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THE PROBLEM OF FLUORINE POISONING

BY

T. K. WADHWANI, B.Sc. (PHARM.), A.I.I.Sc.

AND

N. N. DE, M.B.

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Prof. M. S. THACKER

B.Sc. (ENGG.) (BRI'L), M.I.E.E., F.AM.I.E.E., M.I.E. (IND.), M.INST.F., M.I.R.E. F.A.SC., M.I.I.M.

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THE PROBLEM OF FLUORINE POISONING

By T. K. Wadhwani and N. N. De

Introduction

Ever since fluorine in water and foods has been shown, in animals and humans, to be the causative factor in the production of mottled enamel of the teeth and excessive calcification of the bones, increasing attention has been paid to the study of the subject of fluorine poisoning. This has resulted in considerable data regarding the description and study of the symptoms, the occurrence of the disease and its relationship with the fluorine content of water and foods, the relative toxicity of different fluorine compounds for different animals, the methods for the elimination of fluorine from water and the methods for counteracting the effects of fluorine poisoning by dietary means. Several reviews have been written, dealing with various phases of chronic fluorine poisoning (DeEds, 1933; McClure, 1933; Dean, 1936; Roholm, 1937; Peirce, 1939; and Greenwood, 1940). The earlier reviews (DeEds, 1933; McClure, 1933; and Dean, 1936) are mainly devoted to the study of the symptoms, the occurrence of the disease and the general effects of fluorine poisoning. Comparatively compreshenive reviews have been written by Roholm and Greenwood, covering almost all aspects of fluorine poisoning. Peirce has compiled the data on chronic fluorosis in domestic cattle. In all the reviews, the physiological and biochemical mechanisms involved in fluorine toxicosis have been relatively less adequately covered. The object of writing the present article, besides the study of the more recent literature, is to put together the available data regarding the biochemistry of fluorine poisoning for the renewed study of the problem in experimental animals as well as in humans and animals in the areas of endemic fluorosis.

Prevalence of Fluorosis

As fluorine is widely distributed in rocks and soils and ranks twentieth in quantity in the earth's crust, it would be pertinent to anticipate the prevalence of fluorosis in different stages in many areas where the soil is rich in fluorides and where consequently the water and foods contain more than the permissible quantities of it. Dean (1938, 1939) has shown 375 areas in U.S.A., divided in 26 States, in which mottled enamel of the teeth is endemic. The largest affected area has been found to be the West Texas Panhandle district where 12 to 50 per cent. children are affected. Ainsworth (1934) and Wilson (1939) have reported cases of mottled enamel in school

children in England. The occurrence of fluorine poisoning in different stages has been reported in Africa (Velu, 1931), China (Wang, 1936; Lyth, 1946), Russia (Zelmanova, 1937), Korea (Sugawa, 1939), Dutch East Indies (Liang, 1939), Manchuria (Chang, 1939), Hungary (Straub, 1940; Bodnar and Straub, 1946), Argentina (Capizzano, *et al.*, 1940), Malaya (Tratman, 1940), Japan (OKuno, 1941, 1942), Brazil (Freire, 1946), Australia (Reid and Martin, 1946), New Zealand (Chamberlain, 1946; Denmead, 1946) and Italy (Visintin and Gandalfo, 1947).

History and Prevalence of Fluorosis in India

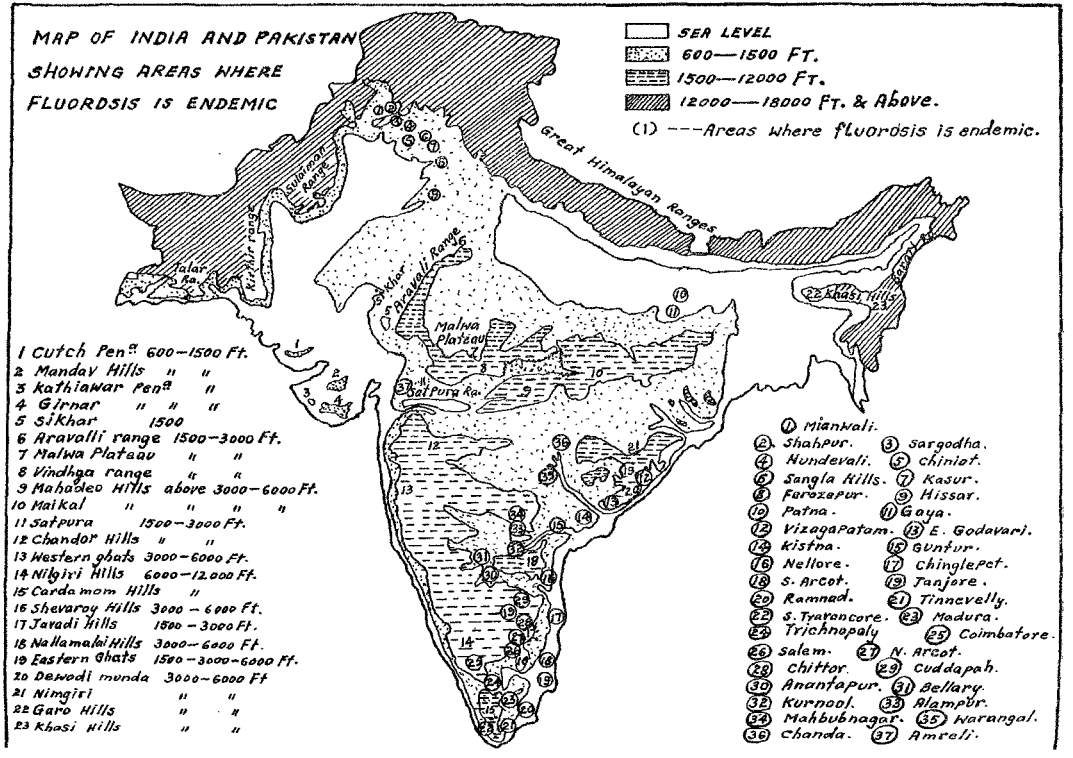
In India, Mahajan (1934–35) reported a peculiar disease in cattle in certain parts of Hyderabad. In the same year, Viswanathan (1934–35) reported a similar disease in humans in Madras Presidency; but Shortt and associates (1937, 1937 *a*) were the first to identify the disease as fluorosis. Khan (1937–38) observed cases of mottled enamel in Kangra Valley in Punjab and suspected a mild form of osteomalacia. Sahai (1937–38) reported two cases of suspected fluorosis in buffaloes in Bihari-Sharif in the district of Patna and in Nawada in the district of Gaya. Cases of mottled enamel in humans were reported by Pillai (1938) in Nagercoil in the Travancore State, by Wilson (1939) and Day (1940) in certain parts of Punjab and by Wilson (1939) and Daver (1945) in Hyderabad. Wilson observed bone lesions also in cattle. Shourie (1945) has observed cases of fluorine poisoning in policemen, recruited from Hissar, Karnal, Ferozepur, Ludhiana, Lahore, Amritsar, Mianwalli, Gujerat, Campbellpur, Jhelum and Sialkot districts. Khan and Wig (1945) have reported two cases of chronic fluorosis with bone lesions in humans. Cases of endemic fluorosis have been detected by the examination of immigrants to Malaya from Nellore (Tratman, 1940).

Nature of the Soil and its Bearing on Flurorine in Water and the Incidence of Flurorine Poisoning

Attempts have been made to correlate the presence and concentration of fluorine in water with the nature of its source. Nichols (1939) has shown that, in U.S.A., the inhabitants of many areas, where cases of mottled enamel have been reported, use artesian waters, originating from or linked with the east side of the Rocky mountain watershed, and he has associated the presence of mottled enamel in areas, adjacent to Mt. Vesuvius in Italy, with the water originating from the laval surfaces of that volcano. Similarly, the fluorine water of the Tjipabelah river in Netherlands East Indies (Liang, 1940) has been found to come from the vicinity of a volcano and the water of hot springs in Korea (Sugawa, 1940) has been reported to contain as

much as 6·4 to 9·2 p.p.m. of fluorine. Wilson (1939), who has reported cases of dental fluorosis in school children in India and England, has explained its occurrence as follows: In India, all the places, where fluorosis has been detected in Punjab, are situated on the Indo-Gangetic alluvium which, ordinarily, is not supposed to contain fluorides. The alluvium, according to geodetic research, has a ridge of rocks below it and the presence of fluoride in the soil and consequently in the water has been explained as due to the rocks forming the ridge, which might include lavas and associated granites and rhyolites. In England, in the Marston Valley, where dental fluorosis is endemic, the clay has been found to contain as much as 450 p.p.m. of fluorine.

Raghavachari and Venkataraman (1940), who have carried out extensive surveys of fluorine-containing waters in certain parts of Madras Presidency, have observed that the water is usually drawn from the well, mostly laid in rocky strata to a depth of 15 to 30 ft. or from bore wells 50 to 200 ft. deep. They have not observed any relationship between the fluorine content of water and the depth of the wells. The wells, very close to one another and of the same depth, have been found to differ widely in their fluorine content. The area surveyed by them has geologically three distinct formations: (i) alluvial, (ii) laterite and (iii) the archæan gneisses. The laterite and alluvial formations have showed little or no fluorine in the ground waters examined, whereas the highest concentration of fluorine has been found in parts lying in the archæan gneisses area. According to Day (1940), the salt range, which runs obliquely across Punjab through Hissar, Ferozepur, Kasur, Sangla Hill, Chiniot, Hundewali, Sargodha, Shahpur and Mianwalli District, is responsible for the fluorine in water. Mazumdar, Ray and Sen (1943) have observed that the suspected fluorosis zones in India are all situated at an altitude of 600 to 1,200 ft. above sea level, in the vicinity of mountain ranges and that many of these places are near sites of old volcanic regions where hot or sulphur springs are still in existence. Lyth, in China (1946), has found that the areas of endemic fluorosis are on the mountain side, where the whole areas have deposits of coal and where often drinking water comes either out of or from very near coal mines. High contents of fluorine have been found in waters from wells in crystalline rocks (Moreaux, 1946) and tufæcous rocks (Visintin, *et al.*, 1947). According to Burkalow (1946), the presence of fluorine in water supplies is often due to the action of sulphuric acid, formed by the decomposition of pyrites, on minerals which contain fluorine, and that, water, containing fluorine, in some cases, is associated with rocks, containing beds of lignite in which fairly large amounts of pyrites commonly occur.


MAP OF INDIA AND PAKISTAN
SHOWING AREAS WHERE
FLUORDSIS IS ENDEMIC
SEA LEVEL
600—1500 FT.
1500—12000 FT.
12000—18000 FT. & Above.
(1) ---Areas where fluorosis is endemic.
Great Himalayan Ranges
Sulaiman Range
Kirthar range
Talar Ra.
Sikhar
Aravalli Range
Malwa Plateau
Satpura Ra.
Khasi Hills
Garo
1 Cutch Penn 600—1500 Ft.
2 Mandav Hills " "
3 kathiawar Penn " "
4 Girnar " " "
5 Sikhar 1500
6 Aravalli range 1500—3000 Ft.
7 Malwa Plateau " "
8 Vindhya range " "
9 Mahadeo Hills above 3000—6000 Ft.
10 Maikal " " " "
11 Satpura 1500—3000 Ft.
12 Chandor Hills " "
13 Western ghats 3000—6000 Ft.
14 Nilgiri Hills 6000—12000 Ft.
15 Cardamom Hills "
16 Shevaroy Hills 3000—6000 Ft.
17 Javadi Hills 1500—3000 Ft.
18 Nallamalai Hills 3000—6000 Ft.
19 Eastern Ghats 1500—3000—6000 Ft.
20 Dewodi munda 3000—6000 Ft
21 Nimgiri " "
22 Garo Hills " "
23 Khasi Hills " "
(1) Mianwali.
(2) Shahpur. (3) Sargodha.
(4) Nundevali. (5) chiniot.
(6) Sangla Hills. (7) Kasur.
(8) Ferozepur. (9) Hissar.
(10) Patna. (11) Goya.
(12) VizagaPatam. (13) E. Godavari.
(14) Kistna. (15) Guntur.
(16) Nellore. (17) ChinglePet.
(18) S. Arcot. (19) Tanjore.
(20) Ramnad. (21) Tinnevelly.
(22) S. Travancore. (23) Madura.
(24) Trichnopaly (25) Coimbatore.
(26) Salem. (27) N. Arcot.
(28) Chittor. (29) Cuddapah.
(30) Anantapur. (31) Bellary.
(32) Kurnool. (33) Alampur.
(34) Mahbubnagar. (35) Warangal.
(36) Chanda. (37) Amreli.

In Fig. 1 is given the physical map of India and Pakistan, showing the places where fluorine poisoning in different stages has been reported to be prevalent. It is seen from the map, as also has been pointed out by Mazumdar, Ray and Sen (1943), that most of the places, where fluorosis is reported to be endemic, are situated at least about 600 ft. high above the sea level. Many places are in the rocky areas and at the foot of the hill. Based on these observations, it is suspected that fluorine poisoning may be prevalent in Cutch and Kathiawar peninsulæ, round about Mandav and Girnar Hills, in some parts of Central Provinces and Rajputana and in places which are located on the sides or at the base of the mountains.

Toxicity of Fluorine

Fluorine, when ingested in small quantities, acts as a systemic poison, but, when taken in large quantities, behaves primarily as a corrosive poison. The symptoms of fluorine poisoning have been described in detail by Roholm (1937). Shortt, *et al.* (1937 *a*), Greenwood (1940), Khan and Wig (1945) and Lyth (1946). Nevertheless, for the purpose of giving a complete picture of the toxicity of fluorine, a brief mention is made here. The symptoms of acute fluorine poisoning, in the first instance, are due to its corrosive effect on the living membranes, causing redness, prolonged burning sensation, thirst, vomiting, abdominal pains and diarrhoea, and in the second, due to its effect on the vasomotor centres, causing salivation, gastro-enteritus, dyspnoea, muscular weakness, tremors, epileptic convulsions, fall of blood pressure and finally stoppage of respiration and heart. Microscopic findings have indicated a pronounced degeneration of the paranchymatous organs, particularly the liver and kidney. In lesser doses, the general metabolic rate in rats has been found to be lowered (Goldemburg, 1930).

The first detectable symptom of chronic fluorine poisoning is the mottled enamel of the teeth, usually observed in the permanent teeth. With high concentrations of fluorine in the drinking water, deciduous teeth have also been repoted to be mottled (Smith, 1935; Shortt, *et al.*, 1937 *a*). No other harmful effects have been observed in the children and according to Shortt, *et al.* (1937 *a*), there appears to be an interval, extending from childhood to about 25–30 years of age, during which few or no ill-effects are exhibited. At about this age, the first symptoms of intoxication appear. " There is a recurrent general tingling sensation in the limbs or over the body in general. Pain and stiffness next appear especially in the lumbar regions of the spine but also involving the dorsal and cervical regions. There is usually anorexia. The final stages in the condition are generally evident in people past forty. There is a complete rigidity of the spine, including

the cervical region and of the joints of both upper and lower limbs. There is fixation of the thoracic walls, so that breathing becomes entirely abdominal" (Shortt, *et al.*, 1937 *a*). "The bone structure is blurred and becomes a diffuse structureless shadow. The bone contours become uneven. These changes are marked in the pelvis, spine and the ribs. The extremities are still in the first phase. In the second phase, the medullary cavity is narrowed down and the ligaments show incipient calcification. In the final stage, the bones show the appearnace of marble white shadow, particularly the central bones, bone contour is woolly, the bones of the extremities show irregular periosteal thickening. There is definite calcification of ligaments and muscle attachments, especially noticeable at the insertion of the intercostal muscles. The cortex of the long bones is dense and thick and the medullary cavity is narrow. There is no evidence of bone destruction" (Khan and Wig, 1945).

Retention and Excretion of Fluorine

The extent of excretion or retention of fluorine is governed by the quantity of fluorine ingested, the chemical nature and the state of the fluorine compounds at the time of ingestion, the age of the animal, the duration of intake and the composition of the diet.

Lawrenz, *et al.* (1940) have observed that the growing rats adapt themselves to the continuous ingestion of fluorine by excreting larger and larger amounts of fluorine in the urine and fæces. According to Machle, *et al.* (1942), in humans, when the daily intake and absorption of fluorine does not exceed 1 mgm., the urinary and the fæcal excretion almost equal the intake. With higher levels of intake and absorption, the urinary excretion increases, particularly with the amounts absorbed. Notwithstanding the increased urinary excretion of fluorine with the amounts ingested and absorbed, the storage in the system occurs when the daily absorption is 2 mgm. The elimination of fluorine from the body is mainly through the kidneys. Brun, *et al.* (1941) found as much as 16 mgm. of fluorine per litre in the urine of cryolite workers as compared to 0·92 mgm. for the controls and even those, who had no exposure to fluorine dust for many years, still excreted about 2·06–9·26 mgm. of fluorine in the urine.

According to Brun *et al.* (1941), fluorine is not absorbed by direct inhalation and in the case of cryolite ingestion, only one third of fluorine ingested is absorbed, as Na_3AlF_6 in the acid medium of the stomach forms, according to the following equation, sodium fluoride and aluminium fluoride and aluminium fluoride is regarded as non-absorbable.

$$Na_3AlF_6 \rightarrow 3Na^+ + AlF_3^- + 2F^-.$$

Marcovitch and Stanley (1938) have observed that rats, receiving 4 p.p.m. of fluorine as NaF in drinking water, retained nearly twice as much fluorine in the body as that retained by the other group of rats, receiving the same amount of fluorine as cryolite in the diet. Lawrenz, *et al.* (1939) have shown that the retention of fluorine in the body is about 20 per cent. less, when it is consumed with the diet than when it is taken in water, provided water is consumed at times such that admixture with the food in the stomach cannot occur. This has not been confirmed by McClure (1939).

Hauck, *et al.* (1933 *a*) have observed that the increase in the concentration of dietary calcium from 0·23 to 0·73 per cent. depresses the total retention of fluorine by 10 to 13 per cent. and to a greater extent, its deposition in teeth and soft tissues. An increase in the phsophorus content of the diet has not been found to affect appreciably the total retention of fluorine in the body. The retention of fluorine in monkeys, receiving 10 mgm. of fluorine as NaF per Kg of body weight, per day, and placed on vitamin C deficient diet, has been reported to be greater than that in the monkeys similarly treated, but placed on a normal diet (Pandit and Rao, 1940). In bulls, Mazumdar and Ray (1946) have observed that the supplement of Ca and Al decreases the retention of fluorine by increasing its excretion in the fæces.

Fluorine is reported to be transferred through the placenta of the cow (Evans, *et al.*, 1938) and rat (Evans and Phillips, 1939) to the fetus. Among the tissues, fluorine is preferentially retained in the teeth and bones and its concentration is greater in certain bones. Roholm (1937) has reported increased amounts of fluorine in the cancellous bone. Muzumdar, *et al.* (1943) have observed that the amount of fluorine in the pelvis or vertebra is much greater than that in the femur and teeth. In general, the amount of fluorine retained in teeth and bones increases with age. It has been observed by Ellis and Maynard (1936) that, for each diet and level of feeding, there is a marked increase in the fluorine content of the bones after 168 days as compared with that after 56 days. In human bones of different ages, according to Glock, *et al.* (1941), there is a general rise of fluorine content with increase of age, the lowest and highest values, with no evidence of fluorosis, being 0·02 per cent. and 0·3 per cent. respectively, and in rats, fed small amounts of NaF, the concentration of fluorine in the bones in relation to age follows a logarithmic curve. In bulls, it has been reported by Mazumdar, *et al.* (1943) that, in the pelvis, the concentration of fluorine per unit weight of the bone is proportional to the age of the animal and the data can be represented by a smooth curve.

Effect of Fluorine on the Metabolism of Calcium and Phosphorus

The toxicity of fluorine depends, besides on its concentration, on the species and age of the animal, the nutritional status and the mode of intake. The toxicity of fluorine ingested in solution appears to be greater than when it is consumed in a solid state (Velu, 1932; Marcovitch and Stanley, 1938; Machle, *et al.*, 1939). The toxicity of fluorine is different for different animals and is distinctly less when its intake is intermittent (Peirce, 1939). An insufficient supply or an imbalance of the essential constituents of the diet has been observed to influence adversely the toxicity of ingested fluorine (DeEds, 1933; Peirce, 1939; Pandit, *et al.*, 1940.) The toxicity of a definite concentration of fluorine has been found to decrease with increasing age (Buckner, *et al.*, 1929; Hauck, *et al.*, 1933 *a*). Depending upon these factors, different results have been reported regarding the effect of fluorine on the metabolism of calcium and phosphorus. No significant differences have been observed in the retention of calcium between the rats, receiving 0·0106 per cent. and 0·0313 per cent. of fluorine as sodium fluoride, and their pair mates. However, the amounts of calcium retained by the rats, receiving high percentage of fluorine, have been found to be smaller than those retained by control pairs (McClure and Mitchell, 1931). Fluorine, when ingested in the concentration of 60–738 mgm. per day, from calcium fluoride or dicalcium phosphate, has been found to cause a decreased retention of both calcium and phosphorus in rats and a slight increase in the calcium retention and a pronounced decrease in the retention of phosphorus in the bovines (DuToit, *et al.*, 1937) and when ingested in the concentration of 0·1 per cent. NaF in the diet, has been reported to cause a very decided decrease in the retention of calcium and phosphorus in rats (Lantz and Smith, 1934) and dogs (Smith, *et al.*, 1935). In both these animals, the path of excretion of these elements has been altered. When fluorine is taken in ordinary quantities, in pigs, the calcium retention is reported to remain stationary (Hart, *et al.*, 1914) or decrease (Forbes, *et al.*, 1921; McClure and Mitchell, 1931 *a*).

The injection of sodium fluoride has been found to reduce blood calcium (Gerschmann, 1930). In fluorine poisoning, serum clacium has been observed to be lowered in young chicks (Hauck, *et al.*, 1933), in heifers (Phillips, 1932) and in rabbits on a low calcium diet (Veselkina, 1940) and to remain unaffected in mature poultry (Hauck, *et al.*, 1933), rats (Channels, 1930) and puppies, receiving 0·45, 0·90 and 2·26 mgm. of fluorine per kg. of body weight per day (Greenwood, *et al.*, 1933). It has been found to increase in dogs, fed small quantities of fluorine (Bogdanovic, 1935). The

behaviour of serum phosphorus, in fluorine poisoning, has been found to be similarly irregular (Cirla, 1938). It has been found to rise in cows (Phillips, 1932), decline in dogs (Pavlovic and Bogdanovic, 1933; Greenwood, *et al.*, 1933), and remain stationary in rats (Hauck, *et al.*, 1933 *a*) and in cattle (Luy and Thormahlen, 1932).

In bulls, placed on high fluorine diet, Mazumdar, *et al.* (1943) have observed that serum calcium is lowered, though not significantly, whereas in the animals on low fluorine diet, serum calcium and phosphorus are increased. In the subsequent report by Mazumdar and Ray in 1946, it is stated that, when fluorine is administered in small doses, the balance of both calcium and phosphorus improves, whereas a high fluorine intake brings about a negative balance of both these elements. It is further stated (1946 *a*) that serum calcium and inorganic phosphorus are not affected in adult animals, placed on a low fluorine diet, whereas in the case of growing animals, similarly placed, the blood phosphorus shows an initial fall and then remains more or less stationary during the experimental period of one year.

In humans, Lantz, *et al.* (1935) showed that there were no significant variations in calcium and phosphorus retention in the case of four girls, whose teeth were severely mottled by drinking water containing 4·5 p.p.m. of fluorine, giving a daily intake of 5·3–7·8 mgm. of fluorine per day. This has been confirmed by Roholm, *et al.* (1937) in the case of cryolite workers with varying degrees of osteosclerosis, whereas Shortt, *et al.* (1937 *a*) found that the serum calcium and inorganic phosphorus were slightly above the upper limit in humans with severe bone fluorosis.

Effect of Fluorine on other Blood Constituents

Chronic fluorine poisoning brings about a condition of anæmia. This has been shown by Leake and Ritchie (1926) and Risi (1931) in dogs, by Valjavec (1932) in rabbits, by Slagsvold (1934) in sheep and by Mazumdar and Ray (1946) in bulls. Such a condition, however, has not been produced in puppies by administering 0·45, 0·90 and 2·26 mgm. of fluorine per kg. weight of body per day, for relatively short period (Greenwood, *et al.*, 1933). In humans with severe bone lesions, Shortt and associates observed a slight degree of anæmia, as revealed by blood counts and hæmoglobin percentages. The differential counts were not distinctive although some cases showed a high eosinophile count. Shortt, *et al.* further observed that the average figure for blood sugar and magnesium was within normal limits, whereas sodium and potassium were above the normal upper limit. In bulls, Mazumdar and Ray (1946 *a*) have found that, except for the decrease in

the magnesium content of the serum, the ingestion of fluorine at the level of 3 mgm. per kg. of body weight, per day, seems to have little effect on the concentration of other constitutents. Though at this level of fluorine intake, a trend to increased values for chlorides and creatinine was observed in the early phases of fluorine poisoning, the final values were found to lie in the normal range found for cattle. Similarly, blood sugar and nitrogenous constitutents have been found within normal limits in dogs, fed 4·5–13·6 mgm. of fluorine as NaF per kg. of body weight per day for four and a half months (Greenwood, *et al.*, 1935).

Larger doses of fluorine, however, have been reported to produce changes in blood constituents (Kick, *et al.*, 1935; Rek, 1935; Crut, 1939; Sugawa, 1939).

Effect of Fluorine on the Composition of Teeth and Bones

The invariable result of fluorine ingestion is its concentration in teeth and bones. Further changes in the composition of teeth and bones depend upon the quantity of fluorine ingested, the composition of the diet, the age and the species. As in the case of the effect of fluorine on the metabolism of calcium and phosphorus, so in this also, depending upon these factors, different results have been reported. Forbes, *et al.* (1921) found that the feeding of rock phosphate to pigs produced weaker bones, characterised by maximum magnesium and phosphorus content and minimum calcium and carbonate percentages. Kick, *et al.* (1933) found that the femurs of pigs, suffering from fluorine toxicosis, contained normal percentages of ash, calcium and phosphorus and increased amounts of magnesium and decreased percentage of carbonate and that the percentages of ash, calcium, phosphorus, magnesium and carbonate in the teeth of the pigs were not significantly affected by fluoride feeding, except for the fact that the fluorine content was proportionately increased. The increased magnesium and fluorine content and decreased carbonate percentage in the bones were directly correlated with the concentration of fluorine in the ration. Schulz (1938) made a similar observation regarding the percentage of magnesium and carbonate in the tibiae, femora and humeri of rats, given sodium fluoride. Bethke, *et al.* (1929) found no changes in the total ash or in the calcium or phosphorus content of the ash of the bones of young growing pigs fed on fluoride rations, whereas according to Cirla (1938), in fluorine poisoning, there is a considerable increase in the phosphorus content of the bones in general.

In rats, McClure and Mitchell (1931) found that when fluorine was fed as sodium fluoride in the concentration of 0·03 to 0·06 per cent., a consistent

increase, averaging 1·3 per cent., was evident in the ash content of the bones and statistically significant, though not as consistent, decrease in the calcium content of the ash, averaging 1·05 per cent. As the phosphorus content of the ash was not affected, the ratio Ca : P in the ash was lowered; but when fluorine was fed as calcium fluoride, there was a decided increase in the percentage of ash in the bones and a significant decrease in the calcium content of the ash of the femur but not of the humerus, whereas in the case of pigs, Mitchell (1933) found that, as a result of calcium fluoride feeding, there was a strong evidence of a decrease in calcium and phosphorus in the ash of the humerus. McClure and Mitchell observed that the insoluble calcium salt was as effective as the soluble sodium salt in bringing about changes in composition and structure of the teeth. Contrary to the results of McClure and Mitchell (1931), Smith and Lantz (1933) observed that when fluorine as sodium fluoride was incorporated in the ration at the level of 0·05 per cent., the analysis of teeth and bones showed no significant variations in the percentages of ash, calcium, phosphorus or in the calcium : phosphorus ratio. With higher concentrations of fluroine, about 0·1 per cent. in the diet, the teeth and bones were both lower in ash content but contained a greater percentage of calcium, low percentage of phosphorus and consequently a high Ca : P ratio, whereas Hauck, *et al.* (1933 *a*) found that addition of 0·15 per cent. of NaF to the diet of young rats produced a variable effect upon the ash content of the bones, depending on the calcium content of the diet.

Assuming the formula of bone salt to be carbonate apatite, $[Ca_3(PO_4)_2]_n$ $CaCO_3$, the lack of significant variation in the composition, save for the increase in fluorine content in the rats, receiving 0·05 per cent. fluorine in the ration, was explained by Smith and Lantz (1933), as being due to the replacement of carbonate by fluoride. Such a mechanism would not result in the increased percentage of ash, calcium or phosphorus, whereas the higher concentration of fluorine in the ration was assumed to lead to the deposition of greater amounts of CaF_2 in teeth and bones, either as free CaF_2 or together with calcium phosphate, resulting in the formation of a compound like collophane, $3Ca_3(PO_4)_2 \cdot 2CaF_2$, and an increase in the percentage of Ca and higher Ca : P ratio.

In bulls, Mazumdar, *et al.* (1943) observed that a high intake of fluorine caused a decrease in the carbonate content and an increase in the magnesium content of the bones. The calcium and phosphorus percentages of the bones were not affected by higher fluorine intake and the increase in the magnesium content was brought to normal level by the administration of extra caclium.

In the man, who had been exposed daily for 18 years to a finely ground rock phosphate dust containing 3·88 per cent. fluorine and had developed chronic fluorine poisoning, Wolff and Kerr (1938) found normal values for Ca, P and carbonate content of the bones.

Effect of Fluorine in the Histology of Teeth and Bones

Fluorine interferes with the calcification of teeth and bones. This interference of fluorine is more marked in the teeth than it is in the bones. In the teeth, the enamel rods have not been found to be properly calcified and the intercementing material, which is normally present between the enamel rods, in some cases, has been reported to be lacking (Black, 1916; Leon, 1918; Williams, 1923; Hauck, *et al.*, 1933 *a*).

In rats, the incremental surface of the organic enamel matrix has been observed to lack its normal arrangement and be covered with hemispherical globules, that stainly deep with hæmotoxylin. There has been found an abnormal distribution of globules within the ganoblastic layer of the posterior and formative portion of the incisors (Schour and Smith, 1934). According to Schour and Smith (1935), this action of fluorine on the enamel and dentine of the incisors is not produced primarily by changes in blood Ca and P, but is direct on the enamel forming cells and odontoblasts. According to Irving (1943, 1944), the action of F on the enamel is independent of the Ca : P ratio but that on the dentine depends on the Ca : P ratio of the blood; whereas, Grinstein (1941) has put forward that the alterations of the adamantogenic process are caused by changes in the structure of the ameloblasts originating in disturbances of the cellular metabolism of the latter.

Changes in bone, due to fluorine poisoning, according to Lang (1939), are similar to those seen in infantile rachitis. In dogs, in long time feeding experiments with NaF, Harndt (1940) has observed osteoplastic alterations and osteoclastic and osteoporotic processes and in the older dogs, hyperplastic bone alterations with special regularity.

In bulls, suffering from chronic fluorine poisoning, Pande (1944) has observed that " the pathological changes produced seem to be influenced by the calcioprive and the osteogenic effects of fluorine and although osteoporosis of the metaphyses of long bones may be said to represent a stage in the development of the final pathological picture, the lesions do not entirely correspond to classical osteomalacia : certain hyperplastic changes in the diaphysis and metaphysis of the long bones and ribs indicate endosteal activity and the resulting lesions are more suggestive of osteosclerosis than of osteomalacia".

In rats, though no gross or radiological changes have been produced, histologically, osteoclastic and osteoblastic activity has been reported to resemble that seen in rabbits (Simada, 1939).

Effect of Fluorine on Other Tissues and Systems

Fluorine has been reported to cause degenerative changes in the kidney (Kick, *et al.* 1935; Phillips, *et al.*, 1934 *a*; Roholm, 1937), liver (McClure and Mitchell, 1931 *a*; Phillips, *et al.*, 1934 *a*; Velu and Zottner, 1934; Roholm, 1937), of pigs, cattle and sheep and in the suprarenals, heart muscle and central nervous system of cattle (Phillips, *et al.*, 1934 *a*; Roholm, 1937). Siegfried (1901) observed that sodium fluoride and fluosilicate caused destruction of the epithelium of the intestine, even though the salt had been introduced into the system through other channels. In humans with bone fluorosis, Shortt, *et al.* (1937 *a*) noted that the kidney function was impaired and in some, markedly so. Pandit and Rao (1940) have made a similar observation in the experimental monkeys, receiving 10 mgm. of sodium fluoride per kg. of body weight per day.

Fluorine has been found to be antagonistic to the proper functioning of the thyroids. It has been reported to cause an increase in the size of the glands of dogs and rats (Goldemburg, 1927). Though this has not been confirmed by Channeles (1928) and Tolle and Maynard (1931), Phillips, *et al.* (1935), in the growing chick, have shown that the non-toxic levels of desiccated thyroid are made distinctly toxic by chronic fluorine poisoning produced by the ingestion of sodium fluoride. According to Wilson (1941), endemic goiter is due to fluorine compounds present in excess in soil, diet and water and the distribution of endemic goiter in Punjab and England is related to the geological distribution of fluorine and to the distribution of human dental fluorosis.

It has been observed that the harmful effect of fluorine on the thyroid does not consist in producing a deficiency of iodine in the gland (Stormont, *et al.*, 1936) but in causing a proliferation of its parenchymatous tissue (Cristiani, 1930).

Feeding of fluorine has been reported to alter the structure and functions of parathyroids (Bergara, 1927; Channeles, 1929; Pavlovic and Tihomirov, 1932; Kochmann, 1934). This has not been confirmed by Hauck (1933, 1933 *a*, 1934) and Kick, *et al.* (1935).

Greenwood, *et al.* (1933) observed that 1·5–5·3 mgmd. of fluorine as NaF per kg. of body weight increased the respiration and 16-31·7 mgm. of fluorine as NaF per kg. of body weight lowered the blood pressure, where-

as Merkel (1933) found no significant variations in the blood pressure from the normal in school children, receiving fluorine water and having mottled enamel. In humans, afflicted with severe fluorosis, Shortt, *et al.* (1937 *a*) found that the chest was almost immobile, due to fixation of the ribs and breathing in some cases was purely abdominal. "There was a generalised wasting of all muscles, sometimes accompanied by pain on pressure. There was diminution in pain and thermal sensation in several cases. Thermal sensation was lost over the lower extremities in the two most severe cases. Tactile and vibration sense was lost over the same area and in the same two cases, there was also loss of sphincter control. The sexual function was found to be normal in the earlier stages but was impaired or completely lost in the final stages."

Effect of Fluorine on Enzymes

Fluorine is regarded as a general inhibitor of enzymes. Its interference in the calcification of teeth and bones has been associated with its inhibiting action on phosphatases (DeEds, 1941). *In vitro*, the inhibitory action of fluorine on enzymes is not irreversible and is determined by such factors as the pH of the reaction mixture, the concentration of fluoride and the concentration of the substrate. Depending upon the conditions of the experiment, different workers have reported very variable and sometimes contradictory results. In vitro, Drill, *et al.* (1944) found that NaF (0·01 M) had a slight activating effect on serum phosphatase of normal dogs, but in dogs with a high serum phosphatase due to hepatic damage, fluorine had only the slight effect noted in normal dogs. The activity of acid phosphatase of liver and kidney extracts is inhibited by F while that of the alkaline phosphatase is not affected. It has been found that NaF can inactivate alkaline phosphatase also, provided it is allowed to react for some time at pH 4·5 (Belfanti, *et al.*, 1935). Massart and Dufait (1939) have found that yeast phosphatase is inactivated by fluorine and that fluorine affects the activation of the enzyme by magnesium. Fluorine has not been found to exert any inhibitory effect on the kidney phosphatase of chickens (Hauck, *et al.*, 1933). Fluorine though retards the rate of synthesis of esters of phosphoric acid in the presence of extracts of kidney and intestine, it has been found that the final equilibrium is not affected (Kay, 1928). Similar observations have been made by Lippman (1928, 1929) with yeast and minced muscle.

In rats, receiving 0·025 per cent. NaF in the ration, no variation has been observed in the value of serum phosphatase (Smith and Lantz 1935), whereas, in rats receiving 0·1 per cent. NaF in the ration, except for an

initial decrease up to the age of 70 days, the serum and bone phosphatase values have been found to be higher than those in the control rats. Irrespective of the age of the rat, on high fluorine diet, the phosphatase content of the incisor teeth has been found to be less than that of the controls (Smith and Lantz, 1935). Smith and Lantz observed that the plasma phosphatase values in adult rats, determined approximately 18 hours after injection of 0·3 c.c. of 2·5 per cent. NaF solution, were not significantly different from those of the controls.

In cattle, Mazumdar and Ray (1946 *a*) found that serum phosphatase content was greatly diminished in fluorosis, whereas Phillips (1932) reported a rise in the plasma phosphatase value in proportion to the level of fluorine intake or nearly so. The results of other observations with cows and sheep (DuToit, *et al.*, 1937) have been similarly variable.

In humans with chronic bone fluorosis, Roholm *et al.* (1937) did not observe any signficant increase in serum phosphatase, whereas Shortt, *et al.*, (1937 *a*) found a higher value for it.

Besides its action on phosphatases, it has been found that fluorine (i) has an inhibitory effect on lipase (Loevenhart and Peirce, 1906-07), urease (Jacoby, 1915, 1928, 1929); (ii) checks the decomposition of starch by pancreatic juice, affects the conversion of starch to maltose but has no effect on the hydrolysis of maltose to glucose (Lang and Lang, 1921); (iii) in high concentration, affects salivary amylase (McClure, 1939); (iv) increases the activity of potato amylase (Doby, 1914), and (v) has no effect on pepsin and trypsin (Vandevelde and Poppe, 1910).

Due to ingestion of fluorine, the clotting period of blood has been found to increase in rabbits and pigeons (Schwyzer, 1913), in dogs (Schwyzer, 1913; Greenwood, *et al.*, 1933), in cows (Phillips, *et al.*, 1934 *a*) and in humans (Stubor and Lang, 1929); whereas, it has been reported to have decreased in poultry (Kick, *et al.*, 1935) and remained unchanged in pigs (Roholm, 1937).

Fluorine has been recorded to have caused transient hyperglycæmia in kids and lambs (Goldemburg, 1928), in dogs (Magenta, 1928) and rabbits (Foit, 1931; Yu, 1940). In rabbits, Yu (1940) observed that, in most cases, hyperglycæmia thus produced could be neutralised with insulin, and that fluorine had no inhibitory effect upon glycolysis and oxidation of glucose but that mobilisation of liver glycogen was the main factor for hyperglycæmia. *In vitro*, fluorine inhibits glycolysis in blood (MacLeod, 1913; Evans, 1922; Bueding and Goldfarb, 1941), in muscle (Embden and Lenhartz, 1924;

Embden and Haymann, 1924; Abraham and Kahn, 1924; Lang and Mayer, 1924) and in other tissues (Dickens and Simer, 1929).

Fluorine causes (i) diminished tissue respiration (Phillips and Stare, 1934), (ii) decreased oxygen consumption and lateic acid production in muscle (Lipmann, 1928, 1929), (iii) a decrease in the anaerobic production of lactic acid from glucose (Loebel, 1925; Lang, 1924), (iv) an inhibition of oxidative as well as glycolytic decomposition of carbohydrate (Dickens and Simer, 1930), (v) interference with the formation of pyruvic acid during muscle metabolism (Meyerhof, 1933, 1935, 1939) and (vi) inhibition of alcoholic fermentation by yeast (Lipmann, 1928).

Vitamain C and Fluorine Poisoning

The following points of similarity have been noted between scurvy and the syndrome of chronic fluorine poisoning: (i) The hæmorrhages of the pyloric mucosa, as in scurvy, have been observed to be common in the rats suffering from chronic fluorine poisoning produced by feeding NaF at a level of 0·15 per cent.

(ii) In some cases, mottled enamel has been found to be without the inter-cementing material, normally found between the enamel rods (Black, 1916; Leon, 1918; Williams, 1923; Hauck, *et al.*, 1933 *a*), and not observed in vitamin C deficiency.

(iii) In experiments with acutely toxic doses of sodium fluoride for rats, it was found (Phillips and Chang, 1934) that 4 c.c. or more of orange juice fed with the diet prolonged the survival period of young growing rats, when fed 0·2 per cent. NaF.

(iv) It has been observed by Pandit, *et al.* (1940) that the production of severe chronic fluorosis in humans is essentially associated with the high fluorine content of domestic water supplies and a pronounced C avitaminosis.

(v) In the experimental fluorosis in monkeys, the changes in the bones noted by Pandit and Rao (1940) are mainly of the nature of diffuse periostitis. According to Ellis (1939), the absence of vitamin C in the diet can cause diffuse periostitis in children.

(vi) The urine of the experimental fluorosis monkeys contained homogentisic acid, indicating an interference with the metabolism of phenylalamine and tyrosine (Pandit and Rao, 1940). The excretion of homogentisic acid and other tyrosine metabolites has been noted in the case of vitamin C deficient guinea pigs (Sealock and Silberstein, 1939, 1940). The excretion of these metabolites in the vitamin C deficient guinea pigs has been prevented

by the administration of vitamin C. The prevention of the excretion of metabolites has been found to be inherent in the antiscorbutic activity of vitamin C.

(vii) There has been noticed a drop in the activity of certain enzymes like liver esterase, phosphatase, succinic dehydrogenase, cytochrome oxidase with the depletion of the vitamin and the development of scurvy (Harrer and King, 1941). Though the opinions regarding the action of fluorine on these enzymes *in vivo* have been conflicintg, *in vitro*, fluorine has been found to inhibit these enzymes.

(viii) The rate of oxygen uptake of the suprarenal tissue from scorbutic and fluorine poisoned guinea pigs has been found to be half of that of the tissue from the normal control animals. The deleterious effects of chronic fluorine toxicosis and vitamin C deficiency have been shown to result from disturbances in specific phases of cellular respiration (Phillips, Stare and Elvehjem, 1934).

Role of Fluorine

Does fluorine play any essential role in the body or in nature? Is fluorine an indispensable element of the diet? Such questions have been asked from time to time during the course of work on fluorine and its toxicity. As long ago as 1914, Gautier, considering the reactivity and wide distribution of fluorine in all tissues, opined that it was but necessary that fluorine should play a specific role in nature, but as a result of the analyses of different tissues for fluorine, he concluded that fluorine plays, in the economy of nature, a very secondary rôle of imparting to the tissues, in which it is contained, strength, resistance and a certain degree of chemical unalterability. He, however, could not explain the presence of very small quantities of fluorine in the organs of intense life, various glands, nervous tissue and muscles. Whether or not, fluorine is an essential element of the diet cannot be satisfactorily answered unless a generation of animals, free from fluorine, is maintained on a diet absolutely free from it. Owing to the occurrence of fluorine in almost every article of consumption and the difficulties involved in its removal, it has been found nearly impossible to prepare a diet, completely free from it. Various attempts have therefore been made to prepare a diet very low in fluorine. Phillips, *et al.* (1934) prepared a diet, permitting an intake of about 4·5 microgrammes of F per rat, per day and found that fluorine, in such concentration, had no essential function in the metabolism of the rat. Sharpless and McCollum (1933), in rats, fed on a diet very low in fluorine, observed that (i) the hair was little coarser than that of the control rats; (ii) the animals lost their

tails; and (iii) there was a slight indication of proliferation of capillaries in the tooth pulp and surrounding bone; but they did not consider these observations to be of much significance. Evans and Phillips (1939) prepared a new low fluorine diet, consisting of mineralised milk and containing, on the basis of dry matter, 1·6 p.p.m. of fluorine, resulting in the intake of 0·05–0·06 mgm. of fluorine per kg. of body weight, per day and reared the rats on this diet for five generations. They found that fluorine even in such low concentrations was transferred through the placenta. They, however, could not prove whether fluorine was necessary for the development of the embryo. However, in the concentration of 0·1–0·20 p.p.m., they did not find fluorine necessary for the rat.

Recently, fluorine has been found to reduce the incidence of dental caries. Based on this observation, fluorine has been assumed to play some part in the development and calcification of teeth. The role of fluorine in the prevention of dental caries may be due to its inhibitory effect on the oral bacteria responsible for the production of acids from carbohydrates or due to its combination with the enamel, resulting in its lower solubility in the acids of the mouth. Unless some direct evidence is produced, it cannot be definitely said that fluorine plays some useful part in the body or is an essential element of the diet.

Methods for Preventing and Reducing the Incidence of Fluorine Poisoning

The mottling of teeth and fluorosis of bones though are due to fluorine poisoning, the production of the two conditions is dependent upon the amount of fluorides ingested. Amounts of fluorine too small to produce bone lesions, may, nevertheless, induce dental symptoms. Various attempts have been made to prevent the development of these two conditions or at least, mitigate the toxic effects of fluorine. The various methods that have been or can be employed may briefly be discussed under the following heads:

(1) *The change of water supply*

The supply of fluorine-free water would obviously be the best method of preventing the incidence of fluorine poisoning. Though such a method can be resorted to in some cases, considering the very wide distribution of fluorides in nature, it cannot be recommended as one universally feasible. Besides tapping of the new sources of fluorine-free water, it would involve either long distance connection with the source of fluorine-free water or large migration of people from one site to another, or in other words, the re-grouping of villages in accordance with the availability of fluorine-free water.

Such difficulties, in some cases, canot be expected to be overcome or even partially solved.

(2) *Removal of F from drinking water*

Under such circumstances, attempts should be made to remove fluorine from the available source of water. Various methods have been developed for the removal of F from drinking water. As the concentration of F in the water is below the solubility of all common fluorine compounds, it has been assumed that the removal of F is accomplished oy physico-chemical processes. Some of the methods employed are given below.

(i) *Methods employing calcium phosphates.*—MacIntire (1938) removed F from water by adding for 1 p.p.m. of suspended matter 30-40 p.p.m. of orthophosphoric acid, and then sufficient $Ca(OH)_2$ to convert the acid into orthophosphate. F was found to be removed with the insoluble phosphate. This process was modified by MacIntire and Hammond (1938) by replacing phosphoric acid with superphosphate and by removing the excess $Ca(OH)_2$ by aeration. Fluorine has been removed by treating the water with bone (Smith and Smith, 1937), purified bone meal (Smith and Davey, 1939), tricalcium phosphate (Behrman and Gustafson, 1938; Adler, 1938), a mixture of tricalcium phosphate and hydroxy apatite (Goodwin and Litten, 1941) and bone black (Burwell, *et al.*, 1945). In the last process, the spent bone black has been either discarded or regenerated with a solution of monosodium phosphate and trisodium phosphate. The loss in fluorine-removing capacity, after first regeneration, is about 12 per cent. Calcium phosphates and bone meal have been activated by washing with sodium hydroxide and by removing the excess alkali with acid. The loss of 4 to 6 per cent. of the material, incurred by this procedure, has been considerably reduced by neutralising the excess alkali with carbon dioxide (Behrman and Gustafson, 1938).

(ii) *Methods employing aluminium salts.*—Fluorine in hard water has been removed by Boruff (1934) by dosing the water with alum and removing the floc by sedimentation and filtration. On a small scale, water is shaken with activated alumina in suitable containers and softened with the addition of excess lime, causing in the process, the co-precipitation of considerable amount of F. The method has been further developed by Boruff, *et al.* (1937). Fluorine has been removed by treatment with calcined alumina (Churchill, 1936), aluminium sulfate (Kempf, *et al.* 1936), partially hydrated alumina (Goetz, 1938), specially prepared aluminium oxide and freshly prepared aluminium phosphate (Walker, *et* al. 1939), activated bauxite (Trelles

and Bach, 1940), water insolubie compounds like precipitated silicate of aluminium, charged with uncombined Al^{+++}ions (Urbain and Steman, 1942) and paddy husk carbon treated with aluminium salts (Venkataraman, *et al.*).

(iii) *Methods employing magnesium salts.*—Trelles and Bach (1940) have removed fluorine from water by boiling it with 1·5 gm. of MgO per litre of water. Magnesium oxide has been employed by Dean and Elvove also (1938). Fluorine has been removed with magnesium phosphate (Behrman and Gustafson, 1941; Adler, 1941), active magnesia (Elvove, 1937; Zottlemoyer, *et al.*, 1947), and with lime and magnesium salts (Wyatt, 1939; Goetz and Tiger, 1947). In the last process, first, the ionic magnesium of water is increased by adding magnesium salts and then lime is added to form a sludge. The mixture is stirred vigorously when fluorine and silica are taken up by the sludge.

(iv) *Methods employing various adsorbents.*—Removal of fluorine from water has been effected by treatment with various adsorbent earths and clays, activated carbon at pH 3·0, Wyoming betonites, Fuller's earth, celite or silica gel at pH 2·5 (McKee and Johnston, 1934, 1937), dried granular metallic oxide gels like hydrated ferric oxide, alumina, borate or the mixed oxides of iron and manganese (Goetz, 1938), bauxite, bog iron ore and activated carbon (Permutit Co., 1938, 1939), exchange material made from barium or ferric chloride and silicic acid (Urbain and Steman, 1939), asphaltic materials heat treated with alkali (Urbain and Stemm, 1943) and ion exchange resins (Venkataraman, *et al.*).

Some of the methods, outlined above, have attained a considerable measure of practical success in other countries, but, under the conditions obtaining here, the methods will be found almost prohibitive in cost. In addition to their prohibitive cost, considering that for the successful working of these methods, a certain degree of technical knowledge and skill is required on the part of the operator and considering also that every locality or house has got its own water supply, the widespread use of these methods in this country does not seem to be immediately possible. The provision of a common water supply by a well-financed governmental authority, however, in some cases, is likely to render the application of these methods feasible.

(3) *Dietary and other methods*

In cases where fluorine cannot be removed from drinking water, attempts can be made to mitigate the toxicity of ingested fluorine by dietary and chemical methods. These methods so far have been employed in domestic cattle

and experimental animals, and are based on the following data. It has been observed that the toxicity of ingested fluorine is greater when the diet is inadequate in its certain essential constitutents. In the areas of endemic fluorosis, it has been observed that it is the poorer people who are more adversely affected. It has been reported by DeEds (1933) that dietary Ca exerts a protective action and that Ca-deficient diets accentuate the symptoms of fluorosis. Hauck, *et al.* (1933 *a*) have shown that the growth of rats was poorer on diet, containing 0·15 per cent. NaF, when the calcium content was lower than when it was adequate and that the supplement of vitamin D reduced the toxicity of F in Ca-poor diet but not in the Ca-rich. Similar observation has been made by Schulz (1938). The protective action of dietary Ca against the toxic action of fluorine has been noted by Lawrenz and Mitchell (1941) and Ranganathan (1941, 1944) in rats, by Velu (1933) in sheep and by Mazumdar and Ray (1946) in bulls. Mazumdar and Ray (1946) have further reported that the addition of calcium or phosphorus salts, in amounts adequate to bring the quantity and the ratio between two minerals to optimum levels, helped in protecting the animals for long periods against fluorine intoxication. Pillai, *et al.* (1944) have reported that the inclusion of sufficient quantities of whole milk powder in the diet of the experimental rats afforded a remarkable protection against fluorine poisoning in the animals. A supplement of bone powder also brought about considerable relief.

Pandit, *et al.* (1940) have observed that the pronounced deficiency of vitamin C is specially associated with the severe incidence of the disease. The administration of vitamin C has been found by Pandit and Rao (1940) to mitigate the toxicity of ingested fluorine in the monkeys. Similar observation has been made in rats by Phillips and Chang (1934).

Based on the observations that fluorine reduces the general metabolic rate and interferes with the carbohydrate metabolism, attempts have been made to reduce the toxicity of ingested fluorine by including in the diet sufficient quantities of thyroid (Phillips, *et al.*, 1935), and the carbohydrate metabolites like glycerol, and lactates (Phillips and Hart, 1935), but no significant result has been achieved. On the contrary, it has been observed that the toxicity of fluorine increases with the administration of thyroid.

Aluminium salts, calcium hydroxide and boric acid, to some extent, have been reported to be capable of saving animals from lethal dose of NaF, when mixed with the latter (Marcovitch and Stanley, 1942). Limitation of fluorine toxicosis with $AlCl_3$ has been observed in rats by Sharpless (1936) and in the bulls by Mazumdar and Ray (1946).

In none of the instances cited above, has it been ever reported that dental lesions, caused by feeding fluorides, have been prevented by treatment with vitamins C and D, or calcium, phosphorus and aluminium compounds or that the development of fluorosis has been completely averted.

Summary and Suggestions

Data have been presented to indicate the very widespread incidence of fluorine poisoning, its relationship with the nature of the soil and fluoride content of water, the nature of fluorine poisoning and the various methods devised and employed to prevent and reduce the toxicity of fluorine. Despite the vast literature that has accumulated, it needs to be emphasised that the present knowledge, regarding the nature of fluorine poisoning in general, and the interference of fluorine in the metabolism of calcium, phosphorus and nitrogen and in the calcification of teeth and bones in particular, is either incomplete or not well established. Work remains to be carried out to determine the exact nature of these and other effects of fluorine ingestion, particularly in man. With a view to evolving an economical process for the removal of fluorine from water, work should be carried out to study the mechanism of fluorine removal by calcium, magnesium and aluminium compounds. The possibility of mitigating the accumulated effects of fluorine in humans and animals, in the areas of endemic fluorosis, with dietary and other methods should be investigated. Methods should be devised for the biological determination of the sub-toxic level of fluorine intake in humans.

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Explanation of Photographs

Skiagrams showing osteophytic outgrowths and increased calcification of human bones in endemic fluorosis.

Plate 1. Cervical vertebrae
2. Lumbar vertebrae
3. Pelvis
4. Tibia and fibula