The initial report concerning the structural changes in the teeth of experimental animals following sodium fluoride ingestion (0.2-0.02%) was made by McCollum (1925). The rats developed overgrown upper incisor teeth without characteristic pigmentation. Chaneles (1929) observed changes in the structure and arrangement of the enamel-forming cells in the teeth of rats fed fluorides. Similar incisor teeth were observed in animals fed rock phosphate (Tolle & Maynard, 1928), cryolite (Smyth & Smyth, 1932), and sodium fluoride and calcium fluoride (Arkansas Agricultural Experiment Station, 1926). McClure & Mitchell (1931) could not produce similar changes in the teeth of swine following sodium fluoride injection (1.03% and 0.06%).

Experimental fluorosis in the white rat was also demonstrated by Smith, Lantz & Smith (1931). The teeth of rats given sodium fluoride (0.02%, 0.05% and 0.1%) either in drinking water or in food showed mottling of enamel after a one-month experimental period. The investigators concluded that sodium fluoride would influence the developing tooth structure irrespective of the mode of administration. Velu (1931) confirmed these findings by feeding calcium fluoride and rock phosphate containing about 3-4% fluorine to white rats. Bethke et al. (1933) demonstrated hypoplasia of tooth enamel in rats receiving fluorine in the diet.

Sebrell et al. (1933) observed changes in the teeth of rats given concentrated drinking water (following evaporation) from an endemic mottled-enamel area. The incisor teeth lost their normal orange colour and appeared white. Distilled water containing 150 ppm sodium fluoride when given to rats as drinking water induced similar alterations in incisor teeth. However, when the concentration of sodium fluoride in such synthetic drinking water was increased to 500 ppm, the water proved to be exceedingly toxic and only a few animals survived. The teeth of these animals were chalky white and brittle. Dean et al. (1934) demonstrated minute striations on the incisor teeth of rats receiving 25 ppm sodium fluoride in drinking water daily for 23 days. The severity of alterations in the teeth of experimental animals was proportional to the concentration of fluoride in the drinking water received by the animals (25 ppm, 50 ppm, 150 ppm, 300 ppm, 500 ppm). The initial appearance of minute striations was followed by the formation of irregular brown patches and, finally, the enamel became white and brittle. Schour & Smith (1934, 1935), and Schour (1934) reported that developing enamel and enamel-forming cells were the first to respond to intraperitoneal injections of sodium fluoride. The disturbances of the ameloblastic layer were reflected in the newly formed enamel matrix, which was poorly mineralized, while the rate of apposition was not affected (Schour & Poncher, 1937). The same workers observed that the cumulative action of fluorine produced a further toxic effect on the ameloblasts, and a disturbance of both appositional growth and mineralization of the enamel matrix. This resulted in hypoplastic defects of enamel.
Histochemical and microradiographic aspects of the influence of various concentrations of sodium fluoride on the developing teeth of rats were investigated by Bhussry (1959b, 1960). Five groups of ten animals, 3-10 days of age, were given intraperitoneal injections of 10, 25, 45, 70 and 90 µg of sodium fluoride daily for up to 20 days. Only two animals in the 90-µg group survived. All experimental animals demonstrated abnormalities of amelogenesis, the degree of severity depending upon the amount of fluoride received. There was a wide zone of pre-enamel matrix, suggesting a delay in homogenization of the Tomes processes of ameloblasts. The apposition and mineralization of enamel matrix was retarded and calcification disturbances were obvious (Fig. 2, I-IV). Large patches of uncalcified enamel matrix were evident and accentuated incremental lines in enamel were occasionally present. There was a distinct reduction in the mucopolysaccharides and glycoprotein-staining components of enamel matrix.

Parikh (1960, 1961) and Weber & Yaeger (1964), using microradiographic techniques, investigated the calcification pattern in the developing teeth of newborn animals receiving toxic doses of sodium fluoride. They reported a disorganization of the ameloblastic layer and the presence of large radiolucent areas in the enamel microradiographs indicating a disturbance in the pattern of enamel mineralization. Allan (1963) observed narrow hypermineralized striae of Retzius preceded by a hypomineralized zone in the forming enamel matrix of 3-day-old pups injected with 2% sodium fluoride in doses of 10 mg/kg to 50 mg/kg body-weight. However, when sodium fluoride was given to pups during the period of enamel mineralization, diffuse hypomineralization of the mature tissue was noted.

The possibility that fluorosis may bear a relationship to calcium metabolism has been suggested by various investigators (Hauck et al., 1933; Lantz & Smith, 1934).

The deposition of elevated levels of fluoride in rachitic animals has been observed by two investigators (Schultz, 1936; Kempf & Nelson, 1941). Morgareidge & Finn (1940) found that 300 ppm fluoride added to the drinking water of rats fed a rachitogenic diet reduced the severity of developing rickets by increasing the bone density.

Zipkin, Likins & McClure (1959) demonstrated an increase in the ash content of the femur and mandible of rachitic animals receiving fluoride. However, the fluoride content in the teeth was not altered by the rachitic condition of the animals. Cicardo et al. (1955) showed that daily administration of fluoride to rats resulted in an increased uptake of radiocalcium by long bones, while Comar et al. (1953) prepared autoradiographs of femurs from pigs following fluoride administration (1000 ppm in diet). He observed the removal of 40Ca originally deposited in the epiphyseal region—an observation suggesting that fluoride intake caused an increased rate of bone resorption in the primary spongiosa. Likins et al. (1959) reported that the percentage of radiocalcium was significantly less in the tooth enamel.
of fluoride-treated rats, but could not find any difference in the deposition of radiocalcium in bone.

Information concerning the histological and histochemical aspects of the effect of fluoride on the developing teeth—and, specifically, on the enamel organ—of rats fed calcium-phosphorus deficient diets is sparse.

Irving (1943a, 1943b) and Irving & Neinbar (1946) demonstrated changes in the calcification of dentine in fluoride-treated animals receiving diets containing various amounts of calcium-phosphorus.

Bhussry (1960) observed that when pregnant rats fed a high-calcium, low-phosphorus diet (4:5:1; Steenbock rachitogenic diet) were given 100 μg of sodium fluoride in water subcutaneously, the developing teeth of their offspring, although not normal, showed an improvement in the quality and mineralization of enamel matrix in comparison with those which did not receive any fluoride. Disturbances in the ameloblastic layer and cells of the stratum intermedium during amelogenesis were not as severe. The enamel matrix demonstrated an unusual increase of mucopolysaccharide and glycoprotein-stained material in the organic matrix.

In the developing teeth of animals which received a vitamin-D supplement (100 IU of Viosterol in cottonseed oil) in addition to sodium fluoride (Bhussry, 1961), the ameloblastic layer demonstrated considerable improvement. The pattern and quality of enamel mineralization appeared similar to that in the teeth of normal control animals of the same age. The enamel matrix, at times, exhibited an accelerated process of maturation.

When pregnant rats fed a vitamin-D deficient diet normal in calcium-phosphorus ratio (chick basal diet) were given 100 μg of sodium fluoride in distilled water subcutaneously (Bhussry & Werth, 1962), the developing teeth of their offspring demonstrated minimal changes in the ameloblasts and the enamel matrix. When these animals received a vitamin-D supplement (100 IU of Viosterol in cottonseed oil), the enamel matrix was of normal texture and staining quality. It could not be distinguished from the enamel matrix of normal developing teeth. These studies suggest a relationship between fluoride intake and calcium-phosphorus ratio in the diet.

**Chemical Studies of Mottled Enamel**

Information regarding the chemical aspects of the organic material in the mottled enamel of teeth is limited. Bowes & Murray (1936) demonstrated a higher protein content in fluorosed enamel than in non-mottled enamel. This finding was confirmed by Bhussry (1959a), who reported a higher nitrogen content in mottled enamel than in sound enamel. He could not, however, detect any significant differences in density determinations (see Table 3).

Chemical analysis of the inorganic content by Armstrong & Brekhus (1937), Bowes & Murray (1936), Montelius & McIntosh (1933), Smith
TABLE 3
COMPARISON OF MOTTLED ENAMEL AND SOUND ENAMEL

<table>
<thead>
<tr>
<th></th>
<th>Density (g/cm³)</th>
<th>N₄ content (mg/g)</th>
<th>N₄ content (mg/cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of teeth</td>
<td>Mean ± SE a</td>
<td>No. of teeth</td>
</tr>
<tr>
<td>Mottled enamel</td>
<td>101</td>
<td>2.88 ± 0.02</td>
<td>105</td>
</tr>
<tr>
<td>Sound enamel</td>
<td>261</td>
<td>2.81 ± 0.02</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td>105</td>
<td>2.17 ± 0.15</td>
<td>243</td>
</tr>
</tbody>
</table>

*a The standard error is based on the within-group standard deviations (pooled estimate), which are: density, 0.29; nitrogen (mg/g), 0.57; nitrogen (mg/cm³), 1.34.

& Lantz (1932) and Ockerse (1943) did not show any significant difference (ash basis) in the calcium, phosphorus, magnesium and carbonate content of mottled and non-mottled teeth. This may partially explain the lack of differences in the density determinations of these teeth (Bhussry, 1959a). It should be mentioned that it has not been possible to find any further investigations dealing with the density and hardness of mottled enamel.

The fluoride concentration in human enamel at various levels of fluoride ingestion has been discussed by Weidmann and Weatherell in Chapter 4, section 3. The data from various investigations suggest that the concentration of fluoride in the surface enamel is linearly related to the fluoride level of the drinking water.

An observation of great theoretical interest is that although the outermost layer of shark’s teeth contains more than a hundred times the fluoride content of human mottled enamel, there are no signs of disturbance in its mineralization. Using biophysical and chemical methods, Glas (1962) demonstrated that the size and orientation of the apatite crystallites in the shark “enamel” and its degree of mineralization was the same as in human enamel. In contrast to the hydroxyapatite occurring in human enamel, the inorganic phase of shark’s “enamel” consists of an almost pure fluorapatite, which is formed during normal mineralization (Büttner, 1966). Unlike human enamel, which is of epithelial origin, the shark “enamel” develops from mesodermal tissues (Kvam, 1950) and has been referred to as “durodentin” and “petrodentin” (Schmidt & Keil, 1958; Lison, 1941). This suggests that the epithelial enamel organ of human teeth demonstrates specific sensitivity to fluorides.

Various investigators (Gedalia et al., 1959, 1961; Gardner et al., 1952; Ziegler, 1956) have reported that fluoride ingested during pregnancy is probably accumulated in the placental tissue. Ericsson and co-workers (Ericsson & Ullberg, 1958; Ericsson & Malmnäs, 1962; Ericsson & Hammarström, 1964) and Dustin (1963), however, demonstrated that the placenta permits a limited passage of fluoride to the foetal skeleton. Using ³¹F they observed accumulations of fluoride in foetal skeletal tissues during intra-
uterine calcification. Brezezinski, Bercovici & Gedalia (1960) found that when pregnant mothers received fluoride (0.55 ppm) in drinking water there was an increase in the fluoride content of foetal femora with advancing age. Gedalia et al. (1964) reported that although fluoride is incorporated in the calcifying foetal teeth, the accumulation is significantly less than that in the femora. Fleming & Greenfield (1954) conducted a histological study to observe changes in the teeth and jaws of mice following administration of very large doses of sodium and calcium fluoride (60-100 μg daily) to the female parent during gestation. Structural alteration of the ameloblastic layer resulted in the retardation of enamel matrix formation and its mineralization. Calcium fluoride seemed to be more toxic to the foetuses than sodium fluoride. It is obvious that there is a considerable lack of histological information regarding the influence of the mothers’ receiving fluoride during pregnancy on the developing teeth of offspring.

Discussion and Summary

Epidemiological studies have verified the association of water-borne fluorides at levels of 1 ppm with the production of significant immunity to dental caries. However, the influence of toxic levels of fluoride in drinking water on the structure of enamel organ during its formation result in the development of an endemic hypoplasia known as “mottled enamel”. Although there appears to be a relationship between the amount of fluoride ingested and the clinical manifestation of dental fluorosis, there are numerous factors which may cause wide individual variations.

The microscopic appearance of human mottled enamel depends upon the severity of the hypoplastic lesion. In mild and moderate dental fluorosis the enamel surface continuity is maintained, while in the severe variety it is broken due to pitting. The outer third of mottled enamel shows pigmentation and a decreased X-ray density suggesting hypocalcification. These areas are less soluble in acids, have a greater permeability to dyes and emit fluorescence of higher intensity than normal enamel.

Investigators using experimental animals have demonstrated that the influence of fluoride on teeth always appears to be identical, regardless of the mode of fluoride administration (in drinking water, in the diet or by injection). The gross changes in teeth include the appearance of minute striations followed by formation of irregular brown patches, and finally the enamel becomes brittle.

Microscopic observations of developing enamel indicate disturbances in the ameloblastic layer and a retardation in the apposition and mineralization of the enamel matrix produced by these cells. The role of reduced mucopolysaccharides and glycoprotein-staining components of enamel in calcification is not well understood. Histological and chemical evidence in
fluoride-treated animals fed diets with varying calcium-phosphorus ratios suggests the possibility that fluorosis may bear a relationship to calcium metabolism.

Although it has been established that fluoride ingested during pregnancy may pass through the placenta and be accumulated to a limited extent in the foetal skeleton and teeth, its effect on the teeth of offspring is not clear.

Chemical investigations of mottled enamel suggest an increase in the organic material, but no significant difference in the calcium-phosphorus ratio of mottled and non-mottled teeth.

It is obvious from the above studies that fluoride influences both the organic and the inorganic phase during development of the enamel organ. The possible mechanisms of action at physiological concentrations have been summarized by Jenkins (1962) as follows:

(a) ionic exchange with hydroxyl of the apatite in the calcified tissues;
(b) influence on the precipitation of mineral from saturated solutions of calcium phosphate;
(c) inhibition and, in some cases with low concentrations, activation of enzymes.

Although there is considerable evidence to support each of these aspects of fluoride action, none of them in itself is conclusive. It is possible that they are all interrelated, and further investigations will be necessary to explain the mechanism of formation of the hypoplastic lesions known as mottled enamel.

3. **CHRONIC TOXIC EFFECTS ON THE SKELETAL SYSTEM**

(A. Singh & S. S. Jolly)

The chronic toxic effects of fluoride on the skeletal system have been described from certain geographical regions of the world where drinking water contains excessive quantities of natural fluoride. This form of chronic intoxication was first described in India from the State of Madras as early as 1937 (Shortt et al., 1937). Subsequently cases of endemic fluorosis have been reported from other parts of India, particularly from Punjab (Singh et al., 1962a, 1962b, 1963), and sporadically from other parts of the world, notably Ceylon (Clark, 1942), China (Lyth, 1946), South Africa (Ockerse, 1942), Japan (Hamamoto et al., 1954), Saudi Arabia (El Tannir, 1959), the USA (Leone et al., 1954; Zipkin et al., 1958), Canada (Kilborn, Outerbridge & Lei, 1950), and Europe (Odenthal & Wienke, 1959). Besides endemic fluorosis, chronic toxic effects of fluoride on the

* The authors wish to thank Dr. M. Singh, Dr. O. C. Mathur, Dr. K. C. Malhotra, and other members of the staff of the Patiala Medical College who helped in the preparation of this section.
The skeletal system have also been observed in relation to industrial exposure to fluorides such as cryolite, and in fact it is the pioneer studies of Roholm (1937) that have paved the way for further contributions on this subject.

The precise dose of ingested or inhaled fluoride which results in well-recognized skeletal changes has not been fully evaluated. However, certain broad conclusions are possible at this stage. In fluoridation studies in adults which envisage a daily intake of 0.5-2 mg of fluoride, no evidence of storage, as defined in terms of abnormal density of bone, has ever been demonstrated.

At higher levels of ingestion—from 2 to 8 mg daily—when signs of fluorosis appear in teeth mineralized during the ingestion period, certain other factors (climatic conditions, malnutrition, age, storage, other constituents of water and, possibly, individual variations in absorption) may be involved. Under such conditions and over a number of years, skeletal fluorosis may arise, characterized by an increased density of bone and demonstrated in adults radiographically. The data put forward by McClure et al. (1945), although no longer regarded as accurate, indicate that the limit of total fluoride which may be ingested daily without hazardous body storage is of the order of 4-5 mg daily. In areas of endemic fluorosis, levels of ingestion of fluoride from diet and water over 8 mg daily are common, although in certain regions in India, changes typical of skeletal fluorosis have been stated to occur at estimated lower dosages (Singh et al., 1962b).

The bone changes and skeletal abnormalities in endemic fluorosis are not as marked as those in industrial fluorosis, although in hyperendemic areas the skeletal changes are almost identical to those seen in the heavy exposure of industrial fluorosis. The severity of the fluorosis indicated by the degree of mottling in the teeth is not proportionally reflected in the bone, which is natural considering the metabolic differences of these tissues and the different periods of development of enamel and bone fluorosis.

**Clinical Features**

The dental and skeletal changes in endemic fluorosis provide important clinical diagnostic criteria. Whereas dental fluorosis is easily recognized (Fig. 3), the skeletal involvement is not clinically obvious until the advanced stage of crippling fluorosis. However, radiological changes are discernible in the skeleton at a much earlier stage and provide the only means of diagnosing the early and relatively asymptomatic stage of fluorosis. Such early cases are usually in young adults whose only complaints are vague pains noted most frequently in the small joints of the hands and feet, in the knee joints and in the joints of the spine. These cases are frequent in the endemic areas and may be misdiagnosed as rheumatoid or osteo-
arthritis. In later stages, there is an obvious stiffness of the spine, with limitation of movements, and, still later, the development of kyphosis. There is difficulty in walking, due partly to stiffness and limitation of the movements of various joints and partly to the neurological lesions of advanced cases. Similarly, some of the patients complain of dyspnœa on exertion because of the rigidity of the thoracic cage. In Roholm's series of industrial fluorosis cases, the gastrointestinal symptoms of lack of appetite, nausea and constipation were as frequent as the symptoms of stiffness of joints, but the former have not been described in the different studies of endemic fluorosis.

The various skeletal changes in endemic fluorosis are best described under the following headings:

**Gross changes in the skeleton**

The gross changes in the skeleton in cases of endemic fluorosis are quite distinctive and characteristic. The excessive quantities of fluoride which are ingested are deposited in the skeleton over the years. Singh et al. (1962a) had a unique opportunity of studying a complete macerated skeleton of an individual who had lived in an endemic area where the water had a fluoride content of 9.5 ppm. All the bones were observed to be heavy and irregular and to have a dull colour due to irregular deposition of fluoride. The sites of muscular and tendinous insertions were rendered abnormally prominent by excessive periosteal reaction with development of multiple exostoses. Irregular bone was laid down along the attachment of muscles and tendons in the extremities as well as in joint capsules and interosseous membranes (Fig. 4 and 5). This irregularity is particularly helpful as a diagnostic feature in doubtful and borderline cases where the density of the bones is not markedly increased.

Maximum changes are detected in the spine with calcification of various ligaments, particularly the yellow, intertransverse and interspinous ligaments, resulting in marked osteophytes. The vertebral bodies are larger than normal and show marked lipping (Fig. 6, I). The vertebrae show altered proportions and measurements in all the planes, but the striking abnormality is the gross reduction of the anteroposterior diameter of the spinal canal. In one of our cases, this diameter was reduced to 2 mm at the level of third and fourth cervical vertebrae (Fig. 6, II). Since the average anteroposterior diameter of the spinal cord in the cervical enlargement is 8 mm and the bulge of the ligamentum flavum has also to be accounted for, it is evident that compression of the cord is almost inevitable. The vertebrae are also fused at many places—a fact which explains the marked limitation of movements and the resemblance of the disease to spondylitis ankylopoietica. The intervertebral foramina are narrowed and rendered irregular—a finding which explains the presence of radicular manifestations. A similar post-mortem
study of an advanced case who had a "poker back" was reported by Lyth (1946). There was fusion of all the vertebrae from the second cervical vertebra downwards with the ribs and bones of the pelvis. There was a fracture at the level of the eighth dorsal vertebra so that the lower dorsal vertebrae, lower ribs, lumbar vertebrae and pelvis came out in one piece and the upper ribs and vertebrae in another. The bones were held together by masses of new bone laid down in the joint capsule, ligaments and tendons. The long bones showed numerous spiky exostoses, especially along the attachment of muscles. The spinal canal was not more than 1.2 mm in diameter at the level of the second cervical vertebra.

In the skull the changes are not so conspicuous, although the bones are thick and heavy with no diploë. The floors of the cranial fossae are irregular and the clinoid process of the sella turcica is fused. The margins of the foramen magnum are also rendered irregular and narrow owing to the projection of osteophytes (Fig. 7). The smaller foramina in the skull are usually not altered, thus explaining the absence of cranial nerve involvement in advanced cases of endemic fluorosis.

The ribs are large, with rough surfaces and osteophytes projecting along the attachments of muscles, membranes and ligaments.

The other bones, including those of the limbs, the sternum and the mandible, have many prominent osteophytes at the attachments of ligaments, membranes, tendons and muscular insertions, thus making the various markings and ridges thick and prominent. The interosseous membranes between the tibia and fibula and between the radius and ulna are calcified in variable degree in most of the cases (Fig. 5, I).

There is thickening and calcification in most of the ligaments and in many of the capsular attachments such as the sacroiliac and sacrotuberous ligaments (Fig. 4, I). The thyroid cartilage is also calcified in most of the cases.

The irregular bone deposition is obvious clinically, in a large percentage of cases, as bony excrescences of varying size. These are usually seen near the knee joint along the anterior border of tibia and near the olecranon. The skeletal changes result in limitation of movements, particularly of the cervical spine, lumbodorsal spine, joints of the lower extremities and joints of the upper limbs, in that order.

Besides the gross structural changes described above, there is an appreciable increase in the weight of fluorotic bones. The total weight of the normal skeleton is variable. It was found to be 4957 g in Americans by Ingalls (1931). In Asians, Lawrence & Latimer (1957) found it to be 2882 g. In a case of fluorosis, the weight of the skeleton was 6190 g, as compared with 2520 g in a normal control of similar proportions (Singh et al., 1962a). The coefficient of weight to length showed that, in general, fluorotic bones were nearly twice the normal weight, but that the vertebral column, pelvis and scapulae were many times heavier.
Radiological changes

The radiological changes of skeletal fluorosis are diagnostic. Roholm (1937) distinguished three stages in the evolution of skeletal fluorosis.

Stage 1. The spinal column and the pelvis show roughening and blurring of the trabeculae.

Stage 2. The trabeculae merge together and the bone has a diffuse structureless appearance. The bone contours become uneven. These changes are most marked in the pelvis, spine and ribs. The medullary cavities may be narrowed and the ligaments show early calcification.

Stage 3. The bones appear as marble-white shadows, this appearance being most marked in the axial skeleton. The configuration is woolly. The bones of the extremities show irregular periosteal thickening with calcification of ligaments and muscular attachments. The cortex of long bones is thick and dense, and the medullary cavity is diminished. The interosseous membrane also shows calcification.

The radiological patterns of endemic fluorosis are almost identical to those of industrial intoxication described in cryolite workers, except that stage 1 is hardly ever seen in endemic fluorosis cases, most of which show the changes of stages 2 and 3. In general, the radiological appearance is as follows:

The most pronounced changes are seen in the vertebral column, particularly in the cervical and lumbar region. Osteosclerosis and irregular osteophyte formation is noted in the vertebral body, the transverse and spinous processes, and the pedicles and laminae. Beak-like lipping and the chalky white ground-glass appearance of the entire vertebral column are the characteristic radiological features. There is calcification of the intervertebral ligaments (Fig. 8 and 9). As a result of irregular exostoses, there is encroachment on the intervertebral foramina and the spinal canal (Fig. 10 and 11). Next to its spinal manifestations, osteosclerosis is most evident in the pelvis, along with calcification of the sacrotuberous and sacrospinous ligaments. Irregular periosteal bone formation is observed along the tendons and fascial and muscular attachments including the interosseous membranes of the forearm and legs, the linea aspera, the deltoid tuberosity, the lower margins of the ribs, the attachment of the Achilles tendon, the tibial tubercle, and the greater trochanter of the femur. Skiagrams of the chest reveal the peculiar contrast of a marble-white bony cage with radiolucent lungs (Fig. 12). The changes in the skull are not very striking, although there is thickening of the vault with sclerosis near the suture lines. The sella turcica and the nasal sinuses are normal and there is no significant narrowing of the basal foramina.
It must be emphasized here that the advanced radiological changes described above and reported from hyperendemic areas like Punjab (Singh et al., 1963) and Andhra Pradesh (Siddiqui, 1955) are not universally seen in the population as a whole. The development of skeletal fluorosis certainly depends on the length and level of exposure to natural fluoride in the water and soil, and possibly on particles suspended in the drinking water (cf. Chapter 2, section 3, and Chapter 4, section 3). It has been suggested that the advanced radiological changes seen in the endemic areas in India are due to malnutrition, although its exact role in the causation of skeletal fluorosis has not been finally elucidated. There is clinical and experimental evidence (Pandit et al., 1940) that malnutrition may predispose to the development of crippling fluorosis, because in other parts of the world where the level of fluoride in the water supply is almost the same the incidence of crippling fluorosis is so low (Leone et al., 1954). It has been alleged that the description of these advanced and bizarre radiological changes has created a bias in the interpretation of the physiological effects of fluoride. However, Leone et al. (op. cit.) also observed increased bone density, with or without condensed trabeculation with a ground-glass appearance, in 10-15% of persons exposed to a water supply containing 8 ppm fluoride. These observations did not bear any resemblance to the advanced findings described in cases of long exposure to cryolite or rock phosphate dust or to those attributed by Indian investigators to excessive fluoride in domestic water supplies.

Histopathology

Although there are many histopathological reports on experimental fluorosis (Weatherell & Weidmann, 1959), the data in human intoxication are scanty. Our observations are based on biopsy specimens obtained either from the tibia or iliac crest or from the spine at the time of laminectomy. In general, the compact bone shows disordered lamellar orientation and an enlarged, poorly formed Haversian system, resembling the changes described in experimental animals (Fig. 13). In the spongy bone, areas of osteoid tissue are found among well-formed trabeculae. Some of the irregular deposits of osteoid tissue extend into the attached muscle. The bone trabeculae are very dense in places and contain a considerable amount of calcium. The areas around the vascular spaces stain deeply with eosin. In some cases the muscular attachments to the bones may show areas of irregular calcification.

Among the effects of high fluoride ingestion may be the calcification of tendons, ligaments and, occasionally, muscles, as well as the stimulation of osteoblastic activity. Some bones are more prone to exostosis formation than others: the vertebrae, ribs and pelvis, for instance, are more susceptible than the long bones. In an advanced case, however, the entire skeleton is
involved. Such localized deposition of new bone, frequently found at the sites of muscle and tendon attachments, would seem to suggest that a significant factor in the development of the lesions is the rich blood supply of these sites. Exostosis formation is not always so restricted —sometimes the entire surface of a bone may be invested with new tissue resulting in an over-all increase in thickness. Blood supply is therefore not the sole factor governing the induction of fluorotic exostoses. The extensive production of new bone in the fluorotic skeleton is usually accompanied by increased bone resorption. It has been suggested that exostoses are formed in order to reinforce a weakened bone (Weinmann & Sicher, 1955). However, the few descriptions of chronic skeletal fluorosis in man suggest that there is a greater tendency towards the formation of new bone than towards the destruction of existing bone. Histologically, the exostoses consist of coarse, primary woven bone in which secondary lamellar replacement is minimal. The low degree of mineralization, as indicated by the calcium: nitrogen ratio of the bone, is partly due to a wide seam of uncalcified osteoid found in the fluorotic bones of both man and animals.

Skeletal fluorosis has been likened to a number of bone diseases: the dense radiographic picture of the skeleton has resulted in comparison with osteosclerosis; the presence of broad osteoid seams has suggested osteomalacia; the way in which bone formation may proceed side by side with bone destruction is reminiscent of Paget’s disease; and the often extensive resorption points to osteoporosis. Certainly, fluorotic bones can exhibit signs common to each of these conditions, but a unique distinction is the presence of high levels of fluoride in the bone.

Geever et al. (1958b) made autopsy studies of 99 bones from 37 persons who had resided 10 years or more in communities where the drinking water contained 1-4 ppm of naturally occurring or artificially added fluoride and 33 controls from areas where the drinking water contained less than 0.5 ppm fluoride. The microscopic examination showed no significant difference between the fluoride-exposed group and the control group. It is, therefore, possible to conclude that the histopathological changes of endemic fluorosis occur only at higher levels of intake than 1-4 ppm.

Chemical Composition of Fluorotic Bones

There are very few studies of the chemical composition of bones in human cases of chronic fluorine intoxication (Zipkin et al., 1958; Zipkin, McClure & Lee, 1960), although considerable literature is available on experimental animals. The skeleton is the most important site of deposition of fluoride in the body. McClure & Zipkin (1958) analysed the fluoride content of the bones of persons exposed to drinking water containing 0.1-4 ppm fluoride and concluded that the concentration of fluoride in the bones increased in an
essentially linear fashion and that, for a given level of fluoride in the drinking water, the iliac crest, ribs and vertebrae contained similar concentrations of fluoride. A recent study of the deposition of fluorides in bones which have also been examined histologically furnishes very valuable information regarding the levels of fluoride tolerated in bone without any harmful effects. McClure, McCann & Leone (1958), from a chemical analysis of the skeletal tissues of two women, have provided additional evidence regarding the threshold level of fluoride which may be tolerated by human skeletal tissues. As much as 0.5-0.6% fluoride in one of the subjects did not prove to be a physiological hazard. It must be concluded in the light of the available evidence that human skeletal tissues may have a very high degree of physiological tolerance to accumulation of fluoride. Roholm (1937) found 0.21-0.89% fluoride in the bones of two cryolite workers whose skeletal tissues showed evidence of increased calcification and trabeculation. The successful management by the body of this deposited fluoride is largely dependent upon the elimination of fluoride via the urinary tract. For this reason, study of the fluoride content of the urine in relation to the fluoride exposure may be of special value as a measure of the suspected health hazard attached to cumulative bone fluorosis. That all fluoride deposited in the skeleton is not fixed irreversibly is shown by its mobilization following a reduction in fluoride intake. Brun, Buckwald & Roholm (1941) reported that men who had absorbed fluoride from cryolite dust maintained a high level of fluoride in the urine for as long as 7 years following the period of exposure. Similarly, Largent & Heyroth (1949) and Largent (1961) found that urinary excretion of fluoride in excess of the intake continued at a progressively decreasing rate for as long as 2 years after the ingestion of large amounts of fluoride.

The deposition of fluoride in the bone takes place mainly by two mechanisms. In the first, fluoride exchanges with hydroxyl ion on the surface of existing crystals. In the second, new bone is formed by osteoblastic and osteoclastic activity. However, the precise mode by which the fluoride exerts its deleterious effects is not known. It is probable that there are initially changes in the chemical composition and deposition of bone salts in the organic matrix, possibly mediated by altered enzyme reactions. Roholm (1937) believed that the fluorides were probably deposited in the form of calcium fluoride along with calcium phosphate of the bone, but the work of Weidmann, Weatherell & Whitehead (1959) demonstrated a decrease of carbonate and an increase of magnesium in the exostotic bone—a finding which suggests replacement of Ca or HCO₃ groups in bone salts and a precipitation of MgF₂ upon or within the bone matrix. Zipkin and his associates (1958) studied fluoride deposition in human bones after prolonged ingestion of fluoride in drinking water, and came to the conclusion that the mean concentrations of fluoride in the various bones were proportional to the fluoride level of drinking water up to 4 ppm, and there is no indication in their data that these human calcified tissues approached their theoretical
capacity of about 3.5% fluoride. Concentrations of fluoride as high as 5480 ppm in dry, fat-free bone and 10 800 ppm in bone ash may be present without producing any apparent tissue damage. The fluoride content in our studies (Singh et al., 1963) ranged from 700 to 7000 ppm (dry weight) against a normal of 200-300 ppm in persons from a non-fluorotic area. Smith & Hodge (1959) pointed out that, in human beings, osteosclerosis would be evident in a small proportion of the individuals with skeletal concentrations of fluoride of the order of 6000 ppm.

Zipkin, McClure & Lee (1960) tried to establish a relation between the fluoride content and the chemical composition of human bone. They studied 69 samples of human bone (iliac crest, ribs and vertebrae) obtained from 23 individuals, 26-90 years of age, who had consumed drinking water containing up to 4 ppm fluoride for 10-87 years. The bones were analysed for calcium, phosphorus, magnesium, sodium, potassium, carbon dioxide and citrate. The percentages of calcium and phosphorus in the dry, fat-free bones were normal, although the bones contained as much as 0.4% fluoride.

Over a tenfold range in concentration, no relation was apparent between the fluoride present in bone ash and either the calcium or the phosphorus content. As the level of fluoride in the ash increased (0.08-0.8%), there was a slight increase in magnesium and a decrease in carbon dioxide. The citrate content decreased markedly with increased fluoride. These data support the hypothesis that fluoride is deposited in mature bone largely at the expense of surface-limited ions like sodium, potassium, magnesium, carbon dioxide and citrate, which are presumed to be confined to the surface of the apatite bone crystals.

As regards magnesium, the apparent increase which accompanies fluoride deposition may be explained by its affinity for fluoride. The observed reduction in citrate concomitant with the increase in fluoride suggests that citrate, which is assigned to positions on the crystal surface, may be replaced by fluoride through ion-exchange processes.

Deformities and Crippling Fluorosis

This advanced stage of fluoride intoxication results from the continuous exposure of an individual to 20-80 mg of fluoride ion daily over a period of 10-20 years. Such heavy exposure is associated with a level of at least 10 ppm in the drinking-water supply. In the areas surveyed by us (Singh et al., 1962b), this level was not only common but was often exceeded. Moreover, besides the fluoride ingested from the water, there were additional sources of ingestion such as vegetables grown in the fluorotic soil and food processed and cooked in the fluoride-rich water. Therefore, it is not surprising that cases of crippling fluorosis are seen in such numbers in endemic areas of Punjab and Southern India.
The crippling deformities are due partly to mechanical factors and partly to the immobilization necessitated by pain and paraplegia. The commonest deformities are kyphosis, flexion deformity of the hips, flexion deformity of the knees and fixation of the chest in the position of inspiration due to calcification of cartilages. The advanced picture of crippling fluorosis is strikingly uniform. The quadriplegic patient bent with kyphosis and with markedly restricted movements of his spine, with contractures of hips and knees, provides a grim picture of the result of excessive fluoride intake (Fig. 14). Owing to the extreme fixation of the spine, the body moves as a single unit with each attempt to straighten any portion of it.

**Neurological Complications of Fluorosis**

The neurological manifestations have been exclusively reported from India. Credit for the earliest description of neurological complications in fluorosis must be given to Shortt, Pandit & Raghavachari (1937), who reported ten such cases from the Nellore district of Madras. A few sporadic cases have also been described from other parts of India (Murthi, Narayana Rao & Venkateswarlu, 1953; Janardhanan & Venkaswamy, 1957; Chhuttani, Wahi & Singh, 1962), but the only authentic study is that of Siddiqui (1955). We have tried to define the neurological pattern of this disease and have designated it as a radiculomyelopathy (Singh & Jolly, 1961). Our interest in this problem was aroused by the fact that while investigating obscure cases of paraplegia in Punjab, we were struck by the osteosclerosis and osteophytosis of all the vertebrae shown on radiography (Jolly, Singh & Singh, 1961). Subsequently it was noticed that nearly all such cases were coming from a limited geographical area of the Punjab.

Such neurological complications occur only in very advanced cases where the ingestion of large quantities of fluorides has continued for at least 20 years. Thus only 42 of our 409 cases of skeletal fluorosis had neurological complications and the description of such complications is based on an analysis of these cases (Singh et al., 1963).

Despite the alarming radiological appearance, the changes in the spine do not produce many symptoms. Usually the only complaint is of vague pains in the back and in the extremities. The symptoms of the spinal-cord lesion tended to develop slowly and progress insidiously. In two cases, the onset was sudden and was related to trauma, which in normal circumstances would not have resulted in sequelae.

Symptoms may be due to a lesion of one or more nerve roots or to involvement of the spinal cord.

*Radicular features*

The most important manifestations were muscular wasting, acropaesthesiae, and pain referred along the nerve roots. Subjective com-
plaints such as acroparasthesiae and pain were almost universal, although such complaints were elicited only after specific questions about them. The most important feature was the weakness and wasting of muscles. This was usually asymmetrical, involving most often the small muscles of one or both hands. This localization was present in twelve cases and in two was the only finding. In the remaining ten it was associated with an extensive radiculomyelopathy. The mechanism is probably similar to that found in cervical spondylosis and due to compression of anterior roots by the lower parts of the foramina. Some muscular wasting may be the result of atrophy from disuse. The accompanying muscle fasciculations and fibrillation often led to a mistaken diagnosis of motor-neurone disease.

Myelopathic features

The earliest symptom of spinal-cord involvement observed in all cases was weakness of both lower limbs. This usually started in one leg, with later progression to the other. In 12 cases, after a variable interval, the upper limbs became involved, producing a spastic quadriplegia. Parasthesiae in one or more limbs were frequent. The pattern resembled in many ways that of spondylitic myelopathy. In general, the symptoms progress fairly rapidly with progressive deterioration and restriction of activity. The signs of fluorotic myelopathy result chiefly from narrowing of the spinal canal or intervertebral foramina, and compression may occur at a single site or at multiple sites. Muscular wasting was not a prominent manifestation in our cases, being noted in only 12 cases. It was usually confined to the muscles of the hand or forearm, being most conspicuous in the former. Fasciculation was observed in only two cases. The site of muscular wasting could not always be correlated with the site of compression. Although wasting of the hands was likely to be severe when the last cervical and first dorsal segments of the cord were compressed, it was at times equally severe with protrusion at a higher level, suggesting interference with the blood supply to the lower segments of the cervical enlargement. Muscle tone in the extremities was usually increased. This was due predominantly to upper motor neurone involvement, although the muscular and skeletal changes of fluorosis were often a contributing factor. In four advanced cases the spasticity was extreme: it was impossible to bend one limb individually and the whole of the skeleton consequently moved as one unit. This was partly explained by development of contractures around the knees and hips. The upper limbs were involved in 18 cases, while the disease was mainly confined to the lower limbs in 19.

Thirty-one of the 42 neurological patients had some type of sensory disturbance, although the sensory changes tended to be patchy. In 12 cases, sensory loss resembled that due to compression by a tumour, all modalities of sensation being affected below a sharp level, usually around the umbilicus.
Light touch was less involved than other sensations. The posterior column was more severely affected than the spinthalamic tracts. In the upper extremities, paraesthesiae and sensory disturbances were confined to a single dermatome distribution in nine cases, while in two others there was a "glove" distribution involving both hands.

The tendon reflexes were usually exaggerated in the lower extremities, although, in advanced cases, contractures of the knee made it difficult to elicit reflexes. The deep reflexes in the upper limbs were exaggerated in 15 cases and absent in three. An inverted supinator jerk was present in nine cases. The abdominal and plantar reflexes were usually compatible with a bilateral pyramidal lesion, the latter being extensor in 37 patients, equivocal in two, and flexor in three. Hesitancy or incontinence of micturition was noted in 22 patients. In advanced cases, paraplegia-in-flexion gradually ensued, with flexor spasms. The active and passive movements of the spine were restricted and painful, and a kyphotic deformity was present in ten patients.

Certain other neurological features, such as impairment of auditory nerve function (Siddiqui, 1955), headache and tetaniform convulsions (Waldbott, 1961), electroencephalographic disturbances (Waldbott, 1955), and meralgia paraesthetica (Chhuttani, Wahi & Singh, 1962) have been described but were not observed by us. It was difficult to enter the subarachnoid space by either the lumbar or the cisternal route, owing to calcification of the intervertebral disks and ligaments. Consequently the composition and dynamics of the cerebrospinal fluid could be studied in only 13 cases. In three, the proteins were increased to more than 200 mg/100 ml. Cerebrospinal fluid pressure was low, indicating a partial block in the subarachnoid space. Myelography was possible in only four cases: in one patient, the dye remained in the cisterna magna for three days; in the second there was delay in the transit of the dye in the cervical region; and in the other two there was a complete block at D8 and C3 respectively.

Thus, the clinical picture of fluorotic myelopathy may closely simulate that of cervical spondylitis, extramedullary and intramedullary tumours of the spinal cord, subacute combined degeneration of the cord, syringomyelia and motor-neurone disease. However, in view of the distinctive clinical pattern and the radiological findings, the diagnosis of fluorosis can be readily established.

4. CHRONIC TOXIC EFFECTS ON THE KIDNEYS
(H. C. Hodge & D. R. Taves)

While there appears to be no doubt that fluoridation is safe for persons with normal kidneys, the remote possibility that fluoride may aggravate intercurrent renal disease has not been conclusively ruled out. Renal fail-
ure should cause fluoride retention, leading to higher tissue fluoride concentrations and a smaller margin of safety than for normal individuals. In this section, the relevant information on the pathological and functional effects of toxic doses is reviewed and current work on the safety of the use of fluoridated water by patients suffering from renal failure is summarized.

Pathology

Fluoride-induced renal pathology, with the causative agent established beyond reasonable doubt, has never been reported from chronic exposures in man. The nearest to such a finding came from the gross and histological studies of tissues of ten former cryolite workers by Roholm (1937), who stated that "poisoning with cryolite produces considerable changes of bones and ligaments, but no changes—or at the most doubtful changes—of the organs". Roholm described the necropsies of two workers in detail: one, a man employed for 24 years in a cryolite factory, showed moderate chronic interstitial nephritis, thus raising some uncertainty as to a possible role of fluoride; the other had been employed for about 9 years.

In the first patient, the kidneys were normal in size. On microscopic examination, the glomeruli were well-preserved. A number of tubuli were dilated, "cystic" in places, and contained serous fluid. Such "a slight grade of chronic nephritis, preponderantly of interstitial type", is at least reminiscent of the pattern of renal pathology in chronically exposed animals.1

In the second patient, the kidneys, normal on gross examination, were, except for some stasis, also normal microscopically. The nephritis of the first worker, by no means proven to be a result of cryolite exposure, thus constitutes the only, and at best doubtful, human example of a chronic fluoride effect.

Autopsy examinations have undoubtedly been conducted on tissues of persons with more than minimal fluoride exposures. Few descriptions have been published, but three can be cited: (1) Neither incidental renal pathology nor renal disease as a cause of death (both recorded by autopsy examination) differed significantly with the duration of exposure to drinking water containing 2.5 ppm F (Geever et al., 1958a). (2) The post-mortem examination of men who had lived in an industrial area of Utah, where chronic fluoride intoxication had been observed in cattle and sheep and vegetation damage recognized, revealed no gross or histological effects in kidney tissues (Call et al., 1965). (3) No renal abnormalities ascribed to

1 After prolonged exposures, macroscopically, the animal kidneys were pale and small, with uneven surfaces. Microscopically, the lesion resembled interstitial nephritis (Bond & Murray, 1952; Taylor et al., 1961a). Varying degrees of degeneration of the tubular epithelium were found, along with evidence of regeneration and greatly increased amounts of fibrous tissue as exposure continued. Dilated tubules were often described at the cortico-medullary junction (Pinedborg, 1957) apparently involving the loops of Henle and the convoluted tubules. Glomerular changes were inconstant. Vascular degeneration was sometimes present. Such pathology has been described in several species—for example, rats, pigs, calves, dogs, guinea-pigs and rabbits.
fluoride were found at the autopsy examination of an elderly woman who for 34 years had consumed water containing 8 ppm F (Leone, Stinson & Sunbury, 1960).

**Acute Effects after a Large Single Dose**

The effects on the kidney of an overwhelming single dose of fluoride, an acute toxic nephritis, have been repeatedly observed in human patients fatally poisoned by accident or intent. The principal findings, which are quite different from the pattern of chronic kidney pathology, are (a) congestion and cloudy swelling of the renal tubular cells; (b) hyperaemia and fatty degeneration of the tubular epithelium; and (c) not limited to the kidney, widely distributed acute visceral hyperaemia. Experimental animals show entirely comparable effects. If the individual survives, regeneration occurs during recovery. Since the acute effects have no applicability in water fluoridation, they will not be discussed further.

**Dose Response**

No renal pathology ascribed to fluoride has been found in experimental animals maintained for protracted periods on diets or drinking water containing 50 ppm F or less. The borderline water concentration at which some individuals of certain species (but not all) exhibit changes is about 100 ppm (Hodge et al., 1964), which in the rat, for example, is roughly equivalent to a daily dose of 10 mg/kg. This dose is far greater (perhaps 10-30 times) than that received by Roholm's cases and held by Matler & Gudjonsson (1932) to cause crippling fluorosis. Only in one report, a study of rats maintained for periods of up to 520 days on drinking water containing 1, 5 and 10 ppm F, has kidney pathology ever been ascribed to fluoride in experimental animals consuming F levels comparable to those in human drinking water supplies (Ramseyer, Smith & McCay, 1957). However, a larger and more rigorous study from the same laboratory (Bosworth & McCay, 1962) failed to show any differences between the control and the treated animals, and identified the pathology as the renal pathology of old, diseased rats and not fluoride effects. The absence of progressive renal pathology in residents who had lived for a long time in a community where the water supply naturally contained 2.5 ppm F (Geever et al., 1958a) is consistent with the absence of renal changes in occupational exposures as well as with the considerable body of quantitative animal data.

**Functional Effects**

The responses of scores of acutely poisoned patients have been summarized in Table 3 of Roholm's monograph (*op. cit.*) and in Table 7 of Hodge & Smith (1965). Goldemberg, in 1930, gave the name of "diabète insipide
fluoride" to a syndrome comprising polyuria, thirst, nocturia and abnormally frequent micturition which developed in patients given intravenously 100 mg of sodium fluoride daily or every other day for 10 to 15 days; neither albuminuria nor glycosuria was detected (see Hodge & Smith, op. cit.).

Efforts to detect functional changes as a result of chronic fluoride exposures have been made in the cryolite industry, in endemic areas of fluorosis in India, and in communities with fluoridated water supplies in the USA. In the 68 cryolite workers examined by Roholm, only a few signs or symptoms referable to the kidney were found: (a) one woman complained of extraordinary thirst; (b) urinary albumin and sugar tests in most cases were normal; (c) signs of chronic nephritis were found in one man; and (d) one woman, a diabetic, had glycosuria. Time lost because of urinary and venereal diseases was minimal for the men but relatively high for the women.

In villagers of the Nalgonda district, not far from Hyderabad, Siddiqui (1955) discovered 32 advanced cases of skeletal fluorosis with neurological manifestations. The nutritional state of the people was deficient; most of the patients showed a mild degree of anaemia. Urea clearance was markedly depressed. In the somewhat similar study of ten hospitalized cases of advanced fluorosis in the Madras Presidency, Shortt et al. (1937) reported renal filtration rates below normal in six cases, but within normal limits or above in three. Urea clearance values were low, in some cases quite low. Kumar & Harper (1963) reported on a group of 19 patients in Aden whose skeletal radiographs revealed osteosclerosis and whose drinking water presumably contained excessive concentrations of F (one well, the water supply for 6 cases, showed "sodium fluoride to be present in 6 parts per million"). Albuminuria, present in 11 of 12 persons examined for it, is ascribed without supporting evidence to fluoride injury of the kidneys. These groups of patients had sustained many stresses—for example, varying degrees of malnutrition, hard work in a hot climate, and unknown intercurrent diseases. Fluoride cannot be held specifically responsible for the changes in kidney function.

A little evidence can be gathered from populations drinking fluoridated water in the USA. The children in the Newburgh-Kingston study excreted similar amounts of albumin and sugar whether the drinking water was fluoridated or not (Schlesinger, Overton & Chase, 1956). No greater incidence of albuminuria or glycosuria was found in populations whose drinking water contained 8 ppm than in residents of a nearby city where the water contained about 0.5 ppm (Leone et al., 1954). McClure found no differences in the urine samples of 101 young men who drank naturally fluoridated water (2.0-5.2 ppm) as compared with those of 394 young men who resided in low-fluoride areas (McClure, 1946).

Animals given sufficient fluoride, in single or repeated doses, excrete large volumes of dilute urine and are thirsty. The urine may or may not give positive tests for albumin, blood or casts; sugar is typically present;
chloride and nitrogen excretion are increased. Clearances of urea, creatinine and p-aminophosphoric acid (PAH) are reduced (see review by Taylor et al., 1961b). These effects reflect severe renal tubular injury in the presence of renal congestion. Caruso (1961) found in acute experiments on dogs that renal tubular transport, as measured by TmPAH and Tm glucose, was also decreased. Large single doses of fluoride in experimental animals promptly increased urine volume; urinary chloride and nitrogen excretions increased (reviewed by Taylor, 1959). Fluoride in large doses can be classed as a depressant of kidney function.

These results can be compared with those of the few studies of kidney function in experimental animals given known amounts of fluoride for protracted periods. Two of 12 rats maintained on drinking water containing 100 ppm for six months had renal lesions, showed polydipsia and polyuria (Taylor et al., 1961a). In a study lasting a little over seven years, Greenwood et al. (1964) and Mangelson (1963) observed the effects of various fluoride supplements on dairy cattle: inulin clearances were normal in cattle whose dry ration contained 93 ppm F. PAH clearances were reduced at 49 ppm but not at 27 ppm. In rabbits, dogs, and rats, doses of 5-10 mg/kg or more for periods of up to nearly a year produced reductions in urea clearance, albuminuria, polyuria, polydipsia, glycosuria, and urine of low specific gravity.

Urinary fluoride excretion is not markedly reduced in children with renal disease (Schlesinger, personal communication, 1957), in elderly patients with advanced kidney disease, or in rabbits with severe renal tubular injury from uranium poisoning (Smith, Gardner & Hodge, 1955). However, these studies do not rule out the possibility of elevations in serum fluoride and accompanying increases in tissue fluoride concentrations. If bone formation is occurring, the elevated serum levels should result in an increased bone fluoride concentration. If no bone is being laid down, on the other hand, the rise in fluoride concentration in serum and soft tissue may be more marked.

Evidence of the efficacy of the skeletal absorption has been provided by Largent (1961, p. 54): fluoride doses given to nephritic patients were stored in abnormally high percentages (75-82%). Nephrectomized animals deposited extra fluoride in their skeletons (Carlson, Singer & Armstrong, 1960). Linsman & McMurray (1943) state that their patient with renal impairment such that death ultimately occurred in uraemic coma, and who had a history of long resident in areas of endemic dental fluorosis, exhibited osteosclerosis, a condition developing only when bone fluoride concentrations exceed about 5000 ppm F (dry, fat-free basis). Call et al. (1965) discerned the end result of this skeletal mechanism, i.e., elevated bone F values in some but not all patients who were suffering from advanced chronic renal disease and whose environment had contributed extra fluoride.

In none of these studies have the serum fluoride concentrations been recorded. The only published data (Singer & Armstrong, 1960) indicated
no increase with renal failure, but more recent investigations, using new methods, revealed a 3-fold to 5-fold increase in the serum fluoride of patients with renal failure (Taves et al., 1968) and in partially nephrectomized rats (Taves & Morrison, unpublished data). The discrepancy is explained by identifying what each method measured: Singer & Armstrong first ashed the serum and then measured total fluoride, most of which has since been shown to be unavailable as fluoride ion prior to ashing. The newer methods, which measure only the fluoride ion, indicate that the fasting "normal" fluoride ion concentration in human serum is about 0.2-0.4 μmol (0.004-0.008 ppm) when the drinking water contains only traces of fluoride, and about 0.5-1 μmol (0.01-0.02 ppm) in a community with fluoridated water. Patients with renal failure occasionally exhibit serum fluoride ion concentrations as high as 5 μmol (0.1 ppm). The risk to health represented by such values cannot be definitively assessed as yet.

In two patients (one during haemodialysis, the other under fluoride therapy in a multiple myeloma study), serum F concentrations of 20-30 μmol (0.4-0.6 ppm) for 6-12 months were observed without obvious adverse effects. Growth was retarded in normal intact rats on high F rations when serum F concentrations reached 15 μmol (0.3 ppm); serious toxic effects developed at 50 μmol (1.0 ppm) (Taves, D.R., Raisz, L. & Yuile, C., unpublished data). There seems therefore to be at least a 3-fold to 5-fold margin of safety, other things being equal, for patients with renal failure.

**Fluoridated Water, Haemodialysis and Bone Disease**

Chronic haemodialysis, now widely employed, enables many patients with little or no kidney function to go on living for many years. It is of interest from the point of view of fluoridation because tap water is often used in the kidney machines, and it has been suggested that fluoride from this source contributes to the bone disease seen frequently in these patients.

During dialysis with fluoridated water, the patient takes up fluoride (10-20 mg per 6-14-hour dialysis) from the dialysis bath (Taves et al., 1968; Backer-Dirks, unpublished data). Such doses would present little or no toxic hazard for an adult with normal kidney function; some of the fluoride would be deposited in the skeleton and the rest rapidly excreted. The patient on haemodialysis, however, frequently has no renal function and poor bone formation; the critical determinant, therefore, is not dose but serum level. Severe osteodystrophy not yielding to therapy with calcium and vitamin D developed in most of a group of patients in the Ottawa General Hospital who underwent dialysis with fluoridated water. The

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1 The non-exchangeable serum fluoride is 3-5 μmol (0.06-0.1 ppm); available information indicates that the magnitude of this fraction does not change with the fluoride concentration of the drinking water (Singer & Armstrong, 1960; Taves, unpublished data).

2 Prolonged maintenance of serum F concentrations of 5-15 μmol (0.1-0.3 ppm) will probably produce osteoclerosis, which under certain circumstances may have a beneficial effect (Taves, 1969).
elevated serum F concentrations found in these patients—average 18 μmol (0.36 ppm)—suggested that fluoride was complicating or causing the bone disease. Patients in another locality, however, who received dialysed water with fluoridated water for a period of three years, did not develop severe osteodystrophy. A causal role for fluoride has not therefore been established. The reasons for the differences are under investigation; it may be that other elements present in the fluoridated water have important influences on bone health. It appears likely that the serum fluoride concentrations reflect the severity of the bone disease, but are not the cause. However, in the Ottawa patients, the elevated serum fluoride concentrations may have made the bone disease more difficult to treat once it had developed. Judgements should not be made prematurely, since the effects of fluoride on bone take years to manifest themselves. Those who for experimental or economic reasons continue to use fluoridated water for dialysis should watch both the bone status and serum fluoride concentrations of their patients.

5. TOXIC EFFECTS ON THE THYROID (V. Demole)

The question of the toxic effects of fluoride on the thyroid is indeed a problem, since formerly fluorides were used as antithyroid medication in Graves' disease (exophthalmic goitre), while nowadays it appears that the same fluorides, when absorbed continually, even in excessive doses, have no harmful effect on the thyroid!

We shall briefly review the literature on this problem. The volume of published work in this field is considerable, so that a selection must be made from the various publications.

1. In the first place, we shall survey clinical experience in regard to the treatment of Graves' disease with fluoride—a form of therapy which led to an erroneous generalization.

2. Secondly, we shall enumerate the main investigations of a possible iodine-fluorine antagonism that have been carried out on animals and man.

3. We shall then review the results of demographic surveys, mainly American, undertaken with a view to determining the alleged goitrogenic effect of water containing fluoride.

4. Finally, we shall mention certain investigations in Switzerland, not because of their extent but because they were carried out in a limited area where endemic goitre was prevalent before it was eradicated by the prophylactic use of iodides.

**Treatment of Graves' Disease**

Among the antithyroid drugs used in the first half of this century, mention must be made particularly of iodine, the oldest antithyroid drug,
which even today occupies the first place in pre-operative preparation to promote involution of the gland, storage of colloid and fall of basal metabolic rate (BMR); while, on the other hand, it is essential to prevent goitre. "The explanation of this paradox is still being sought" (Goodman & Gilman, 1965; Rawson, 1949).

Fluorine has also been used in the treatment of Graves' disease. Prolonged administration of sodium fluoride, 50-100 mg daily, may cause clinical improvement and reduction of the BMR, but the therapeutic action is weak, inconstant and transitory, and some hazard may be involved. Therefore, this medication has been abandoned.

Recent studies with radioactive iodine and fluorine confirm the reduction of BMR effected by prolonged administration (for several months) of a daily dose of 5-10 mg of fluorine to patients afflicted with Graves' disease (Galletti & Joyet, 1958). The signs and symptoms of hyperthyroidism (tachycardia, tremor, loss of weight) were completely relieved in 6 of 15 patients studied. Both the BMR and the plasma PBI (protein-bound iodine) fell to normal levels. In the remaining 9 cases, this fluorine dosage was clinically ineffective, although an improvement of BMR or PBI level was often observed. Young patients did not respond at all to fluorine therapy. No appreciable uptake of $^{38}\text{F}$ by the thyroid could be detected either in the normal or in the hyperactive gland. No inhibition of the thyroidal iodine uptake was observed when fluorine was injected in excess simultaneously with carrier-free iodine.

In normal human subjects, fluorides have no effect (Korrodi et al., 1956). Forty patients with normal thyroid function were given sodium fluoride for several months. Regular observation was possible on 15 of these patients: ten who received 2-3 mg of fluoride daily for 6-14 months, and five who received 5 mg of fluoride per day for 2-5 months. Clinical as well as special thyroid-function tests failed to reveal any pathological findings. The data obtained on blood PBI, radioactive iodine uptake by the thyroid (24-hour values), BMR and serum cholesterol at the beginning and end of the test period showed only negligible variations within normal limits. Any damaging action of fluoride on the thyroid gland was considered improbable.

Additional experiments, on young rats, showed that the radiiodine uptake was not affected by high fluoride intake, either in animals receiving normal food or in those on a low-iodine diet.

On the basis of both the above investigations, it was concluded that there need be no hesitation regarding a general use of fluoride for the prevention of dental caries under the conditions prevailing in Switzerland.

Moreover, in normal animals, fluoride does not decrease the BMR or affect the activity of administered thyroid (Seevers & Braun, 1935; Phillips et al., 1935); nor does it inhibit the deposition of iodine in the thyroid or accelerate the iodine depletion.
Why does sodium fluoride exert a mild antithyroidal effect in hypothyroidic patients if it is inactive in normal persons? Nobody knows. Attempts to develop fluorine-containing drugs which would compete with thyronine have all failed. Substitution of one or several fluorine atoms for iodine atoms in the molecule of thyroxine or thyronine did not produce antithyroidal substances (Cortell, 1949; Roche, 1953). The compound 3-fluorothyronine is said to lower the BMR in mice (Litzka, 1936) and to delay tadpoles’ metamorphosis (Kraft, 1936); however, it seems merely inefficacious in the treatment of Graves’ disease (May, 1935) and certainly less active than several synthetic non-fluorinated preparations—for example, 3,5,3',5'-tetrabromothyronine (Lerman & Harrington, 1949) and 3,5-diiodo-4-hydroxybenzoic acid or DIBB (Sheahan et al., 1951). All these drugs (fluorinated or not) have been swept away by the modern goitrogens thiourea and thiouracil, the first report of whose efficiency was published in 1943 by Astwood.

**Iodine-Fluorine Antagonism**

Baumann & Metzger (1949) suggested that the thyroid has an affinity not only for iodine but also for other members of the seventh periodic group of elements. Such an affinity has been demonstrated to a small extent for chlorine and bromine, but not for fluorine. No correlation was found between the fluorine content of the thyroid of patients with Graves’ disease, the iodine content of the thyroid, the BMR of the patients and the fluoride content of drinking water (Evans & Phillips, 1938).

$^{19}$F investigations have also failed to provide evidence of the affinity for the thyroid of fluorine. For example, no affinity was observed in rat experiments by Wallace-Durbin (1954). No appreciable uptake of $^{19}$F by the thyroid could be detected in tests on normal humans or on patients with hyperactive glands (Galletti & Joyet, 1958). After intravenous injection of $^{19}$F in mice and rats, no concentration of fluorine was found in the thyroid or the salivary glands (Ericsson & Ullberg, 1958).

In rabbit experiments, the $^{19}$F concentrations in the thyroid and pituitary were determined 35-38 minutes after the injection, and compared with the simultaneous concentration in the maternal blood. The $^{19}$F content of the tissues was of the same order as, or lower than, that of the maternal blood (Ericsson & Malmlöf, 1962).

Can plasma fluorine, whether ionized or bound, act on plasma iodine, ionized or bound? Numerous tracer studies on this problem have been reported. All have failed to demonstrate any effect of fluorine on $^{131}$I distribution and metabolism. For example, high doses of fluorine given to rats by mouth during eight days had no influence on $^{131}$I uptake in the thyroid (Demole, 1954). Neither acute nor chronic administration of sodium fluoride to the rat inhibited the uptake of $^{131}$I by the thyroid gland.
The transport of the $^{131}$I through the acinar cell stage into the colloidal phase, and the ultimate distribution in the blood plasma, were of equal magnitude regardless of the dosage of sodium fluoride used (Harris & Hayes, 1955).

In rats suffering from experimental fluorosis caused by administration of NaF or CaF$_2$, the thyroid was not hypertrophied and its histological structure and uptake of $^{131}$I were normal (Demole & Lerch, 1956).

In tests on normal humans, 4 mg F daily, given for 10 weeks, did not affect the iodine-trapping ability of the thyroid (Levi & Silberstein, 1955).

In groups of rats kept on an iodine-deficient diet and receiving 0.005-0.5 mg fluoride in the food daily for 6½ months no goitrogenic effect of the fluoride was observed and the radioiodine uptake was not affected by high fluoride intake either in animals receiving normal food or in those on a low-iodine diet. The increased uptake of $^{131}$I by the thyroid caused by the iodine-deficient diet was clearly evident and independent of fluorine intake (Korrodi et al., 1956).

In the rat, neither F nor Ca nor Ca + F enhanced the goitrogenic effect of iodine deficiency. There was no indication of an antagonism between fluoride and iodine in the thyroid (Puentes & Cremer, 1966).

Jentzer (1955), working with rabbits, claimed to have found pathological changes in the thyroid morphology following fluoride administration. The technique used in this work was, however, open to criticism (Demole, 1956). Gordonoff & Minder (1952) described the inhibition of thyroxine by fluorine in the rat. This paper was marred by faulty calculations (Demole, 1954).

Auskaps & Shaw (1955), Galletti et al. (1955), Mühlemann & Schneider (1956), Ramseyer, Smith & McCay (1957), Willer (1958), Gedalia et al. (1960), Waller (1961) and Hennig & Fritz (1961) have shown that in rats given high fluorine doses the thyroid function is generally not impaired. Later rat experiments, using $^{131}$I-tracing and histological thyroid examinations, have given similar results (Ardelean et al., 1963; Saka, Hallag & Urgancioglu, 1965).

Clinical investigations have also failed to demonstrate any effect of fluorine on the thyroid: in children consuming water naturally fluoridated at 1.25 ppm (Demole, 1951); after tablet administration of 1 mg F daily (Held, 1953); in endemic goitre (Hofmann-Axthelm, 1953); after administration of sodium fluoride (Gedalia et al., 1961); in areas of endemic fluorosis (Siddiqui, 1960); in cases of skeletal fluorosis (Hennig & Fritz, 1961); in workers exposed for 7-20 years to fluorine inhalation with urinary fluoride varying between 5 and 12 ppm (Demole et al., 1951); and in two cases of industrial fluorosis (Roholm, 1937). Similarly, Gabovich and collaborators (Gabovich & Verzhikovskaya, 1958; Gabovich, Bukhovets & Verzhikovskaya, 1960) found no effect on the thyroid $^{131}$I uptake or function from fluoride doses of up to 0.1 mg per kg of body-weight or from drinking water containing 2 ppm F. Velicangil & Eser (1957) found no influence of endemic fluorosis (caused by 4 ppm F in water;
dental signs) on the endemic goitre in a Turkish area. Similar results are reported from India (Chapter 8, section 3).

The publication of Benagiano & Fiorentini (1955) has often been quoted. These authors reported anatomical and functional thyroid change in rural populations near Rome using fluoride-rich drinking water. Their work, however, has been severely criticized on account of lack of precision. It is now generally agreed that iodide concentrated by the thyroid tissue is oxidized to a higher valence state, such as I\(^+\) (iodinium ion), which then displaces hydrogen from tyrosyl residues (Maloo & Soodak, 1963). Anions which behave as iodide in the Hofmeister series or in their interaction with serum albumin have been tested for their combining capacity, in different oxidation states, with albumin (Wyngaarden, Wright & Ways, 1952). Such anions as CIO\(_4\)\(^-\) and SCN\(^-\) combine much more strongly than I\(^-\), and in rat experiments the former ions have discharged iodide from the thyroid, in contrast to fluoride, in 100-\(\mu\)mol doses (Scatchard & Black, 1949).

American Demographic Surveys concerning Fluorine

Large-scale surveys concerning the effect of fluorine on dentition and general health have been carried out in the USA. Some of these surveys are remarkable because of the number of subjects examined, the competence of the examiners, the precision of the investigations, the duration of the examinations and the validity of the controls. No deterioration in the thyroid was reported.

The studies of Leone et al. (1954, 1955) and Geever et al. (1958a, 1958b) concerning water containing 0.5 to 8 ppm fluoride are of particular interest.

Leone et al. carried out a survey of two communities in Texas, one of 116 persons in Bartlett and the other of 121 persons in Cameron. In Bartlett, the fluoride content of the water was 8 ppm until 1952, when an experimental defluoridation unit was installed, reducing it to about 1.2 ppm; in Cameron, the water contained 0.4 ppm fluoride.

The study began in 1943 and the participants, aged 15 to 68, were chosen at random from persons who had resided in the respective communities for at least 15 years. The average length of fluoride exposure at the end of the survey in 1953 was 36.7 years.

In 1943, medical histories were taken and each participant was given a medical, X-ray, and dental examination; blood and urine studies were also performed. These were repeated for all in 1953.

Characteristics studied included arthritic changes, blood pressure, bone changes, cataract and/or lens opacity, thyroid, cardiovascular system, hearing, tumours and/or cysts, fractures, urinary tract calculi, and gallstones. No significant differences between the findings in the two towns were observed except for a slightly higher rate of cardiovascular abnormalities in Cameron and a marked predominance of dental fluorosis in Bartlett.
Geever et al. performed more than 700 post-mortem examinations on persons who had lived for many years in Colorado Springs, where the fluoride content of the water is 2.5 ppm. The duration of residence in the area was over 20 years in 334 cases, 5-20 years in 130 cases, under 5 years in 188 cases, and unknown in 76 cases. The diagnoses were classified and the results tabulated according to the major causes of death. Incidental findings were: thyroid disease, gallstones, renal disease, urinary tract stones, liver diseases, peptic ulcer, diabetes mellitus, and pancreatitis. Comparative statistical analyses of the pathological findings revealed no significant differences that could be related to prolonged residence in the high-fluoride area.

A vital fact that the authors have not felt necessary to point out is that they were working in regions where the iodine intake (either natural or enriched through iodized salt) was sufficient to prevent endemic goitre.

**Swiss Surveys and Experiments showing the Compatibility of Iodine and Fluorine**

It may be mentioned that in Switzerland the prophylaxis of endemic goitre by means of iodized salt (at present 10 mg of KI per kg), commenced in 1922, has led to the disappearance of thyroid hypertrophy and cretinism as well as to a decrease in the prevalence of deaf-mutism.

Two findings are of importance in connexion with the supposed antagonism between iodine and fluorine:

1. The beneficial effect of iodized salt has been experienced by the whole Swiss population (about 6 million) irrespective of whether the fluoride content of the local waters is low (0.01-0.05 ppm), medium (0.1-0.5 ppm), or high enough for caries prevention (1-2 ppm), as is the case at Sembrancher (Valais) and at Kaisten (Aargau).

2. The increasing consumption of salt which has been both iodized and fluoridated (10 mg of KI and 200 mg of NaF per kg—i.e., 90 mg of F) has not led to the reappearance of endemic goitre, even in a minor form (Demole, 1951; Wespi, 1954). No goitrogenic effects have followed the fluoridation of drinking water in Basle (0.8-1.0 ppm) for more than four years, the fluoridation of water in Aigle (1-1.25 ppm) for three years, the daily administration of a fluoride tablet (1 mg of F) to all children in Geneva schools during 10 consecutive years (Held, personal communication, 1967) or the consumption of fluoridated milk in Winterthur (Ziegler, 1964).

The comments by Wespi-Eggenberger (1960) concerning the prevention of thyroid hypertrophy in the foetus by means of iodized and fluoridated salt administered to the mother during pregnancy may serve as a conclusion:

"Various papers ascribe to fluorine a goitrogenic effect, and the introduction of the fluorine prophylaxis has been rejected partly on this ground. The fact, however, that..."
the newborn who have benefited from a combined iodine and fluorine prophylaxis are practically goitre-free, demonstrates that fluorine at the employed doses does not have any goitrogenic property... [and] that the goitre-preventing effect of the iodine is not impaired by the addition of fluorine".

Discussion

It appears that certain drugs which act upon the sick organism are inactive in the healthy organism. Antipyretics which decrease fever do not lower the body temperature of normal men and animals. Thus, it is not surprising that in the treatment of Graves' disease (exophthalmic goitre) fluorides sometimes lower the basal metabolic rate. In normal subjects the same fluorides have no effect on BMR, blood cholesterol or uptake of iodine by the thyroid.

The very instructive example of iodine is also worth stressing here. In the patient afflicted with Graves' disease, iodine promotes involution of the goitre. On the other hand, iodine prevents the development of endemic goitre. This example shows that each case must be considered separately and that generalizations are dangerous.

A tendentious interpretation of certain medical and biological observations led to the erroneous theory of iodine-fluorine antagonism. This theory had two unfortunate consequences. In the first place, it led chemists to synthesize inorganic and organic antithyroid fluorides, all of which were a disappointment. (Of all these drugs, there is not a single one still on the market.) In the second place, it resulted in an unjustified fear that fluoride decreased the thyroid function and encouraged the development of goitre.

Advances in biochemistry, in particular tracer studies, have led to a complete revision of the theory of iodine-fluorine antagonism. We now know that fluorine does not accumulate in the thyroid gland, that its presence does not decrease the uptake of iodine by the thyroid and that it has no effect on the synthesis of thyroxine.

The information derived from the large-scale demographic surveys in the USA, Great Britain and elsewhere indirectly confirms the facts we have mentioned above. Consumption of drinking water containing fluoride, either naturally or artificially, does not impair the thyroid function, nor does it change the morphology and histological structure of the thyroid gland. Even the consumption throughout life of water containing 6 or 7 ppm fluoride does not affect the thyroid function.

Endemic goitre and endemic fluorosis are two separate disease entities. Fluorosis may exist with or without goitre, just as goitre can be present without fluorosis. Each endemic has its own remedy: fluorosis is prevented by defluoridation and endemic goitre by administration of iodine. The two endemics co-exist when both iodine deficiency and an excess of fluorine are present.
In Switzerland, all the doctors of the present writer's generation witnessed the disappearance of endemic goitre and cretinism as a result of prophylactic iodine medication, which is always effective regardless of the fluorine content of the water.

At present, despite the increasing ingestion of fluorine in fluoridated water, fluoridated milk, tablets containing fluoride, etc., goitre has not reappeared, even in its most readily induced form—namely, neonatal thyroid hypertrophy.

Conclusions

The problem of the toxic effects of fluorine in relation to the thyroid may be regarded as settled: a specific toxicity of fluorine for the thyroid gland does not exist.

The main facts behind this statement are:

1. Fluorine does not accumulate in the thyroid.
2. Fluorine does not affect the uptake of iodine by the thyroid tissue.
3. Pathological changes in the thyroid show no increased frequency in regions where the water is fluoridated, either naturally or artificially.
4. The administration of fluorine does not interfere with the prophylactic action of iodine on endemic goitre.
5. The beneficial effect of iodine in threshold dosage to experimental animals is not inhibited by administration of fluorine, even in an excessive dose.

6. SYSTEMIC AND VISCERAL INTOXICATION

(A. Singh & S. S. Jolly)

Since the dental and skeletal manifestations of fluorosis can be easily demonstrated and provide reliable evidence of the disease, other physical abnormalities tend to be overlooked. On the other hand, certain authors have drawn a lengthy list of manifestations attributable to fluorosis. For example, Spira (1953) has mentioned a number of complaints which the persons residing in an area with a high fluoride content in the water may have, including constipation, furunculosis, urticaria, dermatoses, alopecia and brittle nails. Spira's observations were based on the answers to a questionnaire circulated to 5000 military personnel during the Second World War, of whom 20% had mottled enamel. He suggested that fluoride acts on the central nervous system to cause depression and melancholy, and on the central and vegetative nervous systems to affect certain endocrine glands. He postulated that parathyroid dysfunction explained the disturbance of calcium metabolism, brittle nails and changes in the skin and teeth, and that adrenal dysfunction explained low blood pressure, lassitude, and the gonadal involvement which resulted in "feminized males". This hypothesis has,
however, never been substantiated. Similarly, Waldbott (1955) attributed urticaria, cephalgia, electroencephalographic changes and a host of other symptoms to allergic reactions to fluoride.

A sizable number of other biological effects have been ascribed to fluorides. Although many reports of such effects are unsubstantiated, several have been studied sufficiently to deserve a careful summary.

To study the problem of systemic intoxication, Singh et al. (1962c) submitted a detailed questionnaire to the population in some of the villages of Bhatinda district, one of the endemic areas in Punjab where the drinking water had a fluoride content of 10 ppm. There was no significant evidence of underdevelopment or undue anaemia or signs of any unusual nutritional deficiency amongst the population in the affected area. On the contrary, the rural area of Bhatinda district has one of the tallest and best-built male populations in the country. There was no evidence of goitre or hypothyroidism in the affected population. Detailed examination of the cardiovascular system, including electrocardiographic studies, revealed no abnormalities. Thus, the evidence from the clinical studies of fluorosis with regard to systemic intoxication is mostly of a negative nature, with the exception of dental, skeletal and neurological lesions.

**Haemopoietic System**

Various observers have recorded haematological findings in patients with fluorosis. Anaemia—possibly of a secondary type, from nutritional imbalance—was reported in Roholm's (1937) series of cases and recorded as due to partial obliteration of the medullary spaces by dense bone formation. In the series of Singh et al. (1963), the haemoglobin level ranged from 8 to 15.5 g per 100 ml. The principal difficulty lies in separating specific effects of fluoride from other factors such as malnutrition or other nutritional imbalance. In British surveys on industrial fluorosis (Agate et al., 1949) with much higher levels of fluoride intake, blood counts and haemoglobin levels were normal and, in fluorosed livestock, anaemia is not a conspicuous feature. No significant alteration in the factors of coagulation has been reported in any clinical series, but under experimental conditions coagulation is inhibited by fluoride at a relatively low level and fluorides are useful anticoagulants. Whether this is due to inhibition of the enzyme, prothrombokinase, to the precipitation of the Ca salts in an insoluble form, or to some other mechanism is not firmly established.

**Metabolic Effects**

Fluoride has an inhibitory effect on many enzyme systems (see Chapter 6, section 2). Assumptions have been based on *in vitro* findings that this fluoride effect must be exerted to some degree on metabolic processes in general.
However, it is demonstrated in Chapter 6, section 2 that enzyme inhibition in cells and body-fluids requires much higher fluoride concentrations than inhibition of purified enzymes.

While the in vitro toxicity of the fluoride ion for a number of enzymes is universally recognized, it is notable that there are hardly any recognizable clinical manifestations other than the dental and skeletal abnormalities.

**Endocrine Effects**

In the endocrine system, where the intermediary metabolism and synthesis of highly sensitive hormones involves enzymatic action, it is expected that interference with the mechanism by chemical agents would produce early and pronounced clinical effects. Considerable attention has consequently been given of recent years to the behaviour of fluoride in hormone chemistry and to the possible clinical disturbances of endocrine functions, particularly the thyroid gland. The effect on thyroid function is discussed in detail in section 5 of this chapter.

Of particular importance are the effects of fluorosis on the function of the parathyroid glands in regulating the level of calcium and inorganic phosphorus in the blood plasma by controlling deposition or removal from the skeleton and excretion by the kidney. Ritvo (1955), in describing the bone changes in fluorosis, pointed out that in many reports fluorosis and hyperparathyroidism exert a similar action on bone and that the final picture may be a combination of fluorosis and hyperparathyroidism. Differential diagnosis, however, can be easily made on the basis of the history and the serum concentrations of calcium, inorganic phosphorus and alkaline phosphatase. Radiological examination reveals a predominant osteosclerosis in fluorosis, while there may be a generalized decalcification of bone in parathyroid disease. The characteristic and distinct skeletal changes of osteosclerosis and calcification of ligaments occurring in advanced stages of chronic fluorosis might indicate a disturbance of calcium metabolism. An antagonism between fluoride and calcium has been repeatedly assumed, particularly in experimental work, although there are very few detailed studies of calcium metabolism. Singh et al. (1966) studied the parathyroid functions in detail by estimating serum calcium, inorganic phosphorus, and alkaline phosphatase and carrying out phosphate-clearance and calcium-deprivation tests. They did not detect any significant alterations in the parathyroid function as revealed by these tests.

Although the striking and distinctive skeletal changes suggest a disturbance of calcium metabolism, the changes probably take place so slowly (extending over 20 years or more) that they are not reflected in the conventional parathyroid tests available at present. Information concerning the possible function of fluoride in other endocrine organs is lacking.
General Effects

Hagan (1957) has studied the effects of fluoride on general health as reflected in the mortality data collected from the comparison of a non-fluoride community with another in which fluoride is artificially added. This study did not reveal any relationship between mortality experience and the presence of fluoride in drinking-water supplies. Similarly, Leone et al. (1955) did not find any significant physiological or pathological abnormality in the Bartlett and Cameron survey except a high prevalence of dental fluorosis in Bartlett.

7. SUMMARY (S. S. Jolly)

The toxic effects of larger doses of fluoride are predominantly confined to the teeth and the skeletal system, with secondary involvement of the nervous system in advanced and crippling fluorosis. There is experimental evidence of the toxic effects of fluoride in large concentration on the thyroid and the kidney, but overt clinical disturbances in the function of these organs have not been described in endemic fluorosis.

The skeletal changes of endemic fluorosis show irregular deposition of fluorides in different bones of the body, particularly in the axial skeleton. The radiological changes of osteosclerosis along with marked osteophytosis are characteristic. There is a distinctive histopathological pattern in which the Haversian system is disorientated. The chemical composition of the bones is also altered, and there is a marked increase of fluoride content in the bone ash. In very advanced cases, owing to the irregular narrowing of the spinal canal and intervertebral foramina, the complication of radiculomyelopathy is superimposed on the skeletal lesions.

There is no evidence at present to show that the amount of fluoride likely to be absorbed from fluoridated water supplies can produce the type of skeletal defects described in this chapter. In India, some cases of fluorosis have been reported at low water-fluoride levels, but in these areas other factors may play a significant role—for example, other sources of fluorides or constituents of water other than fluorides. Nutritional deficiency may also be an aggravating or superpositioning factor in the endemic fluorosis in India.

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CHAPTER 8

**Fluorides and general health**

N. C. LEONE 1 — A. E. MARTIN 2 — G. MINOGUCHI 3 — E. R. SCHLESINGER 4
— A. H. SIDDIQUI 5

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1. **INTRODUCTION** (A. E. Martin)

The final assessment of the effects of any substance on man can be determined only by observations on man himself, and in making such observations, full consideration has to be given to the variations in the reactions of individuals and to the diverse effects of different environments. Epidemiological studies are therefore of great importance in determining the effects of fluorides on human health. The function of laboratory tests, including those using modern biochemical and tissue-culture techniques, and of experimental studies on animals and on man, is to provide essential background information and to confirm, explain, and, where necessary, fill in the gaps in the knowledge derived from the work of the field epidemiologist.

Epidemiological investigations are frequently difficult to interpret for the design of a study is governed by natural circumstances and by the availability of data. Information on the early signs of general fluorosis is obtained from areas where water supplies contain grossly excessive quantities of fluoride and from occasional cases of industrial fluorosis. Investigations based on comparisons between high- and low-fluoride areas offer some of the best material for research, and particularly convincing results have been obtained in the study of fluoridation projects such as the Newburgh-Kingston project described in Professor Schlesinger's contribution to this chapter. In this investigation baseline information was obtained from

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medical examinations carried out before the start of fluoridation. Such information is obviously not available in natural fluoride areas, but good results have been obtained where an extensive series of observations is available, as in the mortality study of Hagan, Pasternack & Scholz (1954). Where data are more limited, as are those from the smaller series of areas investigated in the similar British mortality study of Heasman & Martin (1962), or where a comparison between a single pair of high- and low-fluoride towns is made, as in the Bartlett-Cameron study of Leone and his colleagues, greater care is needed in interpretation. In the Bartlett-Cameron study useful information was obtained by carrying out repeat medical examinations on the same group of people after a period of 10 years. In these types of investigations, careful attention has to be paid to the meaning which can be attached to aberrant results. Thus, in the study of Heasman & Martin, it was apparent that high fluorides were not the cause of a difference in mortality from cancer of the stomach, since an adjacent town using the same high-fluoride water supply was found not to have a markedly high rate of mortality. Again, the finding of a lower incidence of osteoporosis in Bartlett could be regarded only as a possible indication of a beneficial effect of fluorides until supporting evidence was obtained from further studies in the town of Framingham, and in high- and low-fluoride areas in North Dakota. The US studies of morbidity and mortality are supported by the valuable Soviet survey of the towns of Shchuchinsk and Kokchetav (Knizhnikov, 1958).

While epidemiological studies thus provide some of the most valuable information on the role of fluorides in the human body, it has to be realized that no single epidemiological study can in itself provide a rigorous proof of the safety of fluoridation of water supplies, even though a high degree of significance may be obtained from the findings. Within specified statistical limits individual studies may show an absence of any harmful effects. But the strength of the case for fluoridation is not based on the results of a single study; it is based on the mutually corroborative observations of many different workers. This is the picture which emerges from a consideration of the contributions to this chapter.

2. AREAS OF THE USA WITH A HIGH NATURAL CONTENT OF WATER FLUORIDE (N. C. Leone)

Accumulated evidence derived from studies in the USA indicates that under American conditions the prolonged ingestion of fluorides, in concentrations of up to 8 ppm in a drinking water, does not produce harmful physiological effects in humans except for dental mottling (Leone et al., 1954). Moreover, an objectionable degree of mottling is observed
only when fluorides are consumed during the ages of about 0-12 years and at levels in excess of 2.0 ppm.

While various authors have observed physiological changes by roentgenographic techniques, there is still no reliable evidence to support claims of harmful effects in persons living in high-fluoride areas (up to 8 ppm F) for long periods (15 or more years), when diet, hygiene and all other health factors are taken into consideration and the fluoride is delivered in consistent amounts from a reliable water supply and not in variable amounts from isolated potholes, streams or other unreliable water sources (Azar et al., 1961; Call, Leone & Davis, 1960; Leone et al., 1955, 1960; Stevenson & Watson, 1960). The clarified water from the latter sources may on analysis conform to the range described and studied, but the actual amount of fluoride in the water, as consumed, is greatly in excess of the analysis figures owing to the presence of fluoride-containing sediments which are found in unprocessed or in completely unpurified drinking water.

Actually, the accrued evidence points to a beneficial effect of fluorides on adult bone (Leone et al., 1955) and several clinical studies in which 20-60 mg of fluoride has been administered daily in the control of various bone and calcium-loss conditions bear out this concept (Leone, unpublished data; Purves, 1962; Rich, 1961; Rich & Emsick, 1961).

Recognizable roentgenographic bone changes, attributed to high fluoride intake, have been identified and described by a number of authors, but such changes have never been observed in otherwise healthy subjects consuming a natural water supply containing less than 4 ppm fluoride (Azar et al., 1961; Roholm, 1937). The bone findings described in association with an elevated fluoride intake are increased bone density and coarsened trabeculation of a degree that may be desirable in our aging population. Harmful roentgenographic findings have not been described in man after intakes of up to 8 ppm fluoride in water (Azar et al., 1961; Knizhnikov, 1958; Leone et al., 1955; Stevenson & Watson, 1960).

There is little doubt that nature intended to impose daily contact with fluoride upon us, for 0.1% of the earth's crust is composed of this element in different forms. In a few scattered areas of the world fluoride is found in high concentration in the form of cryolite (54.3% F) and fluorspar (48.0% F).

In the extensive high-fluoride areas of the USA nature has provided an environment of great practical and scientific importance for epidemiological studies. The main high-fluoride areas are in the south central part of the country, though additional areas are found in other parts. Texas, a south central state, with its vast fluoride areas, has provided some of our best epidemiological source material on the effects of fluoride on man. There can be found large stable population groups using water containing more than the desired 1.0 ppm fluoride for many years. Data from such areas are vital to the unbiased evaluation of research findings. A clearer concept of the areas
Areas where mottled enamel has been demonstrated by surveys and/or recorded in the literature.
under discussion can be obtained from the fluoride-distribution map of the USA shown in Fig. 1.

To clarify terminology, waters containing more fluoride than the physiologically desirable 1.0-1.5 ppm are regarded in this discussion as "high fluoride" waters.

Brief reference to the historical background of fluorides in man and, more specifically, to the high-fluoride areas of the USA will provide a better understanding of the nature of the problem and the extent to which it has been studied in the USA.

The earliest information on the effect of fluorides on man's dentition stems from a report by Eager, a US Public Health Service physician who was detailed to examine Italian emigrants in Naples. In his report to the Surgeon General, Eager (1901) stated: "One is struck by the frequency of a dental peculiarity common among the inhabitants of the Italian littoral and known as Denti di Chiaia, a defect first described by Professor Stefano Chiaia, a celebrated Neopolitan."

Specifically, the earlier epidemiological investigations in the USA stem from the astute observations of McKay and Black in Colorado Springs about 1908. These workers were the first to associate dental mottling with domestic water supplies (Black & McKay, 1916; McKay & Black, 1916). McKay, a practicing dentist with an alert, open mind, had epidemiological direction in his thinking. His work gave impetus to Dean and others, who, using epidemiological techniques, proved beyond doubt that fluoride in drinking water produced recognizable dental changes under certain conditions.

These early American investigators found that when water contained concentrations substantially greater than 2 ppm F, there often developed dental defects, ranging from barely detectable white spots called dental mottling at the lower levels to unsightly brown, stained, hypocalcified or hypoplastic teeth at higher levels, i.e., 4-8 ppm F. They also noted a direct relationship between the amount of fluoride in the drinking water and the incidence of dental caries, observing, for example, that 1 ppm fluoride in drinking water, consumed during the tooth formative stage (0-8 years of age), was beneficial and responsible for a significant reduction in dental caries.

It was from these earlier interests and findings that a series of carefully planned, well-controlled studies were initiated to provide reliable information on the physiology of fluorides in man. Many of the studies were designed to be interrelated, each providing specific facets of information. Often they were paralleled by identical animal studies to support the epidemiological or other study results in man and to confirm definitive answers to the many questions that have been posed.

It is difficult to summarize effectively the great number of fluoride studies and the mass of information accrued. Therefore, a tabulation of documen-
<table>
<thead>
<tr>
<th>Area</th>
<th>F level (ppm)</th>
<th>Type of study</th>
<th>Material or effect studied</th>
<th>References</th>
</tr>
</thead>
</table>
| Texas                       | 8.0           | Epidemiological population study | 1. Health status  
2. X-ray — bone  
3. Morbidity  
4. Mortality  
5. Dental  
6. Urinary excretion of F | Leone et al. (1964)  
Leone et al. (1965); Stevenson & Watson (1960)  
Leone et al. (1964)  
Leone et al. (1954)  
Zimmerman et al. (1955)  
Lilien et al. (1956); Zipkin & Leone (1957); Zipkin et al. (1956) |
| Texas and US fluoride areas | 0.0—6.0       | Epidemiological                | Population — X-ray — bone fractures and height-weight (young men)                          | McClure (1944)                                                            |
| US fluoride areas           | 0.0—8.0       | Human autopsy series (Epidemiological) | 1. Human bone — F — chemical analysis  
2. Human soft tissue — chemical analysis  
3. Bone — F — microscopic  
4. Human soft tissue — microscopic | Zipkin et al. (1968); McClure et al. (1958)  
Smith et al. (1960)  
Geever et al. (1956b)  
Geever et al. (1956a); Leone et al. (1964) |
<p>| US fluoride areas           | 0.0 versus 8.0 | Human autopsy study            | Comparative autopsy study of bone and soft tissue (chemical analysis) (2 identical cases)  | McClure et al. (1958)                                                     |
| Colorado Springs            | 2.5           | Autopsy review                 | Pathological studies in man — morbidity and mortality studies (904 cases)                  | Geever et al. (1956a)                                                     |
| US fluoride areas           | 0.0—2.6       | Clinical, epidemiological      | Urinary and biliary tract calculi                                                          | Zipkin &amp; Leone (1958)                                                     |</p>
<table>
<thead>
<tr>
<th>Area</th>
<th>F level (ppm)</th>
<th>Type of study</th>
<th>Material or effect studied</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas</td>
<td>3.5-5.5</td>
<td>Epidemiological</td>
<td>Radiographic survey — osseous development in hands and wrists of children</td>
<td>McCauley &amp; McClure (1954)</td>
</tr>
<tr>
<td>US fluoride areas</td>
<td>0.0-4.0</td>
<td>Epidemiological</td>
<td>Human bone — F content and its relation to chemical composition</td>
<td>Zipkin et al. (1958, 1960)</td>
</tr>
</tbody>
</table>
| Utah                | —*            | Human autopsy study | Bone — microscopic and chemical analysis Soft tissue — microscopic and chemical analysis | Call et al. (1960) 
|                    |               |                |                                                                 | Smith et al. (1960)                |
| Crisfield, Maryland | 0.0-3.48      | Epidemiological| Thyroid function — studies in man — 0.02 ppm and 3.48 ppm F    | Leone et al. (1964)                |
| Texas               | 2.5-8.0       | Epidemiological| Humans — X-ray studies in man with long exposure to F            | Stevenson & Watson (1960)          |
| North Dakota        | 4.0-5.8       | Epidemiological| Lateral lumbar X-ray — humans                                  | Bernstein et al. (1966)            |
|                     | 0.15-0.3      |                |                                                                  |                                    |

* Airborne fluoride from steel mills.
ted evidence describing the source and nature of the pertinent high-fluoride studies is employed as a guide to what is known. By this means, a comprehensive presentation of the selective effects of fluorides on man, as determined through controlled studies, can be reviewed and evaluated, with greater detail available by reference to the original publications. Table 1 lists pertinent US fluoride studies in man with allied studies that have a direct bearing upon the interpretation of information now available; this table is designed to indicate the area, level of fluoride studied, type of study, material or effect studied, and references to original publications. Table 2 is similarly constructed but relates to significant associated fluoride studies in man and animals.

The available documented evidence derived from controlled studies makes it possible to summarize the physiological manifestations in man of long exposure to high fluoride levels. It can now be stated that under the climatic and living conditions met with in the USA:

1. According to epidemiological population studies, no impairment of or effect on the general health status could be detected among persons residing for an average of 37 years in areas where the water supply contains fluoride at the level of 8 ppm, and no systemic abnormalities or abnormal laboratory findings were observed that might be associated with ingestion of fluorides (Leone et al., 1954, 1955).

2. Roentgenographic examination of persons residing in high-fluoride areas showed an increased bone density and coarsened trabeculation with slight thickening of the cortical bone and periosteum in a limited number of those studied, but no harmful skeletal effects were identified. Actually, this X-ray study (Leone et al., 1955) provided evidence, later supported by other studies (Leone et al., 1960; Stevenson & Watson, 1960), that the described "fluoride bone effect" is in fact both beneficial and desirable in adult bone since it counteracts the osteoporotic changes of the aged and the effects of calcium-loss disease (Leone et al., 1955; Rich, 1961; Rich & Ensineck, 1961, McClure, McCann & Leone, 1958).

3. Prolonged high fluoride intakes up to 8 ppm do not affect morbidity or mortality (Leone et al., 1954; Geever et al., 1958a; Hagan, 1957; Knizhnikov, 1958).

4. The frequency of dental fluorosis, an expected finding in the planned studies, was found to be significantly higher in high-fluoride areas, but other dental conditions, such as gingivitis, horizontal and vertical alveolar bone resorption, dental caries, calculus, leukoplakia, soft-tissue abnormalities, pulp stones, periapical rarefaction, condensing osteitis, and dentigerous cysts, were no more frequent than in normal population groups (Zimmerman, Leone & Arnold, 1955). At lower levels of consumption, i.e., 1.0-1.5 ppm fluoride, there was ample evidence of the beneficial anti-caries effect of fluorides. This beneficial aspect is dealt with in detail in Chapter 9 of this monograph.
<table>
<thead>
<tr>
<th>Area</th>
<th>F level (ppm)</th>
<th>Type of study</th>
<th>Effect studied</th>
<th>References</th>
</tr>
</thead>
</table>
| Laboratory            | Toxic levels  | Toxicological study (dogs, mice) | 1. MLD  
2. Toxicity  
3. ERG  
4. Physical effects  
5. Serum calcium | Leone et al. (1955) |
| Utah                  | 12.0-100      | 7½ year F-feeding study (cattle) | Blood system effects:  
1. Peripheral blood  
2. Blood chemistry  
3. Bone marrow  
4. Special studies (a) electrophoresis (b) folic acid (c) vitamin B<sub>6</sub> (d) blood enzyme  
5. Thyroid effects — PBI  
6. Liver function and spleen | Hoogstratten et al. (1965); Leone et al. (unpublished data) |
| Utah                  | 12-100        | 7½ year F-feeding study (cattle) | Growth and development effects  
Fertility  
Reproduction  
Dental effects  
Bone — pathological X-ray chemical analysis (serial bone biopsies) microscopic Placental transfer Genetic, milk production and F content Urinary secretion of F | Shupe et al. (1965) |
| Framingham, Mass.     | 0.04-8.0      | Epidemiological X-ray study (humans) | Low-fluoride population (546 persons) — X-ray findings compared in identical bases with 8.0 ppm F area (Texas) | Leone et al. (1960) |
| Utah                  | 12-100        | Liver-function studies (cattle) | BSP in cattle fed 12-100 ppm F compared with control experimental herd (Beltsville) | Shupe et al. (1960) |
| Bethesda, Md. (NIH)   | 5             | Clinical (humans)       | Rate of F output in normal adults | Zipkin & Leone (1957) |
5. The urinary excretion of fluorides is in direct proportion to the level of F intake and is not directly correlated with age according to studies in which age-groups of 7 through 16 years were compared with age-groups of 20 years and over (Likins, McClure & Steere, 1956; Zipkin & Leone, 1957; Zipkin et al., 1956).

6. Approximately 60% of the fluoride ingested is excreted within the first 24 hours at various intake levels. When there is a decrease in the amount consumed, there is a proportionate gradual but predictable decrease in the urinary fluoride output, indicating that the previously stored fluoride is being mobilized and excreted (McClure, 1944, Zipkin & Leone, 1957; Zipkin et al., 1956).

7. Young males in high-fluoride areas fail to reveal a relationship between bone fractures and fluoride exposure and their height-weight figures compare favourably with those of young men in other areas of the USA, indicating that fluoride exposure does not influence man's growth pattern (McCaulley & McClure, 1954; McClure, 1944).

8. Autopsy studies of persons residing in 0-8 ppm fluoride areas provide clearly defined evidence that:

(a) There is a linear relationship between bone fluoride content and fluoride consumption, the highest bone fluoride content being found at high F levels (McClure, McCann & Leone, 1958; Zipkin et al., 1958).

(b) Soft tissues do not accumulate fluoride, regardless of the level of F consumption or the length of exposure, except the aorta and possibly the kidney where the F is probably adventitious (Smith et al., 1960; McClure, McCann & Leone, 1958; Azar et al., 1961).

(c) Occasionally, small isolated calcific plaques are found in the aorta which contain more fluoride than the immediate surrounding soft tissue. This is due to the affinity of fluoride and calcium for each other. However, in low-fluoride areas, such plaques are found in equal number and size, indicating that fluoride is not a factor in the formation of calcific plaques but a common finding at autopsy in aging adults (Smith et al., 1960; Geever et al., 1958a, 1958b).

(d) Histological examinations of bone from persons residing in communities with 1.0-4.0 ppm fluoride do not show any differences that can be related to fluoride intake. Microscopic changes incidental to aging and to non-fluoride-related conditions are observed in bone from both fluoride and non-fluoride areas (Geever et al., 1958a, 1958b; Azar et al., 1961) substantiating that demonstrable bone changes have not been identified in man by roentgenographic examination up to a level of 4 ppm.

(e) Similarly, no histological changes that might be associated with fluoride can be demonstrated in human soft tissue (Geever et al., 1958a, 1958b) when similarly exposed. Parallel animal studies support this finding (Shupe et al., 1963).
9. Comparative "matched" bone and soft-tissue studies from persons residing in high- and low-fluoride areas clearly demonstrate the effects of fluoride on bone density, increased fluoride and calcium in the bone, and the absence of soft-tissue change or the accumulation of fluorides in soft tissue (McClure, McCann & Leone, 1958).

10. Analyses of the findings of an extensive necropsy series, performed on persons from high-fluoride areas, revealed no significant association of morbidity, mortality, disease entity or other pathological condition which could be related to prolonged residence in a high-fluoride environment (Geever et al., 1958a; Hagan, 1957).

11. The fluoride content of urinary and biliary tract calculi is not affected by the level of fluoride intake according to a study in which renal calculi from high- and low-fluoride areas were compared (Zipkin & Leone, 1958).

12. A radiographic study of the hands and wrists of 2005 children, 7-14 years of age, residing in 3.5-5.5 ppm fluoride areas failed to demonstrate abnormal bone growth or developmental effects (McCauley & McClure, 1954).

13. Supporting human and animal studies demonstrate, through detailed blood studies, that prolonged administration of high concentrations of fluoride (a) does not produce gross histological or functional effects on the thyroid gland or the liver; (b) does not produce significant changes in the serum calcium, phosphorus or numerous other blood constituents studied; (c) may, at the 100 ppm or toxic level, in animals (which normally have a higher eosinophil level than man) slightly raise the total eosinophil count and lower the serum folic acid level; and (d) most important, does not produce anaemia or detectable abnormalities of the bone marrow or otherwise affect the haematopoietic system (Hooogstratten et al., 1965; Leone et al., 1964; Leone et al., unpublished data; Shupe et al., 1960).

14. The prolonged ingestion of fluoride does not affect thyroid gland size or function in either man or animals (Leone et al., 1964; Shupe et al., 1963).

15. The controlled feeding to cattle of fluoride in concentrations of 12-100 ppm for 7½ years does not affect fertility, reproduction or milk production or in any way produce abnormal effects in the offspring through repeated generations (Shupe et al., 1963).

16. The same studies also support the linear accumulation of bone fluoride (as described in man) which parallels the level of consumption, and, further, support human studies showing that while there is a linear increase in fluoride bone levels, the accumulation of fluoride in soft tissue does not occur (Shupe et al., 1963).

17. These and other studies also show a lack of histological evidence of abnormal change or fluoride effect in soft tissues (Shupe et al., 1963).

18. A limited placental transfer of fluoride has been demonstrated through the accumulation of low levels of fluoride in the bones of offspring,
but no growth or developmental effects have been observed (Shupe et al., 1963).

19. Liver-function studies in cattle, applying the same techniques as used in man, have demonstrated that high fluoride does not affect liver function and does not produce gross or microscopic change in the liver of animals fed 12-100 ppm F for 7½ years (Shupe et al., 1960, 1963).

20. Roentgenographic studies provide important information (Leone et al., 1960). When a controlled group of 546 persons in a low-fluoride area (0.04 ppm F) was compared with a group who lived in a high-fluoride area (8 ppm F), a statistically significant greater number of persons in the former group showed a decreased bone density, described by the radiologist as osteoporosis, a finding that supports the concept of a beneficial effect of fluoride on adult bone (Geever et al., 1958b; Bernstein et al., 1966).

In summary, it is evident that except for dental changes, long exposure to fluorides at what might be regarded as “high levels”, i.e., 2.0-8 ppm F, does not produce harmful or otherwise abnormal effects in man but does in fact have an effect on adult bone that is beneficial and most significant to those persons in the post-menopausal or older age-groups.

3. FLUOROSIS IN AREAS OF INDIA WITH A HIGH NATURAL CONTENT OF WATER FLUORIDE (A. H. Siddiqui)

Epidemiology

In India, endemic fluorosis occurs with varying intensity in Andhra Pradesh, Madras, Mysore, Punjab and Kerala (Daver, 1945; Khan & Wig, 1945; Murthy, Narayana Rao & Venkateswarlu, 1953; Pandit & Narayana Rao, 1940; Pandit et al., 1940; Pillai, 1942; Raghavachari & Venkataraman, 1940; Shortt, Pandit & Raghavachari, 1937; Shortt et al., 1937; Siddiqui, 1955; Singh et al., 1962; Venkateswarlu, Rao & Rao, 1952). The pioneer investigations were made by Shortt and his collaborators in 1937. Extensive survey work has been carried out in Andhra Pradesh, Madras and Punjab (Fig. 2, 3 and 4). Singh et al. (1962) have calculated that there is a belt covering at least one-fourth of the Punjab in which the fluoride content of the drinking water is high. This exposes roughly 5 million people to the toxic potentialities of the fluoride ion. An even larger population is exposed to high fluoride ingestion in Andhra Pradesh and Madras. The areas where the incidence of endemic fluorosis is high are shown in Fig. 2. Fig. 3 and 4 indicate the concentration of fluorine in well water and the number of specimens analysed in areas of endemic fluorosis. Singh et al. (op. cit.) recorded 16.2 ppm fluorine in certain areas of the Punjab, the highest figure reported from India.
Most foods are found to be poor sources of fluorine, even when grown in fluorine-rich soils, supposedly because the fluorine in the soil becomes converted to insoluble calcium salts. Tea and some other members of the family Theaceae, which grow in relatively acidic soils, are exceptional in their faculty for taking up fluorine. Fluorine in tea is in inorganic form. Quentin, Souci & Indinger (1960) found the fluorine content of Darjeeling and Assam tea to be 86.7 mg and 98.7 mg per kg dry weight, respectively. Tests on infusions of Assam tea, 3 g to 300 ml of water, allowed to stand for 5 minutes, showed that 90% of the fluorine was extracted by moderately hard tap water as well as by distilled water, and that a cup would supply 0.14 mg of fluorine. In a recent study Singer, Armstrong & Vatassery (1967) found 52-144 ppm F in five black teas and 336 ppm F in one green tea; 41-78% of this fluoride content could be extracted in the first infusion.
Sea foods may be rich in fluorine (5-15 ppm). Venkateswarlu (unpublished data) found the fluorine content of sea salt to range between 14 and 20 µg/g. About 11 g of sea salt are consumed on an average daily in India. Siddiqui (1955) reported high levels of fluorine, 0.09%, 0.11% and 0.15% respectively, in the sediments and mud samples obtained from wells in areas of endemic fluorosis.

Dental fluorosis occurs with varying intensity in the areas of endemic fluorosis (Fig. 3 and 4). Venkateswarlu, Rao & Rao (1952) found 0.9-1 ppm in Indian drinking waters to be associated with mottled enamel: almost the same amount which is being incorporated in the public water supplies in Europe and the USA as a mass caries-control measure. However, the

FIG. 3
FLUORIDE CONTENT OF WELL WATER IN ENDEMIA AREAS — I

○ More than 3 ppm.
□ Between 1 and 3 ppm.
▲ Below 1 ppm.

The numerals indicate the number of specimens analysed.
differences between India on the one hand and Europe and the USA on the other regarding the consumption of water, sediment in drinking water and the nutritional habits and general health status of the population have to be borne in mind in this connexion.

Clinical Observations

Children, apart from dental changes, do not suffer from ill-effects of fluorine-rich drinking water. Susceptibility to mottled enamel is restricted to a sharply defined age-group. The reason is that fluorine is deposited in teeth during the period of calcification of the crown of the permanent teeth.
This period extends from infancy, when the central incisors may be affected, to 16 years of age, when the calcification of the crown of the last teeth, the third molars, has been completed. Both sexes are affected with equal frequency. The condition is largely confined to the permanent teeth, although in areas of marked severity, sporadic instances of deciduous teeth being affected—evidence of placental transmission of fluorine—have been observed.

The changes are of two kinds. First, the enamel is abnormally opaque and chalky white. White blotchy areas are usually interspersed with areas of more or less normal enamel, a condition which has aptly acquired the descriptive term of mottling. This change is observable at the eruption of the tooth. Secondly, after eruption, an irremovable brown or black pigmenitary substance is deposited in the defective enamel. The coloured areas form irregular patches or more regular transverse bands (Fig. 5) (Leone, 1960; Pillai, 1942; Raghavachari & Venkatacharan, 1940; Murthi, Narayana Rao & Venkateswarlu, 1953).

The degree of mottling depends largely on the amount of fluorine ingested. With increasing concentrations of F the effect becomes progressive, so that at 6 ppm the incidence of mottling is 100% (cf. Chapter 7, section 2 and Chapter 9). The most commonly affected teeth are the premolars and the second molars, though any tooth may be involved. The surfaces subjected to attrition show marked lesions. In severe cases of mottling, there is discrete or confluent pitting and the teeth often appear corroded. Caries in the mottled teeth is rare, but the enamel is rather brittle and inclined to chip off in the severe cases.

In the USA manifest mottling is reported to be associated with at least 3 to 4 ppm fluorine—a level at which many workers in India have recorded cases of skeletal fluorosis. In north-western Europe the degree of mottling has been found to be still less than that in the USA (Moller, 1965).

Such highly varying manifestations of fluorine intoxication in different parts of the world lead to the inference that there are factors, peculiar to each country, which influence the effect of fluorine in drinking water. For example, the consumption of water is greater in India than in temperate and subtropical countries. Fluorine-rich sediment in primitive wells has already been mentioned.

Venkateswarlu, Rao & Rao (1952) concluded that the incidence of caries and mottled enamel had a definite relationship with the fluorine content of water. However, the incidence of caries and mottled enamel varies considerably in communities exposed to nearly the same amount of fluorine in drinking water. Owing to the lack of information on the exact relationship between the incidence of dental caries and the fluorine content of waters, Venkateswarlu and co-workers (op. cit.) studied the relationship between the incidence of caries and the over-all manifestation of fluorosis in the community. An index for the degree of manifestation of fluorosis (as revealed by an examina-
FIG. 5
MOTTLING OF TEETH OBSERVED IN ENDEMIC AREAS
tion of mottled enamel prevalent in a community) designated as the dental fluorosis index (DFI) was established. It was concluded that the fluorine content of water remaining the same, the incidence of dental caries varied inversely with the DFI of a community.

This observation does not mean that nutritional and other factors, by lowering the toxicity of fluorine, should increase the chances of caries incidence. On the contrary, such factors, besides lowering the toxicity of fluorine, may by themselves effectively control caries incidence as well. It is interesting to recall in this context an observation by Dean et al. (1939) that the DMF rate per 100 children among Galesburgh subjects with mottled enamel was 200, while among those without mottled enamel it was 186. A low incidence of mottled enamel can co-exist with a low incidence of dental caries. It is therefore desirable to recognize the existence of other factors which contribute to a low caries incidence.

The optimal (sub-mottling) concentration of fluorine beneficial to dental health in India seems to be from 0.5 to 0.8 ppm in water.

Prolonged ingestion of water with a high fluorine content causes skeletal fluorosis in adults. There is an extraordinary uniformity in the signs and symptoms of intoxication. The initial symptom noted in India is a recurrent general tingling sensation in the limbs or all over the body. Pain and stiffness next appear, especially in the lumbar region but also involving the thoracic region and the cervical spine. Extension is more painful than flexion. The stiffness may increase until the entire spine, including the cervical region, appears to be one continuous column of bone. Accompanying the spinal disability, there is stiffness of various joints due to calcification of periosteal tissues, tendinous insertions of muscles and interosseous fasciae. This leads to various other disabilities, such as inability to squat. The bony and cartilaginous skeleton of the thorax is markedly affected and breathing becomes abdominal. The vertebral column becomes rigid and the patient develops a "poker-back". Bony exostoses can easily be seen or felt. By the time this condition is reached, the individual is between 30 and 40 years of age. Skeletal fluorosis, with special reference to conditions in India, is more comprehensively dealt with by Singh and Jolly in Chapter 7, section 3.

The patients exhibit cachexia, there is loss of appetite and signs of spinal root and cord compression appear with loss of sphincter control. The patient is finally bedridden while the mental powers remain unimpaired.

Involvement of the nervous system in skeletal fluorosis has been reported exclusively from India (Murthi, Narayana Rao & Venkateswarlu, 1953; Shortt et al., 1937; Siddiqui, 1955; Singh & Jolly, 1961). The spinal nerves and the cord are compressed by bony ingrowths in the spinal canal. The physical signs depend on the anatomical factors of maximum narrowing of the spinal canal or the intervertebral foramina and whether the compression is chiefly at a single site or is multiple. A patchy type of anaesthesia, muscular wasting, spastic paraplegia with sensory level, absence of vibration sense
and loss of sphincter control are the usual neurological manifestations. The neurological changes resemble to a certain extent the clinical picture of cervical spondylosis. The pathogenic mechanism of root and cord compression is similar. However, the manifestations of cord compression are a more integral part of fluorosis and the root compression is much more common in cervical spondylosis.

Cases exhibiting radiological changes in the skull may suffer from a perceptive type of deafness. In the series reported by Rao & Siddiqui (1962)

![Figure 6: Audiogram indicating hearing loss observed in cases of skeletal fluorosis.](image)

*After Rao & Siddiqui (1962).*

hearing loss commenced at 3000 Hz and was marked (up to 60 dB) at 8000 Hz (Fig. 6). Bone conduction seemed to be affected more than air conduction. Hearing loss was greater for higher frequencies. These workers postulated that hearing loss was the result of pressure on the eighth nerve during its passage through the narrowed and sclerosed internal auditory meatus.

Wilson (1941) reported a high degree of dental fluorosis in the goitrous area of the Punjab, India; however, no mention was made about the iodine intake, water sources were not analysed and the criteria for dental fluorosis did not exclude non-fluorotic mottling. The incidence of simple goitre, cretinism and deaf-mutism was investigated by Siddiqui (1960) in a known area of endemic fluorosis. With the possible exception of temporary thyroid enlargement in pubertal subjects, no relation was found between
the incidence of goitre and the content of fluorine in the water supply. No cases of cretinism or of deaf-mutism were seen. Normal thyroid glands, both macroscopically and microscopically, were reported in two cryolite workers by Rohelm (1937). The fluorine-thyroid problem is more extensively covered in Chapter 7, section 5.

Factors influencing Severity

The severity of fluorosis has a definite relation to the concentration of fluorine in water, to the length of time of ingestion, to meteorological factors (for example, temperature), and possibly to the economic and nutritional status of the people, and the physical strain to which they are exposed.

The degree of disability and the time of onset of symptoms of the disease are related to the concentration of fluorine and to the length of time of its ingestion. Siddiqui (1955) reported that symptoms of intoxication in Kama-guda village appeared in immigrants one to four years after their arrival. The finding that it takes one to four years for symptoms to manifest themselves is at variance with that of Shortt et al. (1937), who concluded that a residence of 30-40 years in an endemic area was required for a definite picture of skeletal fluorosis to develop. An exceptionally high fluorine content of water (11.8 ppm), excessive heat (46.1°C) and a poor state of nutrition, the diet being deficient in calcium and vitamin C (Table 3), may be possible factors responsible for the early development of skeletal fluorosis in Kama-guda. The presence of signs of fluorosis in poultry, which is very resistant to fluorine (Peirce, 1940), also points to the intensity of intoxication in Kama-guda.

<p>| TABLE 3 |
| COMPOSITION OF DAILY DIET IN KAMAGUDA VILLAGE |</p>
<table>
<thead>
<tr>
<th>Constituent</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein:</td>
<td></td>
</tr>
<tr>
<td>animal</td>
<td>5.5</td>
</tr>
<tr>
<td>vegetable</td>
<td>73.1</td>
</tr>
<tr>
<td>Fats:</td>
<td></td>
</tr>
<tr>
<td>animal</td>
<td>8.9</td>
</tr>
<tr>
<td>vegetable</td>
<td>19.9</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>494.9 g</td>
</tr>
<tr>
<td>Total calories</td>
<td>2.618</td>
</tr>
<tr>
<td>Calcium</td>
<td>0.48 g</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.78 g</td>
</tr>
<tr>
<td>Iron</td>
<td>38.1 mg</td>
</tr>
<tr>
<td>Vitamins: carotene</td>
<td>1048 IU</td>
</tr>
<tr>
<td>vitamin A</td>
<td>176 IU</td>
</tr>
<tr>
<td>vitamin B</td>
<td>2 mg</td>
</tr>
<tr>
<td>vitamin C</td>
<td>23 mg</td>
</tr>
</tbody>
</table>

*After Siddiqui (1955).*

Hot weather not only increases the water intake but also increases the concentration of fluorine and leads to the ingestion of abnormal amounts of
TABLE 4

RELATION BETWEEN TEMPERATURE AND FLUORINE CONTENT OF WATER

<table>
<thead>
<tr>
<th>Place of sampling</th>
<th>Temperature at time of sampling</th>
<th>Fluorine content of water (ppm) ¹ ² ³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Well No. 1 ³</td>
</tr>
<tr>
<td>Kamaguda</td>
<td>90°F (32.2°C)</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>115°F (46.1°C)</td>
<td>9.6</td>
</tr>
<tr>
<td>Yedvellí</td>
<td>108°F (42.2°C)</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>115°F (46.1°C)</td>
<td>5.8</td>
</tr>
<tr>
<td>Yellareddyguda</td>
<td>115°F (46.1°C)</td>
<td>5.8</td>
</tr>
</tbody>
</table>

¹ After Siddiqui (1955).
² Estimated by thorium nitrate titration method.
³ The two wells are situated barely 150 yards (90 m) apart.

sediment (Table 4). The protective action of calcium against intoxication by large doses of fluorine has been noted by Ranganathan (1941) in rats, by Majumdar & Ray (1946) in bulls, and by Pandit & Narayana Rao (1940) in monkeys. Pandit & Narayana Rao (op. cit.) and Wadhwani (1952) found that administration of vitamin C lessened the severity of fluorosis in monkeys. This question is discussed in Chapter 6, section 2.

Lower temperatures, ingestion of smaller quantities of water and better nutritional conditions are undoubtedly factors responsible for the absence of crippling disabilities in countries such as Great Britain and the USA. This is well borne out by the studies of Leone (1960) and Stevenson & Watson (1960). A series of well co-ordinated investigations by Leone (op. cit.) in the USA has supported the concept that no clinically significant, adverse, physiological or functional effects, with the exception of dental fluorosis, are to be anticipated in persons whose water supply contains up to 8 ppm fluorine. In a review of approximately 170,000 X-ray examinations of the spine and pelvis of patients, mostly residents of Texas and Oklahoma, osteosclerotic changes were noted in only 23 by Stevenson & Watson (op. cit.). Each of these patients lived his entire life in an area in which the water contained fluorine in concentrations ranging from 4 to 8 ppm. No osteosclerotic changes were evident in this study in persons whose drinking water contained less than 4 ppm fluorine.

The degree of disability is also related to physical strain. It is most pronounced in manual labourers. Subjects pursuing sedentary occupations, such as the local village administrative officials and the school teachers, have less severe symptoms although they utilize the same sources of water supply. Pain and stiffness are most severe in the joints used most by the individual—for example, the wrists, shoulders and neck in the females, who are mostly engaged in household work, and the lumbar spine and the joints of the lower limbs in the males working in the fields. Radiological changes in the skull and the cervical spine, so seldom observed by Roholm and others, are...
frequently encountered in India: a fact which could be ascribed to the same phenomenon of strain. Most of the Indian patients reported were manual labourers who were accustomed to carry heavy loads on their heads.

4. JAPANESE STUDIES ON WATER AND FOOD FLUORIDE AND GENERAL AND DENTAL HEALTH (G. Minoguchi)

Investigations in Areas with a High Natural Content of Water Fluoride

At present, in Japan, water with over 0.5 ppm fluorine is being supplied from 158 sources to 42 communities. The exact number of consumers is unknown, but it is assumed that it is not over 200,000, or about 0.2% of the entire population of Japan, and this number is rapidly decreasing thanks to the advancement of water services. Owing to the geographical features of the Japanese Islands, there are no long rivers and little use is made of underground streams. Most of the fluorine-containing drinking water is obtained from small, shallow wells from which two or three families usually draw their water.

The highest fluorine concentration known today is well water containing 21.0 ppm fluorine which has been used by two or three persons for drinking over a long period (Minoguchi, Okumara & Takenouchi, 1957). In the past, the highest fluorine content in piped water supplies was 2.7 ppm, but at present there is only one district where there is 1.3 ppm (Iizuka, 1964). This means that we are unable to locate many people who drink water of the same fluorine concentration under the same or similar climatic and other environmental conditions. Therefore it is difficult to determine the concentration of fluorine in drinking water that causes dental fluorosis or osteosclerosis.

Dean and his colleagues (Dean, 1946) investigated the threshold of dental fluorosis in the mid-western region of the USA, and set the borderline limit for the appearance of dental fluorosis in the vicinity of Chicago at 1.0-1.5 ppm fluoride. But in Japan, in an investigation around the Kyoto district, it seems that the corresponding borderline limit is 0.8-1.1 ppm, i.e., appreciably lower than that in the central USA.

From the investigations in the Japanese Islands, which are long and narrow to the north and south, it was found that in general the people in the southern districts (which are hotter than the northern ones) seem to be afflicted with dental fluorosis at a lower water-fluoride concentration. In the Kyoto district, dental fluorosis was found in places where the water contained about 0.8 ppm. Many cases of rather severe dental fluorosis can be seen in districts where the fluorine content is over 1.1 ppm. From investigations of scattered small areas with a high water fluorine content, Hirata (1950) has reported the following facts.
He examined 270 schoolchildren afflicted with dental fluorosis in areas where the drinking water contained 1.0-5.0 ppm fluorine, and then divided them into three groups, mild, moderate and severe, according to the degree of dental fluorosis, without reference to the concentration of fluorine in the drinking water. Blood analyses were made in these patients. No changes were determined in the mild group, but in the moderate group a decrease (less than 6000/mm³) in white blood corpuscles was seen in 21.8% and a decrease (less than 3000/mm³) in the neutrophil number was seen in 32.7%. In the severe group, 47.2% showed a decrease in white blood corpuscles and 41.2% a decrease in neutrophil number. However, such abnormalities were not found in pupils beyond the age of puberty. X-ray examinations were made of the bones of the arms and hands of 29 children who showed moderate or severe dental fluorosis and accompanying neutrocytopenia. Abnormal signs, such as hypertrophy of the cortex of bones, shadow increase in the ossification centre of carpal bones, and serrating changes in the metaphyseal cartilage of the radius and ulna, were demonstrated.

Thus, abnormal blood and X-ray findings were not observed in persons with mild dental fluorosis. However, the investigation was mainly conducted during 1947-49, when nourishment and other factors were less satisfactory in Japan.

The results of Hirata's investigation emphasize that effects on the whole body should be considered, and the addition of fluoride to water to prevent tooth decay carried out with great care.

A few years later, Hamamoto (1957) discovered that 58 persons out of the 517 residents in one district in Okayama Prefecture, where 0.1-13.0 ppm fluorine was found in the wells, had reduced mobility in several joints. He estimated the content of fluorine in the drinking water and examined roentgenograms of the bones, and reported that 21 out of 33 persons who had drunk water containing over 5.0 ppm fluorine for over 10 years showed osteosclerosis-like symptoms, as did 2 of 97 children under 10 years of age.

From the above observations, it appears that in the central district of Japan, in communities where water with a fluorine concentration of over 5.0 ppm was continuously used as drinking water for over 10 years, there was a risk of contracting osteosclerosis.

Investigation in Yamashina where Water Fluoridation was introduced in 1952

Caries-preventive fluoridation of the water supply in the Yamashina district in Kyoto was initiated on 1 February 1952 at a level of 0.6 ppm.

As a result of Dean's investigation in the mid-western region of the USA (Dean, op. cit.), most of the fluoridation in the world has been conducted at
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>District</th>
<th>Number of children examined</th>
<th>Number of children affected by caries</th>
<th>Percentage of children affected by caries</th>
<th>Number of permanent teeth examined</th>
<th>Number of DMF* teeth</th>
<th>DMF rate (%)</th>
<th>Average number of DMF* teeth per child</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Fluoridated Control</td>
<td>79</td>
<td>19</td>
<td>24.1 *</td>
<td>512</td>
<td>25</td>
<td>4.9 **</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>152</td>
<td>58</td>
<td>38.2</td>
<td>1,077</td>
<td>127</td>
<td>11.8</td>
<td>0.84</td>
</tr>
<tr>
<td>8</td>
<td>Fluoridated Control</td>
<td>76</td>
<td>32</td>
<td>42.1 **</td>
<td>816</td>
<td>56</td>
<td>6.8 **</td>
<td>0.74</td>
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<tr>
<td></td>
<td>Control</td>
<td>127</td>
<td>91</td>
<td>71.7</td>
<td>1,344</td>
<td>269</td>
<td>20.0</td>
<td>2.12</td>
</tr>
<tr>
<td>9</td>
<td>Fluoridated Control</td>
<td>60</td>
<td>36</td>
<td>60.0 **</td>
<td>791</td>
<td>89</td>
<td>11.3 **</td>
<td>1.48</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>129</td>
<td>107</td>
<td>83.2</td>
<td>1,745</td>
<td>294</td>
<td>16.8</td>
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<tr>
<td>10</td>
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<td>63</td>
<td>37</td>
<td>58.7 *</td>
<td>1,029</td>
<td>109</td>
<td>10.6 *</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>81</td>
<td>63</td>
<td>77.6</td>
<td>1,435</td>
<td>194</td>
<td>13.5</td>
<td>2.90</td>
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<td>11</td>
<td>Fluoridated Control</td>
<td>61</td>
<td>47</td>
<td>77.0 *</td>
<td>1,257</td>
<td>135</td>
<td>10.7 **</td>
<td>2.21</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>96</td>
<td>86</td>
<td>89.8</td>
<td>1,916</td>
<td>301</td>
<td>15.2</td>
<td>3.14</td>
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<tr>
<td>12</td>
<td>Fluoridated Control</td>
<td>72</td>
<td>59</td>
<td>81.9</td>
<td>1,756</td>
<td>200</td>
<td>11.4 **</td>
<td>2.78</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>100</td>
<td>91</td>
<td>91.0</td>
<td>2,405</td>
<td>417</td>
<td>17.3</td>
<td>4.17</td>
</tr>
<tr>
<td>13</td>
<td>Fluoridated Control</td>
<td>53</td>
<td>45</td>
<td>84.9 *</td>
<td>1,396</td>
<td>177</td>
<td>12.7 **</td>
<td>3.34</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>115</td>
<td>108</td>
<td>93.9</td>
<td>3,061</td>
<td>509</td>
<td>16.6</td>
<td>4.43</td>
</tr>
<tr>
<td>14</td>
<td>Fluoridated Control</td>
<td>70</td>
<td>57</td>
<td>82.6 *</td>
<td>1,888</td>
<td>257</td>
<td>14.1 **</td>
<td>3.81</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>145</td>
<td>137</td>
<td>93.8</td>
<td>4,005</td>
<td>775</td>
<td>19.4</td>
<td>5.35</td>
</tr>
<tr>
<td>15</td>
<td>Fluoridated Control</td>
<td>104</td>
<td>91</td>
<td>87.5</td>
<td>2,893</td>
<td>383</td>
<td>13.2 **</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>164</td>
<td>157</td>
<td>96.7</td>
<td>4,574</td>
<td>1,060</td>
<td>23.2</td>
<td>6.46</td>
</tr>
</tbody>
</table>

* DMF = decayed, missing, filled.
* *Significantly differing from control at $P < 0.05$ in $\chi^2$ test.
** *Significantly differing from control at $P < 0.01$ in $\chi^2$ test.
a level of 1.0 ppm; however, according to the investigations in the central
district of Japan, there appeared to be a danger of causing dental fluorosis
and possibly an abnormal blood picture at a concentration of 1.0 ppm.
Moreover, osteosclerosis had been found to occur at a concentration of
about 5 ppm, which was lower than that at which the condition had been
observed in the USA. From the results of the above-mentioned investiga-
tion, it had been assumed that, in general, 0.8 ppm was the borderline of
dental fluorosis occurrence around the Kyoto district, so the optimum fluo-
ride concentration was naturally thought to be 0.6 ppm or 0.7 ppm. The
level of 0.6 ppm was adopted with the aim of keeping well within the safety
margin as regards the occurrence of dental fluorosis.

The Yamashina filter plant, which serves water to about 15,000 people
living in the east side of Kyoto City, was chosen as the test area and the
addition of 0.6 ppm fluorine, as sodium fluoride, started on 1 February
1952. The Shugakuin district, located in the north-east of Kyoto City,
was selected as the control area because it is similar to the Yamashina
district in its environment and in the general occupations of the people.
Since the experiment began, the oral cavity and entire body of school-
children from 6 to 15 years of age have been examined periodically in both
districts.

In October 1964, 12 years and 8 months after the start of fluoridation,
the prevalence of dental caries was as shown in Table 5. In spite of the fact
that caries of the permanent teeth of all the children in Kyoto district
increased remarkably during the period 1952-64 (owing, no doubt, to the
regional dietary changes during the period), the area where fluoride was
added to the water had a considerably lower caries incidence than the control
area. Especially in 7- and 8-year-old children, the number of carious teeth was
reduced, being below 40% of that seen in the control district.

A comparison of the reduction in decayed teeth is difficult because the
cause of tooth decay is complicated; but, as is shown in Table 6, the results
after 10 years of fluoridation in Yamashina at a level of 0.6 ppm are almost
equal to those obtained in Grand Rapids, Mich., at 1.0 ppm and only a
little inferior to those observed among children over ten years of age in
Newburgh, N.Y.

I. Ohmori (personal communication) dissolved with HClO₃ the enamel
of the lingual surfaces of anterior teeth of 12-year-old pupils in the Yama-
shina district, after 13 years of fluoride addition to the water, and estimated
the fluorine content to be 0.16%. This amount is about four times greater
than the usual content of fluoride in the dental enamel. If the increase of
fluorine in the dental enamel reflects an increase of resistance to dental
caries, then it can be said that the purpose of fluoridation has been fully
attained.

We have not seen any cases of dental fluorosis or other unfavourable
side-effects in the people of Yamashina.
### Table 6

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Grand Rapids, Mich.</th>
<th>Newburgh, N.Y.</th>
<th>Brantford, Ont.</th>
<th>Yamashina</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>75</td>
<td>58</td>
<td>39.6</td>
<td>57.9</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>39</td>
<td>42</td>
<td>54</td>
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<td>57</td>
<td>42</td>
<td>38</td>
<td>48</td>
</tr>
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<td>48</td>
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<td>—</td>
<td>36</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>28</td>
<td>—</td>
<td>37</td>
</tr>
<tr>
<td>16</td>
<td>26</td>
<td>21</td>
<td>—</td>
<td>40.9</td>
</tr>
</tbody>
</table>

*Percentage reduction in DMF teeth = \( \frac{\text{No. of DMF teeth per child}}{A} \) \times 100, where \( A = \text{No. of teeth per child at start of fluoridation and } B = \text{No. of DMF teeth per child in control area.}\)

Data from Arnold et al. (1956).

Data from Asa et al. (1956).

Data from Hutton, Linscott & Williams (1956).

### Factors with an Influence on Fluoride Intake in Japan

While fluoridation in Yamashina was conducted at the level of 0.6 ppm, the reduction of decay in this district as compared with the control district was similar to that obtained in Grand Rapids (1.0 ppm added F) as compared with its control, Muskegon, Mich. The present writer would like to comment on why there is this difference in the optimum fluoride concentration.

It has been thought that, the temperature being higher in Japan than in the mid-western region of the USA, the amount of water consumed by the people may be higher. However, there is no actual evidence of any difference in the amount of water consumed in the USA as compared with Japan. In the second place, the Japanese people consume a rather large amount of marine products, such as fish, as their main protein source. This may cause dental fluorosis at a comparatively lower water-fluoride concentration. Besides this, there might be some difference in racial susceptibility to fluoride or other unknown factors. However, it is most appropriate to think that the major variables are the difference in climate and the difference in the amount of fluoride in food.
Climatic variation and fluoride optimum

Maier (1950) discussed the relationship of optimum fluoride concentration to climate and to an increase and decrease in the consumption of water according to seasonal changes in temperature. Since then, Galagan (1953) has compared the results of his investigation of dental fluorosis in Arizona, a hot district, with Dean's investigation in the cooler mid-western region of the USA. This relationship has been demonstrated in a graph with two straight lines showing the Community Fluorosis Index (hereinafter abbreviated CFI) at different concentrations of fluoride in the drinking water according to the different mean annual temperatures—50°F (10°C) and 70°F (21°C)—(see Fig. 7).

Later, Galagan & Vermillion (1957) investigated the relationship of temperature to the consumption of drinking water of children in Antioch and Brentwood, Calif., and derived a formula for calculating the optimum fluoride concentration:

\[ \text{optimum ppm } F = \frac{0.34}{E}, \text{ where } E = -0.038 + 0.0062 \ t \]
(E is the estimated daily water intake for children through 10 years of age, in ounces per pound of body-weight; t is the annual mean of daily maximum temperatures in °F.)

From the formula Galagan calculated the optimum fluoride concentration of Tucson and Chandler in Arizona, which have a mean annual temperature of about 70°F, and found it to be 0.7 ppm.

However, the investigation of the Arizona district, which he had reported earlier, showed the CFI of Tucson (which has a 0.7 ppm fluoride water supply) to be 0.46 and that of Chandler (which has a 0.8 ppm fluoride water supply) to be 0.52. There is thus a risk of moderate dental fluorosis, and 0.7 ppm cannot be considered a safe amount for the people of Arizona. For this reason we think that the optimum fluoride concentration was calculated too high from Galagan's formula.

The difference between the two lines obtained in the Arizona/Mid-West comparison by Galagan (1953) should reflect a difference in physiological response due to the difference in temperature and the difference in the consumption of drinking water. Therefore, with these two trend lines as a basis, we have calculated the optimal fluoride concentration in drinking water as a function of CFI and annual mean temperature under the hypothesis that all the regression lines of the various annual mean temperatures (°F) that can be drawn between the 50°F and 70°F annual mean temperature lines pass through the point \( x = 0.4 \) and \( y = 0.162 \), which is the crossing-point of the 50°F and 70°F regression lines. The angle of the regression line expressed in \( r°F \) and \( y = 0.021 + 0.353x \) is in proportion to the increase in annual mean temperature. This hypothesis may be considered to be established in this narrow space of 50°F and 70°F. As a result, we obtained the following formula:

\[
\text{ppm F} = \frac{\text{CFI} - 0.162}{\tan (1.45585r - 53.3950)} + 0.4, \text{ where } t \text{ is the mean annual temperature in °F.}
\]

What this formula expresses is not only the difference in water consumption as related to seasonal temperature, but also the difference in water consumption due to differences in temperature between various geographical areas. For example, Kuno (1956) found that sweating conditions differ between people born and reared in areas with greatly different mean temperatures.

Our computation is illustrated in Fig. 8. The optimum fluoride concentration, the permissible fluoride concentration, and the limit fluoride concentration at each annual mean temperature are also illustrated in Table 7.
According to this formula, Tucson's optimum fluoride concentration would be 0.6 ppm; this cannot be said to be too high an optimum fluoride concentration in the light of the actual investigation results obtained in Tucson by Galagan (1953). The CFI at optimal fluoride concentration would be 0.374, calculated according to Galagan's formula with \( y = 0.021 + 0.353x \). Dean (1946) stated that a fluorosis index below 0.4 is of little or no public health concern, while indices between 0.4 and 0.6 would be of borderline significance. Above an index of 0.6, the removal of excess fluoride is indicated; CFI = 0.6 thus gives the limit fluoride concentration.

The optimum fluoride concentration of the Kyoto district, which has an annual mean temperature of 57.6°F (14.2°C), can be calculated as 0.762 ppm, the permissible maximum as 0.807 ppm, and the limit as 1.15 ppm. These figures are almost identical to the figures obtained from the investigation of the relation between dental fluorosis and the amount of fluoride in the water near the Kyoto district, which gave the borderline at 0.8 ppm and the limit at 1.1 ppm.
### Table 7

<table>
<thead>
<tr>
<th>Mean annual temperature (°F)</th>
<th>Optimal fluoride concentration (ppm)</th>
<th>Maximum permissible fluoride concentration (ppm)</th>
<th>Limit fluoride concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.000</td>
<td>1.074</td>
<td>1.640</td>
</tr>
<tr>
<td>51</td>
<td>0.956</td>
<td>1.024</td>
<td>1.548</td>
</tr>
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<td>0.979</td>
<td>1.405</td>
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<td>0.880</td>
<td>0.940</td>
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<td>54</td>
<td>0.849</td>
<td>0.905</td>
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<td>55</td>
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<td>0.873</td>
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<td>0.773</td>
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<td>0.785</td>
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<td>0.733</td>
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</tr>
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<td>0.695</td>
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<td>0.682</td>
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<td>0.654</td>
<td>0.685</td>
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<tr>
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<td>0.640</td>
<td>0.670</td>
<td>0.897</td>
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<tr>
<td>66</td>
<td>0.629</td>
<td>0.657</td>
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<tr>
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<td>0.600</td>
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<td>69</td>
<td>0.597</td>
<td>0.621</td>
<td>0.807</td>
</tr>
<tr>
<td>70</td>
<td>0.587</td>
<td>0.610</td>
<td>0.796</td>
</tr>
</tbody>
</table>

*The CFI (Community Fluorosis Index) of optimal fluoride concentration is 0.374, which is calculated in Galagan's trend-line formula, \( y = 0.001 + 0.35x \), as \( x = 1.0 \) fitting (Galagan, 1953).

*The CFI of permissible maximum fluoride concentration is 0.4.

*The CFI of limit fluoride concentration is 0.6.

### Fluoride content of Japanese food

In Japan sea-food and tea are among the staple foods and some particularly fluoride-rich kinds of both are consumed—e.g., shrimps: 30-50 ppm F (Iizuka, 1964; Minoguchi & Sato, 1964); seaweed: 6-14 ppm F (Iizuka and Minoguchi & Sato, *op. cit.*); and green tea: 336 ppm F, of which 66% is extracted in 3 minutes (Singer, Armstrong & Vatassery, 1967).

In order to calculate the amount of fluoride ingested from food daily by the Japanese, Sato, Yoshiyake & Nakanishi (1965) determined the fluoride content of 127 types of food and applied this to the annual average consumption of food throughout Japan according to the 1960 National Nutrition Investigation (results of each food group and chart of nutrition intake) carried out by the Nutrition Section, Public Health Bureau, Welfare Ministry.

As a result, it was calculated that 1.38 mg of fluoride was ingested from food. The largest amounts were from marine products (0.39 mg), rice (0.33 mg), and green tea (0.25 mg) (Minoguchi & Sato, *op. cit.*). These figures are the average for the Japanese nation as a whole and in general correspond to the food intake of children from 13 to 15 years old.

In an investigation of the ordinary food of hospitalized patients in Kyoto University Hospital over one year (April 1963 to March 1964), the figure obtained was lower than the one above, registering 1.2 mg (Sato et al.,
op. cit.). In other investigations, Samejima (1959) has calculated it as 1.6-2.7 mg, Saito (1960) as 2.1-3.5 mg and Iizuka et al. (1963) as 0.48-2.64 mg. In contrast, McClure has reported the amount of fluorine ingested in the USA by children from 10 to 12 years of age as 0.056-0.56 mg (McClure, 1943) and by adults as 0.41-0.91 mg (McClure et al., 1945). Armstrong & Knowlton (1942) reported that the food in Minnesota Hospital contained 0.27-0.32 mg; Adamson et al. (cited by Elliott & Smith, 1960), reporting on Newfoundland residents who were assumed to take 3.1 oz (88 g) of codfish and 6 cups of black tea daily, obtained the figure of 2.74 mg daily, while Ham & Smith (1954), reporting on three women in Toronto, obtained 0.43-0.73 mg.

From all the reports except that of Adamson and co-workers, it appears that the Japanese ingest from 1.0 to 2.0 mg more fluorine daily from food than the Canadians or Americans.

However, these figures do not express the fluorine intake of infants and children from 6 months to 7 years of age—the period during which the main permanent tooth-crowns are being formed and dental fluorosis of the permanent teeth is caused.

Moreover, most of the fluorine in marine products exists in a very stable form bound to calcium phosphate, which is poorly soluble in water. Not all the fluorine can be considered to exert the same physiological action that fluorine dissolved in water ordinarily would.

It can, however, be assumed that Japanese children obtain more fluorine from food than American children of the same age, though the quantity has not been calculated exactly. If this food-borne fluorine shows a similar physiological effect to the water-borne fluorine, then under the same climatic conditions the fluoride concentration in drinking water which causes dental fluorosis would naturally be lower in Japan than in the USA.

**Food Fluoride, Climatic Temperature and Dental Fluorosis**

In fact, as stated earlier, the borderline of fluoride concentration in drinking water that was derived from actual investigation of dental fluorosis around Kyoto District, Japan, is 0.8 ppm, and the limit 1.1 ppm. Moreover, when the above formula derived from investigations in the USA is applied to the Kyoto vicinity, which has an annual mean temperature of 57.6°F (14.2°C), the borderline of fluoride concentration in drinking water is 0.807 ppm and the limit is 1.15 ppm. The latter figures are applicable to the Americans, whose fluorine intake from food is less than that of the Japanese. However, the difference is only 0.07 ppm at the negative borderline and 0.05 ppm at the limit, which can actually be considered zero.

Although the Japanese are thought to ingest a large quantity of foodborne fluorides, the fact that this does not appear as a difference in the sensitivity to fluorine in drinking water would lead to the assumption that a
daily intake of food-borne fluorine corresponding to 1.0-2.0 mg in adults
does not have any physiological effect on dental fluorosis.

What then would the optimum fluoride concentration be in the southern,
subtropical zone of Japan, where the temperature is much higher than in the
temperate zone of the country?

The limits of application of Galagan's formula are 50°F to 70°F (10-
21°C) mean annual temperature. In districts where the annual mean tem-
perature is below 50°F, the formula can hardly be applied because artificial
methods of heating and clothing will prevent extremely low temperatures of
the outside world from affecting the people directly (McPhail & Zacherl,
1965). When the three lines, the optimum fluoride concentration, the per-
missible concentration and limit concentration (according to appearance
of dental fluorosis) are drawn from this formula at each temperature, the
higher the annual mean temperature, the narrower the band width of the
lines. If the interval between the optimum fluoride concentration and the
limit fluoride concentration is considered the margin of safety, this interval
will appear in the mid-western region of the USA, where the annual mean
temperature is 50°F, as 0.64 ppm; in a district where the mean temperature
is 60°F it would be 0.335 ppm, and in a district where it is 70°F it would be
0.199 ppm. That is, with increasing mean temperature, the margin of
safety becomes progressively narrower, at 70°F being one-third of that at
50°F. If this computation were to be applied to a district of over 70°F,
this margin would be 0.13 ppm at 75°F (24°C) and 0.10 ppm at 80°F (27°C),
which indicates that it would be difficult to prevent the occurrence of dental
fluorosis with fluoridation in a high temperature zone.

The relationship between the appearance of dental fluorosis and the nutri-
tion of the residents in different districts was investigated and reported on by
Massler & Schour (1952). In a low-nutrition district, dental fluorosis occured
at a lower fluoride concentration.

At present, in the tropical areas of the world, the inhabitants cannot
be said to be receiving the same adequate nutrition as the people in North
American and European countries. Therefore, in tropical areas the nutri-
tional state of the inhabitants, besides the climatic conditions, contributes
to the risk of fluorosis at a lower fluoride concentration than can normally
be expected.

In addition to temperature differences, there is a physiological difference
in people who are born and reared in districts of high temperature, in that, as
was reported by Kuno (1956), their sweating condition differs.

When we consider the precision that we can guarantee at present in the
apparatus for supplying fluoride to waterworks, and—even more important—
the individual variation in water consumption, the possibility of severe dental
fluorosis occurring would be great in adding fluorine to drinking water in
regions where the annual mean temperature is over 70°F, and in fact we
think it would probably be impossible to avoid occurrence of the condition.
5. HEALTH STUDIES IN AREAS OF THE USA
WITH CONTROLLED WATER FLUORIDATION (E. R. Schlesinger)

Extent of Consumption of Fluoridated Water

The use of controlled fluoridation of public water supplies, at about 1 ppm fluoride, has grown steadily in the USA. By the end of 1967, there were 3827 communities, with a total population of nearly 72 million, which were being served by fluoridated water in the USA and Puerto Rico (US Department of Health, Education, and Welfare, 1968). In addition, some 10 million persons resided in communities in which the water supply contained about an optimal level of fluoride at its source. In recent actions, three populous states—Connecticut, Illinois, and Minnesota—have enacted legislation requiring fluoridation of municipal water supplies.

Besides those persons in the USA who have been receiving water with an optimal fluoride level at its source, more than 17 million persons have been drinking fluoridated water for at least 12 years. Despite this extensive experience with entire population groups—including pregnant women, children throughout their growing period, elderly persons, and persons with all types of long-term illnesses—there have been no well-documented reports of any adverse systemic effects or of symptoms of any kind that could be attributed to fluoridated water, although the medical profession and the general public in the communities concerned were fully apprised of the advent of fluoridation.

On the other hand, it has been a common experience for health officers to receive many complaints from local citizens about digestive disturbances and other disabilities caused by fluoridated water, even in advance of the actual date of initiation of water fluoridation (Hilleboe, 1956).

Controlled Long-term Study of Children (Newburgh-Kingston Study)

In the early 1940s, when water fluoridation was first being considered as a community measure for the prevention of dental caries, there was no body of practical experience to call upon. It is true that water with a fluoride level several times higher than that used in controlled fluoridation had been consumed over the lifetime of a sizable population group without any discernible adverse effects other than mottling of the teeth, and there was no scientific basis for thinking that the fluoride introduced into a community water supply differed in any way, including its physiological effects, from the same level of fluoride leached from the soil and rocks. Nevertheless, it appeared desirable to conduct a long-term controlled study of the health and the growth and development of two groups of children from infancy on, the only known variable in the two groups being the consumption of fluoridated water by the study group. This was the objective of the medical aspects of
the Newburgh-Kingston (New York State) caries-fluorine study which was conducted for a period of ten years starting in 1944 (Schlesinger et al., 1956). The timing of these carefully controlled observations was particularly important, since the public and professional demand for fluoridation might preclude the possibility of long-term studies at a subsequent time.

The cities of Newburgh and Kingston, located about 30 miles (50 km) apart on the west bank of the Hudson River, were selected because of their comparability in size and in their demographic, social and economic characteristics. The two cities had similar upland reservoir water supplies, both of which were deficient in fluoride. The water supply of Newburgh, the study city, was adjusted to a fluoride level of 1.0-1.2 ppm, whereas the fluoride level of the Kingston water supply was allowed to remain at 0.05 ppm.

Since the annual medical examinations, the basic feature of the study, required the voluntary co-operation of the selected families over a period of ten years, a strict random sampling procedure was precluded. The selection of children was based, therefore, on the apparent residential stability of the families, and every effort was directed towards obtaining a broad scattering from all parts of each city, in proportion to population, and comparability of the two groups in respect of social and economic circumstances. With regard to race, for example, 4.6% of the Newburgh study group were Negro, in comparison with 3.6% in the total population of the city at the time; a similar relationship existed in Kingston.

A total of 817 children were enrolled in the Newburgh study group and 711 children in the Kingston control group. Most were enrolled at the start of the study, though small numbers of infants were added each year during the first three years of the study to ensure having in the study group some children whose mothers had been exposed to fluoridated water throughout pregnancy. Of the total Newburgh group, 500, or 61.2%, reported for their final examinations at the end of the study; 405, or 56.9%, of the Kingston group participated in the final round of examinations.

A detailed medical history was obtained by a paediatrician on the first visit to the research clinic, with interval information being added on a cumulative history form on subsequent visits. A physical examination was performed by the paediatrician on each visit, special attention being paid to the status of the skin and mucous membranes, the hair, and the thyroid gland. Physical measurements, including weight, height, and circumference of chest, were also made on each visit.

Laboratory studies were performed on both the Newburgh and Kingston children on the initial and final research clinic visits and on the Newburgh children on every third visit during the course of the study. These laboratory studies consisted of a routine urine analysis (including a microscopic examination of the urinary sediment), a haemoglobin determination, and total leucocyte and erythrocyte counts, with a differential leucocyte count on
children whose total leucocyte count appeared to be outside normal limits.

On the roentgenograms of the right wrist and both knees, which were taken on each visit to the research clinic, special attention was paid to the rate of skeletal maturation and to density of the bone. On the final visit, a lateral roentgenogram of the lumbar spine was also taken, since the lumbar spine is among the earliest sites in the skeletal system to show evidence of osteosclerosis from exposure to excessive amounts of fluoride. The X-ray films were reviewed by an outstanding paediatric roentgenologist without reference to the clinical background or city of residence of the children.

Special ophthalmological and otological examinations were performed on groups of 25 children each year in Newburgh. The ophthalmological examinations included a test of visual acuity using the Snellen chart, plotting of the visual fields, measurement of the size of the blind spot, and slit-lamp examination of the cornea and lens. Otological examination encompassed pure-tone audiometry and a visual examination of the ear, nares and nasopharynx.

The findings from these examinations disclosed no differences of medical significance between the study and control groups that could even remotely be ascribed to fluoride. A threefold higher rate of tonsillectomies observed among the Newburgh children at the start of the study and on subsequent examination was attributable to differences in medical practice between the two cities. Comparable age-sex groups in the two cities followed closely similar patterns in height and weight.

Children with potentially significant health conditions were referred to their family physicians; in Newburgh, 4.0%, and in Kingston, 4.9% were so referred—a total of 39 children in the two cities. Obesity and urinary, blood and roentgenographic findings were the usual reasons for referral in both cities.

Estimation of bone age by two independent observers disclosed no significant differences in the level of skeletal maturation between comparable age-sex groups in the two cities. The second observer deduced the bone age from the X-rays of the wrist and knees, the only information given being the sex of the child under study.

All findings, whether or not considered to be of pathological significance or in any way related to the use of fluoridated water, were recorded. In certain of the findings, such as sclerotic epiphyseal ossification centres and the presence of sesamoid bones in roentgenograms of the hand and wrist, a somewhat higher proportion was found in one city, whereas in other findings, such as benign fibrous cortical defects in the roentgenograms of the knees, a greater proportion was observed in the other city.

No evidence of increased bone density could be discerned on roentgenographic examination. The absence of increased bone density in the lumbar spine after ten years of exposure to fluoridated water added weight to the negative observations of the wrist and knee on earlier examinations.
The haemoglobin level showed no significant differences between Newburn and Kingston children. The mean for the two cities was very close, although a few more children in Newburn had haemoglobin levels below 12.9 g per 100 ml. Similarly, a slightly higher proportion of children in Newburn were found to have total erythrocyte counts below 4 400 000 per ml, but the difference between the two groups was found to be insignificant. The total leucocyte counts were essentially the same in the two cities, with a slightly higher proportion of children in Kingston showing a count over 10 000 per ml. Routine urine analysis also showed no significant differences between the findings in the two cities.

The findings on both the ophthalmological and the otological examinations in the Newburn children fell well within the limits expected of any normal group of children of the age studied.

The quantitative excretion of formed elements in the urine in groups of 12-year-old boys in Newburn and Kingston was the subject of a special study (Schlesinger, Overton & Chase, 1956) carried out because fluoride in highly toxic quantities had been reported to produce pathological changes in the kidneys of experimental animals. The Addis technique was used to detect any possible minimal irritative effect on the kidneys of the prolonged use of fluoridated water. These groups of normally active boys in the two cities failed to show any significant differences in their quantitative excretion of albumin, red blood cells, and casts.

The stillbirth and the maternal and infant mortality rates in Newburn and Kingston were compared for the five-year period prior to the start of fluoridation and during the ten years of the study. The long-term downward trends were similar in the two cities and no change could be detected in the trend in Newburn after fluoridation. The death rates from cancer and cardiovascular diseases were also examined in the two cities. These rates did not change, relative to each other, prior to or during the period of the study.

**Statements on Adverse Systemic Effects from Fluoridated Water**

Publications regarding adverse systemic effects from fluoridated water have often drawn analogies with the acute effects of toxic doses of fluorides or with the chronic effects of high levels of fluoride, particularly in hot climates. The latter observations have been further complicated by the effects of chronic malnutrition and by a high intake of dietary fluoride other than from drinking water. In citing the actual or stated systemic effects of high fluoride intake, the all-important factor of dosage has often been neglected. Many substances essential to life are toxic at excessively high levels, and this applies to oxygen and even to water itself.

The statements of two observers on adverse systemic effects, made in the USA, deserve specific mention. The first of these (Rapaport, 1959) suggests
that Down's syndrome (mongolism) occurs more frequently in communities in which the water supplies contain more than 1 ppm fluoride than in communities with lower levels of fluoride. The numerator of the incidence rates of Down's syndrome presented was the number of cases reported on birth and death certificates, plus the number of children institutionalized for the condition. The denominator was the number of infants born to mothers who resided during their pregnancies in the years and in the communities under study. Based on a total of 48 cases reported, there was an incidence rate of 71.2 cases per 100,000 in the higher-fluoride communities, in comparison with a rate of 34.2 per 100,000, based on 67 cases, in communities with 0.2 ppm fluoride or less. The inadequacy of the case-finding method used is apparent from these figures. Down's syndrome has been found by other investigators to occur most often in the range of one per 600-700 births. In Rapaport's report, Down's syndrome is said to have occurred in only one per 1400 births in the higher-fluoride communities and in one per 2900 births in low-fluoride areas.

A well-conducted study in Great Britain (Berry, 1958, 1962) overcomes these deficiencies in case-finding. In this study, information was sought not only from institutions and vital records, but also from records of health officers which embraced cases detected at school entrance and in occupational centres, and from the personal knowledge of health visitors (public health nurses) and others concerned with the welfare of children with Down's syndrome. The over-all incidence of Down's syndrome was found to be one per 668 births, with insignificant variations in the rates in the communities served by water supplies containing different levels of fluoride.

Another widely cited publication is that describing allergic reactions to test doses of 15 mg sodium fluoride (Waldbott, 1963). These reactions are presented in a brief note and tabulation in an otherwise extensive review of acute fluoride intoxication. Of a selected group of 123 allergic patients tested, five developed a wide variety of symptoms and signs which developed five minutes to three hours after the test dose and lasted from twelve hours to ten days. Of the 21 symptoms and signs reported, only six occurred in more than one patient, and these were mainly of a nondescript nature, such as headache, nausea, vomiting, and epigastric pain. Physical findings such as muscular fibrillations, "cystitis", "spastic colitis", and facial oedema were each found in not more than one patient.

The absence of any suggestion of a clinical syndrome leads to the conclusion that a variety of unrelated conditions were presented as cases of so-called "fluoride intolerance". This was also the situation in an earlier publication (Waldbott, 1962), in which cases are reported from the literature as instances of fluorosis when, in reality, they represent unrelated clinical conditions among persons with vague or undocumented histories of excessive fluoride ingestion. These cases are then used as the basis for asserting that all these conditions are, therefore, manifestations of systemic fluorosis. The
several original case reports in the paper were not documented by any independent observer. No cases of so-called "fluoride intolerance" ascribed to small doses of fluoride have been reported by other observers. In summary, there have been no adequately documented reports of any adverse systemic effects from fluoride ingestion even at levels several times greater than those used in water supplies for the prevention of dental caries.

6. INDUSTRIAL FLUORIDE HAZARDS (A. E. Martin)*

Industries emitting Fluorides

Fluorine is a ubiquitous element and traces of fluorides derived mainly from the combustion of coal and other fuels are to be found in all urban atmospheres. Localized areas of heavier pollution occur in various parts of the world as a result of certain specific industrial processes and may have a serious effect on agriculture.

The major sources of fluorine compounds in the atmosphere are well-known and in 1961 it was estimated that some 25,000 tons expressed as fluorine were emitted annually in England and Wales. Twelve thousand tons were derived from the industrial use of fluorspar (of which 10,000 were emitted during the manufacture of steel), 5000 tons from the industrial and domestic use of coal, 4500 tons from the heavy clay industry, 600 tons from the treatment of iron ores, 500 tons from the cement industry, and 150 tons from the pottery industry. Emissions from blast furnaces, from the chemical industry and from the manufacture of hydrofluoric acid, fertilizers, phosphorus and zinc production were negligible.

Such figures are of limited value for it is the localized areas of high pollution which may constitute the hazard. Moreover, the fumes may be discharged from tall chimneys giving satisfactory dispersal or alternatively they may be discharged at a low level with resulting heavy ground pollution. Heavy particulate matter will be deposited in the immediate vicinity of the emission whereas aerosol particles and gases will be dispersed over a wide area and a proportion will diffuse upwards and not reach ground level.

It is apparent that hazards may exist either from the deposition of fluoride particles on the ground and on herbage, or from the presence of fluorides in the atmosphere, where they may be inhaled by animals or man. Crops may be damaged and plant growth restricted by either, but it is the physical contamination of herbage which gives rise to the principal hazard, animal fluorosis.

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Measurement of Fluorides

The amounts of fluoride deposited may be measured by the standard deposit gauge, the material collected being analysed and the results expressed either as total fluoride or subdivided into soluble and insoluble fluorides. This method is frequently used for monitoring emissions from individual industrial establishments.

Deposits in a rural area of England (Essex) have been found to average 0.69 g of soluble fluoride per 100 square metres per month, whereas in London values ranging from 0.58 to 2.6 g per 100 m² have been obtained, the excess over rural areas presumably being largely due to the combustion of coal. Measurements by local authorities at sites in Warwickshire have varied from 0.5 to 1.08 g per 100 square metres, the latter figure being recorded downwind from an aluminium works. In contrast to these readings, a monthly average of 4.5 g per 100 m² was measured near the centre of Rotherham at a distance of approximately 1½ miles (2.5 km) from a steelworks at that time using fluor spar in open-hearth furnaces, and an average of 3.64 per 100 m² was obtained at a site near the centre of the pottery industry in Stoke-on-Trent.

Deposit gauge readings are, however, of limited value for they are essentially an index of local pollution representative only of a small area round the gauge. The alternative method of measuring fluoride emissions is to use a volumetric apparatus to measure the gaseous and particulate matter in the atmosphere. Samples taken in the centre of London indicate a normal winter pollution of particulate matter of 0.05-0.09 μg per cubic metre expressed as fluotrine. The concentration of gaseous fluorides is less than 0.05 μg per m³ so that the total fluoride content of the normal London air would be of the order of 0.1-0.15 μg per m³. During a period of exceptionally heavy pollution associated with severe fog, the amount of particulate fluoride rose to 0.8 μg per m³. In contrast, measurements of total particulate and gaseous fluoride over the winter months yielded an average of 0.7 μg per m³ at Rotherham and 1.9 μg per m³ at Stoke-on-Trent.

Similar, and in some cases rather higher, atmospheric concentrations have been reported from urban and rural areas of the USA (Cholak, 1960).

The Industrial Hazard in Man

In spite of continual vigilance by industrial health authorities, few cases of human industrial fluorosis have been identified and incidents have mostly been of a relatively trivial character. An exception was in the Danish cryolite industry where cases were identified and investigated by Roholm (1937). His descriptions still provide the classical account of severe human fluorosis due to the inhalation of fluoride dusts.
The cryolite industry

The mineral cryolite contains some 50% of fluorine and at the time of Roholm's investigations, many workers had been exposed to very heavy concentrations of the dust for long periods. Typical atmospheric dust concentrations were 30-40 mg per m³ and in two enclosed areas of the works concentrations of up to more than 9000 mg per m³ were found. Many of the exposed workers complained of acute gastric symptoms or shortness of breath, but it was difficult to say how far these might have been toxic symptoms due to cryolite, and how far they might have been a physical effect of the very heavy dust concentrations. Most of these symptoms disappeared quickly on leaving work. The most typical symptoms of fluorosis were complaints related to skeletal and muscular systems and 35% of the workers complained of pains, stiffness or rheumatic attacks. On radiological examination, 84% of exposed workers were found to exhibit evidence of osteosclerosis, the severity being related to both the duration of exposure and the concentration of dust inhaled. Faint or moderate pulmonary fibrosis was found in half the workers.

Roholm also traced previous workers in the industry. Although they were known to have been exposed to concentrations of dust at least as heavy as or heavier than workers currently employed in the industry, the number and severity of the cases of osteosclerosis was proportionately much lower. This was considered by Roholm to be a clear indication of the reversibility of the condition, a hypothesis confirmed by Likins, McClure & Steere (1956) who observed at Bartlett, Texas, that when a population ceased to be exposed to a high fluoride intake, fluoride excretion rates continued at a high level for a considerable time. A higher incidence of spondylitis deformans was found in workers who had left the industry. Cases of pulmonary fibrosis did not show any evidence of having deteriorated since leaving.

Roholm estimated that the workers engaged in the industry probably absorbed between 0.2 and 1 mg per kilogram of body-weight per day, the former figure being the more likely. The urinary excretion of two workmen, both with osteosclerosis and much exposed to dust, was 2.45 and 2.09 mg fluorine per day, as compared with two normal subjects whose daily excretion was 0.22 and 0.1 mg, respectively.

British experience: the Fort William incident

In Great Britain, apart from one incident, only occasional cases of human industrial fluorosis have been described and most of these have been asymptomatic. Thus Bridge (1941) described radiological changes in the workers at a factory using hydrogen fluoride. Wilkie (1940) similarly found radiological osteosclerosis in two workers employed in the manu-
facture of hydrogen and aluminium fluorides, and Bowler et al. (1947) found a case in an employee in a magnesium factory. Murray & Wilson (1946) described an episode where a family living adjacent to ironstone workings where calcining took place were exposed to heavy fumes over a period of years. Members of this family were found to be excreting from 1.6 to 4.6 ppm fluorine in the urine. They complained of muscular and joint pains, which they were convinced were due to the fumes, but radiological examination revealed no evidence of osteosclerosis.

The most notable incident in Great Britain occurred in an aluminium factory near Fort William, Scotland, and was investigated by the Medical Research Council during the years 1945-48 (Agate et al., 1949). Concentrations of fluorides in the factory atmosphere ranged from 0.14 to 3.13 mg per m³ in the furnace room, while outside they varied from 0.22 mg at a distance of 200 yards (180 m) to 0.04 mg in the centre of Fort William, 1 mile (1.6 km) away.

None of the factory workers had complained of any symptoms and the incidence of aches and pains in the furnace-room workers was no greater than in other workers in the factory or in local residents. There was a suggestion that the furnace-room workers had rather more frequent digestive disorders and coughs, and the investigators themselves noted the irritating nature of the furnace-room fumes. No dyspnoea on exertion was found and no increased liability to suffer from fractures. There were no physical signs of skeletal fluorosis, but one furnace-room worker was suffering from ankylosing spondylitis which was thought by the investigators to be unconnected with fluorides. Among the other factory workers there was one case of chronic pulmonary fibrosis, and one of emphysema with a rigid barrel-shaped chest. Radiological examination revealed signs of osteosclerosis in 48 of the 189 furnace-room workers who were radiographed, the proportion of cases increasing with the time of exposure. Radiological signs included lipping of the dorsal and lumbar spines with beak-like exostoses, a granular, amorphous, and somewhat dense appearance of the pelvis, often with short bony exostoses, and plaques of dense bone on the tibia and fibula.

Workers in the factory showed an increased urinary excretion of fluoride, the amount being closely related to the severity of exposure; the average excretion of 65 heavily exposed workers in the furnace room was 9.03 mg per day. Outside the factory no clinical signs or symptoms among local residents were found and the incidence of mottled teeth in children in the vicinity did not differ appreciably from that in unaffected areas.

Other studies on industrial fluorosis

Other incidents resulting in human industrial fluorosis have been noted by Hodge & Smith (1965). A recent investigation is that of Derryberry, Bartholomew & Fleming (1963) in an American phosphate fertilizer
factory in which a group of 74 workers exposed to relatively high fluoride concentrations was compared with a matched control group of unexposed workers. In this study the fluoride exposure of the individual workers was estimated by repeated examinations of urine samples taken at the end of the night shift, and the percentage of specimens containing 4 mg per litre or more was calculated as an index of exposure for each person.

No disability attributable to fluoride was found in any of the workers. Minimal or questionable degrees of increased bone density were found radiologically in 23% of exposed employees, but in no case were the bone changes sufficient for them to have been recognizable as increased osseous radiopacity in routine radiological practice. No increase of abnormal findings relating to gastrointestinal, cardiovascular, metabolic or haematological conditions was observed in the exposed group. Respiratory conditions, however, were more frequent, though these might have been due to the irritating properties of the acid gases. An apparent increase in albuminuria in the exposed group was found by Derryberry to be significant only at the 10% level of probability.

Miller (1955) quotes a report by Babayants from a super-phosphate factory with no purifying or recovery plant in the USSR. In a series of 56 tests during 1938-39, an average concentration of 0.98 mg per m³, with a maximum concentration of 18.4 mg, was recorded at a distance of 1000 metres from the factory. In a further series of 61 tests on the leeward side of the factory after the introduction of safeguards, the average concentration was found to be 0.050 mg per m³ at the same distance.

The Fluoride Intake of the Population

Suggestions have occasionally been made that where water is fluoridated at 1 ppm, the additional fluoride intake of the population in areas where there is industrial pollution might create a hazard. In most circumstances such fears may easily be discounted. The average man engaged on moderately strenuous work is known to inhale approximately 20 cubic metres of air per day. If, therefore, the fluoride pollution of the air of any place is known, it is a simple matter to calculate as an upper limit the maximum fluoride uptake on the assumption that all the fluorides inhaled are retained.

Using this method it was found that in Central London the fluoride intake of the average man would be of the order of 0.003 mg per day normally and 0.03 mg during a day of thick fog with exceptionally heavy pollution. Stoke-on-Trent and Rotherham have been among the most heavily polluted areas of the country. In the former, where the pollution was a generalized one covering the entire city and its environs, the intake of the average man would be of the order of 0.04 mg per day, and in Rotherham, where the pollution was more localized, the intake would be 0.01-0.02 mg. It is evident, therefore, that with these levels of pollution, even when allowance is made
for the increased air intake of a workman engaged in a very strenuous occupation, the amount of fluoride absorbed from the atmosphere would be but a fraction of that shown by McClure (1949) and Longwell (1957) to be contained in his diet. By contrast, however, Lindberg (1964) has reported atmospheric fluoride concentrations of from 0.098 to 0.485 mg per m³ near a super-phosphate plant in the USSR. This suggests maximum possible adult intakes of from 1.9 mg to 9.7 mg and high levels of fluoride intake were, in fact, confirmed by the finding of dental fluorosis and a low incidence of dental caries in schoolchildren in that area. Somewhat earlier, in an investigation of two USSR aluminium plants, Sadilova (1957) reported average atmospheric fluoride concentrations of 0.01-0.13 mg per m³ in the ambient air in the vicinity of the plants, with maximum concentrations of 0.89 mg per m³ at one plant and 0.61 at the other. An investigation of 2483 children in the vicinity was reported by this author also to have revealed increased dental mottling and diminution in the incidence of dental caries.

Other possible hazards are more remote. It has been shown that the increase in the fluoride content of the milk from cows suffering from fluorosis is negligible. There is no significant accumulation in the soft tissues and the prolonged boiling of bones from such animals has shown that there is no hazard in the making of soups and stews (Allcroft, 1956).

No appreciable increase occurs in the fluoride content of vegetables grown on soils rich in fluorides, and any hazard if it exists would arise from surface contamination of vegetables. From our knowledge of the amounts of fluoride deposited in affected areas of the United Kingdom, of the amounts of vegetables consumed by man, and from the practice of washing vegetables and discarding the outer and older leaves, it is apparent that any additional intake in the diet would also be negligible.

The relative unimportance of atmospheric fluorides as a human hazard has also been demonstrated in a recent study by Call and his colleagues (1965) of material from 127 autopsies in the State of Utah, where air pollution from industry was known to give rise to atmospheric fluoride concentrations of up to 0.8 µg per m³, with a mean annual value of 0.24 µg.

Animal Fluorosis

It was the effects on animals in polluted areas which first drew attention to the importance of industrial fluorosis, and many reports have been published over the past 50 years. In the USA, the problem has been reviewed by Phillips et al. (1960) and, in Great Britain, a detailed investigation of the problem over an 8-year period has recently been completed (Burns & Allcroft, 1964; Allcroft, Burns & Herbert, 1965).

Cattle are the animals principally affected in Britain. As in man, dental lesions are the most sensitive clinical sign, but skeletal abnormalities are
the most characteristic feature in severe cases and lameness is frequently the
first sign noted by the farmer. An important cause of lameness in British
cases is fracture of the pedal bone. Debility and a loss of milk production
are a frequent result of the lameness, but in only a small number of cases
are dental lesions severe enough to cause difficulty in grazing and mastication.

Part of the British investigation was a survey of herds in industrial areas
to establish the distribution of animal fluorosis in England and Wales.
Fluorosis severe enough to cause economic loss was found on 170 farms in
17 different areas. Of these, 9 farms were so badly affected that cattle were
no longer kept, 61 were classified as severely and 100 as slightly affected.
In addition, a considerable number of farms were found to have cattle show-
ing only dental lesions.

Control Measures and their Effectiveness

Standard methods for controlling fumes and arresting particulate emis-
sions have done much to eliminate fluorine hazards in industry, and in the
United Kingdom it is now many years since a case of industrial fluorosis
occurred in a factory employee. Changing methods in industry have also
eliminated many of the sources of pollution. Thus, the sintering of iron
ores is replacing the older calcining process and a high proportion of the
fluoride is retained in the final sinter. In the pottery industry the use of
defluoridated Cornish stone and of higher chimneys is reducing pollution.
Emissions from the brick industry are still substantial and at present no
satisfactory method has been discovered for removing fluorides from the
fumes.

The major hazard is an agricultural one. The occasional farmer in a
heavily polluted area has had to give up animal husbandry and confine him-
self to arable farming; other farmers use flying herds in which cows are
brought to the farm as adults and stay for only a few lactations.

An important part of the British investigation was to examine the pos-
sibility of alleviating the effects of fluorosis in a self-contained dairy herd
in a polluted area of the pottery industry in Stoke-on-Trent. The results
showed that the feeding of mineral supplements, such as aluminium sulfate,
with or without additional calcium and phosphorus compounds, delayed
the effects of excessive fluorine intake but did not prevent them sufficiently
to be of practical value, and that good farming practices—in particular,
good pasture management—provided the best means of mitigating the ill-
effects.

7. SUMMARY (A. E. Martin)

By their wide distribution in nature, their inevitable presence in man’s
food and drink and their consequent presence in the tissues of the human
body, fluorides form a natural part of man's environment, yet when present in excess they are known to be harmful. Studies of the geographical distribution of dental mottling in the USA were begun during the early decades of the century and the identification of fluorides in water supplies in 1931 led to a comprehensive survey designed, in the first place, to find the threshold limit for the avoidance of dental fluorosis and, later, to ascertain the concentration in a water supply necessary for optimum dental protection. When the artificial fluoridation of water was first considered, this survey provided a useful starting-point for a programme of specific epidemiological and experimental studies which, over the past three decades, has yielded a mass of data confirming the safety of fluoridation. This has been supplemented by independent studies from other countries which have provided further supplementary material for use in defining the upper limits of a safe fluoride intake. The results have shown that for the climatic, nutritional and environmental conditions under which the surveys have been carried out, a level of approximately 1 ppm fluoride in temperate climates has no harmful effects on the community. The margin of safety is such that it will cover any individual variation of intake to be found in such areas.

High levels of fluoride in drinking waters are found in some hot countries, such as India, China, Japan and parts of the Middle East and Africa, and some cases of osteosclerosis and crippling fluorosis have been observed. Occasionally, instances of harmful effects in these countries have been reported where there appear to be relatively low levels of fluoride in the drinking waters, and these findings were at first hard to reconcile with those of the American and European studies. In many of the reports, accurate medical histories are lacking and it is hard to ascertain how long or how consistently a person has consumed a particular water. Many of the reports also have been written primarily from a clinical angle and fluoride levels are found to be judged on inadequate analyses of water, often from shallow wells or water-holes where the mineral content may fluctuate from season to season.

Hot climates result in fluid intakes probably much higher even than those in the Arizona and Texas studies, and in addition populations have sometimes been exposed to severe nutritional deficiencies to a degree not experienced in the USA or Europe. Nevertheless, the apparent differences between countries have been puzzling and it was not until recently that information became available on which to base more accurate assessments. Dr Siddiqui has shown in his contribution the importance of taking into account a person's total fluoride intake as national dietetic habits may be responsible for considerable differences. The importance of considering the total fluoride intake emerges also in Professor Minoguchi's study of Japanese experience. Variations in total fluoride intake are therefore factors which must be taken into account when determining a country's fluoridation policy, for similar total fluoride intakes may be found where a water supply con-
tains, for instance, 1 ppm in a temperate climate or 0.7 ppm in Arizona or 0.6 ppm in Japan. Each country should, therefore, make its own assessment of the desirable optimum concentration of fluoride in its water supplies.

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CHAPTER 9

Fluorides and dental health

P. ADLER

1. INTRODUCTION

Although some earlier papers (Bunting, 1927; McKay, 1929; Dean, 1933) contain references to the low prevalence of caries among populations suffering from mottled enamel, the systematic investigations of Dean and co-workers (after the cause of this anomaly in development had been found to be excessive fluoride consumption) were the first to provide definite proof of the protective action of fluoride against dental decay. It had been repeatedly stated in the older literature that fluoride salts afforded protection against caries, but no adequate proof of this had been given.

The conditions under which mottled enamel appears were elucidated in the USA (Dean, 1954):

(a) Mottling occurs only when the dentition is permanently exposed to excessive fluoride during the development and calcification of the teeth. The permanent teeth are affected more frequently and to a greater extent than the milk teeth.

(b) As a rule, mottling is caused by the consumption of drinking water which is too rich in fluoride. The minimal threshold value at which a just perceptible change appears in the developing enamel of the permanent teeth was found to be 1.0-1.1 ppm for the people in the USA living in the temperate zone. At this concentration a small number of spots, gleaming like mother-of-pearl and hardly differing in colour from the rest of the enamel, develop on a limited number of teeth in scattered individuals. These spots are not noticeable to the layman and are in no way disfiguring. It is only after the fluoride concentration in drinking water exceeds 1.4-1.6 ppm that the first signs of more serious dental fluorosis appear: some of the teeth of a few

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members of the population then show circumscribed spots, coloured light-yellow to brownish. When the fluoride content exceeds 2.0 ppm, then brownish spots, varying from small to large in size, can be seen on numerous teeth in the great majority of the members of the exposed community. When the fluoride content is more than 2.5 ppm, the enamel loses its smoothness: signs of serious dental hyperfluorosis appear, with hypoplastic zones and an often quite dark discoloration affecting extensive areas of the enamel of several teeth in the persons affected. The degree of mottling thus runs parallel to the fluoride content of the drinking water, but this parallelism is by no means absolute, since, in addition to the fluoride content, the amount of water consumed—i.e., the quantity of fluoride ion ingested—also plays a part. When the average annual temperature is high, then—because of the increased water consumption—small fluoride concentrations have a more harmful effect on the enamel than they do in the temperate zone (Galagan & Lamson, 1953). Living and eating habits are also important; in cases of malnutrition, for example, the enamel has been found to be more susceptible (Schour & Massler, 1947). In comparison with the amount consumed in water, the fluoride content of solid food plays only a minor role; however, in some special circumstances it, too, may be of practical importance (see Chapter 2, section 3 and Chapter 8, section 4).

(c) A change in the drinking-water supply (conversion from water with excessive fluoride to fluoride-poor drinking water) causes the mottling to disappear in children born after the conversion (Dean & McKay, 1939), but mottling in already formed enamel is unaffected.

(d) Disfiguring mottling is the first sign of a lesion caused by increased fluoride consumption, but it appears only at a late stage, on the eruption of the mottled teeth. The ameloblast active in enamel formation is the most sensitive of all kinds of cells of the body to fluoride. Other tissues, organs and functions are only affected by considerably higher fluoride concentrations.

After elucidating the question of the threshold of harmful concentration, the protective effect against caries was ascertained quantitatively. Next, the naturally favourable conditions for the dentition occurring by chance in many places were artificially reproduced by enriching fluoride-poor drinking water with fluoride ion until the optimal concentration was reached. Almost at the same time an attempt was made to bring about the desirable fluoride consumption by means of vehicles other than drinking water, primarily in order to provide protection against decay for population groups without a piped water supply.

In addition to increasing fluoride consumption to a desirable level, local fluoride application was also tried, after it had been shown that even fully developed enamel can take up fluoride from outside and that this also ensures a protective action against caries. This local application took the form, on the one hand, of repeated brief application of fluoride solution to the teeth
by the dentist or an auxiliary (referred to in the literature as “topical application”) and, on the other, the use of toothpastes and mouthwashes containing fluoride.

In the following we shall first recapitulate the observations which led to the artificial enrichment of drinking water with fluoride. We shall then review the results given so far by this health measure and compare them with those achieved by other means of fluoride application, in an attempt to indicate the best method of caries prophylaxis with fluoride.

2. EFFECT OF FLUORIDE INGESTION ON CARIES EXPERIENCE

Fluoride Ingestion with Water

Caries of the permanent dentition in school-age children and adolescents consuming domestic waters with naturally occurring fluoride

Dean and co-workers (Dean, 1945, 1954) have clearly shown by systematic examination of 12- to 14-year-old children of both sexes in 21 cities in the

<table>
<thead>
<tr>
<th>City</th>
<th>Number of examinees</th>
<th>Domestic water content (mg per litre)</th>
<th>Total hardness (DSF)</th>
<th>CER (DMF) count</th>
<th>First molar mortality</th>
<th>Upper incisor proximal surface caries</th>
<th>Percentage of caries-free examinees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorado Springs</td>
<td>404</td>
<td>2.6</td>
<td>27</td>
<td>246</td>
<td>4.7</td>
<td>4.7</td>
<td>28.5</td>
</tr>
<tr>
<td>Galesburg</td>
<td>273</td>
<td>1.9</td>
<td>247</td>
<td>236</td>
<td>15.0</td>
<td>15.0</td>
<td>30.8</td>
</tr>
<tr>
<td>Elmhurst</td>
<td>170</td>
<td>1.6</td>
<td>323</td>
<td>252</td>
<td>11.8</td>
<td>11.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Joliet</td>
<td>447</td>
<td>1.3</td>
<td>339</td>
<td>323</td>
<td>19.3</td>
<td>19.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Aurora</td>
<td>633</td>
<td>1.2</td>
<td>329</td>
<td>291</td>
<td>14.6</td>
<td>14.6</td>
<td>28.5</td>
</tr>
<tr>
<td>East Moline</td>
<td>152</td>
<td>1.2</td>
<td>276</td>
<td>253</td>
<td>15.6</td>
<td>15.6</td>
<td>28.5</td>
</tr>
<tr>
<td>Maywood</td>
<td>171</td>
<td>1.2</td>
<td>75</td>
<td>258</td>
<td>11.7</td>
<td>11.7</td>
<td>28.5</td>
</tr>
<tr>
<td>Kewanee</td>
<td>123</td>
<td>0.9</td>
<td>415</td>
<td>343</td>
<td>29.3</td>
<td>29.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Pueblo</td>
<td>614</td>
<td>0.6</td>
<td>302</td>
<td>412</td>
<td>20.2</td>
<td>20.2</td>
<td>28.5</td>
</tr>
<tr>
<td>Elgin</td>
<td>403</td>
<td>0.5</td>
<td>103</td>
<td>444</td>
<td>20.3</td>
<td>20.3</td>
<td>28.5</td>
</tr>
<tr>
<td>Marion</td>
<td>363</td>
<td>0.4</td>
<td>209</td>
<td>556</td>
<td>25.1</td>
<td>25.1</td>
<td>28.5</td>
</tr>
<tr>
<td>Lima</td>
<td>454</td>
<td>0.3</td>
<td>223</td>
<td>652</td>
<td>55.9</td>
<td>55.9</td>
<td>28.5</td>
</tr>
<tr>
<td>Middletown</td>
<td>370</td>
<td>0.2</td>
<td>329</td>
<td>703</td>
<td>65.9</td>
<td>65.9</td>
<td>28.5</td>
</tr>
<tr>
<td>Zanesville</td>
<td>459</td>
<td>0.2</td>
<td>291</td>
<td>733</td>
<td>99.6</td>
<td>99.6</td>
<td>28.5</td>
</tr>
<tr>
<td>Elkhart</td>
<td>278</td>
<td>0.1</td>
<td>220</td>
<td>823</td>
<td>34.2</td>
<td>34.2</td>
<td>28.5</td>
</tr>
<tr>
<td>Michigan City</td>
<td>236</td>
<td>0.1</td>
<td>141</td>
<td>1,037</td>
<td>80.1</td>
<td>80.1</td>
<td>28.5</td>
</tr>
<tr>
<td>Quincy</td>
<td>330</td>
<td>0.1</td>
<td>88</td>
<td>796</td>
<td>71.2</td>
<td>71.2</td>
<td>28.5</td>
</tr>
<tr>
<td>Portsmouth</td>
<td>489</td>
<td>0.1</td>
<td>90</td>
<td>722</td>
<td>72.8</td>
<td>72.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Waukegan</td>
<td>423</td>
<td>0</td>
<td>134</td>
<td>810</td>
<td>79.9</td>
<td>79.9</td>
<td>28.5</td>
</tr>
<tr>
<td>Oak Park</td>
<td>359</td>
<td>0</td>
<td>132</td>
<td>722</td>
<td>31.0</td>
<td>31.0</td>
<td>28.5</td>
</tr>
<tr>
<td>Evanston</td>
<td>256</td>
<td>0</td>
<td>131</td>
<td>673</td>
<td>42.6</td>
<td>42.6</td>
<td>28.5</td>
</tr>
</tbody>
</table>
USA that there is a definite relationship between the fluoride content of drinking water and caries experience: the higher the fluoride content, the lower the caries experience (Table 1).

Caries experience was expressed by the sum total of overtly carious, filled or extracted permanent teeth per person—DMF (decayed, missing, filled) or CER (caries, extractio, restauratio) count. The investigation was limited to children who had been born in the district concerned, had always resided there, and had always consumed the local water. In order to check the effect of the presence or absence of a drinking-water constituent (i.e., a varying concentration of fluoride), it was necessary to select for the survey localities whose water supply had undergone no change, at least during the lifetime of the subjects, but where the fluoride content of the water varied within given limits. The caries experience of children aged 12-14 years was investigated, since children in this age-group could still be completely reached in the schools. Apart from wisdom teeth, the permanent teeth have already erupted in the majority of children of this age, and numerous teeth known to be liable to caries (first molars, upper incisors, upper first premolars) had already been exposed for several years to cariogenic influences in the oral cavity.

While a considerable degree of regularity was evident in the antagonism between the fluoride content of the water and caries experience (Fig. 1), no

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**FIG. 1**

RELATION BETWEEN DENTAL CARIES AND FLUORIDE CONTENT OF WATER

![Graph showing the relationship between fluoride content of water and DMF count per 100 examinees.](https://example.com/graph)

*Based on the data obtained by Dean and co-workers from the examination of the permanent teeth of 7297 schoolchildren aged 12-14 years in 21 cities of the USA. (After Dean, 1954)*
connexion could be detected between caries experience and water hardness (Fig. 2), which had been regarded as a determining factor in the development of caries since the time of Röse (1904).

As can be seen from Table 1 and Fig. 1, minor deviations from the general rule are visible in all the fluoride concentration ranges studied, so that caries experience is not strictly inversely proportional to fluoride content. Consequently, the data from the individual localities are best considered, not separately, but grouped according to the fluoride content of the water. For example, in Fig. 3, the average DMF count per 100 examinees

![Figure 2](image)

**Figure 2**

**RELATION BETWEEN DENTAL CARIES AND HARDNESS OF WATER**

*Data from 16 of the 21 cities referred to in Fig. 1. (After Dean, 1945, 1954)*

![Figure 3](image)

**Figure 3**

**DATA FROM THE 21 CITIES REFERRED TO IN FIG. 1 GROUPED ACCORDING TO FLUORIDE CONTENT OF WATER**

<table>
<thead>
<tr>
<th>Number of cities studied</th>
<th>Number of children examined</th>
<th>Number of DMF teeth per 100 examinees</th>
<th>Fluoride content of water (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>3867</td>
<td>![Fluoride content]</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>3</td>
<td>1140</td>
<td>![Fluoride content]</td>
<td>0.5 - 0.9</td>
</tr>
<tr>
<td>4</td>
<td>1403</td>
<td>![Fluoride content]</td>
<td>1.0 - 1.4</td>
</tr>
<tr>
<td>3</td>
<td>847</td>
<td>![Fluoride content]</td>
<td>&gt; 1.4</td>
</tr>
</tbody>
</table>

*After Dean (1945, 1954).*
is shown for four—intentionally limited—ranges of concentration—namely, $>1.4$, $1.0-1.4$, $0.5-0.9$, and $<0.5$ ppm. This removes the small irregularities mentioned above (produced by minor differences in nutrition, general way of life, etc.) and clearly reveals the regular inverse correlation.

When mottling of the enamel in the various localities is also taken into account, it is found that a certain range of concentration exists where there is still no danger of any harmful dental hyperfluorosis, nor even of slight discoloration of the teeth, although the fluoride concentration already provides definite protection against caries. This protection is almost as great as that given by higher fluoride concentrations, including those causing a disfiguring mottling of the enamel. As can be seen from Fig. 4 (Hodge, 1950), this protective concentration is about 1.0-1.2 ppm for the temperate zone of the USA.

FIG. 4
RELATIONSHIP BETWEEN FLUORIDE CONTENT OF DRINKING WATER, CARIES EXPERIENCE AND DENTAL FLUOROSIS

$\diamondsuit$ Fluorosis index,
$\triangle$ DMF count.

* After Hodge (1950).

The above data, derived from the older schoolchildren, were subsequently confirmed in other parts of the USA as well as in other countries and continents, and also extended. In particular, it was found that the protective effect on the permanent teeth exists already in children commencing school. Its extent appears to remain the same during the whole of the school-attendance period. Furthermore, the effect, expressed as a percentage of the caries
experience of the unprotected population, was *practically the same* in all parts of the world. As compared with the results mentioned above, there were differences between the various investigators in regard to the grouping of the children by age and of the localities according to the fluoride content of the drinking water, as well as in regard to the system used to characterize caries experience.

**FIG. 5**

Caries experience of Hungarian schoolchildren in relation to fluoride content of water

In Fig. 5 we show, as an example, the results of investigations made in Hungary. Although the ranges of concentration of fluoride in the drinking water vary from those chosen by Dean, Fig. 5 clearly demonstrates the parallelism between fluoride content and protective effect, and this in a
population appreciably less attacked by caries. The protective effect can be seen to exist in all annual age-groups up to school-leaving age. The percentage protection is about the same in the individual age-groups and no distinct variation between the sexes can be detected (Fig. 6).

**Fig. 6**
Caries prevalence and caries protection in children consuming water with a medium (M) or high (H) content of fluoride, expressed as a percentage of that in children consuming water with a low (L) content of fluoride.

According to Dean (Fig. 3), a fluoride content of 0.5 ppm is usually taken as the threshold value for the protective effect. In the case of a population whose composition, social structure, eating habits, general living standards and customs are all uniform, even small differences in the “sub-threshold” concentration range cause distinct variations in the caries experience of school-age children (see Fig. 7, concerning two adjacent villages in the Hungarian plain). The fluoride content of certain wells is higher in the village whose children have better teeth, even though the presumed
TABLE 2
Comparison of the fluoride level in the waters from artesian wells in the Hungarian villages of Nagyléta and Vértes

<table>
<thead>
<tr>
<th>Fluoride level (mg per litre)</th>
<th>Number of wells with the particular fluoride level at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nagyléta</td>
</tr>
<tr>
<td>Lower than 0.1</td>
<td>0</td>
</tr>
<tr>
<td>Between 0.1 and 0.2</td>
<td>6</td>
</tr>
<tr>
<td>Between 0.2 and 0.3</td>
<td>4</td>
</tr>
<tr>
<td>Between 0.3 and 0.5</td>
<td>2</td>
</tr>
</tbody>
</table>

* Data from Csengura & Kovács (1953).

Threshold value of 0.5 ppm is not reached in any of them (Table 2). Nevertheless, the small difference in fluoride content was sufficient to bring about the changes in caries experience shown in Fig. 7.

FIG. 7
Caries experience in two adjacent Hungarian villages with small differences in the fluoride content of the water

* The black columns indicate the standard error; the figures at the top of the columns denote the number of children examined.
### TABLE 3
**COMBINATION OF THE CARIES-PROTECTIVE EFFECT OF WAR-TIME DIET AND INCREASED FLUORIDE INGESTION IN ENGLAND**

<table>
<thead>
<tr>
<th></th>
<th>1943</th>
<th>1949</th>
<th>1943</th>
<th>1949</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>North Shields</td>
<td>South Shields</td>
<td>North Shields</td>
<td>South Shields</td>
</tr>
<tr>
<td>Mean F level of domestic water (mg per litre)</td>
<td>0.25</td>
<td>1.4</td>
<td>0.25</td>
<td>1.4</td>
</tr>
<tr>
<td>Children of 12 years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of caries-free examinees</td>
<td>4.8</td>
<td>25.8</td>
<td>26.4</td>
<td>50.6</td>
</tr>
<tr>
<td>Mean CEW (DMF) count</td>
<td>4.3</td>
<td>2.4</td>
<td>2.4</td>
<td>1.3</td>
</tr>
<tr>
<td>expressed as percentage of North Shields count</td>
<td>100</td>
<td>55.8</td>
<td>100</td>
<td>54.2</td>
</tr>
<tr>
<td>expressed as percentage of 1943 count</td>
<td>100</td>
<td>100</td>
<td>55.8</td>
<td>54.8</td>
</tr>
<tr>
<td>Children of 5 years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of caries-free examinees</td>
<td>11.6</td>
<td>27.0</td>
<td>26.4</td>
<td>28.0</td>
</tr>
<tr>
<td>Mean CEW (def) count</td>
<td>6.6</td>
<td>3.9</td>
<td>4.4</td>
<td>3.5</td>
</tr>
<tr>
<td>expressed as percentage of North Shields count</td>
<td>100</td>
<td>59.1</td>
<td>100</td>
<td>79.5</td>
</tr>
<tr>
<td>expressed as percentage of 1943 count</td>
<td>100</td>
<td>100</td>
<td>56.7</td>
<td>89.7</td>
</tr>
</tbody>
</table>

* Data from Weaver (1950).
* The number of children at each examination in each age-group was 500.

### TABLE 4
**CER COUNTS AND DISTRIBUTION INTO DIFFERENT CER CLASSES OF BOYS AND GIRLS, AGED 16-18 YEARS, IN HUNGARY, ACCORDING TO THE FLUORIDE LEVEL OF THE DOMESTIC WATERS**

<table>
<thead>
<tr>
<th></th>
<th>F level lower than 0.35 mg per litre</th>
<th>F level higher than 0.35 mg per litre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>Number of examinees</td>
<td>2217</td>
<td>2126</td>
</tr>
<tr>
<td>Number of CER teeth per examinee</td>
<td>4.91</td>
<td>4.81</td>
</tr>
<tr>
<td>Standard error</td>
<td>0.071</td>
<td>0.089</td>
</tr>
<tr>
<td>Percentage of caries-free examinees (CER O)</td>
<td>17.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Percentage with 1 CER tooth</td>
<td>11.5</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>11.8</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>11.2</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>10.3</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>8.9</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>12.3</td>
<td>20.4</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Highest number of CER teeth observed in one person</td>
<td>21</td>
<td>22</td>
</tr>
</tbody>
</table>

* Data from Adler (1957).
* The groups consuming domestic waters containing more than 0.35 mg F per litre include all pupils of the grammar schools (gymnasium) in Szekszard and Hatvan who were born and continuously resident in the respective city, or whose residence there began before the end of the 6th year of life. While in Szekszard a public water supply exists, in Hatvan domestic waters are drawn from individual artesian wells. In no instance does the sum of the percentages, which have been corrected to one decimal place, in the columns differ from 100 by more than 0.5%.
We regard as significant the finding that the protective effect of fluoride can combine with other factors in reducing caries experience. Thus in England the protective effect of fluoride-rich water on the permanent teeth has been demonstrated both alone and in combination with the caries reduction resulting from war-time diet (Table 3).

The protective action is not restricted to school-age children; it is also found in adolescents. For example, Table 4 shows the caries distribution among Hungarian adolescents aged from 16 to 18 years (Adler, 1957) who had consumed drinking water with a fluoride content above or below 0.35 ppm, respectively.

On the basis of data collected in the suburbs of Chicago, in particular, Arnold (1943) forecast that artificial enrichment of drinking water with fluoride would bring about:

(a) a fall of nearly 60% in caries intensity;
(b) a sixfold increase in the number of children still caries-free at school-leaving age;
(c) a decrease of about 75% in the losses of first permanent molars during this period of life; and
(d) a fall of about 95% in caries attack on the approximal surfaces of the upper incisors.

The success of this prediction will be commented on in the following.

*Caries of the permanent dentition in school-age children consuming domestic waters with artificial addition of fluoride*

The suggestion made initially by Cox (1939) that the protective action of increased fluoride consumption—confirmed epidemiologically and in animal experiments—should be utilized for public health purposes was first adopted in North America in the middle 1940s. Systematic studies on the various consequences of increased fluoride ingestion following the addition of fluoride to drinking water, studies extending over several years, were carried out in four towns—namely, Brantford, in Canada (control towns: Sarnia and Stratford), and Evanston, Grand Rapids and Newburgh, in the USA (control towns: Oak Park; Muskegon and Aurora; Kingston). The fluoride content of the drinking water was increased by the addition of sodium fluoride to about 1.2 ppm in Brantford and to 1.0 ppm in the other towns.

It should be remembered that this dosage applies to North American towns, and to inhabitants of the temperate zone. When the annual average temperature is higher, a lower fluoride level suffices to produce the same effect, and this also holds true in the case of dietetic habits involving increased consumption of liquid or fluoride-rich foods.

In view of the general interest in these studies, the partial results were published seriatim, leading many communities to introduce fluoridation without awaiting the completion of the investigations. Unfortunately, this
also happened in Muskegon, the fluoride-poor control town of the Grand Rapids study, in the sixth year of the studies. The results obtained in the four studies are not only basically similar, but to a large extent even quantitatively identical. Nevertheless there are differences in presentation, in the time when the interim researches were made, in the grouping of the examinees by age, in the findings deemed worthy of communication, etc. Because of this it is not possible to summarize the results in a uniform manner. We can only enlarge on individual points in the results communicated. In addition, we shall refer to other studies carried out later elsewhere, so far as these results contribute to an understanding of questions which remain unsettled.

FIG. 8
GRAND RAPIDS: CARIES REDUCTION IN CHILDREN WITH LIFE-LONG CONSUMPTION OF FLUORIDATED WATER (1.0 ppm) 

*For comparison, the caries prevalence in Aurora, with 1.3 ppm naturally occurring fluoride in the water, is shown.*
The extent of the protection against caries attack on the dentition as a whole has been shown by concurrent findings to depend on the age when ingestion of fluoridated water commenced and the age when the results were recorded. The longer the period of “dental life” in an environment characterized by increased—presumably optimal—fluoride ingestion, the more distinct the protective action. The protective action throughout the compulsory school-attendance period and even afterwards is quite apparent (see Fig. 8, which shows the separately published longitudinal results of the Grand Rapids study combined into a single graph).

As regards the previously mentioned predictions of Arnold regarding the results of water fluoridation, it was found that:

(a) The fall in caries intensity among 12- to 14-year-old children was well up to expectations. As can be seen from Table 5, the protective effect

<table>
<thead>
<tr>
<th>Period of fluoridation (years)</th>
<th>CER (DMF) count per 100 children of 12-14 years of age, born and continuously resident at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grand Rapids</td>
</tr>
<tr>
<td>Before start</td>
<td>958</td>
</tr>
<tr>
<td>2½</td>
<td>833</td>
</tr>
<tr>
<td>5½</td>
<td>762</td>
</tr>
<tr>
<td>6</td>
<td>762</td>
</tr>
<tr>
<td>7½</td>
<td>951</td>
</tr>
<tr>
<td>10½</td>
<td>951</td>
</tr>
<tr>
<td>12</td>
<td>477</td>
</tr>
<tr>
<td>15</td>
<td>415</td>
</tr>
</tbody>
</table>

\(^a\) After 10 years of fluoridation in Newburgh the CER count per 100 children aged 13-14 years amounted to 610, as compared with 1176 in non-fluoridated Kingston.

is augmented in the case of increased fluoride consumption from birth (as compared with increased fluoride ingestion only at a later age). Thus it is not surprising that caries experience in Grand Rapids and Brantford, after 15 years of water fluoridation, fell to about 43-44% of the initial figure, and in Evanston and Newburgh, after about 10 years’ fluoridation, to only about 52-54% (of the initial figure or of the figure determined contemporaneously in the control town).

(b) In regard to the number of caries-free dentitions among 12- to 14-year-old children, the predicted sixfold increase had already been attained in Brantford after fluoridation had been under way for 8 years. In the 14th year of the study, such dentitions were about 9 times as numerous as in the fluoride-poor control town of Sarnia. After 18 years, 11.8% of 16- to 18-year-old Brantford examinees had a caries-free dentition, as compared
with only 0.41% of the same age-group in Sarnia. After 10 years of fluoridation, 13.5%, 10.7% and 5.6%, respectively, of 12-, 13- and 14-year-old schoolchildren in Grand Rapids were free from caries, whereas in Muskegon (where fluoride-enriched water had at that time already been consumed for more than 3 years) the corresponding figures were only 4.4%, 1.6% and 0%, respectively, giving an average of 9.9% for these three age-groups in Grand Rapids and 2.0% in Muskegon.

(c) In regard to the loss of the first molars, most reports contain no comparable figures. However, there are numerous comparable data (Table 6) on the over-all loss of teeth, involving chiefly the first molars. In Brantford, tooth mortality among 12- to 14-year-old children fell after 14 years of fluoridation (in comparison with data collected after the study had been under way for 3 years) by almost three-quarters; in Grand Rapids the figure fell after 15 years' fluoridation to almost the level found in Aurora at the outset. In New Britain, Conn., tooth mortality per examinee fell in 10 years from 0.93 to 0.23. In brief, the figures in Table 6 show that in this respect, too, fluoridation fulfilled expectations. Nevertheless, it should be remembered that in Sarnia—without any change in the drinking water—tooth mortality fell between 1948 and 1959 from 1.37 to 0.75 per person. Since loss of teeth depends not only on caries attack and progression but also, inter alia, on possibilities of treatment, the social status of the population, and the attitude of the dental profession to treatment of children in

### TABLE 6

<table>
<thead>
<tr>
<th>City</th>
<th>Level and duration of fluoridation</th>
<th>Tooth mortality per 100 examinees</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurora</td>
<td>Natural, 1.2 ppm</td>
<td>25</td>
</tr>
<tr>
<td>Grand Rapids</td>
<td>F-deficient, before start of fluoridation F-fluoridation to 1.0 ppm through 10 years F-deficient control city, in 1945</td>
<td>84, 41, 27, 94, 98</td>
</tr>
<tr>
<td>Muskegon</td>
<td>F-deficient control city, in 1945 6 years later</td>
<td>25</td>
</tr>
<tr>
<td>Stratford</td>
<td>Natural, 1.3 ppm—contemporaneously with examination at Brantford after 14 years of fluoridation</td>
<td>137</td>
</tr>
<tr>
<td>Brantford</td>
<td>Fluoridation to 1.2 ppm through 14 years F-deficient control city, in 1948 6 years later</td>
<td>22.5, 22.3, 75</td>
</tr>
<tr>
<td>Sarnia</td>
<td>F-deficient, before start of fluoridation F-fluoridation to 1.0 ppm through 10 years</td>
<td>137</td>
</tr>
<tr>
<td>New Britain, Conn.</td>
<td>Fluoridation to 1.2 ppm through 10 years</td>
<td>93, 33</td>
</tr>
<tr>
<td>Ely, Minn.</td>
<td>Fluoridation to 1.2 ppm through 10 years; children born and continuously resident in city children with partial exposure to fluoridated water</td>
<td>18, 35</td>
</tr>
</tbody>
</table>
general and to root treatment in particular, as well as the attitude of the population to dental treatment in general, it is not certain that the impressive improvements revealed by the figures in Table 6 can be attributed solely to the favourable effect of fluoridation.

(d) The individual reports contain no specific data on the number of DMF upper incisor approximal surfaces. As the collected data of the Brantford study in Table 7 show, the number of DMF upper incisor teeth fell quite considerably as a result of fluoridation without reaching, however, the predicted 95% reduction. But these figures include the foramina coeca decay foci also so that they cannot be directly compared with Arnold's forecasts. However, in the Netherlands (Tiel-Culemborg study) the results were again close to those predicted, the protective influence of fluoridation on the approximal surfaces being greater than that on fissures and pits. The protective action exerted on the approximal surfaces also varies according to the type of tooth (weakest for the molars, strongest for the upper incisors) and even between the mesial and distal surfaces of the same tooth (Fig. 9), although it is true that these findings apply to teeth whose morpho-differentiation was already complete when fluoridation commenced (Backer Dirks, 1963).

Of the studies made elsewhere, Minoguchi's report on the results in Yamashina (control town, Shugakuin) is of fundamental importance (Minoguchi & Sato, 1964). After 11 years' fluoridation (0.6 ppm) caries experience in 12- and 13-year-old children rose from 1.49 and 1.85, respectively (average 1.67), to 2.46 and 2.64 (average 2.55), but nevertheless a protective

---

**Table 7**

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>Year of examination</th>
<th>Number of CER (DMF) upper incisors per 100 children born and continuously resident at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Brantford</td>
</tr>
<tr>
<td>9-11</td>
<td>1948, 1959</td>
<td>34, 3</td>
</tr>
<tr>
<td>12-14</td>
<td>1948, 1959</td>
<td>105, 20</td>
</tr>
<tr>
<td>14-15</td>
<td>1961</td>
<td>25, 19</td>
</tr>
<tr>
<td>16-18</td>
<td>1963</td>
<td>22, 30</td>
</tr>
</tbody>
</table>


Flouridation at Brantford (to 1.0 ppm) started in 1945.
effect can be definitely shown to exist! For during the same period, there was an increase in the control town from 0.85 and 1.96, respectively (average 1.425), to 3.73 and 4.46, respectively (average 4.095). Thus, although in Yamashina caries experience rose by 53%, despite fluoridation, there was a protective effect of about 72% in comparison with the data for Shugakuin (since caries experience in the control town increased by 187% over the same period). Conditions similar to those in Japan may well exist in many other countries where the general living and eating customs and the social structure of the population have undergone extensive changes over a comparatively short period of time, with a resulting increase in caries experience. This shows that the periodic examination of the population in control towns also is of the greatest importance!

Protection of the teeth in adults

The far-reaching similarity between caries experience in children and adolescents following water fluoridation and that observed in subjects living
### Table 8

**Numbers of CER (DMF) teeth per 100 adults in areas with high and low fluoride levels in the domestic water, and differences between the two types of area (in England, Hungary and the USA)**

<table>
<thead>
<tr>
<th>Age group</th>
<th>England</th>
<th>Hungary</th>
<th>United States of America</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>B−A</td>
</tr>
<tr>
<td>1</td>
<td>1 060</td>
<td>1 650</td>
<td>620</td>
</tr>
<tr>
<td>2</td>
<td>1 230</td>
<td>1 930</td>
<td>680</td>
</tr>
<tr>
<td>3</td>
<td>1 620</td>
<td>2 150</td>
<td>530</td>
</tr>
<tr>
<td>4</td>
<td>1 920</td>
<td>2 280</td>
<td>360</td>
</tr>
<tr>
<td>5</td>
<td>2 200</td>
<td>2 640</td>
<td>440</td>
</tr>
<tr>
<td>6</td>
<td>1 096</td>
<td>1 413</td>
<td>317</td>
</tr>
<tr>
<td>7</td>
<td>1 365</td>
<td>1 536</td>
<td>171</td>
</tr>
</tbody>
</table>

* Compiled from: Adler (1951, 1953); Bruszt (1960); Englander & Wallace (1960); Forrest, Parfitt & Bransy (1951); Russell & Elyov (1951).

1. 1 = 21-25 (20-24) years
2. 2 = 26-30 (25-29) years
3. 3 = 31-35 (30-34) years
4. 4 = 36-40 (35-39) years
5. 5 = 41-45 (40-44) years
6. 6 = 46-50 (45-49) years
7. 7 = 51-55 (50-54) years
8. 8 = 56-60 (55-59) years

The age-groups in parentheses apply to group B in Hungary and to all groups in the USA.

A = CER (DMF) count in the "fluoride" areas (South Shields, Slough and Colchester in England, with 0.92, 1.45 and 0.8 ppm, respectively; Kunszentmarton in Hungary, with about 1.1 ppm; Colorado Springs, with about 2.5 ppm, and Aurora with 1.2 ppm, in the USA).

B = CER (DMF) count in F-deficient areas (North Shields, Ipswich and Reading in England, with 0.07, 0.3 and 0.1 ppm, respectively; 12 agricultural communities in southern Hungary, with less than 0.5 ppm; Boulder, with less than 0.1 ppm, and Rockford, with 0.1 ppm, in the USA).

100 A

\[ \% = \frac{100 - B}{B} \]
in places where the drinking water has a naturally high fluoride content justifies the assumption that the protective effect of fluoridation also remains the same in later years, like that of a naturally fluoride-rich water. It is therefore of interest to review the available data on the caries protection in adults afforded by naturally fluoride-containing water. Table 8 shows the results of four surveys—one in England, one in Hungary (only among women) and two in the USA (among both men and women). The statistics reveal that the protection continues up to—and beyond—the age when periodontal disease commences to play a large part in tooth mortality, even in advanced countries. But it is noteworthy that the absolute difference in the DMF count between “protected” and “unprotected” subjects decreases with advancing age in England, in Hungary and in the Aurora-Rockford study, whereas in the Colorado Springs—Boulder investigation it increases slightly. However, in Colorado Springs the fluoride content of the drinking water is appreciably greater than in the protected localities of the three other studies. Moreover, if the protective effect is expressed in the usual way, as a percentage of the caries experience of the unprotected control group, then there is a distinct tendency for it to fall with increasing age in Colorado Springs also.

**Effect on caries of the deciduous teeth**

For characterization of the caries experience of milk teeth, the cer (def) count—al analogous to the CER (DMF) count of the permanent teeth—can be regarded as reliable only before the second dentition commences. So as to exclude the loss of milk teeth by natural exfoliation, the cer (def) \(^1\) count of the milk teeth is sometimes related to the number of milk teeth present. This number, however, depends not only on caries attack, but also on the quality and quantity of paedodontic care. It is therefore unsuitable for the unambiguous characterization of over-all caries experience. There is a time gap between the change of the incisors and that of the canines and molars, so that in early school age the temporary cuspids and molars can be used to assess caries experience in the (remaining) temporary dentition (number of cer or def temporary molars and canines per 100 examinees, where “e” indicates missing, presumably extracted, teeth). A refinement is to neglect missing temporary teeth when the corresponding permanent teeth have already erupted (Adler, 1953). The need to determine the caries experience of milk teeth during school age arises because of the difficulty of examining an unselected, representative part of the individual annual age-groups in preschool age. Another suitable index number—at least for comparative purposes—is the percentage of examinees with caries-free milk teeth in the various annual age-groups. This number, too, gives a picture which is better than the actual state of affairs.

\(^1\) “e” means here “indicated for extraction”.

## TABLE 9

**CHANGES IN DENTAL CARIES PREVALENCE IN THE DECIDUOUS TEETH AFTER FLUORIDATION OF THE PUBLIC WATER SUPPLY**  
(IN THE UNITED KINGDOM* and THE USA)

<table>
<thead>
<tr>
<th>Study area</th>
<th>Mode of caries assessment</th>
<th>Duration of fluoridation (years)</th>
<th>Age (years)</th>
<th>Change in the car count per 100 examinees in fluoridated area</th>
<th>Change in the car count per 100 examinees in control area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>from to</td>
<td>%</td>
<td>from to</td>
<td>%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>380 129 — 66.1</td>
<td>353 332 — 5.9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>539 251 — 57.1</td>
<td>518 483 — 6.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>581 291 — 49.9</td>
<td>566 539 — 4.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6</td>
<td>6</td>
<td>649 481 — 25.9</td>
<td>632 622 — 1.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7</td>
<td>7</td>
<td>706 605 — 14.3</td>
<td>708 689 — 2.7</td>
</tr>
</tbody>
</table>

USA (Grand Rapids)  
Muskegon:  
<table>
<thead>
<tr>
<th>Study area</th>
<th>Mode of caries assessment</th>
<th>Duration of fluoridation (years)</th>
<th>Age (years)</th>
<th>Change in the car count per 100 examinees in fluoridated area</th>
<th>Change in the car count per 100 examinees in control area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>from to</td>
<td>%</td>
<td>from to</td>
<td>%</td>
</tr>
<tr>
<td>Grand Rapids</td>
<td>3</td>
<td>6-10</td>
<td>4</td>
<td>419 219 — 48.0</td>
<td>505 446 — 11.7</td>
</tr>
<tr>
<td>Muskegon</td>
<td>3</td>
<td>7-10</td>
<td>5</td>
<td>537 245 — 54.4</td>
<td>680 595 — 23.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-10</td>
<td>6</td>
<td>643 293 — 54.4</td>
<td>717 567 — 20.9</td>
</tr>
</tbody>
</table>

* Data from Ministry of Health, Scottish Office & Ministry of Housing and Local Government (1962).

1 = number of carious, extracted and filled deciduous teeth (total deciduous dentition);  
2 = number of carious, extracted and filled deciduous molars and canines;  
3 = number of carious, extraction-indicated and filled deciduous teeth.

In Grand Rapids the post-fluoridation car counts are the averages of published figures for 6, 7, 8, 9 and 10 years of fluoridation for the 4-year-old, for 7, 8, 9 and 10 years for the 5-year-old, and for 8, 9 and 10 years for the 6-year-old children. In the control city Munkegon the second assessment was made 7 years after the first one.

As concerns the caries experience of the temporary dentition and the fluoride protective effect at school age (in cases where naturally fluoride-rich water is consumed), it has been found (Adler, 1953) that the milk teeth are appreciably less protected than the permanent teeth of the same children.

In the case of water fluoridation, it appears that—as with the protection of the permanent teeth—the effect is increased when ingestion has continued for a long time, perhaps since birth. Table 9 gives a few results of the action of fluoridation on the temporary dentition; Table 10 shows that the protective effect on the milk teeth of younger schoolchildren is less marked than that on the permanent teeth, even when fluoride-enriched water is consumed.

Nevertheless, a protective effect can definitely be shown during school age. Whereas the above-mentioned 12 milk teeth were caries-free in only 11.1%, 4.7%, and 1.8% (average 5.5%), respectively, of 6-, 7- and 8-year-old children in Kingston, the corresponding figures in Newburgh after 10 years of fluoridation were 37.0%, 27.9% and 24.9% respectively (average 29.6%). In Sarnia, as well as in Stratford, there was no change in the percentage of children with caries-free milk teeth after 11 years of un-enriched drinking water, whereas in Brantford the frequency of such teeth rose over the same period from a level originally the same as that in Sarnia to the same height as that in Stratford.
TABLE 10
CARIES REDUCTION IN THE DECIDUOUS AND PERMANENT TEETH OF CHILDREN 6-8 YEARS OLD AFTER FLUORIDATION OF THE PUBLIC WATER SUPPLY (IN CANADA AND THE USA)

<table>
<thead>
<tr>
<th>City</th>
<th>Year and conditions</th>
<th>First caries assessment</th>
<th>Second caries assessment</th>
<th>CER count per 100 examiners</th>
<th>First assessment</th>
<th>Second assessment</th>
<th>Percentage reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brantford</td>
<td>1948/49 prior to</td>
<td>1953/46 after start of</td>
<td>1948/49 first assessment</td>
<td>1953/46 second assessment</td>
<td>495</td>
<td>252</td>
<td>140</td>
</tr>
<tr>
<td>Evanston</td>
<td>1946 prior to</td>
<td>1958 after start of</td>
<td>1946 first assessment</td>
<td>1958 second assessment</td>
<td>537</td>
<td>366</td>
<td>150</td>
</tr>
</tbody>
</table>

The reason why the milk teeth—even when ingestion of an increased (optimal) amount of fluoride commences before conception—are less protected than the permanent teeth is an unsolved problem. The fact that morpho-differentiation and the commencement of mineralization occur \textit{in utero} and that the placenta acts as a barrier against the entry of increased fluoride into the foetal circulation may play some part (reviews: Chapter 4, section 4; Zipkin & Babeaux, 1965). This barrier is already effective against fluoride concentrations in drinking water. Carlos, Gittelsohn & Haddon (1962) showed that fluoride ingestion by the mother during pregnancy causes no difference in caries experience. Other studies of the same problem in the USA have given contradictory results (review: Babeaux & Zipkin, 1966), which might indicate that the fluoride ingestion that is regarded as optimal for the mother is of borderline significance for the expected child.

At the same time, however, it should be borne in mind that the milk teeth of 6- to 8-year-old children are approaching the end of their life and therefore cannot be compared with the permanent teeth of the same children, which are commencing their existence. A more suitable comparison is with the permanent teeth of adults at an advanced age (Table 8); such a comparison at least hints at a certain parallelism. No definite conclusions can be drawn, however, from the available data in regard to the causation of the definitely proven difference in the effect on the temporary and the permanent teeth.
Fluorides and Dental Health

Fluoride Ingestion with Salt

As a general vehicle for ensuring adequate fluoride ingestion, cooking salt comes next to drinking water; its enrichment with iodine already provides a reliable means of preventing goitre. Following recommendations to this effect, Wespi (1956) succeeded in having salt enriched with sodium fluoride put on the market in Switzerland, and the consumption over the whole country increased from 100,000 kg in 1955 to 3,134,900 kg in 1961 (Wespi, 1962). In addition to 10 mg of potassium iodide, this salt contains 200 mg of sodium fluoride per kilogram, corresponding to 90 mg of fluoride ion. The daily salt consumption per head of the adult population in Switzerland amounts to about 7 g, so that the enrichment ensures the consumption of at most 0.63 mg of fluoride daily. It can be assumed that the fluoride intake with salt is smaller in children, particularly infants.

Nevertheless, this enrichment (which is at least 50% below the optimum for adults) has led to a statistically significant fall in caries experience as indicated by the CER—tooth surfaces count after 5½ years’ unsupervised use as table and cooking salt (Marthalen & Schenardi, 1962). In extent and distribution over the various tooth surfaces, this reduction is similar to the one observed in Tiel by Backer Dirks, Houwink & Kwant (1961) following water fluoridation. The extent of the reduction achieved ranges in both boys and girls from 8% to 28% in the various annual age groups. The report also shows the difficulties and inaccuracies in the selection of examinees and their allocation to the experimental and control groups.

Fluoride Ingestion with Flour

Flour has been used in some countries as a vehicle for calcium, iron, iodine and/or some vitamins, and it has also been suggested as a carrier for fluoride. It has been shown that the variations in flour consumption may be smaller than those in water consumption in some countries—for example, Denmark and the Netherlands. Fluoridation of flour, like salt, would have the advantages of requiring much less of the chemical and, with large-scale production, much simpler control measures than fluoridation of piped waters. However, before fluoride enrichment of flour or any other staple food can be recommended on a large scale a number of investigations have to be performed: mapping of the consumption variations in different countries and areas, testing of the systemic and dental absorption of fluoride from the respective vehicles, and clinical testing of the caries-preventive effects.

Fluoride Ingestion with Milk

On the daily administration over 3½ years of 1 mg of fluoride in the milk with school meals, a very distinct fall in caries was observed by Rusoff
et al. (1962) in the multicuspitate teeth erupting during this period in children aged 6-9 years at the beginning of the experiment. The caries rate was 0.34 CER teeth per child in the experimental group as compared with 1.70 in the control group (corresponding to a drop of 80%). The protective effect was still detectable 18 months after stopping the enrichment of the milk, but had fallen to 50%. Because of the considerable divergence in caries attack affecting the first molars in the two groups at the beginning of the experiment, and in view of the smallness of the groups (65 and 64 children), the lower CER rate noted in the experimental group during the enrichment period can hardly be regarded as a valid proof of the alleged effect.

The results for a larger, but still insufficient, number of subjects in Winterthur, Switzerland, are shown in Table 11. The protective effect is definitely visible.

**TABLE 11**

DENTAL CARIES EXPERIENCE OF CHILDREN AFTER 6 YEARS OF CONSUMING FLUORIDATED MILK (1 ppm F) AND OF CONTROLS IN WINTERTHUR, SWITZERLAND *

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of examinees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age when milk fluoridation started (months):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CER count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>522</td>
<td>625</td>
<td>22</td>
<td>212</td>
<td>277</td>
<td>310</td>
</tr>
<tr>
<td>Control group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of examinees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>car count per 100 examinees</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CER count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>713</td>
<td>99</td>
<td>69</td>
<td>325</td>
<td>452</td>
<td></td>
</tr>
<tr>
<td>Percentage caries reduction:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the deciduous teeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the permanent teeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.6</td>
<td>19.2</td>
<td>9.5</td>
<td>20.9</td>
<td>14.8</td>
<td></td>
</tr>
</tbody>
</table>

* Data from Ziegler (1964) and Wirz (1964), collected in 1964.

The two experimental series cited give proof, which *a priori* seemed beyond doubt, that increased fluoride consumption can be suitably achieved by means of milk fluoridation too.

**Fluoride Ingestion with Tablets**

Protective ingestion of fluoride by systematic administration of fluoride tablets is feasible on a large scale primarily during school age, when it is possible to distribute the tablets in school and see that they are taken under the supervision of the teacher. Thus such administration is restricted to the days when children are attending school. Both these factors are disadvantageous as concerns the protective effect. Consequently, it
is not surprising that the results of this method, as reported in various studies, are far behind those given by water fluoridation. However, several reports have indicated that increased fluoride ingestion beginning only at school age exerts a protective effect, not only on teeth erupting later on but also on first molars, which have already appeared when tablet administration commences. Some reports show that the effect persists for several years after the cessation of tablet administration, although it becomes weaker (Held & Piguet, 1956; Berner et al., 1959); other reports even mention an increasing effect (Schützmannsky, 1965).  

When tablet administration commences at an early age, the results are quantitatively better; indeed, in the somewhat small number of examinees reported on by Arnold et al. (1960), they were quite comparable to those given by water fluoridation. However, these subjects were not only few in number (only about half remaining of the original test group) but also a selected group of children of scientific workers at the US National Institutes of Health.

In the various trials carried out different doses were used, and sometimes even changed during the course of one and the same trial. Because of the fear that the tablets might cause mottling, the dose was often kept below the optimum level, which again may be responsible—at least in part—for the comparatively small effect.

Fluorides have been combined with vitamins A and D, and sometimes also with other protective factors, in a number of preparations as tablets, lozenges and drops, particularly in the USA (Wurdack, 1965). The philosophy behind these preparations has been that it would be easier to obtain the collaboration of the families for the distribution of preparations containing several recognized protective factors. The caries-preventive effect of such preparations is probably of the same order as that of simple fluoride tablets (Hennon, Stookey & Muhler, 1966; Margolis, Macauley & Freshman, 1967; Hamberg, 1967). For a good effect on already erupted teeth these preparations obviously have to be administered in a form that ensures contact with the tooth surfaces.

3. EFFECT OF LOCAL FLUORIDE TREATMENT ON CARIES EXPERIENCE

Since the discovery that the fluoride ion readily reacts with calcium phosphates, even with the apatite in dental enamel, great efforts have been made to develop efficient methods for incorporating fluoride ions into the enamel surface of erupted teeth locally, by topical fluoride applications. Such treatment was expected to promote dental health primarily through its

---

3 This conclusion, however, was based on the percentage of DMF teeth in relation to the tooth count, which, because of the increasing number of permanent teeth erupting with advancing age, may vary in an erratic manner.
local effects upon the tooth surface, and secondarily—though to a minor
degree—by retention and absorption of F.

Some F is retained after every local application of fluoride, particularly if
high concentrations are used. Studies of this problem are summarized in
Chapter 2, section 4.

The caries-protective effect apparently varies both with the method of
application and with factors such as posteruptive tooth-age, previous cleaning
and drying of the teeth, supply of fluoride from other sources, etc.

Many methods have been tested, beginning with the manual (topical)
applications of rather concentrated solutions of sodium fluoride to the tooth
surfaces. Later developments have included the use of solutions of different
fluorides, such as stannous fluoride, fluoride—orthophosphoric acid combina-
tions, and sodium monofluorophosphate; elaborate methods, such as the daily
application of a fluoride gel in a splint specially fitted to the dental arch or the
use of electrophoresis in order to accelerate ionic movement; and simpler
methods, such as the use of fluoride-containing toothpastes and mouth-
washes.

As regards the mode of action of topically applied fluorides, reference is
made to Chapter 6, section 4. A detailed report on the extensive and rapidly
growing literature on local fluoride applications has been regarded as falling
outside the scope of this monograph. Only a few summarizing statements
will be made in addition to references to some reviews and key articles
(Campbell & Widner, 1958; Mühlemann & König, 1961; Brudevold, 1967;
Torell & Ericsson, 1965).

Rather great variations are apparent in the reports on the caries-protective
effects of even similar or identical topical fluoride applications. This
may reflect the well-known difficulties of clinical caries registration, small
but none the less important differences in experimental conditions, and
inadequacies in the quantitative estimation of caries protection.

The careful, repeated manual painting of the tooth surfaces of children
with 2% sodium fluoride solution seems to reduce the caries attack by a
maximum of 40% during the following year, but thereafter little seems to be
left of the protection. The reports on similar or single applications of
stannous fluoride solutions vary between much higher and much lower
figures.

The purpose of combining sodium fluoride and phosphoric acid—pH
about 3.0—has been to obtain the markedly greater fluoride uptake by the
enamel at lower pH while at the same time counteracting by the high concentra-
tion of phosphate ions the splitting of the apatite, with liberation of
phosphate and formation of unstable CaF₂. Initial optimistic reports have
been followed by more modest figures.

Mouth-washing or tooth-brushing with weak solutions of NaF at
intervals of two weeks or more have been widely employed in Scandinavian
schools with good reported results.
The incorporation of fluorides into toothpastes offers great promise for the daily, and practically automatic, application of F, but obviously only in persons who brush their teeth regularly. This incorporation has met with some difficulties regarding the compatibility of the fluoride and the polishing agents commonly used in toothpastes. A number of clinical tests with different formulations of fluoride toothpastes (generally containing 0.1% F) have given reductions of 20-30% in caries rates in schoolchildren; higher protection figures have also been reported, particularly with daily supervised toothbrushing.

The effects of topical fluoride applications in adults and the benefits of such applications in areas with optimal water fluoride concentrations cannot yet be regarded as quantitatively settled.

Few studies have been made on the possible reaction of the gingival tissues to local fluoride applications. Provided that the pH values of applied solutions are not so low as to cause superficial etching per se, the gingiva does not seem to react to topical applications of fluoride containing up to 2% NaF.

4. EFFECT ON SHAPE AND SIZE OF THE TEETH

It could hardly fail to escape the notice of investigators in fluoride-rich districts how greatly the appearance of the teeth differs from that in fluoride-poor districts. In fluoride-rich districts the teeth have a fine lustre, which tends to be yellowish rather than blueish, lower cusps with flatter slopes, and wide, easily visible sulci. At the beginning of our field studies, some of the writer's young clinical assistants endeavoured to determine—on the basis of the appearance of the teeth and without waiting for the results of the chemical water analysis—whether the district concerned was a fluoride-rich one. However, these differences were not described more closely, mainly because of their non-quantitative nature. Measurable differences in the form of the teeth were first reported in the Evanston study—namely, a fall in the frequency of deep but not carious fissures (termed "pre-caries") after the introduction of fluoride; this decrease became more and more pronounced as the period of fluoride consumption increased (particularly in children aged 6-8 years, but also in those aged 12-14 years). Nevertheless, on a more thorough study of the reports it is noticeable that the decrease in frequency was already distinct after water fluoridation had existed for only a short time—i.e., it was manifest also in the case of teeth whose morpho-differentiation had taken place and mineralization commenced in a fluoride-poor environment, which had at most become a favourable one only in the final stage of mineralization (decrease in the number of pre-caries fissures in 8-year-old children after 12-22 months' fluoridation, from 107.65 to 68.63; after 9 years' fluoridation, however, reduction to 24.04). Subsequent experience with fluoridation has shown that there is no, or hardly any, notice-
able protective action on the occlusal surfaces of first molars whose morpho-
differentiation and mineralization have taken place in a fluoride-poor
environment (Backer Dirks, 1963; Russell & Hamilton, 1961).

Apparently contradictory reports on the influence of fluoride on tooth
size in humans and experimental animals are referred to in Chapter 6,
section 4.

Measurement of the Carabelli cusp (a fifth, not always well-marked,
cusp of the upper first molar) in children at Newburgh and Kingston gave
greater values at Newburgh. The fact that this difference is not statistically
significant indicates, however, that genetically determined dental charac-
teristics are unlikely to be changed by increased fluoride consumption
(Cox, Finn & Ast, 1961).

5. EFFECT ON PERIODONTAL HEALTH

The multifaced antagonism between dental decay and periodontal disease
renders specially important the question whether (and, if so, to what extent)
the protection against caries afforded by increased fluoride ingestion is
associated with an adverse effect on the health of the periodontal structures.
Although suspicions of this nature have been expressed, there is evidence
that increased fluoride consumption in no way harms the periodontium and
may even be advantageous. The fact that continuous consumption of
fluoride-rich water in childhood does not bring about or maintain any
inflammatory condition of the gums was shown, inter alia, in the case of
children aged 14-15 years by Russell (1957) (comparison between Newburgh,
with 1 ppm fluoride, and Kingston, with about 0.2 ppm) and in 16- to
18-year-old children by the present writer (Adler, 1957) (comparison be-
tween Szekszárd, with about 0.75 ppm, Hatvan, with about 0.4 ppm, and
Eger, with about 0.2 ppm fluoride in the drinking water). Jirásková
(1961) in Czechoslovakia, as well as Englander & White (1963) in the
USA, found the periodontium to be in better condition among teenagers
living in fluoride rich districts than among those in fluoride-poor districts,
in regard to the number of teeth affected per person and the percentage
of subjects with periodontal pockets (the Russell periodontal index
remaining the same).

We feel that the comparisons made by Russell & White (1959) in the USA
on the basis of studies of adults are more important. These studies, carried
out in localities with a high fluoride content in the drinking water (Colorado
Springs, 2.5 ppm; Bartlet, about 8 ppm), concerned the frequency of pockets
and the numerical value of the Russell periodontal index; the findings were
in no way worse than those in fluoride-poor control districts. The present
writer, too, found among the female population of a fluoride-rich village
that the number of permanent teeth lost up to an advanced age was not
greater than that observed in fluoride-poor areas.
To sum up, data based on various criteria justify the conclusion that the possibility of increased fluoride consumption having an adverse effect on the periodontium can be definitely excluded. At all ages the reduction in the number of teeth lost as a result of smaller caries experience should have a favourable influence on the position of as well as on the load borne by the remaining teeth, and consequently also on the periodontium. This is probably the main explanation of the lower prevalence of periodontal pockets which is repeatedly encountered in fluoride-rich districts. However, it is worth mentioning that experimental osteoporosis in alveolar septa, provoked by steroids in animals, has been prevented or reduced by fluoride administration (Zipkin, Bernick & Menczel, 1965; Gedalia & Binderman, 1966; Levy et al., 1968).

6. EFFECT ON LOSS OF THE DECIDUOUS AND ON ERUPTION OF THE PERMANENT TEETH

As part of epidemiological investigations under the direction of Dean, it was shown by Short (1944) that 12- to 14-year-old children of both sexes in areas with fluoride-rich drinking water had fewer erupted permanent teeth per subject than those in localities with fluoride-poor water. With a fluoride content of 2.5 ppm, the difference was statistically significant, while with a lower content, already affording, however, a high degree of protection against caries (1.2-1.9 ppm), this was no longer the case. Consequently Short excluded the possibility that this phenomenon could result from smaller caries experience of the milk teeth. Meanwhile, a more refined method of investigation made clear the basic causes involved (Adler, 1951a). It was shown later that the “apparent delay in eruption” of certain permanent teeth—and at the same time the delay in the loss of individual milk teeth—does not depend directly on the fluoride content of the drinking water but on the caries experience of the deciduous molars (Adler 1). The deciduous molars and the permanent premolars are practically the only teeth affected by this delay in exfoliation or eruption, respectively. Findings in Finland (Scheinin et al., 1964) and Denmark (Møller, 1965) support this conclusion.

In regard to the influence of water fluoridation, the reports from Grand Rapids, Brantford and many other places in North America and Europe give no details regarding the number of milk teeth and permanent teeth in the various annual age-groups of boys and girls. The relevant figures given in the Newburgh-Kingston study (although unfortunately not broken down by sex) agree very well with the explanation given above (Table 12): among 9- and 10-year-old children—but not in younger age-groups—the number of teeth in Newburgh after 8 years of fluoridation was distinctly smaller, as compared both with the prefluoridation value and with the control-town

1 Academic dissertation, Budapest, 1956.
TABLE 12
MEAN NUMBER OF ERUPTED PERMANENT TEETH BEFORE AND 8 YEARS AFTER FLUORIDATION OF THE PUBLIC WATER SUPPLY

<table>
<thead>
<tr>
<th>Age</th>
<th>Newburgh 1944-45</th>
<th>Newburgh 1953-54</th>
<th>Kingston 1945-46</th>
<th>Kingston 1953-54</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4.8</td>
<td>5.16</td>
<td>4.9</td>
<td>4.46</td>
</tr>
<tr>
<td>7</td>
<td>8.8</td>
<td>8.53</td>
<td>8.9</td>
<td>8.08</td>
</tr>
<tr>
<td>8</td>
<td>11.4</td>
<td>11.22</td>
<td>11.7</td>
<td>10.72</td>
</tr>
<tr>
<td>9</td>
<td>14.7</td>
<td>12.95</td>
<td>14.0</td>
<td>13.07</td>
</tr>
<tr>
<td>10</td>
<td>18.3</td>
<td>18.79</td>
<td>17.8</td>
<td>17.80</td>
</tr>
</tbody>
</table>

*Data from Ast, Finn & Chase (1961) and from Ast et al. (1955).*

figures. In general, Carlos & Gittelsohn (1965) found no delaying effect on the change in dentition. Again, unpublished provisional data from Norrköping, Sweden (personal communication from A. Syrrist) show, after 6-9 years’ fluoridation, no appreciable difference in the number of teeth (broken down according to type) compared with the control area either among 7-year-old or among 14-year-old boys and girls. Findings in the two fluoridation studies with younger children indicate that no general delay in the eruption of the permanent teeth is caused. Rather, premature loss of the deciduous molars, as a cause of the early emergence of the permanent premolars, is largely prevented. There seems to be no effect on the eruption of the milk teeth (Tank & Storvick, 1964).

7. EFFECT ON ORTHODONTIC ANOMALIES

When fluoride ingestion from water is adequate, there is less undesirable migration and tilting in the remaining teeth after loss of individual milk teeth and permanent teeth than there is when fluoride-poor water is consumed. As a result, anomalies of occlusion are also rarer. Thus, in Evanston, the frequency of malocclusion among 6- to 8-year-old children fell after 8 years of fluoridation from 37.51% to 29.54%, and among 12- to 14-year-old children, after 10 years of fluoridation, from 55.83% to 46.32%, while in Oak Park over the same period there was a slight increase in frequency. Before fluoridation, a second deciduous molar was lost in at least 6.2% of 6- to 8-year-old children, and this was combined with malocclusion in 3.4% of cases. These frequencies fell to 2.9% and 0.4%, respectively, after fluoridation. Of all the occlusion anomalies encountered, 13.4% before fluoridation and only 1.3% after 8 years’ fluoridation were associated with the loss of one or more second deciduous molars (Hill, Blayney & Wolf, 1959). In older children, loss of the first permanent molar plays a great part in the etiology of anomalies in the positioning of the teeth. For
example, Ast, Allaway & Draker (1962) found that among 50 children aged 13-14 years in Kingston who had lost one or more first molars there was not one with normal occlusion. In Kingston, 35.2% of children had lost a first molar and in Newburgh only 8.1%. Consequently, it is not surprising that class I anomalies (Angle's classification) were found more often in Kingston than in Newburgh. Surprisingly enough, however, in Kingston the frequency of class II and class III (Angle's classification) anomalies was also greater than in Newburgh, even among children who had not lost any first molars. A causal connexion of the last-mentioned differences in frequency with fluoridation seems to us all the less probable in that increased fluoride ingestion has been shown to have no effect on the growth and proportions of the facial bones (Ast, 1955; Salzman & Ast, 1955). None the less, it is true that differences in the frequency of distoclusion and mesioclusion were also found by Plater (1949), between Madison, with fluoride-poor drinking water, and Union Grove, with 1 ppm fluoride in the drinking water.

8. CONCLUDING REMARKS

It has been shown that a certain level of fluoride consumption—especially when this is continuous from earliest childhood—affords considerable protection for both permanent and milk teeth against caries, without exerting any unfavourable influence on the appearance of the teeth or on the periodontium. The best way to ensure adequate fluoride consumption is by fluoridation of drinking water, which is a collective measure of benefit to all those drawing water for drinking and cooking purposes from a central water supply system. When nutrition is adequate, enrichment of the water so that it contains 1.0-1.2 ppm is advisable in temperate zones. In warmer regions the content should be smaller.

Experience to date indicates fluoridated drinking water to be superior to all other vehicles, since these do not ensure permanent and optimal ingestion of fluoride. For districts without a piped water supply system, the best alternative at present appears to be enriched cooking salt. Another possible vehicle is flour, whose consumption in some countries does not vary more markedly than that of water or cooking salt. Nevertheless, certain precautions are called for in the use of fluoridated salt and flour which are unnecessary with water fluoridation (risk of introduction into fluoride-rich areas).

The use of fluoridated milk is less promising, bearing in mind the wide variations in its consumption and its frequent distribution from small dairies or even farms, difficult to control.

Any hope of ensuring the continuous, large-scale administration of fluoride tablets or similar preparations in families is equally slim. However, in groups such as school-classes the administration of tablets may be feasible,
and the distribution of fluoride together with vitamins A and D to pre-school children may obtain sufficient interest and collaboration from many parents. A caries-preventive effect of these measures seems established.

Methods of local fluoride application also carry promise in direct proportion to their caries-preventive effectiveness but in inverse proportion to the personal effort and orderliness or professional working time required. These considerations clearly point towards the use of fluoride-containing toothpastes or mouthwashes.

The outstanding ability of fluoride to prevent dental caries by mechanisms that are not yet fully understood warrants great efforts both in basic and applied research and in practical application of methods that can safely and effectively be utilized for the attainment of improved dental health, which is an integral part of human general health.

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