to fluorine in the gaseous state (F_2).

Concentrations of fluoride in feed products, soil, forage, animal tissues, or water are usually expressed as parts per million by weight. These values are readily converted to metric units, in that 1 ppm equals 1 mg/kg stated material, or 1 mg/liter water.

Bases for expressing concentrations other than ppm occur frequently in the literature; these should be clearly stated. For example, fluoride concentrations in soft tissues have been expressed on a fresh-, dry-, or ash-weight basis by various investigators, and fluoride concentrations of skeletal tissues have been expressed on a dry-, dry fat-free, or ash-weight basis. Obviously, values obtained on the basis of bone ash will be considerably higher than those based on dry fat-free tissue, whereas the values expressed on a fresh-weight basis would be the lowest.

Data on fluoride as an atmospheric pollutant are expressed as "ppb in air," which indicates volumes of fluoride per billion volumes of air. To convert ppb in air to milligrams per cubic meter involves certain assumptions regarding a standard atmosphere. The assumptions and conversion factors have been discussed elsewhere (NRC, 1971).

Sources of Fluorides

FLUORIDE CONSTITUTES APPROXIMATELY 0.06–0.09 percent by weight of the upper layers of the lithosphere (Koritnig, 1951; Leech, 1956). It is present in varying amounts in soil, air, water, and in plant and animal tissues. Feed and water are sources from which animals usually acquire fluoride, but inadvertent consumption of other fluoride-containing materials can also contribute significantly to intake.

The fluoride content of soils varies greatly from one location to another, due mainly to differences in geologic origin of the soils and to fertilization practices. While soil is undoubtedly the principal source of fluoride in plants, there is ample evidence that no consistent relationship exists between total fluoride in soil and in plants (MacIntire *et al.*, 1949; Hansen, 1953; Adams, 1956; Hansen *et al.*, 1958; Garber, 1966; Jacobson *et al.*, 1966; Garber *et al.*, 1967). There is, however, some indication that acid soils promote fluoride uptake and that liming of those soils reduces it.

Most review papers indicate that natural forage normally contains 2–20 ppm F on a dry-weight basis. Although instances are rare, certain crops grown on high-fluoride soils in nonindustrial areas have been found to be so contaminated with soil blown or splashed onto the vegetation that they contain as much as 300 ppm F on a dry-weight basis (Merriman and Hobbs, 1962). Suttie (1969) has analyzed 107 samples of alfalfa hay from areas in the United States thought to be free of industrial pollution and found fluoride concentrations ranging from 0.8 to 36.5 ppm F, with a mean of 3.6 ppm and a median of 2 ppm. The grain portions of cereal plants, in contrast to forages as consumed, contain remarkably little fluoride (Hitchcock *et al.*, 1964). The fluoride content of plants varies with

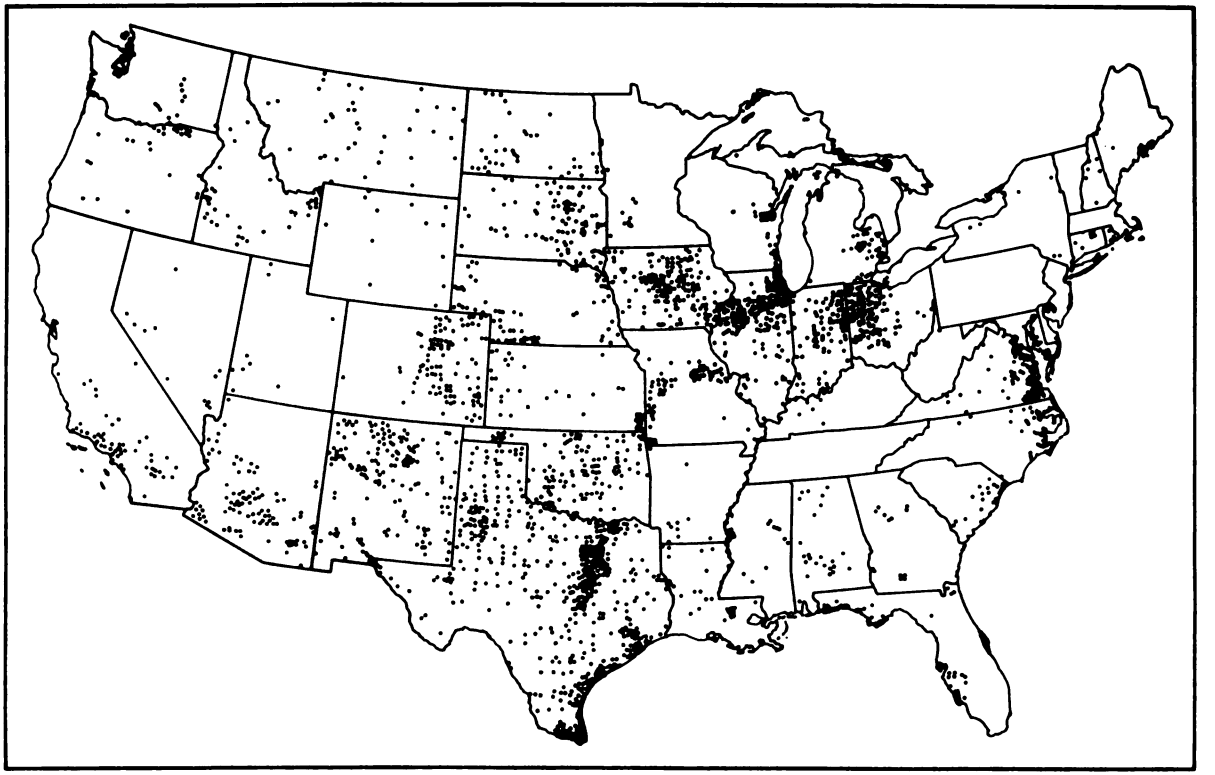

FIGURE 1 Distribution of communities in the United States with 0.7 ppm F or more natural fluoride in community water supply systems.

Source: USDHEW (1969)

age, species, variety, specific plant part, and soil on which the plant is grown (Garber, 1967a,b; Garber *et al.*, 1967). The ingestion of soil fluoride by animals when grazing forage too closely, or of forages contaminated by windblown soil and rain splash, is also of considerable importance.

Most waters naturally contain some fluoride; this source should be taken into consideration in estimating the total daily intake by animals. In river and irrigation waters the amounts vary widely, being lowest in calcareous regions. As indicated in Figure 1 (USDHEW, 1969), there were 2,630 communities (about 8 million people) in the United States in 1969 with a drinking water supply having a natural fluoride concentration of 0.7 ppm F or more. Certain spring waters, especially hot springs, contain relatively high amounts of fluoride derived from local mineral deposits. It has been estimated that intake by cattle of water containing 1 ppm provides 0.05–0.10 mg F/kg of body weight per day (Mortenson *et al.*, 1962), a quantity that is not of health significance in cattle.

Substantial quantities of fluoride are present in certain mineral and rock formations. The most important fluoride-containing minerals are fluorite (CaF_2), fluorapatite [$3Ca_3(PO_4)_2 \cdot CaF_2$], and sedimentary rock phosphate. Fluoride is also present in minor amounts in a number of such other naturally occurring minerals as calcite and aragonite. Fluorspar is used as a flux in the smelting of certain ores and in the ceramic industry. Phosphate rock is used in the production of phosphatic fertilizers, industrial chemicals, and elemental phosphorus. Major deposits and production plants in the United States are shown in Figure 2 (USDI, 1970).

In various industrial processes, fluorides may be driven off in one of three principal forms: hydrofluoric acid, silicon tetrafluoride, or particulate matter. Observations on man and laboratory animals (Largent, 1961) indicate that direct inhalation of fluoride, even from the ambient air around industrial plants, does not contribute significantly to the total fluoride accumulation in livestock. These emissions, however, may contaminate the vegetation, soil, and water to varying degrees and, as a result, find their way into feed and water. Gaseous fluorides are more toxic to plants than to animals and because they are absorbed and translocated, little is lost from the plant once they have been incorporated. Particulate fluorides, on the other hand, are likely to accumulate on vegetation surfaces, from which they can to some extent be washed off. They are usually relatively inert and their toxicity is probably related to solubility (Pack *et al.*,

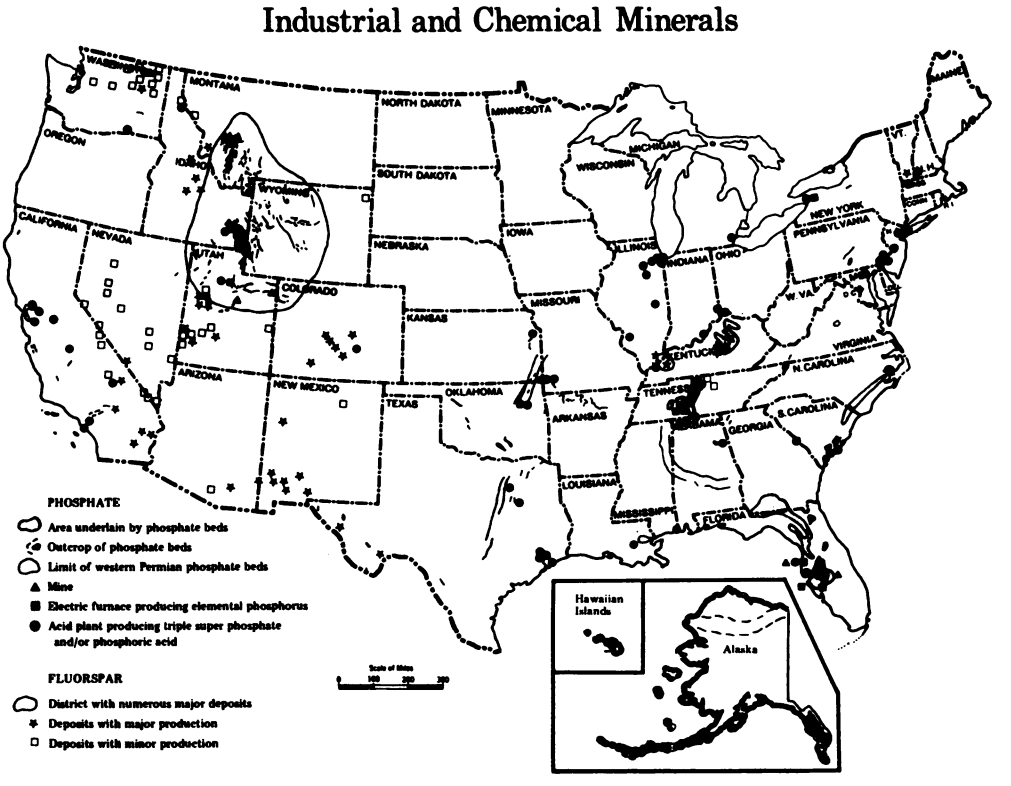

FIGURE 2 Major deposits and industrial production plants related to the use of phosphate ores and fluorspar deposits in the United States.

Source: USDI (1970)

1960). The fluoride content of vegetation therefore depends on (1) the amount and kind (particulate or gaseous) of fluoride escaping into the atmosphere, (2) the distance of the vegetation from the source of contamination, (3) the type and kind of vegetation and its growth rate, (4) a number of environmental factors, (5) duration of exposure, and (6) distribution patterns as affected by wind and topography.

In the normal feeding of animals, primary sources of dietary fluoride are the mineral supplements and related feed ingredients. These products vary greatly in fluoride content, depending on origin and manufacturing processes. The majority of domestic feed phosphates originate from rock phosphate deposits having fluoride levels ranging from 2 to 5 percent F and averaging approximately 3.5 percent (Van Wazer, 1961). Fluoride is to a large extent removed from most commercial feed-grade phosphates. A phosphate compound, to be classified as defluorinated, must contain no more than one part of fluorine to 100 parts phosphorus (AAFCO, 1973). Thus defluorinated phosphates can be used to meet the total phophorus requirements of animals without incurring any adverse effects. A 450-kg finishing steer, for example, requires 0.22 percent P in its total daily ration (NAS-NRC, 1970). A phosphate source that met the criteria for classification as defluorinated would thus add no more than 22 ppm F to the total ration if it were used to furnish the total phosphorus requirement, which is a level below the fluoride tolerance level for beef cattle. (See "Tolerance of Various Animal Species" chapter, p. 47.) Feed phosphate supplements manufactured from feed-grade phosphoric acid (by either defluorinated wet process or electric furnace) and feed phosphates thermally defluorinated by calcination qualify for classification as defluorinated phosphate. The compounds of this class in common commercial use include mono-, di-, and tricalcium phosphates; defluorinated phosphate; mono- and diammonium phosphates; mono- and disodium phosphates; feed-grade phosphoric acid; and ammonium and sodium polyphosphates. Typical phosphorus and fluoride contents of compounds in common commercial use are shown in Table 1, as well as analyses of various high-fluoride phosphate compounds. Such unprocessed phosphatic minerals as soft rock phosphate, ground rock phosphate, and ground low-fluoride rock phosphate, when used in feeds, add substantially to the fluoride intake of animals. A more serious difficulty, however, arises from the use of undefluorinated fertilizer-grade chemicals in animal feeds. These high-fluoride sources include wet-process phosphoric acid,

TABLE 1 Typical Fluoride Content of Phosphate Compounds[a]

Compound	Phosphorus Content (%)	Calcium Content (%)	Sodium Content (%)	Nitrogen Content (%)	Fluoride Content (%)	Fluoride Contribution from Compound at 0.25% Phosphorus[b] (ppm)
Defluorinated phosphates manufactured from defluorinated phosphoric acid						
monocalcium phosphate	21.0	16.0	–	–	0.16	19
dicalcium phosphate	18.5	21.0	–	–	0.14	19
defluorinated phosphate	18.0	32.0	–	–	0.16	22
monoammonium phosphate	24.0	0.5	–	11.0	0.18	19
diammonium phosphate	20.0	0.5	–	18.0	0.16	20
ammonium polyphosphate solution	14.5	0.1	–	10.0	0.12	20
defluorinated wet-process phosphoric acid	23.7	0.2	–	–	0.18	19
Defluorinated phosphates manufactured from furnace phosphoric acid						
monocalcium phosphate	23.0	22.0	–	–	0.03	3
dicalcium phosphate	18.5	26.0	–	–	0.05	7

tricalcium phosphate	19.5	38.0	–	–	0.05	6
monosodium phosphate, anhy.	25.5	–	19.0	–	0.03	3
disodium phosphate	21.5	–	32.0	–	0.03	4
sodium tripolyphosphate	25.0	–	30.0	–	0.03	3
ammonium polyphosphate solution	16.0	–	–	11.0	0.02	3
feed-grade phosphoric acid	23.7	–	–	–	0.03	3
High-fluoride phosphates						
soft rock phosphate	9.0	17.0	–	–	1.2	334
ground rock phosphate	13.0	35.0	–	–	3.7	710
ground low-fluorine rock phosphate	14.0	36.0	–	–	0.45	81
triple superphosphate	21.0	16.0	–	–	2.0	238
diammonium phosphate (fertilizer grade)	20.0	0.5	–	18.0	2.0	250
wet-process phosphoric acid (undefluorinated)	23.7	0.2	–	–	2.5	264

[a] International Minerals and Chemical Corp., Libertyville, Ill., unpublished data.
[b] Commercial dairy feeds commonly contain 0.25 percent P from added phosphatic minerals. Phosphate compounds at dietary levels to furnish 0.25 percent P would contribute fluorine levels as indicated.

normal and triple superphosphates, fertilizer-grade mono- and diammonium phosphates, ammonium polyphosphates, and by-product gypsum recovered from the manufacture of wet-process phosphoric acid.

Since approximately 99 percent of the fluoride retained in the body is stored in bone, animal by-products used as feed ingredients vary widely in fluoride content, depending on bone content and the previous diet and husbandry of the animals and poultry from which the by-products were derived. Bone normally contains less than 1,500 ppm F (calculated on an ash basis) and contributes only minor amounts of fluoride to diets. The fluoride content of bone increases in relation to the fluoride content of the diet; it is, however, possible for bone meal from certain geographic areas to contain relatively high levels of fluoride, even exceeding that of low-fluoride phosphate rock. For example, cattle grazing on fluoride-contaminated forage can have bone ash containing over 10,000 ppm F, which would represent 5.5 parts fluorine for each 100 parts of phosphorus.

In addition to bone meal, the fluoride in such animal by-products as fish meal, meat and bone scraps, and poultry by-product meals should be taken into account in determining the total fluoride intake (Jones, 1972). Because bone by-product wastes from poultry processing plants are utilized in poultry feeds, it is possible that the fluoride content of poultry bone tissue, especially in integrated operations, will gradually increase over time as the material is recycled. A significant contribution to total dietary fluoride can derive from certain feed ingredients, as indicated in a study on the fluoride content of 168 samples of dairy feed (16 percent crude protein) from seven different states (Suttie, 1969). Although 90 percent of the samples contained less than 30 ppm F, some had over 200 ppm.

Pesticides containing fluoride in various forms that may be harmful to animals if accidentally ingested include sodium fluoroacetate and fluoroacetamide, which are used as rodenticides. Although these two compounds do not contain inorganic fluorides, sodium fluorosilicate (used as an insecticide) and sodium fluoride (occasionally used as an ascaricide) do.

Essentiality of Fluoride

RECENTLY DEVELOPED SENSITIVE PROCEDURES for fluoride determination have made it possible to detect at least traces of fluoride in practically every natural water supply and foodstuff analyzed. This fact has an important bearing on the question as to the essentiality of fluoride, because it has not been possible for most investigators, until recently, to prepare nutritionally adequate diets that are either wholly devoid of fluoride or sufficiently low to demonstrate conclusively that it is or is not required (Evans and Phillips, 1939; Muhler, 1951; McClendon and Gershon-Cohen, 1953; Maurer and Day, 1957; Wuthier and Phillips, 1959).

McClendon and Gershon-Cohen (1953) have reported that fluoride is an essential nutrient, but confirmation of this has not been reported by most investigators. More recently, Messer *et al.* (1972a) reported that there is a marked impairment in fertility of female mice having a low-fluoride (0.1–0.3 ppm F in the diet) intake. Messer *et al.* (1972b) found that the anemia of mice produced under the stress of pregnancy and growth before weaning is more severe when the fluoride intake is low. Schwarz and Milne (1972) have observed a favorable growth response when small increments of fluoride were added to the control diet of rats. These findings suggest a deficiency state that is specific for fluoride. Although the question of whether fluoride is an essential nutrient has not been completely resolved, trace quantities of the element have been shown to be beneficial to the development of caries-resistant teeth and may also be beneficial in preventing excessive demineralization of bone (osteoporosis) in aged individuals.

Metabolism of Fluoride

THE METABOLISM OF FLUORIDE AND THE EFFECTS of normal and abnormal intake of fluoride on body processes have been investigated extensively in well-controlled studies with man, small animals, and livestock and through *in vitro* techniques. This section of the report of necessity includes pertinent information concerning the metabolism of fluoride irrespective of the species used and assumes a large measure of universality in the animal kingdom in this regard. There is little reason to believe that ruminants or other domestic animals metabolize fluoride in a way substantially different from laboratory species.

The concentration of free fluoride is generally considered to be more significant than total fluoride in assessing the effects of excessive fluoride intake on the normal metabolism; however, if fluoride binds to the enzyme, to the substrate, or to the co-factor of a given enzymic process, the bound fluoride will affect the overall process. Although the importance of ionic fluoride is generally recognized, it is the total fluoride rather than the ionic concentration that has been reported in most publications.

FLUORIDE ABSORPTION

The gastrointestinal absorption of fluoride appears to be passive and not to involve active transport. The rapid absorption of fluoride has been demonstrated in rats (Volker *et al.*, 1941; Wallace, 1953; Durbin, 1954; Zipkin and Likins, 1957; Stookey *et al.*, 1964a) and man (Carlson *et al.*, 1960a). *In vitro* studies with inverted rat intestinal sac preparations (Stookey *et al.*, 1964b; Parkins *et al.*, 1966; Parkins,

1971) have suggested, but have not provided conclusive evidence for, an active transport of fluoride.

Observations on man (Carlson *et al.*, 1960a), rats (Stookey *et al.*, 1962; Wagner, 1962; Yeh *et al.*, 1970), and on domestic animals (Perkinson *et al.*, 1955) have suggested that fluoride is absorbed in the stomach. Experiments involving both sheep and cattle (Perkinson *et al.*, 1955) have shown that fluoride absorption is rapid, that it probably occurs in the rumen and that there is a selective localization of ^{18}F in the skeleton similar to the distribution of radioactive calcium. These authors have also shown that some of the ingested ^{18}F given to chickens and cattle was deposited in various parts of eggs and milk. Approximately half the fluoride absorbed by man is excreted in the urine; the remainder is stored primarily in the calcified tissues. There is no evidence of significant accumulation of fluoride in soft tissues. The urinary excretion of fluoride promptly increases with an increase in dietary intake. There is considerable evidence that fluoride progressively increases in bone and teeth with advancing age, provided a constant level of fluoride is ingested.

HOMEOSTASIS

Fluoride is concentrated in the skeletal and dental tissues as the inorganic mineral fluorapatite. Only minor concentrations of fluoride occur in body fluids and soft tissues. An individual on a long-term, relatively constant fluoride intake reaches an equilibrium between intake and retention, at which time the fluoride uptake by the skeletal tissue is reduced and the concentration of fluoride in the urine approximates that of the drinking water (Zipkin *et al.*, 1956). The regulation of fluoride levels in body fluids will be discussed later.

CALCIFIED TISSUES

Bone has great affinity for fluoride and incorporates fluoride into hydroxyapatite, forming fluorapatite. Fluoride accumulates in all calcified tissues, as well as in abnormally calcified tissue, and its concentration in these tissues increases with the duration and rate of fluoride intake. Once the ion is incorporated in the apatite of bone, it cannot be removed without resorption of the unit crystalline structure of the mineral phase. In bones, fluoride has been reported to increase the size of apatite crystals, to stabilize the unit cell, and to decrease the solubility of mineral (Zipkin *et al.*, 1964). The ingestion

of a large amount of fluoride by rats (Singer *et al.*, 1965) did not interfere with the utilization of dietary calcium for bone and tooth formation. The solubility of bone, enamel, and dentin containing high-fluoride concentrations has been clearly demonstrated to be less than that of comparable low-fluoride tissues (Singer *et al.*, 1965). The sequestering of fluoride by the skeleton is influenced by the previous fluoride exposure, by the skeletal fluoride concentration, and by the age of the individual (Largent, 1961). Some evidence has accumulated that, in man, the optimal fluoride intake in early life may provide some protection against senile osteoporosis and atherosclerotic calcification (Bernstein *et al.*, 1966).

Even at low levels of fluoride intake, appreciable levels of fluoride will in time accumulate harmlessly in calcified tissues. For example, the fluoride content of bones from normal mature cattle fed a basal diet (3–5 ppm F) for 5½ years contained less than 1,000 ppm F on a dry fat-free basis (Suttie *et al.*, 1958). The bones of animals receiving 10 ppm F in hay for 588 days have been reported to contain 320–528 ppm F on a dry fat-free basis (Shupe *et al.*, 1962). The amount of fluoride stored in bone can increase, within limits, over a period of time, irrespective of any demonstrable changes in structure and function of the tissues. However, in some cases, if high levels of fluoride are thus ingested, structural changes in bone associated with fluorosis become evident (Shupe *et al.*, 1963b).

The effectiveness of low-fluoride intake in reducing dental caries in man, rats, and hamsters is well documented. In human populations 1 ppm F in the municipal water supply has resulted in well over a 50 percent reduction in the incidence of dental caries in individuals who consume it from infancy (Quimby, 1970). Fluoride in the diet of man and small animals has been reported to have beneficial effects on tooth form, appearance, eruption time, and the frequency and severity of peridontal disease (Quimby, 1970). Highly excessive fluoride intake has resulted in such mineralization maladies in bone as disordered lamellar patterns, periosteal hyperostosis, calcification of ligaments, and fusion of bones, as well as mottled enamel (see "Fluoride Toxicosis" chapter, p. 20).

Fluoride is incorporated into the tooth mineral as fluorapatite at the time of calcification. It is only the developing or calcifying tooth, however, that is affected adversely by excess fluoride intake. Teeth, once calcified, do not have the same biologic responsiveness to fluoride as does bone. Enamel, because it is so compact, does not change significantly in fluoride concentration except at the surface, which

comes in contact with oral fluoride. By contrast, dentin does in time show an increase in fluoride levels. Dental lesions in animals are therefore indicative of the exposure of the animals during the period of tooth development; the histology of fluoride-induced dental changes has been described by Schour and Smith (1934).

PLASMA FLUORIDE

Armstrong and Singer (1970) have reviewed available information on distribution of fluoride in body fluids and soft tissues of man and animals. Fluoride, unlike chloride, occurs in intracellular fluid. The erythrocytes, on a water volume basis, have a fluoride content that is 40–50 percent that of plasma. About 75 percent of the total fluoride of blood is in the plasma (Carlson *et al.*, 1960b) and about 5 percent of this, in turn, is bound to protein. Further attention has been given to the partition of the total plasma fluoride into ionic and bound forms (Taves, 1966, 1968; Singer and Armstrong, 1969, 1971). The ionic concentration of fluoride in bovine and rat serum has been reported to be 0.01–0.04 ppm F, representing between 15 and 70 percent of the total plasma fluoride (Singer and Armstrong, 1964). A considerable fraction of the total plasma fluoride is ultrafilterable and results indicate that the compounds in plasma responsible for most of the fluoride binding have molecular weights less than that of albumin (L. Singer and W. D. Armstrong, unpublished data). Most of the reports in the literature that cite the concentration of fluoride in tissue, fluids, foodstuffs, etc., give data on total fluoride.

The plasma fluoride content is maintained within narrow limits by regulatory mechanisms that involve principally the skeletal and renal tissues (Smith *et al.*, 1950; Singer and Armstrong, 1960, 1964), even when there is considerable variation of dietary intake. The ability of body-regulating mechanisms to maintain the constancy of the internal environment is influenced by such factors as the skeletal fluoride load, the anatomic and physiologic status of the skeleton and kidneys, previous fluoride exposure, and the rate and amount of fluoride consumption at the time. The regulatory mechanism can be exceeded by sustained increased intakes, but apparently a new equilibrium between bone, plasma, and body fluids is quickly reached and re-established (Smith *et al.*, 1950; Singer and Armstrong, 1964). This was demonstrated during periods of high-fluoride intake or long periods of food deprivation in carefully controlled studies with rats (Singer and Armstrong, 1964).

FLUORIDE IN MILK

In radiofluoride studies on dairy cows, the concentration of the isotope in milk was similar to but lower than that found in blood, indicating that the ionic fluoride contents of milk and blood are similar (Perkinson *et al.*, 1955). The total fluoride contents are not necessarily similar, since tightly bound fluoride in either fluid may not be in equilibrium with the ionic fluoride pool. Ericsson (1958) found trace quantities of fluoride bound to fat and to the albumin–globulin fraction and about 25 percent of the total fluoride in whole milk bound to casein. Zipkin and Babeaux (1965) and Armstrong and Singer (1970) have summarized much of the literature dealing with the concentration of fluoride in animal milk. Cattle receiving feed containing 3–5 ppm F have been found to produce milk containing 0.1 ppm; when their intake was increased to 50 ppm, the milk contained only 0.4 ppm (Suttie *et al.*, 1957b). Greenwood *et al.* (1964) found that whole milk of Holstein cows consuming 10, 29, 55, or 109 ppm F from 3 to 4 months of age to about 7½ yr of age contained in the fifth lactation 0.06–0.10, 0.14, and 0.20 ppm, respectively. Human milk has been reported to contain less than 0.05 ppm F (Ericsson, 1969). These concentrations of fluoride are low and are of no significance to human or animal health. Such concentrations show that the mammary gland does not excrete fluoride in sufficient quantities for it to be considered important in this regard.

SOFT TISSUE FLUORIDE

Many investigations of the fluoride content of soft tissues and its relation to other factors have been carried out with rats. Singer *et al.* (1967) have clearly demonstrated that the adjustment of the fluoride content of muscle tissue may be more efficiently regulated than that in plasma. In these studies, rats fed a diet containing 0.5 ppm F had a mean total plasma elemental fluorine content of 0.17 ppm ± 0.020 (SE), whereas the plasma fluoride of animals receiving food containing 100 ppm F was only 0.47 ppm ± 0.075 (SE). The fluoride content of fresh muscle in the two groups of animals was, however, very similar, i.e., 0.20 ± 0.031 and 0.21 ± 0.026 ppm F, respectively.

The early literature on soft tissue fluoride was surveyed by Gettler and Ellerbrook (1939), who found no evidence of appreciable accumulation of fluoride under normal circumstances in any of the vital organs of man or dog. The fluoride content of soft tissues of cattle

(Shupe *et al.*, 1963b), on a fresh-weight basis, was similar to that of the spleen, heart, liver, and muscle of man, dog, and rat. Insignificant amounts of fluoride in the soft tissues were reported in cattle receiving up to 93 ppm F for 7½ yr. Because urine is retained in tubules and collecting ducts, the kidney had the highest content of fluoride of all normal soft tissues.

It is not surprising that the tendon (Armstrong and Singer, 1970), aorta (Ericsson and Ullberg, 1958), and placenta (Gardner *et al.*, 1952) have higher fluoride contents than do most soft tissues, since it appears that much of the fluoride in these tissues is bound rather than free and that the high calcium and magnesium contents of these tissues play an important role in the acquisition and retention of fluoride.

No histologic changes in human (Geever *et al.*, 1958) or bovine (Shupe *et al.*, 1963b) soft tissues associated with fluoride intake have been demonstrated. Further, Hoogstratten *et al.* (1965) established that fluoride fed to cattle daily in concentrations up to 100 ppm F for more than 7 yr does not have gross, histological, or functional effects on the thyroid gland or liver.

ROLE OF KIDNEY

The kidney is important in regulating the fluoride content of body fluids, although it is apparently secondary to the skeletal tissues in this respect. The clearance of fluoride by the kidney exceeds that of chloride many fold and increases with urine volume. Urinary fluoride excretion occurs by glomerular filtration, with variable amounts of tubular resorption. It has been shown that the dog kidney, in producing urine, can concentrate fluoride from the plasma by a factor of 10–20 times and that it functions effectively even when the plasma fluoride is elevated to a level more than 10 times normal (Carlson *et al.*, 1960c). Studies on the physiologic responses of the rat to a large fluoride challenge (as a result of preloading the skeleton) provide evidence that rats can control plasma fluoride and dispose of fluoride by urinary excretion. The kidney appears to function normally even under considerable stress and variation in fluoride intake (Yeh *et al.*, 1970).

Livestock fed different diets and consuming varying quantities of water may excrete identical amounts of fluoride, although the specific gravities and volumes of the urine vary considerably under the influence of dietary constituents other than fluoride. The urinary

fluoride concentrations appear to vary with specific gravity of the urine and age of the animal. At a given fluoride intake level, older livestock will void more fluoride in the urine than will younger animals. In this case the older animal retains proportionately less of the consumed fluoride in its bones as the concentration of fluoride in the bone increases. The fluoride content of the urine of normal cattle ingesting a normal diet fluctuates, but it is usually less than 6 ppm F. Under carefully controlled conditions a correlation can be demonstrated among the concentration of fluoride in the urine, the amount of fluoride in the dry matter consumed, and the duration of fluoride ingestion (Shupe *et al.*, 1963a). Extreme caution must be used in applying this correlation to field conditions. The degree of saturation of the skeletal tissue of animals maintained on a constant level of fluoride is a factor that affects the amount of fluoride excreted in the urine. It has been found that farm animals shifted from high levels of fluoride intake to low levels will reduce their urinary fluoride excretion and at the same time will mobilize some fluoride from skeletal tissues. It has also been demonstrated with rats that growing animals incorporate large amounts of fluoride in the skeleton when they are fed a high-fluoride intake and lose a moderate amount of fluoride from the bone when the intake is so modified as to provide little fluoride (Savchuck and Armstrong, 1951; Miller and Phillips, 1953).

PLACENTAL TRANSFER

Whether there is a placental barrier to the transport of fluoride from the maternal circulation across the placenta to the fetus has not been settled. Some species difference may exist in the extent to which the placenta is a barrier to fluoride.

Examinations of calves from cows that received various levels of fluoride in long-term feeding trials demonstrated that fluoride did pass the placental barrier and that the fluoride levels in the bones of the calves could be correlated with the amount of fluoride ingested by the dam and with the amount in her blood (Bell *et al.*, 1961; Shupe *et al.*, 1963a). It has been shown that radioactive fluoride (^{18}F) administered intravenously to pregnant cattle is removed rapidly from the blood, but its distribution suggests that there is a barrier for the free passage of fluoride to the fetus even though ^{18}F was found in fetal tissue (Bell *et al.*, 1961).

Bawden *et al.* (1964) injected ^{18}F into the fetus of pregnant sheep; the subsequent recovery of activity from the maternal circulation clearly demonstrated that fluoride was transferred across the placenta to the maternal blood. Fetal plasma levels of radiofluoride were low compared with the maternal plasma when the ^{18}F was administered to the maternal circulation. These observations suggested that the placenta may limit the transfer of fluoride to the fetus in pregnant sheep.

A significant placental transfer of fluoride occurs in guinea pigs receiving 1–50 ppm F during gestation (Hudson *et al.*, 1967). Several investigations (Gedalia, 1970) suggested that the rat placenta may act as a partial barrier to the transport of fluoride to the fetus.

One can conclude, therefore, that fluoride does cross the placenta but that there is often some inhibiting effect.

REPRODUCTION

McClendon and Gershon-Cohen (1953) reported that reproduction was impaired in rats raised on a diet prepared from hydroponically grown components low in fluoride. Females fed the fluoride-free diet did not produce viable offspring when mated with normal males. Muhler (1954a), in experiments with rats raised on a highly purified low-fluoride diet, reported that reproduction was adversely affected. Venkateswarlu (1962) suggested that a low-fluoride diet fed to rats through three generations resulted in some impairment of reproduction. Since purified diets used by Muhler (1954a) and Venkateswarlu (1962) did not adequately sustain normal reproduction even when fluoride was supplemented, there is still some doubt that fluoride is required by the rat for normal reproduction. Recent evidence has shown, however, that fluoride is required to maintain normal rate of reproduction by female mice (Messer *et al.*, 1972a). Cattle fed rations with low-to-moderate concentrations of fluoride have not exhibited any abnormalities in fertility or reproduction (see "Fluoride Toxicosis" chapter, p. 34).

Fluoride Toxicosis

EXCESSIVE FLUORIDE INGESTION CAN INDUCE either an acute toxicosis or a debilitating chronic condition that has been referred to as chronic fluoride toxicity, fluoride toxicosis, or fluorosis. Although such specific conditions as osteofluorosis and dental fluorosis are definable, the general term fluorosis does not lend itself to a clear-cut definition. The term fluoride toxicosis is used here to describe conditions that result from an excess ingestion of fluoride. An understanding of the clinical manifestations and a thorough knowledge of the pathogenesis and lesions of fluoride toxicosis are essential for a correct diagnosis and accurate evaluation of the disease.

ACUTE FLUORIDE TOXICOSIS

Acute fluoride toxicosis has neither been studied as extensively nor elucidated as well as has chronic fluoride toxicosis. This is due, at least in part, to the fact that acute fluoride toxicosis is relatively rare. Acute fluoride toxicosis has most frequently resulted from accidental ingestion of high levels of such fluoride compounds as sodium fluorosilicate used as a rodenticide and sodium fluoride used as an ascaricide in swine. Several cases of accidentally and experimentally induced acute responses have been reviewed (Cass, 1961).

Depending on a number of factors, various types of toxicologic response may occur. The rapidity with which the symptoms appear will depend on the amount of fluoride ingested. The following symptoms and changes are usually observed: high fluoride content of blood and urine, restlessness, stiffness, anorexia, reduced milk production, excessive salivation, nausea, vomiting, incontinence of urine

and feces, clonic convulsions, necrosis of mucosa of digestive tract, weakness, severe depression, and cardiac failure. In one of the best-documented cases of acute fluoride toxicosis, Krug (1927) reported that 18 dairy cows died within 12–14 h after ingesting sodium fluorosilicate (Na_2SiF_6) that had been erroneously added to the diet. Convulsions, exaggerated chewing motions, and hyperemia were observed.

A distinction between acute and chronic toxicosis is not always practicable. Severe but nonlethal effects have been observed in animals that ingest high concentrations of fluoride in the ration. Hobbs *et al.* (1954) have shown that extreme inanition occurred within 18 days after pregnant beef heifers were fed 600, 900, or 1,200 ppm F as NaF. The inanition that occurred without additional symptoms is not typical of either acute or chronic fluoride toxicosis (Hobbs and Merriman, 1962; Shupe, 1967).

CHRONIC FLUORIDE TOXICOSIS

Chronic fluoride toxicosis is the response that has been most often observed in livestock and certain wildlife (Shupe *et al.*, 1972). The development and onset of this condition are usually insidious. Some of the symptoms of the disease may be confused with those of certain other trace element toxicoses or deficiencies, or with such chronic debilitating diseases as osteoarthritis. It is difficult to define a precise point at which fluoride ingestion becomes harmful to the animal. It can vary from case to case and may be influenced by the following factors:

- Amount of fluoride ingested
- Duration of ingestion
- Fluctuations in fluoride intake with time
- Solubility of fluoride ingested
- Species of animal involved
- Age at time of ingestion
- General level of nutrition
- Stress factors
- Individual biologic response

Fluoride toxicosis is complicated by such factors as the interval between ingestion of elevated levels of fluorides and any clinical, gross, or microscopic manifestation of the symptoms and lesions of chronic fluoride toxicosis (Shupe, 1970).

No single criterion should be relied on for diagnosing and evaluat-

ing fluoride toxicosis (Figure 3). All clinical observations, necropsy findings, histopathologic, radiographic, and chemical evidence must be carefully evaluated and correlated before a definite diagnosis and evaluation of fluoride toxicosis are made (Shupe, 1972a,b). The following symptoms, lesions, and analytical determinations are of particular diagnostic importance: degree of dental fluorosis; degree of osteofluorosis; intermittent lameness; and the amount of fluoride in the bone, urine, and components of the diet.

DENTAL FLUOROSIS

Developing teeth are extremely sensitive to excessive fluoride ingestion (Roholm, 1937). Teeth that have erupted, however, are not influenced adversely by subsequent fluoride ingestion (Garlick, 1955). Fluorotic lesions in permanent dentition are among the most obvious symptoms of excessive fluoride ingestion during the period of tooth formation (Brown *et al.*, 1960; Bhussry, 1970; McClure, 1970). The

FIGURE 3 Seven-yr-old Holstein cow with fluoride-induced severe lameness and bone lesions.

Courtesy of J. L. Shupe and A. E. Olson, Utah State University

period of crown formation of the permanent teeth of cattle has been elucidated by Brown *et al.* (1960). Enamel matrix formation precedes this radiologically demonstrable calcification process. The period during which the developing teeth in cattle are sensitive to excessive fluoride extends from approximately 6 months to 3 yr of age. Thus animals not exposed to excessive fluoride ingestion until they are more than 3 yr old will not develop typical dental lesions when excessive fluoride is ingested. Although dental fluorosis usually results from continual ingestion, Suttie (1969) and Suttie and Faltin (1971) have shown that short periods of exposure can cause severe lesions and that this should be taken into consideration when establishing fluoride ingestion standards.

Gross fluorotic lesions of the incisor enamel are generally described as mottling (white, chalk-like patches or striations in the enamel), chalkiness (dull white, chalk-like appearance), hypoplasia (defective enamel), and hypocalcification (defective calcification). Teeth affected to a moderate, marked, or severe degree are often discolored (creamy yellow to brown or black), are subject to more rapid attrition, and in some cases show erosion of the enamel. Several standards have been developed for classifying degrees of dental fluorosis. These various standards do not differ significantly. Following is a standard for the classification of dental fluorosis:

(0) *Normal* smooth, translucent, glossy white appearance of enamel; tooth having normal shape.
(1) *Questionable Effect* slight deviation from normal, exact cause not determinable; may have enamel flecks but is not mottled.
(2) *Slight Effect* slight mottling of enamel, best observed as horizontal striations with transmitted light; may have slight staining, but no increase in normal rate of wear.
(3) *Moderate Effect* definite mottling; large areas of chalky enamel or generalized mottling of entire tooth; tooth may have a slightly increased rate of wear and may be stained.
(4) *Marked Effect* definite mottling, hypoplasia, and hypocalcification; may have pitting of enamel; with use, tooth will have increased rate of wear and may be stained.
(5) *Severe Effect* definite mottling, hypoplasia, and hypocalcification; with use tooth will have excessive increase in rate of wear and may have erosion or pitting of enamel. Tooth may be stained or discolored.

Examples of dental lesions are shown in Figures 4 and 5.

Dental fluorosis in animals is usually diagnosed by examining the incisor teeth. Cheek (premolar and molar) teeth are more difficult to examine in the live animal because it is difficult to restrain the animal properly, illumination of the teeth is often poor, the tongue and unswallowed food may interfere, and discoloration resulting from factors other than fluoride complicate the examination. The criteria used in diagnosing and evaluating incisor lesions are not the same as those used in diagnosing and evaluating cheek teeth for den-

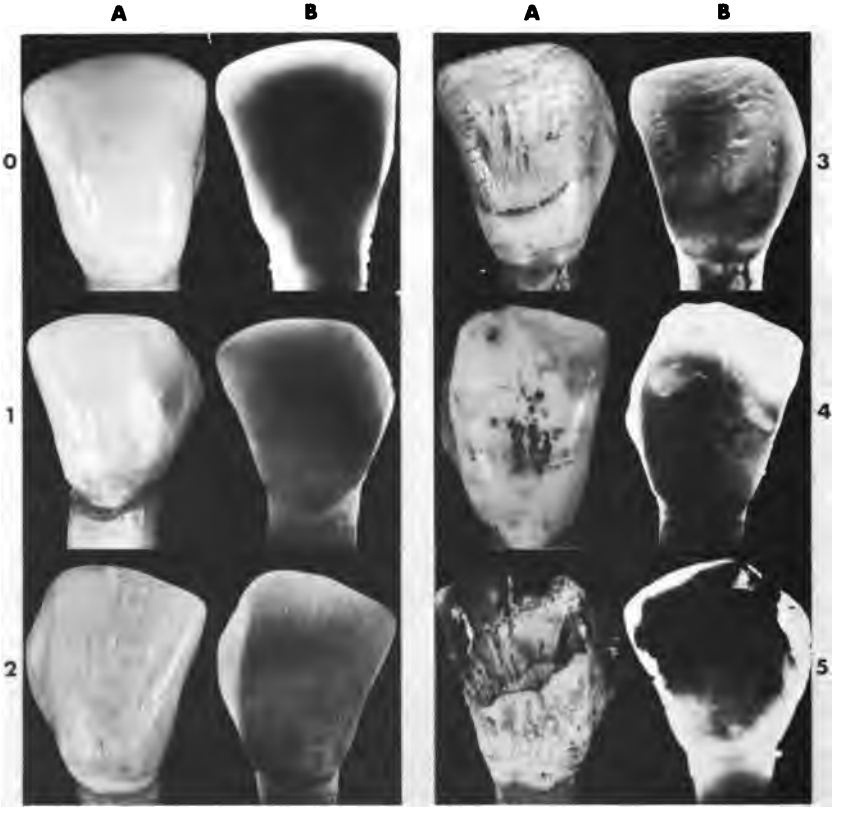

FIGURE 4 Clinical standards used in diagnosing dental fluorosis. Teeth shown are permanent bovine incisors: (A) photographed with front lighting; (B) photographed with back lighting. 0 = normal, 1 = questionable effect, 2 = slight effect, 3 = moderate effect, 4 = marked effect, 5 = severe effect.

Courtesy of J. L. Shupe and A. E. Olson, Utah State University

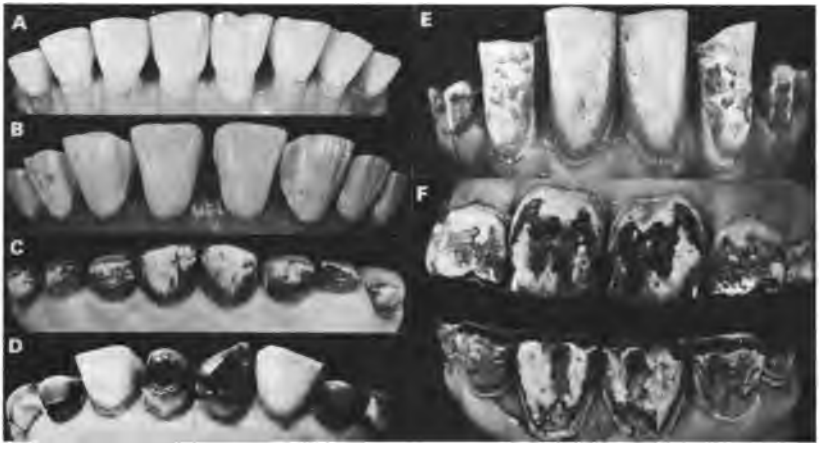

FIGURE 5 Dental fluorosis in incisor teeth. A = bovine, normal, 7 yr old; B = bovine, moderate effect, constant excessive ingestion of fluoride, 8 yr old; C = bovine, severe effects, constant excessive ingestion of fluoride, 4 yr old; D = bovine, severe effects, intermittent periods of excessive ingestion of fluoride, 5 yr old; E = ovine, severe effects, constant excessive ingestion of fluoride, 5 yr old; F = equine, severe effects, constant excessive ingestion of fluoride, 4 yr old.

Courtesy of J. L. Shupe and A. E. Olson, Utah State University

tal fluorosis. Fluorosis of premolars and molars is estimated on the basis of the degree of selective abrasion and is correlated with the degree of incisor fluorosis (Shupe, 1967). Premolar and molar abrasion appears to be somewhat delayed beyond that of incisor teeth. Abraded cheek teeth (Figure 6) are protected by adjacent sound teeth that are not abraded. Such abrasive feeds as coarse, fibrous, tough roughage will increase the rate of dental abrasion. In diagnosing and evaluating chronic fluoride toxicosis in animals, the cheek teeth should be examined and the findings correlated with other fluoride-induced symptoms and lesions.

The degree of fluoride-induced dental lesions that develops under controlled experimental conditions has been correlated with such factors as the amount of fluoride ingested, duration of excessive fluoride ingestion, the age of the animal, and the severity of osteofluorosis (Shupe *et al.*, 1963b). The dental lesions, therefore, are useful in clinical diagnosis of chronic fluoride toxicosis; however, to be most meaningful, fluoride dental lesions should be correlated with other tissue changes and symptoms (NAS-NRC, 1955; Suttie *et al.*, 1957a; Shupe, 1969).

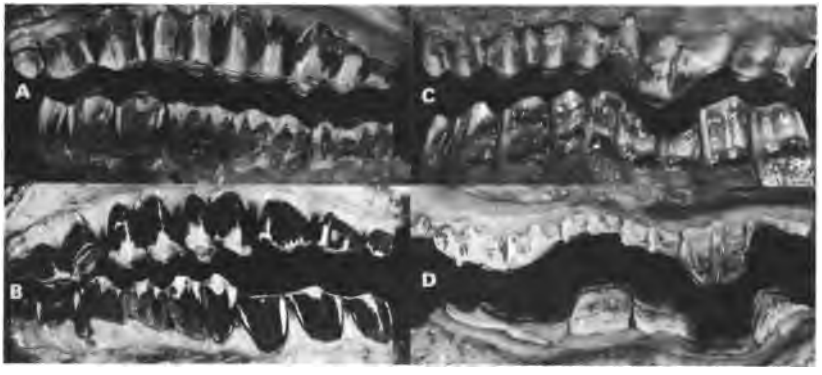

FIGURE 6 Dental fluorosis in cheek (premolar and molar) teeth. A = bovine, normal, 8 yr old; B = bovine, moderate effect, 4 yr old; C = ovine, marked effect, 4 yr old; D = equine, severe effect, 4 yr old.

Courtesy of J. L. Shupe and A. E. Olson, Utah State University

OSTEOFLUOROSIS

The level of fluoride storage in bone can increase over a period of time with no apparent changes in bone structure or function. If the level of dietary fluoride ingestion is sufficiently above normal for an appreciable length of time, structural bone changes will become evident (Shupe *et al.*, 1963b; Johnson, 1965). The degree and type of progressive bone structural changes are determined by various factors, cited elsewhere in this report, that influence the general degree and manifestation of fluoride toxicosis.

In livestock, the first clinically palpable bone lesions usually occur bilaterally on the medial surface of the proximal third of the metatarsal bones. Subsequently, palpable bone lesions occur on the mandible, metacarpals, and ribs. The severity of osteofluorotic lesions appears related in some measure to the stress and strain imposed on various bones and to the structure and function of the bones. This is exemplified by the more severe osteofluorotic lesions characteristic of the ribs, mandible, and metaphyseal areas of the metatarsal and metacarpal bones as compared with the less severe lesions appearing on the diaphyseal areas of the metatarsal and metacarpal bones (Shupe *et al.*, 1963b). Experiments with dairy heifers and cows have shown that there is an increase in bone alkaline phosphatase when the dietary fluoride is increased (Miller and Shupe, 1962).

Grossly, bones that are severely affected by fluoride appear chalky

white, have a roughened irregular periosteal surface, and are larger in diameter and heavier than normal. Examples of metatarsal bones affected by osteofluorosis are shown in Figure 7. The type of bone changes depends on the level and duration of fluoride ingestion; one or more of the following conditions may occur: osteosclerosis, osteoporosis, periosteal hyperostosis, osteomalacia, or osteophytosis (Johnson, 1965; Shupe, 1969). Characteristic histological changes are associated with the gross lesions of osteofluorosis and have been illustrated and described (Johnson, 1965; Shupe and Alther, 1966; Shupe, 1969). Some of the gross and histological changes characteristic of osteofluorosis resemble bone lesions and alterations that are also associated with other bone diseases. Therefore, in making a definitive diagnosis, the lesions observed must be correlated carefully with other lesions and symptoms.

Radiographically, osteoporosis, osteosclerosis, osteomalacia, hyperostosis, and osteophytosis, or any combination of these conditions, have been observed in animals that have ingested excessive levels of fluoride for long periods of time (Roholm, 1937; Johnson, 1965; Shupe, 1969). The radiographic findings (Figures 7B,D and 8) vary, depending on the interaction of factors influencing fluoride toxicosis.

LAMENESS AND STIFFNESS

The impaired movement of animals that is characteristic of fluoride toxicosis is more frequently a nonspecific stiffness than a specific lameness. In some severe cases, animals become progressively worse and may eventually refuse to stand, moving instead on their knees. However, in most cases, periods of stiffness and lameness are intermittent. In advanced cases of fluoride toxicosis, where the animals have marked periosteal hyperostosis, there may be a spurring and bridging of the joints that eventually leads to marked rigidity of the limbs and spine.

The stiffness and lameness that appear in more advanced cases of fluoride toxicosis seem to be associated with osteofluorotic lesions and calcification of periarticular structures and tendon insertions. The specific lesions responsible for the condition are not known but they can deter the affected animals from standing at the feeder or grazing; subsequently, this reduction in feed intake may adversely affect levels of performance.

Initial stages of the bone lesions associated with fluoride toxicosis are not intra-articular. In contrast, lesions associated with osteoarthri-

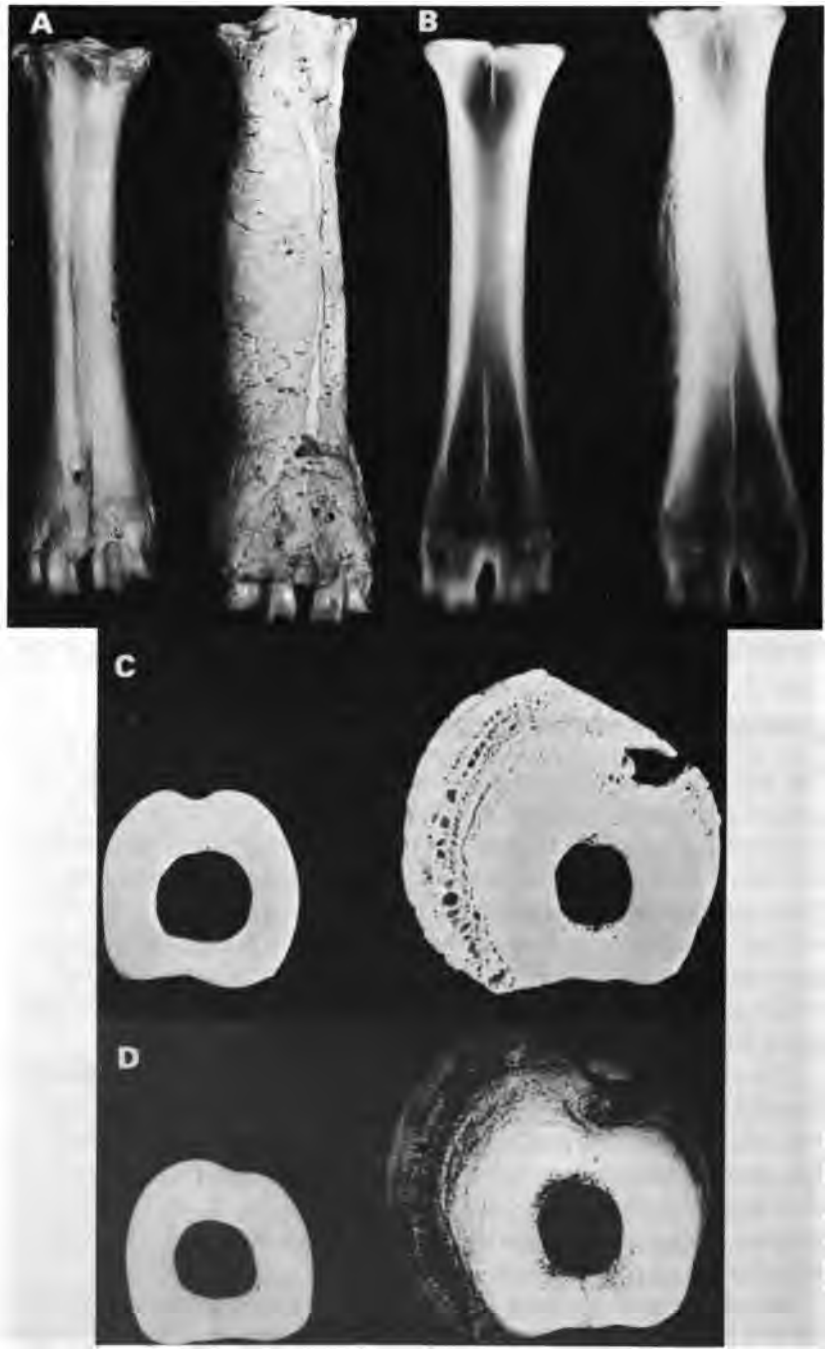

FIGURE 7 Effects of excessive fluoride on bone. A = bovine metatarsal bones: (left) normal; (right) severe effect; B = radiograph of bones shown in (A); C = cross sections of bones shown in (A); D = radiograph of cross sections of bones shown in (A) but taken at a different location than those in (C).
Courtesy of J. L. Shupe and A. E. Olson, Utah State University

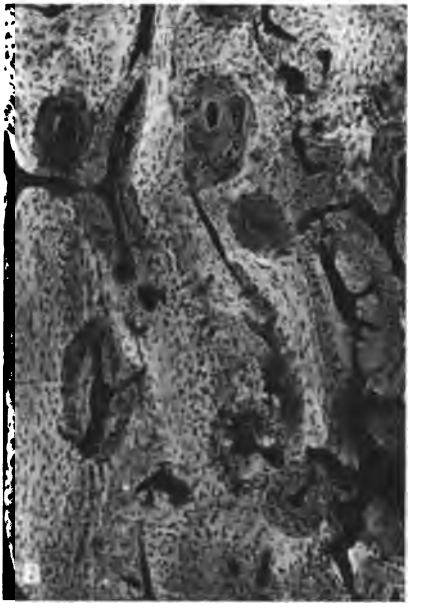

FIGURE 8 Microradiographs of bone. A = normal (X56); B = severe effect of fluoride (X56); C = section showing zones of severe effect resulting from intermittent ingestion of excessive fluoride (X10).

Courtesy of J. L. Shupe and A. E Olson, Utah State University

tis are intra-articular and, secondarily, may become periarticular (Shupe, 1961, 1967). Crepitation, or grating of joints, is a symptom of osteoarthritis and does not appear in uncomplicated cases of fluoride toxicosis. Varying degrees of osteoarthritis have been diagnosed in certain field cases of severe fluoride toxicosis. However, such arthritic changes and such symptoms of acute inflammatory arthritis as elevated body temperature, hot swollen joints, and suppressed ruminations are not associated with the characteristic intermittent stiffness and lameness of advanced fluoride toxicosis (Shupe, 1967). Stiffness and lameness are observed rather frequently in livestock, but in the absence of supporting evidence they are inconclusive measures of fluoride toxicosis.

Lameness associated with the fracture of the distal phalanx (Burns and Allcroft, 1964) and arthritis of the hip (Jones, 1972) have been reported to be associated with fluoride toxicosis in England. These conditions have been observed infrequently in other geographic areas or in experimental studies.

FLUORIDE RETENTION IN TISSUES

The most definitive evidence that animals have ingested increased amounts of fluoride includes elevated fluoride levels in the diet, bone, and urine. Excretion and retention are dependent on a number of factors, i.e., the fluoride content of the diet, duration of ingestion, solubility of the fluoride, age of the animal, composition of the diet, and amount of fluoride in the bone.

In a number of long-term experimental studies with dairy or beef cattle, wherein as much as 100 ppm F as sodium fluoride was added to the diet, the skeletal retention of fluoride was approximately proportional to the amount ingested. This information is illustrated in Figure 9. The rate of increase of skeletal uptake of fluoride decreases with time, a fact that was observed in experiments with dairy cattle in which serial biopsies were taken (Shupe *et al.*, 1963b).

The amount of fluoride in different bones of the bovine skeleton varies appreciably, depending on the structure of bone. Cancellous bones such as the frontal, ribs, vertebrae, and those of the pelvis have a higher fluoride content than the more compact metatarsal and metacarpal bones (Suttie and Phillips, 1959; Shupe *et al.*, 1963a). There is also a marked variation in the fluoride content of such different anatomical areas of bone as the metatarsal or metacarpal; the diaphyseal portion has a lower fluoride content than the metaphyseal

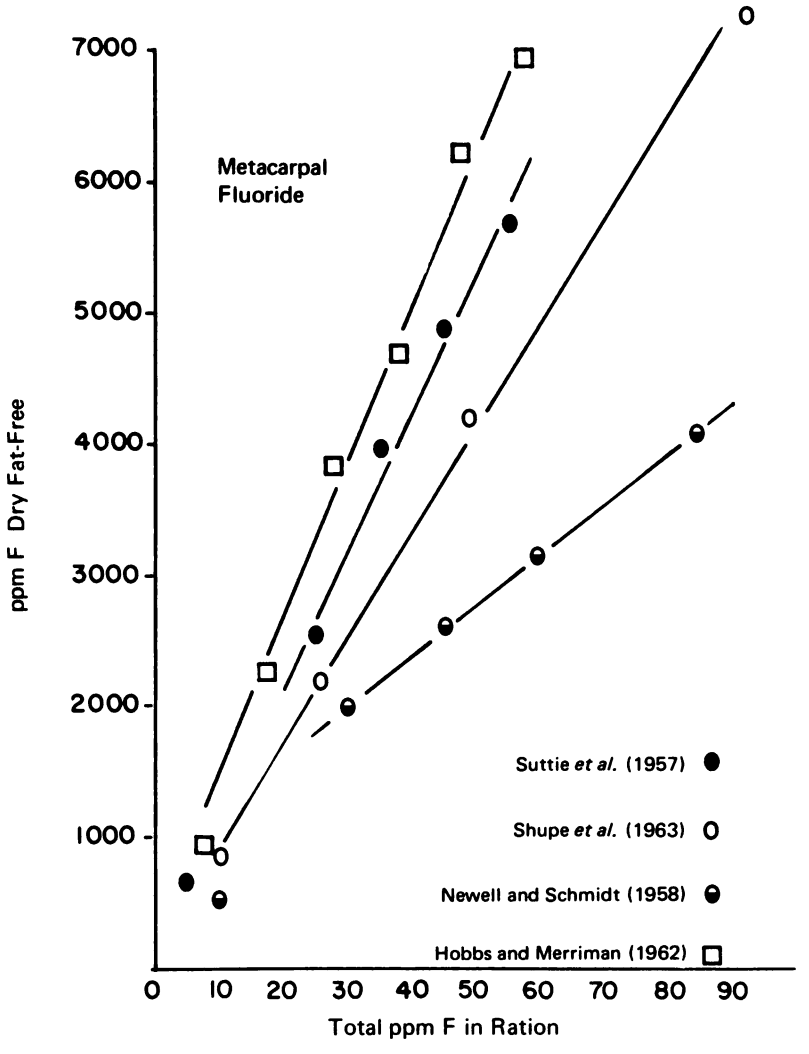

FIGURE 9 Comperison of bone fluoride content as reported by various investigators.

Compiled by J. W. Suttie

portion (Shupe *et al.*, 1963a; Ammerman *et al.*, 1964). This difference in fluoride distribution is reflected in concentration differences between the periosteal and endosteal surfaces as compared with dense cortical bone (Suttie and Phillips, 1962).

Under experimental conditions in which there is a constant level

of fluoride intake, the amount of fluoride in the diet can be estimated if the bone fluoride content and the period of exposure are known (Shupe *et al.*, 1963b). This cannot be assumed in field cases, as can be seen from the data of Mortenson *et al.* (1964), which indicate differing degrees of dental damage in range cattle with similar bone fluoride concentrations. Experiments with controlled feeding of alternate high and low concentrations of fluoride indicate, however, that the fluoride concentration of bone is a good indication of total fluoride intake, but not necessarily of the concentration of fluoride in a given diet (Suttie *et al.*, 1972).

Techniques for obtaining coccygeal vertebra and rib samples for analysis by biopsies have been developed (Burns and Allcroft, 1962; Purvance and Transtrum, 1967). A correlation has been established between the fluoride content of the coccygeal vertebrae and the metacarpal or metatarsal bones (Suttie, 1967). Urine fluoride analyses can be a useful diagnostic aid and urine fluoride levels are correlated to some extent with dietary intake. The urinary fluoride level, however, is affected by a number of important variables, including the duration of fluoride ingestion, time of day sampling is conducted, and total urinary output (Shupe *et al.*, 1963b). Because of variations in urine output, the results of urine fluoride analysis are usually expressed on a common specific gravity basis. Individual random samples of urine have limited value for indicating the fluoride intake of a herd of animals. Information concerning the number and frequency of samples that must be obtained to be representative of the entire herd has been reported (Shupe *et al.*, 1963b). Urine fluoride concentration will remain high for some time after the removal of animals from a higher fluoride diet (Blakemore *et al.*, 1948; Phillips *et al.*, 1963; Allcroft *et al.*, 1965); therefore, it is not an ideal indicator of current exposure.

The ingestion of excessive amounts of fluoride by livestock will result in slightly increased concentrations of fluoride in blood and soft tissues (Suttie *et al.*, 1957a; Shupe *et al.*, 1963a). Advances in analytical methods have made it possible to measure blood-plasma fluoride with sufficient accuracy to demonstrate a correlation between fluoride intake and plasma-fluoride concentration and to show that plasma-fluoride concentrations change rapidly with changes in fluoride intake (Suttie *et al.*, 1972). Plasma-fluoride levels, however, no not appear to be practical aids in the diagnosis of chronic fluoride toxicosis.

The levels of fluoride in milk have been shown (Stoddard *et al.*, 1963a) to increase when the level of dietary fluoride was increased

but did not exceed 0.2 ppm F even when the cows ingested 109 ppm F for extended periods of time. Within such levels of fluoride ingestion, the fluoride content of the milk was low and within safe levels for human consumption. The mammary gland has been shown to serve as a minor route of fluoride excretion.

Examinations of calves from cows that received various levels of sodium fluoride have demonstrated that fluoride passed the placenta (Suttie *et al.*, 1957a; Bell *et al.*, 1961; Shupe *et al.*, 1963a). The amount of fluoride in bone of the offspring varied with the level of fluoride ingested by the dam. In subsequent gestations, the amount of fluoride transmitted through the placenta did not increase, regardless of the duration of fluoride ingestion. The level of fluoride in the skeletal tissue of the offspring was correlated with the fluoride content of maternal blood, but was not correlated with the levels of fluoride in the maternal osseous tissue.

Calves from cows that had ingested high levels of fluoride performed normally when compared with calves from cows that had ingested low levels of fluoride (Shupe *et al.*, 1963a). Suttie *et al.* (1961) found that calves from cows previously exposed to fluoride performed similarly in a subsequent experiment to calves from normal cows, and Rosenberger and Gründer (1967) have shown that calves born to cows that had been removed for 1 yr from a very high exposure level of 9 mg F/kg body weight were normal.

MILK PRODUCTION

Milk production is not directly affected by ingestion of low levels of fluoride (Schmidt *et al.*, 1954; Suttie *et al.*, 1957b; Stoddard *et al.*, 1963a). Even when fluoride toxicosis is sufficiently severe to alter metabolic function or impair dental and skeletal structure, any effects on milk production are likely to be directly attributable to these alterations and impairments rather than to interference with lactogenesis (Stoddard *et al.*, 1963a).

Studies (Suttie *et al.*, 1957b) have demonstrated that cows first exposed to fluoride at 4 months of age can consume 40–50 ppm F in their diet for two or three lactations without measurable effect on milk production. However, milk production of these cows was reduced in the fourth and subsequent lactations. A diet containing 93 ppm F reduced milk production in the third and subsequent lactations and may have affected milk production in the second lactation (Stoddard *et al.*, 1963a).

Variations in fluoride tolerances among individual animals may

affect the amount and the duration of fluoride intake that precedes any impact on milk production. Irrespective of the tolerance level or duration of fluoride uptake by individual animals, the subsequent clinical manifestations of primary symptoms and lesions associated with fluoride toxicosis will usually precede any alteration of milk production. The lesions and symptoms that result from fluoride toxicosis may adversely affect milk production secondarily: for example, advanced osteofluorosis (with marked periosteal hyperostosis that may induce spurring and bridging of the joints and intermittent lameness), which limits the time affected cows stand at the manger to feed; molar abrasion that makes mastication difficult; reduced feed intake that very likely results from the two previous factors; and possibly metabolic impairment.

REPRODUCTION

As measured by services required per conception, prolonged ingestion of excessive fluoride under controlled experimental conditions had no direct effect on reproduction. Severe fluoride toxicosis can influence reproduction indirectly by altering the function of body systems, with a resultant impairment of generalized body health.

GENERAL CONDITION

Appetite impairment, resulting in general unthriftiness and loss of condition, can result from excessive fluoride ingestion (Hobbs *et al.*, 1954; Stoddard *et al.*, 1963b; Harris *et al.*, 1964; Crampton, 1968). Impairment of feed intake is not in itself a good diagnostic aid, since many toxicities and deficiencies can bring about the same result. Abnormal and excessive molar abrasion can also affect feed intake. A generalized unthriftiness, characterized by dry hair and thick, nonpliable skin, has been observed in animals that had other unequivocal symptoms and lesions of fluoride toxicosis (Roholm, 1937; Shupe *et al.*, 1963a).

Extensive experimental studies and observations in endemic fluorotic areas have not shown any correlation between fluoride intake and growth and shape of hoofs (Schmidt *et al.*, 1954; NAS-NRC, 1955, 1960; Suttie *et al.*, 1957a, 1961; Hobbs and Merriman, 1962; Shupe *et al.*, 1962, 1963a; Greenwood *et al.*, 1964; Shupe and Olson, 1971). More variation occurred within single fluoride treatment groups than between groups. Furthermore, reports of high incidences of diarrhea

(Udall and Keller, 1952) have not been confirmed in controlled experimental studies or careful field investigations (Hobbs *et al.*, 1954; Schmidt *et al.*, 1954; Suttie *et al.*, 1957a, 1961; Shupe *et al.*, 1962, 1963a; Burns and Allcroft, 1964).

BLOOD AND SOFT TISSUES

Dairy cattle fed diets containing as much as 109 ppm F for 7½ yr evidenced no change in blood morphology or adverse effects on the hemopoietic system. Wider variation could be found within a single treatment group than between different treatment groups. No correlation was found between the amount of fluoride in the diet and the concentration of calcium, inorganic phosphorus, or alkaline phosphatase in the blood serum (Hoogstratten *et al.*, 1965). Beef cattle fed diets containing 7–107 ppm F as sodium fluoride for approximately 4½ yr showed normal hematology (Hobbs *et al.*, 1954). These studies indicate the capacity of the hemopoietic system to cope with widely varying fluoride intakes.

Only small amounts of fluoride are retained in the soft tissues of animals that ingest excessive fluoride for prolonged periods. No significant gross or histologic changes were noted in the brain, pituitary, liver, kidneys, adrenals, spleen, pancreas, thyroid, ovaries, mammary glands, uterus, rumen, reticulum, omasum, abomasum, or intestines (Shupe *et al.*, 1963b). In kidney-function tests using inulin, renal clearances were not significantly reduced as the dietary fluoride was increased. On the basis of the bromsulfophthalein (BSP) liver function tests, no correlation existed between fluoride treatments and BSP clearance (Shupe *et al.*, 1960). In field cases of fluoride toxicosis, interpretation of the pathologic changes in the soft tissues may be difficult because of associated conditions that are unrelated to fluoride levels consumed. The kidneys were routinely higher in fluoride than was other soft tissue, probably because of their role in eliminating fluorides from the body. To date, no characteristic, unequivocal histologic, or significant functional changes in the soft tissues of animals can be correlated to ingestion of fluoride levels high enough to induce chronic fluoride toxicosis.

RECOVERY FROM FLUORIDE EXPOSURE

There have been only a few investigations of the performance of cattle after they are removed from a diet containing toxic amounts

of fluoride. Blakemore *et al.* (1948), Hobbs and Merriman (1962), Allcroft *et al.* (1965) and Gründer (1967) have made observations on cattle after they have been removed from an area where they were exposed to fluoride as an industrial pollutant, and Phillips *et al.* (1963) have studied the recovery of cows removed from an experiment where they were being fed sodium fluoride.

In these experiments, a decline in the level of skeletal fluoride, which varied from as low as 10 percent in 2 yr to as much as 50 percent in a 4- to 5-yr period, has been found. Studies in progress (J. L. Shupe, personal communication) have shown that as much as 40 percent of 11,000 ppm F (calculated on an ash basis) retained in the rib bones of cattle exposed to high dietary fluoride for 1 yr was lost within 6 months after transferring them to a control diet. It appears from these data that the magnitude of the loss varied inversely with the time that it took to reach a particular level of fluoride concentration in the skeletal tissue. This would suggest that cattle exposed to a high level of fluoride for a short time will mobilize and excrete more fluoride during a subsequent recovery period than will animals that built up the same skeletal level over a longer time at a lower level of intake.

Suttie *et al.* (1972) have shown that plasma-fluoride concentrations decrease to near normal a day or two after cows are removed from a high fluoride diet, and the available data (Hobbs and Merriman, 1962; Phillips *et al.*, 1963) indicate that urinary fluoride concentrations fall at a slower rate. Phillips *et al.* (1963) noted also that an animal that had over 11,000 ppm F in the vertebral ash at the time it was changed from a high- to a low-fluoride diet was still excreting urine containing 15 ppm F 2 yr later. These data clearly indicate that there are periods during which urinary fluoride concentrations do not reflect either current intake or skeletal fluoride concentrations, and their use in diagnosis could therefore be very misleading, unless properly interpreted.

Incisor teeth that are formed and calcified after animals are removed from a high-fluoride diet will not have lesions, but teeth that have been severely damaged by fluoride will continue to show an increased rate of attrition in subsequent years. Hobbs and Merriman (1962) have provided excellent photographic documentation of these responses.

Gründer (1967) noted an increase in body weight and improved nutritional status when cattle were taken from an area of heavy (up to 9 mg F/kg of body weight) industrial fluoride exposure. However,

Phillips *et al.* (1963) noted that one cow that had suffered a systemic reaction to high-fluoride ingestion during her first two lactations was not greatly improved during her third lactation when she was no longer receiving excessive fluoride. Available information along these lines is very limited, and it is difficult to draw unequivocal or firm conclusions about the subsequent performance of animals subjected to damaging levels of fluoride. The response of animals transferred from a high to low dietary intake of fluoride will vary with many factors, and each case must be individually evaluated. In animals where reduced feed intake and performance are associated with excessive incisor and molar wear or marked osteofluorosis, there will be limited improvement upon removal from a high fluoride diet. If, however, the feed intake repression was due to a systemic reaction, it will improve as plasma fluoride concentrations fall.

EXTRAPOLATION OF EXPERIMENTAL FINDINGS TO CLINICAL CONDITIONS

Individuals undertaking the diagnosis and evaluation of fluoride toxicosis in animals should be properly trained, knowledgeable, and experienced. All available records, data, and findings that relate to the animals involved should be examined.

The diagnostician should make detailed clinical examinations of all animals suspected of being adversely affected. Each animal should be properly identified with an ear tag (for short-term identification) or ear tattoo (for permanent identification). Regardless of monitoring and sampling data related to the source(s) and levels of fluoride in the vegetation, each animal should be evaluated as to its individual expression of fluoride toxicosis.

It is advantageous to compare suspected animals with others that have experienced approximately similar exposure but under different management practices. Important factors may be overlooked if animals in adjacent areas are not thus observed. Some manifestations thought to be abnormal due to excessive fluoride may not in fact be so, and some animals thought to be normal may actually be adversely affected. The variability that can occur between individual animals within and between herds must also be considered (Shupe, 1967).

Under field conditions, the levels of fluoride ingested, the duration of excessive fluoride ingestion, and management practices are usually subject to wide variations. In some instances extremely high or low amounts of fluoride may be ingested intermittently. Such as-

pects of management as preventive medical programs and housing facilities, type, quantity, and quality of feed, breeding program, and characteristics of routine animal care can influence expression of fluoride-induced symptoms and lesions. Crampton (1968) emphasized that inadequate nutrition of dairy cows resulted in poor physical condition and loss of body weight very similar to the condition observed with continued ingestion of excess fluoride in an otherwise satisfactory diet.

The relationship of animal age to excessive fluoride intake and lesions is also important. For example, molar abrasion usually occurs whenever first, second, or third pairs of incisor teeth (I_1, I_2, I_3) are severely affected and indicates a different significance than do severely affected corner incisor teeth (I_4), which usually show little or no molar abrasion if the first, second, and third pairs of incisor teeth do not have marked lesions themselves (Newell and Schmidt, 1958; Shupe, 1967). Additional factors to be considered are the type of farming operation (i.e., dairy or beef) and whether it is a fattening, replacement, or cow-and-calf enterprise. All findings must be properly considered and interrelated before a final evaluation is made.

Borderline cases of fluoride toxicosis may be difficult to diagnose and evaluate accurately. Chronic fluoride toxicosis is usually progressive and subject to varied manifestations. The interval between ingestion of excessive levels of fluoride and manifestation of clinical symptoms complicates the clinical syndrome. The subtle effects in some cases may interfere with performance and productivity. Certain symptoms and lesions due to other causes may resemble those associated with borderline fluoride toxicosis. The disease is such that no single criterion should be used in diagnosing fluoride toxicosis (Shupe, 1967).

Symptoms and visible lesions are sometimes not definitive enough to warrant an unequivocal diagnosis of fluoride toxicosis. In such instances—or to further substantiate a reasonably certain diagnosis—additional verification can be sought in several ways. When properly interpreted, urine analyses can be a useful diagnostic aid (see section on Role of Kidney, p. 17). Bone radiographs can provide useful information. Biopsies or necropsies of properly selected animals can be used to obtain tissues for gross and histopathologic evaluations and chemical analyses for fluoride content. Correlation of symptoms, lesions, and chemical analyses of tissues with the measured fluoride content of the animals' water and forage sources can often help sub-

stantiate suspected instances of fluoride toxicosis. All findings must be evaluated carefully before a definite diagnosis is made.

Prevention and control of fluoride toxicosis in livestock can be achieved, but only when the complexity of the disease is recognized and the pathogenesis, symptomatology, and lesions are properly correlated, interpreted, and evaluated and when the source(s) of excessive fluorides are eliminated.

BIOLOGIC FOOD CHAIN

The adverse effects of excessive fluoride intake have been observed in both domestic and wild animals and in humans. Hazards to humans have occurred in certain areas of the world and appear to result primarily from consuming water with a high fluoride content.

The major hazard, however, is agricultural as it affects plants and animals. The damaging effects of fluoride occur primarily in animals that ingest rations high in fluoride. Indeed, domestic animals can serve as a protective barrier for humans. Approximately 99 percent of the fluoride retained in the body is stored in bone, and only slight increases in the concentration of soft tissue fluoride occur even at high levels of dietary fluoride intake. Milk from cows consuming high levels of fluoride shows only slightly elevated fluoride, indicating that the mammary gland is not a primary route for excretion. There is therefore little danger to humans from the consumption of meat or milk from domestic animals even if the animals have ingested excessive fluoride. A few meat and fish products prepared for human consumption contain portions of comminuted bone that may contribute to a higher fluoride content. The proportion of the total diet represented by these products, however, would generally be very small indeed.

Factors Influencing Fluoride Toxicosis

THE SEVERITY OF FLUORIDE TOXICOSIS DEPENDS on the total dietary intake of the element rather than on its concentration in a particular portion of the diet. Total intake may include fluoride consumed with forages, in water, or in supplemental minerals and feeds. Any reduction of dietary fluoride through the use of supplemental feeds relatively free of fluoride, or the employment of proper pasture management practices that reduce fluoride contamination, reduces toxicity of the total diet. Besides total intake, it is important to consider other factors that influence toxicity; i.e., the form in which fluoride occurs, the nutritional status of the animal, and certain dietary nutrients or additives that may alleviate the toxicity.

SOURCE OF FLUORIDE

Inorganic Compounds

The toxicity of a fluoride compound generally increases as its solubility in water increases. Mitchell and Edman (1952) reviewed extensive studies in which the relative toxicity of fluoride compounds was determined. In research conducted primarily with the rat, sodium fluoride (NaF) and sodim fluosilicate (Na_2SiF_6) were the most toxic; calcium fluoride (CaF_2) was the least toxic compound tested. The fluoride in cryolite (Na_3AlF_6) and in rock phosphate and certain of its processed derivatives was intermediate in toxicity. These authors concluded that the fluoride in sodium fluoride was about twice as toxic as that in cryolite or rock phosphate. Shortly thereafter, Hobbs *et al.* (1954) showed that, on the basis of skeletal storage of fluoride

by rats, the toxicity of various compounds could be ranked from high to low in the following order: potassium and sodium fluosilicate, potassium and sodium fluorides, rock phosphate, natural and synthetic cryolite, calcium and magnesium fluosilicates, and calcium fluoride. Most recent studies with animals of domestic importance have been conducted with sodium fluoride.

In studies with beef heifers fed for approximately 1½ yr, Hobbs and Merriman (1962) found that fluoride in rock phosphate was considerably less toxic than that in sodium fluoride, as judged by voluntary feed intake, dental fluorosis, and bone fluoride levels. In research with finishing steers (Ammerman *et al.*, 1964), deposition of fluoride in the bone indicated that the fluoride in soft phosphate was much less available than that in sodium fluoride but at least twice as available as the fluoride in calcium fluoride. Research with swine (Plumlee *et al.*, 1958) indicated that more than three times as much fluoride was deposited in the femur from soft phosphate than from calcium fluoride when they were fed at equivalent levels of fluoride (373 ppm F).

Elevated fluoride vegetation levels result from accumulation of fluoride within plant tissue and from atmospheric pollution or soil contamination caused by rain splash. Data on dental effects and on bone changes, including fluoride concentration, show that contaminated high-fluoride hay (62 ppm F) containing fluoride emitted from a steel-processing operation was as toxic to growing dairy heifers as an equivalent amount of fluoride in the form of sodium fluoride (Shupe *et al.*, 1962). In the same study, calcium fluoride proved much less toxic than either sodium fluoride or the fluoride-contaminated hay. In studies with beef cattle (Hobbs *et al.*, 1954), it appeared that fluoride from forage obtained near an aluminum reduction plant affected the animals' teeth less severely than did a similar amount of fluoride as sodium fluoride. The available evidence would indicate that fluoride from industrial sources is no more toxic than is that present in sodium fluoride.

Waterborne Fluoride

A significant portion of fluoride intake may be obtained from water (Rand and Schmidt, 1952; Neeley and Harbaugh, 1954; Merriman and Hobbs, 1962). Skeletal retention of fluoride was similar when weanling rats received equal amounts of fluoride from either naturally fluoridated water or redistilled water to which sodium fluoride

was added (Wagner and Muhler, 1957). Other studies with rats (Harvey, 1952; Wuthier and Phillips, 1959) have indicated that fluoride in both naturally and artificially fluoridated waters is comparable in toxicity with equal intakes of soluble fluoride fed in a dry diet. Ingestion of water containing 4–5 ppm F as a natural constituent has resulted in fluoride toxicosis in cattle (Rand and Schmidt, 1952; Neeley and Harbaugh, 1954). Studies on beef cattle (Merriman and Hobbs, 1962) showed increased skeletal fluoride in animals that drank pond water contaminated with fluoride when compared with animals drinking low-fluoride water.

LEVEL OF NUTRITION

Although the adequacy of nutrition in relation to fluoride toxicosis in domestic animals has been studied by several investigators, no clearly definable relationship has emerged. Merriman and Hobbs (1962) investigated combinations of "high-" and "low"-fluoride intake with "good" and "low" nutrition over a 3 yr period with beef cattle on pasture. The results of the study, however, were undoubtedly complicated by variations in fluoride intake. The conditions of shorter, less dense pasture and closer grazing that characterized the low-nutrition treatment resulted in the forages having higher fluoride concentrations and in an increased bone fluoride accumulation. Bone-fluoride levels for the low-nutrition cattle were significantly greater than those for the good-nutrition groups in one of the 3 yr. In another study by Suttie and Faltin (1973), Holstein heifers were individually stall-fed either 60 or 100 percent of the recommended allowance of total digestible nutrients and 40 ppm dietary F for 4½ yr. Cows receiving adequate nutrition were heavier and their intake of fluoride (mg F/kg of body weight) was elevated for the first year but was equal to the other group for the remainder of the experiment. Incisors of the low-nutrition group were slower to erupt and showed greater effects of fluoride. Dietary fluoride at levels up to 100 ppm F as sodium fluoride did not influence nutrient digestibility by cattle consuming equal levels of feed (Hobbs *et al.*, 1954; Shupe *et al.*, 1962; Harris *et al.*, 1964).

VARIATIONS IN INTAKE

Although most experimental studies have involved the feeding of a constant amount of fluoride over an extended period, exposure of

animals to fluoride in areas where forage is contaminated by fluoride from industrial sources can be extremely variable. Experimental studies (Suttie *et al.*, 1972) have shown that exposure of young cattle to alternating periods of high- and low-fluoride intake was more damaging than was exposure to a constant level that provided the same yearly intake. This experiment substantiates observations made in areas of endemic fluoride toxicosis.

ALLEVIATION OF TOXICOSIS

Certain dietary additives or natural components have been tested, at least experimentally, as a means of alleviating fluoride toxicosis. Much of this research has been conducted with laboratory animals and the materials tested have been only partially effective. They have had only limited use under practical conditions.

Calcium and Phosphorus

The beneficial effect of added calcium has been shown in the rat (Lawrenz and Mitchell, 1941; Ranganathan, 1941; Weddle and Muhler, 1954, 1957; Boddie, 1957), in man (Peters, 1948; Danowski, 1949), and in cattle (Suttie *et al.*, 1957a; Boddie, 1960). In one trial (Majumdar and Ray, 1946), the addition of calcium carbonate to a high-fluoride diet for cattle failed to improve performance, but the results may have been influenced by low dietary phosphorus intake. Boddie (1960) reported the results of a 3 yr study in which two groups of cattle were rotated on different pastures contaminated with fluoride. All cattle received 2 lb of concentrate daily and one group, in addition, received daily 1 oz/head each of calcium carbonate and aluminum oxide. Dental fluorosis was less severe in the incisor teeth of cattle receiving the alleviator, but fluoride concentration in the incisor teeth and in the mandibular and metacarpal bones was similar for both groups.

In a study with dairy cattle (Suttie *et al.*, 1957a), young cows were fed, in addition to a complete diet, either 50 ppm F as sodium fluoride or 50 ppm F plus 200 g $CaCO_3$/head daily through five lactations. Effects of fluoride on teeth were less severe when $CaCO_3$ was fed in that the condition of the teeth was similar to that of animals receiving a diet containing only 40 ppm F. Fecal fluoride concentration was greater for cows fed $CaCO_3$, which supports the hypothesis that calcium salts alleviate fluorosis by converting soluble

fluoride ions to calcium fluoride (CaF_2) in the intestinal tract. This effect, however, was not sufficient to decrease storage of fluoride in ribs. Rats given a diet high in calcium and phosphate prior to ingestion of fluoride retained more fluoride in the intestinal tract and less in the skeleton than did controls (Ericsson, 1968). Increasing the phosphorus content of the diet from 0.7 to 1.0 percent did not alter the toxicity of fluoride to chicks (Gardiner *et al.*, 1961).

Magnesium

Results of research with rats have been contradictory and suggest that magnesium has no effect on fluoride toxicosis (Schuck, 1938; Gardiner *et al.*, 1961) and that it decreases fluoride toxicosis (Ranganathan, 1941; Weddle and Muhler, 1954). In studies with poultry (Gardiner *et al.*, 1961), the inclusion of 0.25 percent magnesium in combination with 800 ppm F as sodium fluoride caused a greater depression in growth and greater incidence of leg weakness in chicks than occurred when either magnesium or fluoride was added to the diet singly.

Aluminum Compounds

Certain aluminum compounds have been relatively effective in alleviating fluoride toxicosis. In studies with rats and rabbits, both aluminum chloride (Sharpless, 1936; Hobbs *et al.*, 1954) and aluminum sulfate (Kempf *et al.*, 1937; Marcovitch and Stanley, 1942; Venkataramanan and Krishnaswamy, 1949; Hobbs *et al.*, 1954) have reduced fluoride toxicosis. The effect of feeding sodium fluoride in combination with aluminum sulfate to beef cows was studied (Hobbs *et al.*, 1954; Hobbs and Merriman, 1959). The animals were barn-fed and received 8, 28, 38, 48, or 58 ppm dietary F, with and without aluminum sulfate, as 0.5 percent of the total diet. The cows were 18 months old initially and remained on test for 8 yr. The aluminum sulfate reduced bone fluoride storage in cattle in each treatment by 30–40 percent and decreased dental fluorosis. Gross bone hypertrophy of the metatarsals and mandibles occurred in cows receiving 48 and 58 ppm F, but this condition was not observed when aluminum sulfate was also fed. In studies by Greenwood *et al.* (1964), heifers ingesting aluminum sulfate showed 30–42 percent less fluoride deposition in their ribs than did control animals that consumed high dietary

levels of fluoride during an experiment approximately 4 yr in length. Aluminum sulfate, fed over a 5-yr period as 1 percent of the total dry matter intake to dairy cows grazing contaminated forage, resulted in a reduction of about 22 percent in bone fluoride (Allcroft *et al.*, 1965). In these studies the aluminum sulfate was fed twice daily and the average fluoride content of the available forage varied from about 45 to 105 ppm F. In other experiments, aluminum sulfate fed to grazing cattle, free choice, in a mineral mixture was not effective in reducing bone fluoride storage (Merriman and Hobbs, 1962). The authors questioned whether there was continuous ingestion of the aluminum sulfate adequate to provide alleviation of the fluoride effects when the animals were given free access to the supplement.

Research was conducted by Hobbs *et al.* (1954) on growing lambs in which the influence of aluminum, as aluminum sulfate or aluminum chloride, on fluoride and phosphorus balance was determined. The lambs were fed either 0.1 or 0.5 percent aluminum sulfate or 0.1 percent aluminum chloride in a natural-type diet containing 100 ppm F as sodium fluoride or 106 ppm total F. Feed intake, nutrient digestibility, nitrogen balance, and weight gains were similar for all treatments. There was a slight reduction in the percent of fluoride retained and in the concentration of fluoride in the bones of those lambs fed the aluminum compounds. The main effect of additives, however, was to decrease phosphorus retention. Control sheep retained 41.8 percent, whereas treated sheep retained 12.5–18.6 percent of their phosphorus intake. Adverse effects of aluminum on phosphorus utilization have also been observed in poultry (Storer and Nelson, 1968) and rats (Street, 1942; Alsmeyer *et al.*, 1963). These results suggest that aluminum compounds increase the dietary requirement for phosphorus by making some of the dietary phosphorus unavailable for absorption. Thus, if they were to be used in the alleviation of fluoride toxicosis, compensating levels of phosphorus should be fed.

In addition to the above compounds, Hobbs *et al.* (1954) reported that aluminum acetate reduced bone fluoride storage in rats when fed at dietary levels of 0.5–2 percent of the total diet. Aluminum oxide, which is relatively insoluble, alleviated fluoride toxicosis only slightly when added to the diet. In the same studies, dietary aluminum compounds were ineffective in hastening the depletion of fluoride stores already deposited in the skeletal system of rats.

Other Compounds

Sodium chloride, added to the diets of rats, depressed skeletal uptake of radioactive fluoride (Ericsson, 1968). The author suggests that competition between chloride and fluoride ions for transport across the gastric or intestinal wall may have reduced the absorption of fluoride. In the same studies, additional lysine reduced toxicity, whereas olive oil used as the source of dietary fat did not reduce fluoride toxicity to the rat. The implantation of 12 mg diethylstilbesterol in finishing lambs, or feeding 20 g oxytetracycline/ton feed, did not influence tolerance to fluoride (Harris *et al.*, 1963).

Tolerance of Various Animal Species

TOLERANCE LEVELS FOR FLUORIDES IN THE DIET of domestic livestock must be established with due consideration of the economic usefulness and the well-being of the animal and with an understanding of how the various fluoride-induced biological responses that have been discussed influence this usefulness. The tolerance levels presented for various species are based primarily on observations of animals fed soluble fluorides.

BREEDING CATTLE

Much of the available experimental work has dealt with the effects of excessive fluoride ingestion by dairy or beef cattle. Most of the practical concern about fluoride in animal diets has also involved cattle. Results of the experimental work are summarized in Table 2, which includes appropriate references to the original literature. The material in Table 2 has been further summarized in Table 3. The statements "yes" and "no" in Table 3 are derived from a critical assessment of the available published data and should be interpreted as indicating that a given response would or would not be expected to be manifest at this level. The term "no" is therefore defined as meaning that the incidence of a given effect would not be expected to be significant at this intake level.

The data in Tables 2 and 3 indicate that there is no direct effect of fluoride on lactogenesis, but that prolonged excessive ingestion may eventually decrease animal performance. Cattle, although shown to tolerate 40–50 ppm F in their diet for three lactations, did show some adverse effect during subsequent lactations. At a higher intake (93 ppm F) milk production has been influenced during the third

TABLE 2 Fluoride Tolerance of Cattle

	Experiment						
	A[a]	B[b]	C[c]	D[d]	E[e]	F[f]	G[c]
	Highest F level fed (ppm)[g]						
	54	54	58	85	90	93	108
	Initial age (yr)						
	2	4	1	2	0.3	0.2	1.5
	Length of experiment (yr)						
	5.5	3	10	5.5	4	7.5	8
Response	Lowest Fluorine Level (ppm) To Give Response						
Decrease in growth rate	NE[m]	NA[l]	NE	NE	NE	NE	NE
Significant decrease in total milk production	NE	NE	NA	NE	NE	93	NA
Interference with individual lactations	54	NE	NA	NE	NE	49	NA
Food intake repression	NM[h,n]	NM	48	NM	NM[i]	93	58
Tooth class (4)	34	NA	38	45	55	49	48
Tooth class (2)	24	NA	18	33	35	27	28
Moderate gross periosteal hyperostosis	44	54	48	60	55	49	58
Significant incidence of lameness	44	NE	NE	85	55	49	NE
5,000 ppm F in skeleton at 5 yr[j]	54	NA	48	85	55	93	48
25 ppm F in urine[k]	34	34	38	85	55	93	38

[a] Suttie *et al.* (1957a,b, 1958) and Suttie and Phillips (1960).
[b] Suttie and Phillips (1959).
[c] Hobbs *et al.* (1954) and Hobbs and Merriman (1962).
[d] Newell and Schmidt (1958).
[e] Suttie *et al.* (1961).
[f] Harris *et al.* (1964), Shupe *et al.* (1963b), and Stoddard *et al.* (1963a,b).
[g] Total F added (as NaF) plus amount in diet. In experiments D and E, intake was in terms of mg/kg, converted to ppm from data in original paper or from Stoddard *et al.* (1963b) and Suttie *et al.* (1957a).
[h] Temporary effect at 44 ppm.
[i] Temporary effect at 70 ppm.
[j] Based on metacarpal or metatarsal dry fat-free weight, in most cases extrapolated from other data in original references.
[k] Based on values taken after 2 yr on experiment, expressed after correction to specific gravity of 1.04, except for experiment F, which is on as-is basis.
[l] NA = not applicable.
[m] NE = no effect at highest level fed.
[n] NM = not measured.

and subsequent lactations. The lack of a generalized response on milk production is consistent with the observation that dietary fluoride must be in excess of 50 ppm F before feed intake is significantly depressed. The severe lameness and skeletal lesions that have been observed in animals whenever more than 50 ppm F has been included in the diet may also influence the animals' ability to graze or to consume dry feed and thus influence production.

A tooth classified as (4) in the classification system (see p. 23)

TABLE 3 Relationship between Fluorine Content of the Diet and the Development of Various Symptoms in Cattle[a]

Symptom	Total Fluorine in Diet (ppm)			
	20–30	30–40	40–50	>50
Discernible dental mottling[b]	yes	yes	yes	yes
Enamel hypoplasia [score number (4)][b]	no	no	yes	yes
Slight gross periosteal hyperostosis	no	yes	yes	yes
Moderate gross periosteal hyperostosis	no	no	yes	yes
Significant incidence of lameness	no	no	no	yes
Decreased milk production	no	no	no	yes
Skeletal F equivalent to 5000 ppm at 5 yr[c]	no	no	no	yes
Urine F of 25 ppm[d]	no	no	yes	yes

[a]Based on data summarized in Table 2. The statements "yes" or "no" indicate if the symptom would be reproducibly seen at this level.
[b]Only if fluoride is present during formative period of the tooth.
[c]Metacarpal or metatarsal bone, dry, fat-free basis.
[d]Based on values taken after 2–3 yr of exposure; specific gravity = 1.04.

represents the first category in which a definite increased rate of incisor and molar attrition is to be expected. Teeth classified (2) have been shown to have a normal rate of wear, whereas those classified (4) or (5) may abrade rapidly. The concentration of fluoride in the diet that produced a class (4) tooth varied somewhat from one experiment to another, but has tended to average 34–49 ppm F.

At a constant level of excessive fluoride intake, the fourth incisors (or canines) are usually more severely affected than are the other incisors. The chronology of dental development is such that dental fluorosis of these teeth is not associated with an increased rate of molar attrition if they are the only incisor teeth affected.

At ingestion levels much below those required to induce a class (4) tooth, a trained observer can detect fluoride-induced changes in dentition. These animals also have an increased fluoride content in urine, skeletal tissue, and slight but insignificant increases in some soft tissues. Histologic changes in bone and tooth structure also may appear at low levels (20–30 ppm F).

When these considerations are taken into account, it appears that the fluoride concentration of the diet of young cattle being raised for milk production or as replacements for beef herds should not exceed 40 ppm F. Available experimental data also indicate that beef or dairy cattle first exposed to elevated fluoride intakes at 3–4 yr of age can be fed as much as 50 ppm F in their diet without influencing performance.

FINISHING CATTLE

There is little need for concern about dental lesions in the case of beef heifers or steers being fed for slaughter. These animals will not be held for a sufficient time for this effect to become serious. The overriding concern therefore appears to be feed intake. Studies by Hobbs *et al.* (1954) and Hobbs and Merriman (1962) have shown that fluoride must be present in excess of 100 ppm F in the diet of beef heifers before their feed intake decreased. Harris *et al.* (1964) have also shown that growing dairy heifers consuming 109 ppm F in the diet had normal dry-matter intakes at 1½ and 2½ yr of age, but that intake decreased at 4½ yr. It is suggested that 100 ppm F can be tolerated in the diet of cattle being finished for slaughter.

BREEDING SHEEP

Although most of the extensive experimental work on fluoride effects has involved cattle, other species have been studied; in general, the symptoms of the disease are similar (Shupe *et al.*, 1972).

The fluoride tolerance of ewes maintained for lamb or wool production is higher than that of cattle. Hobbs *et al.* (1954) fed yearling lambs, for a period of 3 yr, a basal diet containing 6 ppm F to which 25, 50, or 100 ppm F were added as NaF. They found no difference in feed consumption, weight gain, or reproduction under those conditions. Extensive studies on the effect of waterborne fluoride have been carried out by Peirce (1952). Yearling lambs were raised for 3½ yr with rainwater, or rainwater plus 2.5, 5.0, 10, or 20 ppm F added as NaF, as their sole water source. From data on feed consumption (Peirce, 1952) and comparisons with other studies by Peirce (1938, 1954, 1959), it can be calculated that 20 ppm F in the water furnished about the same amount of fluoride as would have been consumed in a diet containing 70–75 ppm F. There was no effect on general health, feed consumption, or wool production at this level of intake. These animals had a lower body weight at 2½ yr, but not at the termination of the experiment. Pronounced mottling was seen on incisors that were formed when the animals were drinking water containing 10–20 ppm F, but seriously uneven molar wear was seen only in the 20-ppm F group. It was later shown (Peirce, 1954) that mature ewes could tolerate 10 or 20 ppm F in their drinking water for 26 mon with no adverse effect. In a later experiment (Peirce, 1959),

lambs were exposed, from birth to 7 yr of age, to water containing 10 or 20 ppm F. The animals were pastured in an arid desert region and the consumption of water (and therefore fluoride intake) varied five- to tenfold from summer to winter. Neither treatment influenced reproduction, but there was some decrease in wool production accompanied by the appearance of characteristic dental lesions in both groups. Because of the variable nature of the exposure in this experiment, it is almost impossible to relate these fluoride intakes directly to a particular concentration of fluoride in the diet. In a separate experiment, Peirce (1938) fed yearling sheep a calcium–phosphate supplement containing F equivalent to about 45, 90, and 120 ppm in the diet for 3.5 yr. The sheep receiving the lower two levels grew normally, consumed feed at normal levels, and were in good health throughout the experiment. They had only minor skeletal lesions and, although they had some incisor lesions, molar wear was not excessive. At the highest intake, there was a decrease in feed consumption and body weight after 1 yr in the experiment, and bones, incisors, and molars were severely affected. None of the fluoride intakes influenced wool production.

These studies indicate that sheep being raised for lamb or wool production can tolerate 60 ppm F as a soluble fluoride in their diet.

FINISHING LAMBS

The addition of fluorine as sodium fluoride at the rate of 100 ppm in the diet had no deleterious effects on feed consumption, weight gain, or wool production of lambs over periods of 12–20 weeks and did not bring about any clinical signs or any histological changes in their organs (Hobbs *et al.*, 1954; Harris *et al.*, 1963). A level of 200 ppm in the diet, however, resulted in reduced feed consumption and decreased weight gain. In another experiment, Harris *et al.* (1958) fed sheep a basal diet containing 14 ppm F, and levels of 20, 40, 80, and 160 ppm F, for 14 weeks. The fluoride levels fed did not produce a significant difference in feed consumption, rate of gain, market grade, dressing percentage, or carcass grade. Wool weights of animals from all fluoride treatment groups averaged heavier than did the basal groups. Wool staple length, fiber length, and fiber diameter were not significantly affected by dietary fluoride levels. These studies indicate that finishing lambs can be fed levels up to 150 ppm F in their diet.

HORSES

No carefully controlled studies have been conducted to determine the effects of excessive fluoride ingestion on horses. Several workers have noted that affected horses are found in the same geographic areas in which cattle have been injured by industrial effluents. Shupe and Olson (1971) have described some of the effects of such ingestion and have provided photographs of the dental and skeletal lesions. Analysis of pastures in these areas (Shupe, 1972a,b) suggests that 60 ppm F is the tolerance level for this species. Although evidence is not available, it is felt that thoroughbreds, quarter horses, and other breeds being trained and developed for racing at an early age, during the period of rapid bone growth, may have a lower tolerance for fluoride in the diet.

SWINE

In an extensive series of experiments, Kick *et al.* (1935) demonstrated that finishing pigs that were fed more than 290 ppm F (as either NaF or rock phosphate) showed depressed growth in some experiments, whereas levels of fluoride in excess of this consistently caused decreased weight gains and distinct skeletal lesions. Fargo *et al.* (1938) reported that 140 ppm F in the diet (as rock phosphate) had no effect on weight gain in feeder pigs, whereas a variable effect was noted at 217 and 293 ppm F. Comar *et al.* (1953) found no effect on weight gain when 200 ppm F (as NaF) was added to the diet, and Gobble *et al.* (1956) fed as much as 550 ppm F, as soft phosphate with colloidal clay, with no effect on weight gain. Kick *et al.* (1935) have also studied the long-term effects of fluoride on breeder sows and have observed no effect on reproduction when up to 650 ppm F (as rock phosphate) was added to the diet. However, feed consumption and, subsequently, lactation were influenced adversely when the diet contained more than 290 ppm F. Spencer *et al.* (1971) have raised young pigs through three lactations and found that 1 mg F/kg of body weight had no influence on growth, feed intake, or reproduction. This level provided 40–90 ppm F in the diet, depending on the period of the study. Although there are few studies where different levels of fluoride were fed in the same experiment, the available data indicate tht both finishing pigs and breeding sows can tolerate at least 150 ppm F in their diet.

CHICKENS

Interpretation of much of the data on the fluoride tolerance of poultry is complicated by the fact that phosphate content as well as fluoride level varied in many of the experimental diets. Because birds have no teeth, which are important diagnostic aids in other species, diagnosis and evaluation of fluoride toxicosis in poultry is more difficult. Kick *et al.* (1933) found that the growth rate of day-old chicks was unaffected by 360 ppm F in the ration, and Gerry *et al.* (1947) noted no effect on chick growth of a diet containing 318 ppm F (as rock phosphate) but a slight depression in growth was noted at about 400 ppm F. They later reported (Gerry *et al.*, 1949) that a diet containing 330 ppm F as rock phosphate was safe for both growing chicks and layer hens. Snook (1958) found that neither egg production nor hatchability was impaired by a diet containing 530 ppm F as rock phosphate. Smith *et al.* (1970) found no effect on the properties of eggshells when up to 87 ppm F was added to the diet of hens. Halpin and Lamb (1932) also found 350 ppm F (as rock phosphate) to be without effect on the growth of young chicks and that egg production was unimpaired by 350 or 700 ppm F. Growth depressions resulting from NaF in the diet have been noted at 410 ppm F (Phillips *et al.*, 1935), 500 ppm F (Weber *et al.*, 1969), 800 ppm F (Gardiner *et al.*, 1959, 1968), and at 600 or 900 ppm F by Suttie *et al.* (1964). In these same experiments, 300, 320, and 600 ppm F has been fed with no depression in growth rate. Gardiner *et al.* (1968) have concluded that about half of the decreased growth rate caused by 800 ppm F was due to a decrease in feed intake and that the remainder resulted from a lower efficiency of energy utilization.

These data suggest that growing chicks can tolerate 300 ppm F in their diet and that laying hens can tolerate 400 ppm F.

TURKEYS

Anderson *et al.* (1955) have studied the effect of the addition of NaF to the diet of 10-week-old turkeys. The levels of fluorine as NaF in the dry diet were 43, 100, 200, 400, 800, and 1,600 ppm F. They were fed for the usual length of time necessary to produce market turkeys.

Feed consumption was normal at 400 ppm F, slightly decreased at 800 ppm F, and severely curtailed at 1,600 ppm F. The growth rate

of the female birds was slightly depressed at 800 ppm F, with a significant depression at the 1,600-ppm F level. In the case of the male birds, there was a slight, but statistically significant, decrease in growth rate at the 200- and 400-ppm F level and a marked effect at 800 and 1,600 ppm F. In view of this, it is suggested that the tolerance level be 400 ppm F until additional data are obtained.

DOGS

Although dogs have often been used in the study of pharmacological responses to fluoride, there are few data available to establish a tolerance level for this species. Greenwood *et al.* (1946) fed 5 mg F/kg of body weight to young dogs in the form of sodium fluoride, bone meal, or rock phosphate. This amounted to about 50 ppm F in the diet and had no effect on growth. Bunce *et al.* (1962) found that 250 ppm F as sodium fluoride adversely influenced the growth rate of dogs, and Chiemchaisri and Phillips (1963) noted a slight growth depression at 200 ppm F. However, Pyke (1965) found no effect of 200 ppm F as sodium fluoride on the growth rate of magnesium-sufficient pups. On the basis of available data, there is no doubt that young pups can tolerate 100 ppm F with no adverse effect on growth. Data are inadequate to determine if the dental effects caused by this level of ingestion have an adverse effect on mature dogs.

FISH

The fluoridation of domestic water, as well as the fluoridation of the aquatic environment from natural sources, has stimulated interest in the effect of fluoride on fish. Potable waters in the United States have been reported to contain 0–16.0 ppm F (Bell and Ludwig, 1970) while Neuhold and Sigler (1960) indicate that hot springs and geysers of Yellowstone National Park may contain from 25 to 50 ppm F. In research by Ellis *et al.* (1948), fish eggs subjected to 1.5 ppm F were delayed 7–10 days in hatching time, compared with eggs exposed to water containing no fluoride. Further studies by Neuhold and Sigler (1960) indicated that at levels of 100, 200, and 300 ppm F, there was a linear decrease in hatching time. The sensitivity of growing fish to fluoride was dependent on several factors that included size and species of fish, temperature of medium, and calcium and chloride concentrations in the medium. Because research is limited and be-

cause so many factors influence fluoride toxicity to fish, no fluoride tolerances are set forth in this report.

HONEY BEES

Literature bearing on the toxicity of fluoride to honey bees has been reviewed by Lillie (1970). Pesticides, rather than industrial emissions, are primarily responsible for fluoride poisoning of honey bees. Pesticides characteristically produce acute intoxication and high mortality of bees within a few days. Destruction of bees by industrial emissions may occur slowly over the entire season during which the bees are feeding from flowers on which fluoride deposits have accumulated. In research cited by Lillie (1970) a fluoride content of more than 1 μg F per bee was indicative of fluoride pollution. In another study, normal and poisoned bees contained 7.39 and 23 to 47 μg F per bee,

TABLE 4 Dietary Fluoride Tolerances for Domestic Animals[a]

Animal	Performance[b] (ppm F)	Pathology[c] (ppm F)
Beef or dairy heifers	40	30
Mature beef or dairy cattle[d]	50	40
Finishing cattle	100	NA[e]
Feeder lambs	150	ID[f]
Breeding ewes	60	ID
Horses	60	40
Finishing pigs	150	NA
Breeding sows	150	100
Growing or broiler chickens	300	ID
Laying or breeding hens	400	ID
Turkeys[g]	400	ID
Growing dogs	100	50

[a]The values are presented as ppm F in dietary dry matter and assume the ingestion of a soluble fluoride, such as NaF. When the fluoride in the ration is present as some form of defluorinated rock phosphate, these tolerances may be increased by 50 percent.
[b]Levels that, on the basis of published data for that species, could be fed without clinical interference with normal performance.
[c]At this level of fluoride intake pathologic changes occur. The effects of these changes on performance are not fully known.
[d]Cattle first exposed to this level at 3 yr of age or older.
[e]NA = not applicable.
[f]ID = insufficient data.
[g]This level has been shown to be safe for growing turkey females. Very limited data suggest that the tolerance for growing male turkeys may be lower. (See p. 53.)

respectively. It is not possible to relate these levels to a toxic ambient air level.

COMPARATIVE TOLERANCES

On the basis of the data considered above, suggested tolerances for fluoride ingestion by domestic animals are shown in Table 4. These values assume continual ingestion of fluoride by the animals. They take into account the economic usefulness of the various classes of livestock and poultry and are meant to assure that this role is not impaired. In addition, levels of fluoride above which pathologic changes occur are presented where sufficient data are available. The suggested tolerances are for fluoride in the form of sodium fluoride or other soluble fluorides. There are insufficient data available in most cases to determine an accurate tolerance based on the fluoride that is present in various phosphate supplements. In some cases, fluoride as sodium fluoride has been shown to be nearly twice as toxic as that in rock phosphate because the former is more readily absorbed. It seems reasonable to assume that when all of the fluoride in the diet is derived from phosphate, a given tolerance might be increased by 50 percent. These suggested tolerances differ somewhat from, but are in the same range as, those that have been established by the Association of American Feed Control Officials (1973).

Research Needs

IT IS EVIDENT FROM THE MATERIAL REVIEWED IN this report that there are important gaps in information concerning the effects on animals of prolonged intakes of moderate and high dietary fluoride.

More precise information is needed on the relationship of such factors as lesions, pathogenesis, age, nutrition, and stress to the response of certain animal species to various levels of fluoride intake. For some species, information upon which tolerance levels for fluoride can be established is inadequate. This information is very limited for fish, pets, horses, turkeys, and wild animals.

The effect of management practices on the ability of animals to tolerate moderate or high levels of fluoride has not been sufficiently investigated. Clinical and epidemiological observations tend to show that good management and nutrition enable animals to tolerate levels of fluoride intake that under other circumstances might be harmful, but this has not yet been fully established. Although some experimental evidence shows that certain mineral compounds reduce the toxic effects of excessive fluoride, these measures have not yet been successfully applied in the field.

It is not known how much of the reduced feed intake resulting from high levels of fluoride intake is due to metabolic or systemic effects and how much is due to dental abrasion. This information is needed. There is a definite need to establish upper levels of fluoride tolerance for animals under a variety of environmental and physiological conditions. Unquestionably, this will require definitive studies to elucidate further the effect of fluoride on production, reproduc-

tion, lactation, and growth, wherever these physiological processes are matters for concern. Considerable variation in fluoride tolerance exists between poultry and most other species of livestock. A study of the metabolic basis for this variation could lead to new means for alleviating fluoride toxicosis.

Experimental evidence has not shown any deleterious effect on human health from the consumption of edible products from animals that have ingested high levels of fluoride. Only rarely has fluoride toxicosis occurred when livestock have consumed high-fluoride animal by-product feeds. There may be differences in biological availability of fluoride in various food products and these should be investigated.

The tolerance levels suggested in this report are based on the toxicity of soluble fluoride, such as sodium fluoride. Although much of the early literature dealt with the effect of fluoride in rock phosphate, almost all of the more recent studies utilized sodium fluoride. Critical comparisons of the relative toxicity of these two forms of fluoride are therefore difficult to make. The tolerance of animals to more insoluble forms of fluoride, assumed in this report, should therefore be considered as approximations based on the limited data available.

Additional studies on the uptake and concentration of fluoride in fish and fish products are desired. Certain animal by-products are frequently used as feed ingredients, especially for poultry and swine. The possible impact of recycling animal by-products containing fluoride needs further investigation.

Although there is considerable information on the tolerance of livestock to fluoride in feed, there is a paucity of experimental information on tolerance of some domestic animals to waterborne fluoride. Because of seasonal and physiological variation in water requirements of animals, large variations occur in water consumption and may influence expressions of fluoride toxicosis. More research is needed on ingested excessive waterborne fluorides.

Fluoride is bound tightly within the crystalline structure of bone. More research is needed to determine if there is an adverse effect of fluorides on specific processes in animals where mobilization of calcium and (or) phosphorus is an important factor. Further information is needed on the relationship of fluoride intake to other metabolic processes in livestock and poultry.

Almost all of the published information on fluoride toxicosis has been based on the consumption of a constant concentration of fluoride in the diet over an extended period. The exposure of animals to

fluoride in the field is very often intermittent, under various types of management and climatic conditions, and information on the effects of this type of exposure to animals is needed. Interaction of fluorides with other elements and nutrients should also be investigated.

Summary

ANIMALS ARE EXPOSED TO VARIOUS FORMS AND amounts of fluoride from ingested vegetation, water, feed supplements, and the atmosphere. Inhalation contributes only a negligible amount to the total fluoride intake. With the expansion of certain types of industrial operations that emit appreciable amounts of fluoride in the vicinity of livestock, fluoride toxicosis in animals has become an important problem. Vegetation with high-fluoride contamination is the major source of excessive fluoride in the diets of animals.

Animals normally ingest low levels of fluoride without adverse effects. Fluorides in small amounts may be beneficial and may even be essential in some species. When excessive amounts are assimilated, adverse effects are induced.

Ingestion of excessive fluoride by animals induces certain characteristic lesions. Developing teeth are very sensitive to fluoride, and dental fluorosis is one of the more obvious symptoms of excessive fluoride ingestion. Excessive fluoride ingestion can also induce bone lesions, intermittent lameness, and reduced feed intake, leading to decreased weight gain and diminished milk production. The amount of fluoride in bones, urine, and to some extent blood, can be used as a measure of the level of fluoride ingested by animals.

Many symptoms and lesions of fluoride toxicosis in animals have been characterized. The lesions observed in livestock and various species of wildlife are similar. The available evidence indicates that dairy cattle are the most sensitive of domestic animals. It has been concluded that the level of fluoride ingestion that is safe for dairy cattle will also be safe for other species of livestock.

Controlled experiments have indicated that long-term ingestion of fluoride in concentrations greater than 40 ppm F in the diet of dairy

cattle is needed before there is a significant incidence of severe dental fluorosis, severe osteofluorosis, intermittent lameness, or any appreciable deleterious effect on feed intake, growth, and milk production. Developing teeth and bone are sensitive to short-term ingestion of excessive fluoride, and for this reason there can be no assurance that limiting the fluoride intake to a specific yearly average will fully protect animals from severe dental fluorosis, osteofluorosis, and secondary adverse effects. Therefore, if adequate protection is to be ensured, limits must be placed on the length of time during which high fluoride levels can be tolerated.

On the basis of experimental data, fluoride tolerances (Table 4) for various species of animals and a dental classification chart (p. 23) as an aid in diagnosing fluoride toxicosis in animals have been compiled. Prevention and control of fluoride toxicosis in animals can be achieved when the nature of the disease is recognized; when the pathogenesis, symptomatology, and lesions are properly diagnosed, interpreted, and evaluated; and when the source of excessive fluorides is eliminated.

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