A REVIEW OF THE LITERATURE

(Effect of fluoride on other body constituents)

Fluoride metabolism is affected by various substances. Weddle and Muhler (1954) found that various cations decreased absorption and retention of fluorides. Wagner and Muhler (1958) studied the effect of Ca\(^{++}\), Mg\(^{++}\), Fe\(^{+++}\), PO\(_4\)^{---} ions and found no significant difference in retention of fluoride in carcass by these ions, if added separately. Lesser retention was found when all these salts were mixed together. Considering the affinities for complex formation, Feldman, Morken and Hodge (1957) thought that the effect on fluoride were in the order of aluminium > magnesium > calcium. The order stated here is of stability constants. The amount of binding in drinking water would depend on the relative concentrations of magnesium, calcium, aluminium. It was inferred that the effect may be due to combination of different ionic effects and not due to a single ion. The inter-relation of metabolism of fluoride and some of the substances is as follows:

Fluoride and Calcium

Fluoride has a strong affinity for calcium ion. Prissok (cited by Held 1957) inferred that toxic effect of fluoride might be due to calciprivic power of fluoride. In acute poisoning, the blood calcium may be lowered to about 50 per cent (Jodlbauer 1932). Roholm (1937) considered that the toxicity of fluoride might be due to calcium precipitation.
In case fluoride bind serum calcium, its amount ought to be less. It was found experimentally that fluoride did not block the blood calcium (Grand 1955) and that, in particular, no tetanic convulsions were seen in cases of accidental ingestion of large quantities of fluoride (Held 1957). McClure (1946), Majumdar and Ray (1946), Greenwood, Hewitt, Nelson (1934) found no effect on the concentration of calcium in blood due to fluoride. According to Schour and Smith (1934, 1935) the toxicity of fluoride was not due to its effect on blood calcium or phosphorus. Irving and Ninaber (1946) were also of the same view.

Calcium salt fed with the ingested fluoride decreases the action as well as toxicity of fluoride (Weddle and Muhler 1957; Lawrenz and Mitchell 1941; Greenwood, Playney, Skinsnes, Hodge 1946; McClure and Mitchell 1931). It was found that a high calcium intake reduces the fluoride retention (Smith 1936; Jackson 1955). Largent (1954) observed that lesser fluoride was retained by those rats which received greater calcium. Weddle and Muhler (1954) found that all cations reduce but calcium appeared to be most effective of all cations in reducing fluoride retention. Steyn (1964) considered two probable reasons for lesser toxicity of calcium fluoride namely (a) calcium fluoride is much less soluble and (b) in calcium fluorides the fluoride atom was already accompanied by the calcium atom and this would prevent, in a measure at least, the fluoride atom from attaching itself to ionised calcium in the blood and tissues, thus deionising and rendering it unavailable for important physiological processes.
Marcovitch and Stanley (1942) considered calcium salts as an antidote for fluoride. Thus the more serious symptoms of fluorosis may be modified with the help of calcium salts (Ranganathan 1941; Pillai, Rajagopalan and Day 1944). Shourie (1946) found that tolerance limit of fluoride was increased in presence of excess of calcium. Massler and Schour (1952) concluded from their studies that lower the calcium intake, more prevalent the mottled enamel.

Conversely, addition of fluoride to diet caused a decrease in calcium retention in concentrations above 0.06 percent of diet (McClure and Mitchell 1931; Smith 1936).

Glock (1940) found slight decrease in calcium in bones of rats when administered fluoride. Suttie and Phillips (1939) noticed no effect on ash or 45Ca content of long bones or whole skeleton by fluoride. Majumdar and Ray (1946) found that when fluoride was administered in small amounts the balance of calcium improved, but higher doses brought about a negative balance. Dunstone and Payne (1959) observed a greater uptake of radioactive calcium in the ends of bones from salts given fluoride than in those of control. The ash content of teeth was found to be lowered by fluoride consumption regardless of Ca/P ratio in the diet (Smith and Lantz 1933).

Lantz and Smith (1934) found that fluoride caused increased excretion of calcium in the faeces as well as urine. Fluck (1955) observed greater excretion of calcium in goat's milk on administration of fluoride. Wagner and Muhler (1959)
... found no effect either in concentration or in total amount.

Loss of radio-active calcium has been found to be greater in the tissues in the presence than in the absence of fluoride. (Likins, Scot, Zipkin and Steere 1955; Likins and Zipkin 1954; Likins, Zipkin, McClure and Steere 1953; Likins, Zipkin, Steere and McClure 1954).

Fluoride and phosphorus.

McClure and Mitchell (1931) showed that the phosphorus contents of diet affect markedly the action of fluoride on teeth. Majumdar and Ray (1946) found that fluoride in small amounts improved the balance of both calcium and phosphorus, but higher amounts produced a negative balance due to their increased elimination in urine. They further noted that symptoms of fluorosis were precipitated in animals kept on low phosphorus diet, but were delayed when adequate phosphorus was supplied. Lantz and Smith (1934) also found that fluoride caused increased excretion of phosphorus in faeces and urine, indicating perhaps an interference in the absorption of these elements. According to Wagner and Muhler (1958) phosphorus appears to facilitate somewhat storage of fluoride but not significantly. DuTact, Smuts and Malan (1937) observed loss of phosphorus by dairy cattle on administration of fluorides and considered that fluoride produced symptoms of osteomalacia by inducing a condition of phosphorus shortage. This hypothesis has not been substantiated by Majumdar and Ray (1946); Majumdar, Ray and Sen (1943). Jackson and Weidmann (1955) found that absorption of phosphorus decreased in proportion to amount of fluoride accumulated in the bones and teeth. Though it has been reported that fluoride
affect the phosphorus retention, yet the converse of it has not been found true (Lawrenz and Mitchell 1941). Why it is so, has not been found.

According to McClure (1946); Majumdar and Ray (1946); Kasliwal and Solomon (1959); Majumdar, Ray and Sen (1943) there was no effect on phosphorus levels in serum due to fluoride.

Gautier and Clausman found that in human and cow’s milk there was a certain parallelism between the fluoride and phosphorus concentration (Held 1957).

**Fluoride and Magnesium**

Schuck (1938) noted that magnesium did not protect the animals against fluoride when ingested together. But other workers (Czernyesi 1956; Goldenberg and Sobel 1951) considered that a certain metabolic antagonism existed between fluoride and magnesium, so that, in particular, similar complaints may be attributed to a lack of magnesium or an excess of fluoride and vice versa. Inhibitory action on phosphatase and stimulation of a salivary secretion due to excess fluoride can also be brought about by lack of magnesium. Weddle and Muhler (1954) found the Mg$^{++}$ decreased fluoride retention. Sodium fluoride decreased in vitro, the power of calcification of rachitic cartilage (Robinson and Rosenheim 1934); this effect was also decreased by magnesium (Goldenberg and Sobel 1951).

**Fluoride and Aluminium**

Administration of aluminium salts causes the formation of poorly absorbed compound, and the absorption of fluoride is thus reduced (Kempf and Nelson 1936; Sharpless 1936; Marcovitch and Stanley 1942).
Fluoride and Iodine

Iodine content of thyroid was found to be less in fluoride intoxicated rabbit than normal by Jentzer (1959). Harris and Hayes (1955), on the other hand, found that the accumulation of iodine was not affected by fluoride in smaller amounts. Creek, Parker, Hauge, Andrews and Carrick (1958) observed greater reduction in growth rate of chickens at a low iodine level than higher iodine level when given fluoride.

Fluoride and Molybdenum

According to Stookey and Muhler (1959) molybdenum appears to decrease the retention of fluoride.

Fluoride and Strontium

Muhler, Stookey and Wagner (1959) observed that Sr did not increase retention of fluoride nor did fluoride increase retention of Sr in whole carcass or femur in rats.

Fluoride and Vitamins

It is well known that the dietary nutrients greatly affect the fluoride intoxication. Green leafy plants or fresh cut grass ameliorated toxic effect of fluoride (Henke, Maneke 1931; Hobbs, Moorman, Griffith, West, Merriman, Hansard and Chamberlain 1954; Phillips, Bohstedt, Fargo and Hart, 1934).

Vitamin A

Carr (1954) found that toxicity of fluoride increased with low vitamin A and panthothenic acid diet. 200 international units of the vitamin slightly delayed the onset of the symptoms of fluoride intoxication.
Vitamin B

Spira (1950) reported that vitamin B complex helped in the tolerance of toxic effects of fluoride.

Vitamin C

Schour and Massler (1947) found that toxicity threshold of fluoride was lowered when there was a vitamin C deficiency. Pandit, Raghavachari, Rao and Krishnamurthi (1940), associated a severe incidence of fluoride intoxication to pronounced deficiency of vitamin C.

Pandit and Narayana Rao (1940) and Wadhwani (1955) found that ascorbic acid seemed to mitigate the toxicity of fluoride. Phillips (1933); Phillips, Stare and Elvelijem (1934); Phillips and Chang (1934); Pandit and Raghavachari, Rao and Krishnamurthi (1940) and Wadhwani (1954) studied the relation of vitamin C with fluoride and concluded that it had beneficial effect.

The vitamin C contents were found to increase in supra renal s, pituitary, kidneys and liver in cases of fluoride poisoning in guinea pigs. Phillips and Chang (1934); Phillips and Stare (1934) considered it to be due to inhibition of enzyme systems in which vitamin C plays a part. A deficiency of vitamin C produced symptoms almost opposite to fluoride poisoning and animals subjected to fluoride and vitamin C deficiency at the same time showed teeth more normal in appearance than those of animals suffering from either conditions alone. Muhler (1958) showed that vitamin C caused an increased storage in skinned carcass of rat.

Vitamin D

Hauck (1934), Morgareidge and Finn (1940) studied the
effect of vitamin D in fluoride intoxication and found that it reduced the toxic effect in a diet low in calcium but not in diets rich in calcium.

**Fluoride and Enzymes**

It is well known that the fluoride ion is able to inhibit enzyme processes. Its action may be due to formation of complex metallic salts with various enzyme activators (Reiner 1946) e.g. Ca, Mg, Mn, Fe etc. or combination with prosthetic groups of many phosphoproteins to form fluorophosphoprotein. Fluoride ion at certain concentrations affect urease, phosphatases, lipase, esterases, enolase and enzymes engaged in glycolysis, oxidation and reduction mechanisms.

Some of the enzymes affected by fluoride are listed below:

1. **Fluoride and enzymes engaged in carbohydrate metabolism**
   
   Bramstedt, Kroncke and Naujoks (1956) found that fluoride interferes with carbohydrate catabolism. Warburg and Christian (1942) studied the inhibition of enolase by fluoride and showed it due to magnesium ion displacement.

2. **Fluoride and enzymes engaged in lipid metabolism**
   
   Johnson and Lardy (1950) demonstrated the inhibition of fatty acid oxidase activity by 0.01 mol of fluoride. The closely related acetate activating system is inhibited in vitro by 0.0001 to 0.0005 mol of fluoride (Aisenberg and Potter 1955). Succinic dehydrogenase (Slater and Bonner 1951), lipase (Rothschild 1929) were affected by fluoride. Linde (1959) estimated fluoride by its inhibition of lipase.

3. **Fluoride and enzymes engaged in bone metabolism**

The
Acid phosphatases was found to be inhibited by fluoride. Optimum pH for this inhibition was 5.5 (Lammers and Hafer 1956).

Naujoks (1957) found by histochemical method that topical application of fluoride on human gums resulted in partial inhibition of alkaline phosphatase but no effect on acid phosphatase. Phillips (1932) found an increase of phosphatase in blood but a reduction in bones. Majumdar and Ray (1946) showed an initial increase in alkaline phosphatase followed by constant fall.

According to Maplesdon, Motzok, Oliver and Branion (1960) alkaline phosphatase activity of plasma, kidney, liver residue, intestinal mucosa, bone of rat and rabbits did not change when they were given diets containing high levels of fluoride. They considered alkaline phosphatase levels of no value for diagnosis of fluorosis. Kaliwal and Solomon (1959) found normal serum alkaline phosphatase levels in fluorosis.

Fluorides inhibit the tyrosine-tyrosinase and dopa tyrosinase reaction (Lerner 1952).

Function of gastric mucous membrane are interfered by fluoride. Sodium fluoride abolished the effect of histamine on acid production (Bowie, Darlow and Murray 1953). Activity of Fumaric dehydrogenase and enolase (Jacobson and Tapadinas 1935) were inhibited.

Larger doses affect cholinesterase activity but lower doses containing 0.05 sodium fluoride had no effect on the amount of cholinesterase in the brain (Dybing and Loe 1956). In cats brain slices, Strickland (1954) found that fluoride
inhibited the incorporation of phosphorus.

In muscle metabolism, DeEds (1933) found inhibition of lactic acid formation. Probably a precursor of lactic acid (heptose-6-phosphate) is converted into a stable compound (glucose-6-phosphate).

Enzyme studies are considered to be of little value. According to Frajola (1959) the substrate of one enzyme system is the product of the other and a dynamic equilibrium exists due to activity of various enzymes. In considering the fluoride action, the concentration is of great significance. Therefore, studies of isolated enzyme system, that is, the enzyme activity measured in tissue homogenates, extracts or fraction, cannot be a sure indication of inhibition in the system. Studies of enzyme patterns in serum is considered to be more reliable but normal data is not yet available (Frajola 1959).

Fluoride and Hormones

It is surprising that in view of enormous advances in hormone chemistry during recent years, little work has been done to find the effect of fluoride on these.

The biological antagonism between fluoride and iodine has been repeatedly suggested in connection with effect of fluoride on thyroxine and its storage in thyroid gland. Wespi (1954) found that regions which are rich in fluoride are poor in iodine. Baumann and Metzger (1949) suggested that thyroid had affinity not only for iodine but other members of the seventh periodic group of elements. The thyroid was found to concentrate fluoride (Chang, Phillips, Hart and Bonstedt 1934), Chloride (Remington 1938), bromide (Perlman and Morton & Chaikoff 1941);
astatine (Shellaberger, Godwin 1956; Hamilton, Durbin and Parrot 1954); manganese (Ray and Deyssach 1942), technetium (Baumann, Searle, Yalow, Seigel and Leidlin 1952) and rhenium (Baumann, Lizmor, Oshry and Leidlin 1940).

Galletti and Joyet (1958) considered that the action of fluoride on thyroid physiology is not the result of simple competition between halogens for receptor site within the gland. The amount of fluoride accumulated by the thyroid has been a subject of controversy. It has been stated by some workers that thyroid accumulates relatively large amounts of element (Chang and Phillips, Hart and Bonstedt 1934; Hein, Smith and Brudevold 1954; Phillips, Stare and Elvelijem 1934). Fluoride is not considered by others to accumulate in greater proportions in the thyroid (Galletti and Joyet 1958; Harris and Hayes 1955; Harris 1954). The changes in thyroid are observed by Spira (1950) whereas no effect was noticed by Demole (1951). Decrease in basal metabolism under the influence of fluoride was found by Jentzer (1954) whereas no effect on basal metabolic rate was observed by Held (1953).

Effect on constituents of blood

Kniznikov (1958) found no change in the amount of hemoglobin in fluoride intoxicated rats.

Kasliwal and Solomon (1959) observed that the total proteins were normal in a fluorotic patient. Leone, Shimkin, Arnold, Stevenson, Zimmermann, Geiser, Liebermann (1954) found normal blood picture in their famous Bartlett-Cameron survey.

Fluoride and Nutrition

The fluoride intoxication may be related to nutritional status. Under-nourished may show the effect of fluoride poisoning
in a more striking way (Schour and Massler 1947; Massler and Schour 1952). It is not precisely known which particular constituent of the diet is responsible to increase the toxicity of fluoride.