INTRODUCTION
Fluorine is considered now as essential trace element in view of its beneficial effect in small amounts upon tooth structure and in the prevention of dental caries. However high intake of fluoride is known to cause toxic effects causing a debilitating condition clinically referred to as 'Fluorosis'. Endemic fluorosis has been a public health problem in several parts of the world (Singh and Jolley, 1970). Due to the presence of high levels of fluoride in drinking water it is estimated that in India several millions of people residing in the states of Andhra Pradesh, Punjab, Rajasthan, Uttar Pradesh, Karnataka and Tamil Nadu are exposed to the risk of fluorosis (Pandit et al., 1940; Daver, 1945; Siddique, 1955; Singh and Jolly; 1961; 1970; Teotia et al., 1969; 1971). Shortt et al. (1937) first described the disease from their studies carried out in parts of Andhra Pradesh (formerly Madras state). Several investigators studied different aspects of the problem such as the clinical, biochemical and epidemiological nature of the disease. More recently it has been reported that fluorosis exists in endemic form in parts of Uttar Pradesh (Teotia et al., 1971), Rajasthan (Jolley, 1974), Tamil Nadu (Ganesan, 1973) and Karnataka (Myaia, 1974).
In some parts of South India fluorosis has taken a new and serious dimensions in the form of 'genuvalgum' among communities exposed to high levels of fluoride in drinking water (Krishnamachari and Kamala Krishnaswamy, 1973; 1974).

In nature fluoride occurs in several forms and enters the human system by several routes, mainly through drinking water. India stands distinctly among the countries where disease in man due to fluoride toxicity in endemic forms has been identified. High levels of fluoride in water have been described from all the continents in the world (Anonymous, 1970).

Fluorine comes under the group VII A elements. The four elements, fluorine, chlorine, bromine and iodine are classed together under the name halogens or salt formers. The name was given by Berzelius to those non-oxygenated radicles, simple or compound, which combine with metals to form salts. The binary compounds of these elements are usually called haloid salts.

The halogens are found in combinations and are very widely distributed. Metallic chlorides are very numerous; bromides, iodides and fluorides occur in small quantities. The elements themselves are scarcely found
in the free state in nature. Iodine is said to exist in minute quantities in sea water. Fluorides of all the elements are known except Br, C, Cl, N, O and some ten or twelve metals. The affinity of fluorine for hydrogen and the stability of its salts is much higher than it is with other corresponding halogens.

**Distribution of fluorine**

Fluorine constitutes approximately 0.077 per cent of the earth's crust and as such ranks thirteenth among the elements in order of abundance. Sea water contains about 1.4 ppm which makes fluoride rank twelfth in order of concentration. The waters of all oceans contain between 1 and 1.5 ppm fluoride. In the human body only a trace exists (but never the less here also it is thirteenth in abundance) (Maier, 1963).

**Biogeochemistry of fluorine**

The distribution of fluorine in nature is given below (Bowen, 1966).

Igneous rocks : 625 ppm, Shales : 740 ppm, Sandstones : 270 ppm

Fresh water : 0.09 ppm, Sea water : 1.3 ppm.

Air : < 0.01 μg.m⁻³.

Soils : 200 ppm; fixed in many clay minerals and in apatite.
Marine plants: 4.5 ppm.
Land plants: 0.5 - 40 ppm. Accumulated by Dichapetalum cymosiflum.
Marine animals: 2 ppm. Accumulated by the sponge Dysidea crawshayi, the mollusc Archidoris britannica and by fish bones.
Land animals: 150 - 500 ppm in mammalian soft tissues, 15000 ppm in bones.

Most commonly found minerals containing fluorides are fluorspar (which contains calcium fluoride), cryolite (which contains fluoride combined with aluminium and sodium) and apatite (which usually is a calcium compound of fluorides, carbonates and sulphates)(Maier, 1963).

Topaz and fluorite are the only common rock minerals in which fluorine is an essential constituent. In other common rock minerals, e.g. apatite, mica etc., fluorine replaces hydroxyl groups. This is possible because fluorine has the same valance and radius (1.33 Å) as OH (1.40 Å). Fluorapatite are common in soils that are not highly weathered but the mineral would not be a ready source of fluorine.
Studies on soil formation from granite in an acid soil from near Alice springs indicated that in the granite much of the fluorine was present as fluorapatite but in the soil, fluorite was present in the clay fraction and occurred as a sharp layer with 3% fluorine at the base of a diffuse carbonate horizon. These results suggested that fluorite was more soluble than calcite and would not persist in leached soils (Nicholas and Egan, 1975).

Most raw (untreated) waters contain fluorides. Surface water fluoride content (these sources comprising rivers, lakes, ponds, canals, cisterns etc.) generally do not exceed 3 ppm except when contaminated with industrial waters or sewage.

To what extent the structural fluorine replaces available hydroxyls (OH) of clays is not known, but it would not be a ready source of fluorine. However clays can exchange reversibly fluorine and OH, probably at crystal edges (Hofmann *et al.*, 1956; Hukner, 1969) and fluorine in this form would be available to plants.

After a rain, water percolates down through the soil and becomes what is called 'ground water'. Some of the water later reappears in the form of springs or from wells and galleries. In passing through the earth
the ground water dissolves in varying amounts of the minerals with which it comes in contact. Fluorides are also found naturally in many waters. These are dissolved from fluorine containing minerals occurring in the passages of the water, as it flows through the earth. Fluorides are found in almost all water supplies in varying concentrations (Maier, 1963).

An aluminium plant on the South bank of the St. Lawrence river, South West of Cornwall island, Ontario, Canada, emitted 0.816 metric tons of fluorine daily since 1973, considerably higher amounts were emitted from 1959-1973. Chronic fluorine poisoning was manifested clinically by stunted growth and dental fluorosis to a degree of severe interference with drinking and mastication in Cornwall island cattle (Krook and Maylin, 1979).

The below reaction occurs when phosphate rock containing fluorapatite is treated with sulphuric acid to make fertilizer

$$\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2 + 7 \text{H}_2\text{SO}_4 \rightarrow 3 \text{Ca(H}_2\text{PO}_4)_2\text{H}_2\text{O} + 7 \text{CaSO}_4 + 2 \text{HF}$$

The HF produced in the reaction can cause significant air pollution problems. Fluorides are also
emitted to the atmosphere in steel making and aluminium production. There is some evidence that fluorides rather than sulphur dioxide may have been responsible for human deaths in air pollution episodes at Donora, Pennsylvania and the Maas Valley in Belgium.

Endemic fluorosis has been reported from several parts of India (Fig. 1) (Shortt et al., 1937; Siddiqui, 1955; Singh et al., 1963) and the neighbouring Ceylon (Senewiratne et al., 1974). Endemic fluorosis with skeletal involvement has been recognised as a public health problem in several parts of the country, particularly in the States of Andhra Pradesh, Punjab, Rajasthan, Karnataka and Tamil Nadu.

Tamboli et al. (1980) studied about the prevalence of fluorosis at Pratabpura and Surajpura villages in Ajmer district, Rajasthan (India), where fluorine contents in water were 14.3 ppm and 13.9 ppm, respectively. Dental fluorosis and skeletal fluorosis was present in 86.5% and 26.9% persons, respectively in both villages and was found slightly more often in males than in females.

In the two states of Andhra Pradesh and Punjab, extensive work had been carried out in the epidemiological and clinical aspects of the disease (Shortt et al., 1937; Daver, 1945; Singh et al., 1963). Jolly et al. (1980)
Geographic distribution of 'Fluorosis' in India.
(Tandon and Gopinath, 1984).
observed that no cases of genuvalgum syndrome, which is reported in Andhra Pradesh, were encountered in the endemic fluorotic villages of Punjab.

In Andhra Pradesh, Nalgonda and Prakasam districts are most affected by endemic fluorosis. In addition to these two, three or four more districts also lodge a few fluorotic villages (Krishnamachari and Kamala Krishnaswamy, 1973). Nalgonda has 5 taluks in which a majority are affected with fluorosis. Half of the Prakasam district is endemic for fluorosis. The taluks of Darsi and Podili are worst affected (Krishnamachari and Kamala Krishnaswamy, 1973). Several investigators carried out clinical, epidemiological and metabolic studies in subjects with fluorosis.

The incidence of endemic fluorosis in human beings in Anantapur district is reported to be considerably high due to the high fluoride content in natural waters of the area (Raju et al., 1979). The fluorine content in about 60 to 70% of the samples collected in various parts of the district was found to be high from permissible limit of 1.5 to maximum of 5 ppm (Table A) which caused dental fluorosis in general and skeletal fluorosis in some
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<th>Place</th>
<th>Fluoride content in ppm</th>
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<tbody>
<tr>
<td>Ajmukur, Prisoner’s farm, Madakasira, Kothacheruvu and Jambuladinne</td>
<td>&gt; 1.0</td>
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<tr>
<td>Pandameru river, Guddapalapalle, Kottampalli, Paturayi, Nayanivaripalli, Pamurayi, Raptadu, Madakaleru river, Advibrahmasnapalli, Oruladevera cheruvu, Talupula, Tanakal, Maddalapuram, Anantapur town, Narpala, Salakamacheruvu and Gooty town</td>
<td>1.6 - 2.0</td>
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<td>Anantapur tank, Hamapauram, Kuduru, Mandabandapalli, Singanamala, Penukonda town, Mauled B.T.P. Colony, Narpala, Salakama cheruvu and Anantapur town</td>
<td>2.1 - 2.5</td>
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<th>Places</th>
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<td>Poguru (Gooty taluk), Kadvakllu, Guntakal (Timmamcherla), Rekulapadu and Narpala</td>
<td>2.6 - 3.0</td>
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<td>Bandamidapalli, Marutta, Tamallapalli, Dharmavaram town and Urvakonda</td>
<td>3.6 - 4.0</td>
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<td>Bapanakunta</td>
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specific cases. Out of the six samples collected from the municipal water supply bore wells of Anantapur urban area, three samples indicated fluoride with more than the permissible limit of 1.5 ppm (Raju et al., 1979). In general it is found that area of high slopes in pink granite have high incidence of fluorine.

The range of distribution of fluoride in natural waters of the area i.e. 1 - 5 ppm could account for the incidence of dental and skeletal fluorosis. The incidence of dental fluorosis and skeletal fluorosis was reported to be 50-70% and 10%, respectively. It may be stated that high incidence of fluorosis is because of a variety of factors such as geological, geochemical, climatological, social and economic factors. The people affected are economically backward and suffer from malnutrition. It is suggested that substantial quantities of fluoride may also be made available through sources other than drinking water. Sea salt contributed about 14 - 16 ppm fluoride (Raju et al., 1979).

Fluorine in the exogenic cycle of the fluorosis belt is almost wholly contributed by the granite and pegmatitic rocks. There is no evidence that the contribution of the fluorine is by a deep seated source through
volcanic fumaroles or hot springs. There may be however an insignificant addition of fluoride to the soil by the use of phosphate fertilisers containing fluorine. On account of extreme backwardness of the region from the industrial point of view it is unlikely that there is any addition of fluoride to the environment by artificial means. Although data is not available it is not unlikely to expect any pollution in cultivated vegetation by use of fluorine insecticides (Raju et al., 1979).

The factors that govern the distribution of fluoride in natural waters is dependent on the amount of fluorine in the source rocks, soils, duration of contact of water with rocks and soils, temperature, rain fall, vegetation and oxidation-reduction reactions.

The dissolved solids including fluoride in waters increase considerably due to high evapotranspiration under the hot, semi-arid climatic conditions prevalent in the region. This might also lead to increased salinisation of soils by precipitation of various slats including fluoride.

A major part of the district is occupied by granites and greisses and to some extent by Schistose rocks in the southern and eastern parts (parts of
Peaukonda and Kadiri taluks). Shales and Slates are exposed towards the north-eastern part of the district (Tadpatri taluk).

The principal fluoride bearing minerals of these rocks are the acid soluble minerals such as fluorite and fluoroapatite and the refractory minerals like hornblende, mica, epidote. Fluorite and apatite are the minerals that are responsible for high concentrations of fluoride under normal pressure and temperature conditions whereas the refractory minerals like hornblende etc. will release only at high temperature.

The other factors that control the amount of fluoride in waters is dependent on the degree of weathering to which the granite rocks of the area were subjected. In regions where the granitic rocks were subjected to extensive physical, chemical and biological weathering resulting in the development of thick mantle of decomposed rock and soil carrying abundant clay, minerals and organic matter, ground waters are expected to contain higher concentration of dissolved solids, including fluoride. In regions where the ground water occurs along fractures and joints of granite rocks subjected to little chemical
weathering very little concentration of dissolved solids including fluoride is expected (Raju et al., 1979).

**Food and fluoride:**

Fluoride analysis of some typical foods used in the American dietary have been made in nine field stations in the eastern, central, western sectors of the United States (Elifford, 1947).

Of all the foods only fish and fish products, dry beans and tea contain more than 1 ppm of fluoride. Milk was very low in the mineral (0.09 ppm); most of the fruits, meats and vegetables contained less than 0.30 ppm of fluoride (Wilson et al., 1959).

No significant differences were observed in the copper content of the grain from fluorosis and non-fluorosis areas (Deosthale et al., 1977). Zinc content was significantly higher in sorghum and lower in pearlmillet from fluorosis areas than in non-fluorosis areas. The concentration of zinc in rice either milled or brown, from the fluorosis and non-fluorosis areas was not significantly different. From fluorosis areas both sorghum and pearlmillet contained about 60% more molybdenum than from the non-fluorosis areas. The molybdenum content was
significantly lower in milled rice than in brown rice (Deosthale et al., 1977).

Extra fluoride may be introduced to the diet from fluoride containing insecticides and sprays that are used as fruit and vegetable pest control. In addition to this, vegetables absorb the mineral when they are cooked in fluoride containing water (Wilson et al., 1959).

At a concentration of 1 ppm, fluoride is supplied in nutritionally adequate amounts (Pike and Brown, 1970). When the drinking water in a given area contains less than 1 ppm, it is regarded as commendable public health practice to add fluoride to water supply (fluoridation) in order to raise its concentration to an appropriate level.

In areas where the fluoride content of drinking water is low, the incidence of dental caries in children can be significantly reduced either by administration of fluoride tablets to children or to women during pregnancy and lactation or by topical application of fluoride preparations to the teeth (Harpe et al., 1979).

Fluorine occurs in many tissues notably the teeth, thyroid and skin, but there is no evidence that it is nutritionally essential for general health. Interest in
the element arises chiefly out of its efficiency in preventing dental caries (Cantarow and Schepartz, 1961).

Metabolism of Fluorine

The use of fluoride for the treatment of patients with metabolic or neoplastic bone disease has stimulated renewed interest in studies of fluoride metabolism in man (Osis et al., 1974).

Data of the dietary intake of fluoride (Armstrong and Knowlten, 1942; Machle, 1942; McClure, 1949; Martin 1951) and urinary fluoride excretions were reported many years ago (Machle et al., 1942; McClure et al., 1945, Zipkin et al., 1956; Singer and Armstrong, 1965).

The determination of fluoride balances in man requires the analysis of the diet, of urine and of stool. These were carried out in research unit under strictly controlled conditions (Osis et al., 1979).

Fluoride is readily absorbed from the intestines (Cantarow and Schepartz, 1961). It is also believed that fluorine may undergo surface adsorption by the hydroxyapatite crystals of the enamel forming a protective layer of acid resistant fluorapatite (Cantarow and Schepartz, 1961).
Serum fluoride was directly correlated with previous intake and appear to reflect bone fluoride stores (Suttie and Kolstad, 1977; Feerskov et al., 1979; Waterhouse et al., 1980).

The fluoride in plasma is present in ionic and bound form with diurnal variations, the level being maximum in the night and minimum in the morning (Patterson et al., 1977; Cowell and Taylor, 1981). Jenifer and Riggs (1978), reported ingestion of Ca (1.3 g) decreased the blood fluoride values (by 22%).

Teotia et al. (1978) reported that plasma fluoride levels in patients living in endemic areas were elevated.

Singer and Ophaug (1979) reported no significant difference between the mean levels for ionic, bound and total fluoride concentration in the plasma of male and female subjects of the same age. Significantly higher levels of ionic and total fluoride concentrations in plasma in older age group than in younger age groups was observed.

Fluoride has been shown to get concentrated in liver and muscle within 2 to 3 hours after I.V. injection, the accumulation being more in liver than in muscle (Armstrong and Singer, 1980).
Diets containing dairy products was found to decrease the bio-availability of fluoride (Ekstrand and Ehrnebo, 1979). Aluminium inhibited intestinal absorption of fluoride in animals, increased fecal fluoride excretion, and significantly decreased plasma and urinary fluoride levels (Herta et al., 1980; 1981). Stookey and Muhler (1962) reported that molybdenum promotes fluoride retentions.

Shearer et al., (1980) reported cadmium did not influence caries development or alter the coriostatic effectiveness of fluoridated drinking water and did not influence fluoride uptake on to erupted enamel.

The bones of newly born baby contains very little fluorine and as years pass by a portion of the fluorine through water daily is added cumulatively to the bones when fluoride is digested by people in small amounts. Physiologic saturation of bones with the ingested fluorine can never take place during their life time. But if the water containing more than about 2.4 ppm under Indian conditions or more than 8 ppm under American conditions is consumed continuously for a period of more than 10 - 20 years they develop skeletal fluorosis or osteoporosis (Wilson et al., 1959).
Wix and Mohamedally (1980) reported that fluoride levels of human iliac crest correlated with age.

A direct correlation between the fluoride intake and urinary excretion was observed by Bagga et al. (1979). Cantarow and Schepartz (1961) reported that 75% of ingested fluoride was excreted mainly in the urine and the remainder mainly in sweat. However, Ekstrad et al. (1977) in their pharmaco-kinetic studies of fluoride in man, reported that nearly 50% of the fluoride was excreted in the urine indicating a considerable accumulation in the body. The urinary fluoride excretion was affected by the aluminium ingestion (Herta et al., 1980).

Types of staple consumed might also modify fluoride retention. Diets based on sorghum resulted in significant retention of fluoride (Lakshmaiah and Srikantia, 1977). This increased retention was due to the changes in urinary excretion of fluoride but not in the intestinal absorption (Krishnamachari, 1978).

Urinary excretion of fluoride was greater in animals whose diet were less in vitamin C and protein than to fluoride exposed guinea pigs on adequate diets (Parker et al., 1979). Parker et al., (1979) reported an increased fluoride deposition in bones of the guinea pigs fed low protein diets.
Maternal ionic plasma fluoride concentrations were significantly decreased during pregnancy. After delivery the ionic plasma fluoride concentration returned to usual levels despite onset of excretion of milk (Hanhijarvi, 1981). Teotia et al. (1979) reported that ionized fluoride concentration in maternal urine decreases during the course of pregnancy. The fall in maternal plasma and urine fluoride concentration during pregnancy was believed to be due to increased accumulation of fluoride in the rapidly mineralizing fetal skeleton.

At intakes of 4 to 5 mg of fluorides per day, it has been shown that almost all of the fluoride ingested was eliminated (McClure et al., 1945) in as much as equilibrium in the body was maintained by the loss of the mineral through kidney and skin. But at daily intakes of 12 - 25 mg, almost one half of the absorbed amount was stored in the body tissues (Largent and Heyroth, 1949). However when the individuals on these high levels of intake were returned to normal intake pattern of the mineral absorption and excretion returned to normal.

**Beneficial effects of fluorine:**

Fluorine is proved to be essential to mammals (Maura and Day, 1957) for dental health and for the development
of teeth and bones. Fluoride is now accepted as a required mineral nutrient.

Minimal amounts of fluoride have been showed to benefit men by providing an increased resistance to dental caries (Wilson et al., 1959). The protective effect of fluoride in tooth development is most important during infancy and early childhood because these are the periods that coincide with tooth development, although the caries preventive activity of fluoride continues into adulthood (Harper et al., 1979).

The effect of minimal amount of fluorides on the skeletal tissues of man has been studied, both radiologically and histologically (Weidman et al., 1963). Singer and Armstrong (1960) found that the fluoride content of the plasma to be constant for individuals who use fluoridated water within the range of 0.15 and 2.5 ppm.

In addition to this appropriate levels of dietary fluoride decrease the incidence of osteoporosis, a defect in the maintenance of bone structure that occurs in older people notably in women after menopause. It is essential for growth in rats and for fertility in mice. Fluoride appears to exert an inhibitory effect on enzymes of cariogenic bacteria.
At a concentration of 1 ppm fluoride is supplied in nutritionally adequate amounts. In certain districts when the natural fluoride content is less than 1 ppm artificial fluoridation of water has been adopted.

In areas where the fluoride content of drinking water is low, the incidence of dental caries in children can be significantly reduced either by a administration of fluoride tablets to children or to women during pregnancy and lactation or by topical applications of fluoride preparations to the teeth.

**Toxic effects of fluorine:**

Fluorosis occurs only in geographic areas where the water naturally contains high concentrations of fluoride. Fluoride is very toxic in large doses. Foods high in fluoride, excessive placental transfer and deposition in the fetus during pregnancy, appears to be the source of fluoride toxicity. Hot climate and malnurition may aggravate the toxicity (Bagga et al., 1980).

Ingested fluorides accumulate in the hard tissues of the body, the teeth and bones. Changes in the teeth as well as pathological lesions of the body tissues have been observed in animals when fed with either toxic amounts of fluoride or lesser amounts that proved to be toxic after
continuous ingestion for a period of time (Wilson et al., 1959). If the children consume water containing more than 1 ppm during the period when their permanent teeth are growing they develop dental fluorosis or mottling.

Intake of abnormally large amounts during childhood results in 'dental fluorosis' (mottled enamel) characterized by a patchy chalky or brownish mottling of the enamel, frequently with pitting of the surface and fracture and chipping of the enamel which is abnormally fragile. Symptoms of dental fluorosis include development of lustless spots, chalkiness, yellowish to brown transverse bands. This is a reflection of imperfect formation of enamel (Cantarow and Schepertz, 1961).

Anonymous (1978) reported that non-skeletal changes of fluorosis occurs early in the disease before dental and skeletal changes became apparent. The soft tissue organs affected by fluoride are in the order—-aorta, thyroid gland, lungs, kidneys, heart, pancreas, brain, spleen and liver (Anonymous, 1978; Zhavoronkov, 1977).

**Clinical and physiological studies:**

Petraborg, (1977) reported preskeletal fluorosis due to artificially fluoridated water. The affected patients presented a wide spectrum of symptoms among which polydipsia,
general pruritus, head aches and gastrointestinal symptoms were the most important. The affected made a full recovery when they discontinued the use of fluoridated water for drinking and cooking their food (Petrabor, 1977).

Skeletal fluorosis is characterised clinically by restricted movements of the joints, stiffness of the spine, deformities of spine such as kyphosis, bony exostosis and in some unfortunate victims by paraplegia due to spinal compression (Singh, 1967; Krishnamachari and Kamala Krishnaswamy, 1973).

Endemic fluorosis is a well defined clinical entity characterised by dental and skeletal changes (Krishnamachari and Kamala Krishnaswamy, 1973). Bone changes characterised by osteosclerosis, ligamental calcification and calcification of membranes and tendinous insertion, had been reported among adults and children living in areas of endemic fluorosis (Siddiqui, 1955; Singh and Jolly, 1961; Teotia et al., 1971; Krishnamachari and Kamala Krishnaswamy, 1973).

The symptoms of skeletal fluorosis include lethargy, body pains, tingling sensation in extremities of limbs, stiffness of spine joints, difficulties in breathing and in performing natural movements and development of osteophytic
over growth. In advanced cases the victims exhibit extreme leanness, loss of appetite, loss of sphincter control and onset of impotence. They finally became immobile and bedridden.

Runge et al. (1979) found an increase of bone mineral content and the bone width which was dependant on the fluoride exposure level and time. Franke et al. (1980; 1981) observed an increase in bone mass in the age group of 16 - 20 among those who had been drinking fluoridated water since birth.

Christie (1980) reported painful crippling deformities in Tanzania children from an area of endemic fluorosis. Excessive fluoride ingestion in pregnant women may possibly poison and alter enzyme and hormonal system in the fetus, causing disturbances in osteoid formation and mineralization. Knock-knee, bowlegs and Saber shins develop when walking begins. Combination of osteomalacia, osteoporosis and osteosclerosis result in a spectrum of bone changes from an early age. Male hormones and dietary, dietary and genetic deficiencies may aggravate individual response of actively growing bones.

The relationship between fluoride and tooth physiology was recognised first as a public health hazard.
In certain areas of the world and in this country, it was noted that the enamel of human teeth was mottled. These teeth were dull and chalky in appearance, some showed evidence of pitting and corrosion and in severe cases the teeth were stained with a color ranging from yellow to black (Wilson et al., 1959).

Chiro, (1977) reported from his histological studies that the prodentin of the molars and precementum of fluoride treated rats were remarkably wider. No marked histologic changes were seen in the gingiva, the periodontal ligament and the alveolar bone.

In rat the tooth enamel becomes chalky and brittle and the incisor teeth continue to grow forming an elongated tusk like incisor that is no longer useful in securing food. The skull of the rat becomes thickened, when excessive amounts of the mineral are fed to the rat (Wilson et al., 1959).

In cattle and swine the enamel of the teeth wears away, exposing the pulp cavity and it becomes difficult for the animals to ingest food and water because of the sensitiveness of the teeth. Fluoride poisoning was manifested clinically by stunted growth and dental fluorosis (Elifford, 1947; Krook and Maylin, 1979). Hillman et al., (1979)
observed that cattle afflicted with fluorosis developed hypothyroidism, anemia and eosinophilia, and affected the health and performance of some cows.

Fluorosis of bone, a condition clinically similar to arthritis, has been reported in population living for many years in areas of high fluoride content in water of at least 8 ppm and results from an excessive accumulation of fluoride in bone (Pike and Brown, 1970).

Czerwinski and Lankosz (1978) reported that in industrial fluorosis the changes were less advanced than in endemic fluorosis. Generalised sclerosis, alteration in the bone structure and periosteal reactions were the most typical features of the skeletal fluorosis. Ossification of the interosseous membranes and muscle attachments were less characteristic.

Erickson (1980) observed positive association between the frequency of human Down syndrome and the fluoridation of drinking water.

The workers of aluminium plant with fluorosis showed incidence of degenerative dystrophic skeletal effects when compared with control group who were not chronically exposed to fluorine compounds (Kuzina, 1977).
Whitford et al. (1979) reported early signs of acute fluoride toxicity in all animals during the 1st hour of fluoride infusion, which included diuresis, falling of urinary osmolality and glomerular filtration rate.

Decamargo and Merlelv (1980) reported that the rats treated with fluoride did not present any abnormalities with respect the weight gain, morphology, behaviour and macroscopic appearance of liver and kidney. Histochemically the polysaccharides and the acid and alkaline phosphatases were not visibly altered. Long term treated animals showed zones of deposition of lipid in the liver and kidneys.

Kidneys were adversely affected by prolonged use of NaF. The most consistent changes in the kidney were cloudy swelling of the tubular cells, marked necrosis of tubular cells, atrophy of the glomerule and areas of interstitial infiltration of round cells were found (Kour and Singh, 1980).

Studies of Kour and Singh (1980) established a different relationship between fluorosis and damage to the testis in mice. There was a lack of maturation and differentiation of spermatocytes, spermatogenesis had stopped and the seminiferous tubules had become necrotic.
Makhni et al. (1979) reported that in fluoride treated rabbits, parathyroids were hyperplastic and exhibited degenerative changes and the nuclei of chief cells became enlarged.

Walash and Mu&hir (1980) studied the influence of sodium fluoride on the developing chick embryo. At the dosage of 10 mg/egg all the embryos died. 5 mg/egg did not show any effect related to the phenotype or weight of the embryos. 2.5 mg/egg revealed an enhanced growth. This increase of growth was not accompanied with any embryonic phenotype abnormalities.

It was believed earlier that mottled enamel and crippling skeletal deformities occur only in persons who had resided for over 3–4 decades in areas of high fluoride content in drinking water. However recent studies carried out at the National Institute of Nutrition have brought to light that in several villages of Andhra Pradesh and Tamil Nadu, crippling bone deformity in the form of 'genuvalgum' can occur in adolescents and young adults and even in children under 7 years of age among communities exposed to high levels of fluoride (Krishnaswamy, 1974). The peculiarity of this syndrome is the association of osteosclerosis of the spine.
and extensive osteoporosis of the limb bones. Genuvalgum makes the appearance among children among 8 - 10 years of age residing in endemic fluorosis villages. More males were affected than females with a sex ratio of over 10:1 (Krishnamachari and Sivakumar, 1976). Clinical features showed that most of the patients were between the ages of 10 and 30 years. All had dental changes. Genuvalgum, which became prominent while walking was a striking feature. There was internal rotation and adduction of the hip. As a result, the gait was slow, laborious and awkward (Krishnamachari and Kamala Krishnaswamy, 1973).

A syndrome called 'Kenhardt bone disease' whose clinical picture is very similar to the genuvalgum syndrome had been reported from a small village close to Adam, in South Africa where chronic toxicity was also seen (Jockson, 1962). It is interesting that both in Andhra Pradesh and in Coimbatore the syndrome of genuvalgum appears to have come into existence in the vicinity of dams after their construction (Krishnamachari, 1974).

Studies carried out in Karnataka revealed that skeletal fluorosis was widely prevalent in an area, Mundargi where the fluoride content of water varied between 3 and 7.6 ppm with no incidence of genuvalgum.
Interestingly this area is situated far from any dam. In contrast to this, a few cases of genuvalgum were seen in villages nearer to Hospet Dam, where the fluoride levels in the drinking water ranged between 1 and 3 ppm. During these studies it was also observed that communities exposed to the same level of fluoride where the staple was sorghum or bajra (pearl millet) had higher incidence of genuvalgum than those which subsisted on rice (Krishnamachari and Sivakumar, 1976). It is reasonable therefore to assume that building up of a dam in the vicinity of fluorosis affected area modifies soil mechanics and trace element composition of soil, food grains and drinking water considerably. These alterations may influence or modify the soil fluoride-water-men relationship adversely (Krishnamachari, 1974). The molybdenum content of some cereals grown in areas where fluorosis is endemic has been found to be significantly higher than that in cereals grown in areas where fluorosis does not exist (Anonymous, 1973).

Radiological studies:

Anterio-posterior views of the cervicothoracic and limbodorsal spine showed the presence of osteosclerosis in majority of patients. In most cases typical 'bamboo spine' was seen due to spinal ligament calcification.
Calcification of interosseous membrane of the fore arm was observed. In addition, sclerosis of humerus, scapulae, ribs, fore arm bones and pelvis together with calcification of muscular attachments were seen. The most striking radiological feature, however was marked osteoporosis of the lower end of the femur and of the tibia and fibula and rarefacting of the metacarpal bones (Krishnamachari and Kamala Krishnaswamy, 1973; Krishnamachari and Sivakumar, 1976).

Socio-economic influence:

It was observed that invariably the poorest segment of the village was the one affected most. While the village head-men, business community and land-owners had evidence of dental fluorosis and had been living in the same village for generations, they did not suffer from genuvalgum as much as the poor. However persons over 40 years of age had suffered like others from kyphosis and from spinal osteosclerosis (bamboo-spine) due to chronic fluoride toxicity (Krishnamachari and Kamala Krishnaswamy, 1974).

Sex prediction

Males were predominantly affected. The overall ratio between males and females affected was about 10:1,
among children; 20:1 among adolescents and young adults. There were several families in each village in which more than one person were affected. In some families all the male members were affected.

**Dietary influence:**

Osteomalacia related to endemic fluorosis was reported by Jackson and co-workers in areas where drinking water was high in fluoride (Roholm, 1973). They observed rickets-like changes in inadequately nourished black children who were economically poor. Such changes did not occur among age matched children residing in the same environment.

No correlation between the amount of toddy consumed or the intake of calcium and the incidence of genuvalgum in a community was observed (Krishnamachari and Kemala Krishnaswamy, 1974).

Griffiths et al., (1975) recently observed evidence of osteomalacia in monkeys on a low calcium diet which received high doses of fluoride for 60 months. In contrast, monkeys fed high fluoride and adequate calcium diets develop osteosclerosis. A third group kept only on a low calcium diet developed osteoporosis. Roholm (1973), observed
that upon feeding small amounts of fluoride growth of bone was stimulated (osteosclerosis) but large doses led to osteomalacia with uncalcified osteoid.

Group of monkeys fed high levels of fluoride were found to develop radiological changes, characteristic of fluorosis much earlier when their diets were low in either calcium or in ascorbic acid. Animals maintained on diet in which protein was inadequate however showed equivocal changes (Krishnamachari, 1978).

It was considered possible that the type of staple consumed might also modify fluoride toxicity. It was shown that diets based on sorghum resulted in significant increase in retention of fluoride, mean increase in retention being 12.2 per cent as compared to diets based on rice at identical intakes of fluoride (Lakshmaiah and Srikantia, 1977). The increased retention was not due to changes in the intestinal absorption of fluoride but in the urinary excretion of fluoride (Krishnamachari, 1978).

It has been reported that molybdenum promotes fluoride retention (Stookey and Muhler, 1962) and the molybdenum content of sorghum has been found to be somewhat higher than that in rice (Deosthale et al., 1977). Whether there are other factors as well needs to be examined.
Alterations in bone metabolism is a basic feature of the disease and hence of calcium. \(^{45}\)Ca kinetics showed that the cumulative retention of radioactive calcium was high in all animals which received fluoride as compared to those that did not receive fluoride, but was highest in animals which received low calcium diets. Also there existed a parallelism between the concentration of fluoride in the bone on the one hand and specific activity of \(^{45}\)Ca on the other (Sriranga Reddy and Narasinga Rao, 1971). These data thus clearly show that the level of dietary calcium influences fluoride toxicity (Krishnamachari, 1978).

The commonly available food materials like cereals, vegetables etc. may also contribute much fluorine. Another factor that is equally of importance is the habit of most of the natives to remain almost through their lives at the same place, consuming locally available food and water which are fluorine rich (Raju et al., 1979).

Jolly et al. (1980) reported that residents of Punjab consume trace elements Mo, Cu and Zn in lesser quantities, than in Andhra Pradesh where a new syndrome (genuvalgum) was reported. In villages of Punjab with endemic fluorosis consume less Mo and Zn while Cu consumption is higher.
Recently Krishnamachari and Krishnaswamy (1973; 1974) reported endemic genualgum among residents of areas where fluorosis is endemic. It has also been reported that in fluorotic areas where the incidence of genualgum is high, the copper content of water is significantly lower than in areas where there is no genualgum (Krishnamachari, 1976) though the fluoride content of water is equally high in both the areas. Both copper and fluoride play an important role in bone formation and molybdenum has been reported to promote absorption of fluoride (Underwood, 1971).

**BIOCHEMICAL STUDIES:**

Biochemical studies in fluoride toxicity were mainly confined to the skeletal and dental tissues, with particular reference to the absorption, deposition and excretion of fluoride and to turnover of calcium. Reports on the toxic effects of fluoride on non-skeletal tissues are scanty.

Contrary to earlier reports the normal levels of serum calcium, Pi and alkaline phosphatase were found to be normal in these subjects (Krishnamachari and Kamala, 1973; Krishnamachari, 1978). Chronic fluoride toxicity was associated with increased calcium retention in the body and this may be explained by the increased formation of bone and decreased resorption of high fluoride containing
bones in this disease (Srikantia and Siddique, 1965; Narasinga Rao et al., 1968; Sriranga Reddy and Narasinga Rao, 1971; Rao and Susheela, 1979). Increased exchangeable calcium pool and increased bone mineralization rate were seen in chronic fluoride toxicity. These changes were in line with the clinical observation that fluorosis was associated with new bone formation as well as increased density of the bone (Narasinga Rao et al., 1979).

It was observed that the daily loss of body calcium (external calcium turnover) in fluorosis and genuvalgum was less compared to age matched control subjects. The turnover and bone mineralization rates were higher in patients with genuvalgum than in those with fluorosis. The calcium kinetic measurements were higher in younger subjects than in older subjects. The increase in calcium accretion rate was of greater magnitude in patients with genuvalgum than in those with fluorosis (Narasinga Rao et al., 1979). Inspite of osteoporosis the bone mineralization rate was higher in genuvalgum than in fluorosis. This may be due to acute immobilization (Heany, 1962), hyper parathyroidism (Krane et al., 1956), and acromegaly (Bell and Bartter, 1967). The bone resorption rates also were even higher than bone formation rate in these instances resulting in osteoporosis. It is then possible that in
genualgum, where osteoporosis co-exists with osteosclerosis, increased bone formation rate might be accompanied by a much greater increase in bone resorption rate (Narasinga Rao et al., 1978).

Studies carried out at the National Institute of Nutrition, Hyderabad, had revealed that excess molybdenum in the diet can cause copper deficiency due to increased excretion of copper in the urine. It was reported that molybdenum content of certain grains was high in endemic areas of fluorosis and the content of copper in the bones of the patients was found to very low (Krishnamachari, 1976). Thus it was concluded that the composition of trace elements in the diet of the region appear to influence the prevalence of fluorosis (Deosthale and Gopalan, 1974; Smith et al., 1975; Krishnamachari, 1976; 1978).

Herta et al. (1977) reported supplemental fluoride ranging from 10–45 mg/day did not affect the magnesium balance during calcium intakes that ranged from 200 – 2200 mg/day and during Pi intake that ranged from 300 – 1900 mg/day.

Determination of the hormonal profile in these subjects, showed that the concentration of parathyroid hormone was considerably higher in subjects with fluorosis as compared
to normals, but the levels were higher in those with genuvalgum than in those without (Sivakumar and Krishnamachari, 1976). On the other hand levels of plasma calcitonin were somewhat depressed in subjects with genuvalgum (Anonymous, 1976). Concentration of circulating growth hormone was markedly elevated in subjects with genuvalgum as compared to either normal subjects or subjects with fluorosis without genuvalgum (Shivkumar, 1977). The hormonal profile of subjects with genuvalgum was thus different from that seen in fluorosis subjects without genuvalgum. The circulating immunoreactive parathyroid hormone was found to be elevated in both cases (Sivakumar and Krishnaswami, 1976; Shivkumar, 1977).

Tokar (1980) reported that patients with fluorosis displayed specific temporary shifts in the maximal estrogen excretion peaks and also significant increase in estriol concentration in the urine. Changes in the estrogen concentration in the urine of patients with fluorosis apparently were connected with disturbed metabolism of the steroids and not with elevation of their production.

Kour et al., (1978) reported that there was significant fall in the total serum protein and inversion of the albumin/globulin ratio. Hongslo et al., (1979) reported
sodium fluoride exhibited a dose dependent inhibitory effect on protein and DNA synthesis in mouse fibroblasts. However Tausch et al., (1977) observed no effect on DNA metabolism in lymphocytes of patients with osteoporosis.

The protein content of adrenal gland was found to be increased by fluoride treatment and was attributed to increase in collagen (Rao and Susheela, 1979). The increase in the weight of the adrenal gland and the generalized hypertrophy of the cells observed in rabbits was correlated with the increased content of protein and collagen (Rao and Susheela, 1979).

Fluoride decreased the initial active uptake of 2-aminoisobutyric acid in mouse fibroblast cells, only at high concentrations and after several hours of exposure. The cellular levels of some natural amino acids were also reduced by fluoride. Cells resistant to fluoride showed equally lowered levels of amino acids (Holland and Hongslo, 1979).

Patients affected with endemic fluorosis showed low urinary levels of free and total hydroxy proline (Rao et al., 1978). However the total urinary hydroxyproline excretion was almost twice as high in subjects with genuvalgum compared to that in normals suggesting an increased bone turnover.
and bone loss mediated perhaps through increased levels of parathyroid hormone (Krishnamachari, 1978).

Collagen biosynthesis was reported to be impaired in osseous and nonosseous tissues (Susheela and Mukerjee, 1981). Susheela and Sharma (1960) suggested that the decrease in plasma glycoproteins levels in rabbits treated with low doses of fluoride might be due to increased deposition of the same for new bone formation. But high doses was found to enhance the glycoprotein level in plasma. This was attributed either to the inhibition of lysosomal enzymes like neuraminidase by fluoride ions or to the stimulation of synthesis of glycoproteins due to tissue injury.

The reduction of ascorbic acid content and the depletion of steroid dehydrogenase activity in the adrenal glands of rabbits treated with fluoride, especially at the zona glomerulosa, led to the conclusion that fluoride toxicity may interfere either in the synthesis or utilization of ascorbic acid and impaired steroid production (Rao and Susheela, 1979). This in turn may inhibit collagen synthesis (Singer and Armstrong, 1960; Risteli, 1977). Yu and Driver (1978) reported that fluoride treatment in growing chicks decreased ascorbic acid concentration in the heart, spleen,
brain, gizzard, pancreas and pectoralis, while its levels were elevated in lungs and kidneys.

Uslu and Burhan (1961) reported that the haemoglobin and hematocrit values in human subjects residing in an endemic flurotic area were within normal range. Susheela and Sharma (1981) observed differential response with regard to the plasma fibrinogen levels in rabbits fed with moderately high and very high fluoride. It was suggested that administration of low doses of sodium fluoride induce new bone formation, enhancing fibrinogen level. But high doses of sodium fluoride, which moderate tissue damage, results in high levels of plasma fibrinogen.

The serum total lipid, cholesterol and α-tocopherol levels were increased by fluoride toxicity. Increase in total lipid and α-tocopherol levels were also observed in the liver. The increase in liver α-tocopherol was proportional to the increase in total lipid content. It was also found specific effect of fluoride on the serum α-tocopherol levels in fluoride toxicity (Vatassery et al., 1980). Fatty degeneration of hepatocytes was found in rats receiving 10 and 20 mg/Kg of sodium fluoride (Dominiczak et al., 1981).

Holland (1977) observed that fluoride had no effect on glycerol production in vitro from rat epididymal
adipocytes irrespective of the presence or absence of calcium and magnesium.

Mcgown and Suttie (1979) reported the hyperglycemia which accompanies acute fluoride toxicity in the rat is mediated by epinephrine. Holland and Hongalo, (1978) showed long term exposure to fluoride induced decreased production of lactate in cultured, fluoride resistant L-929 rat (Lewis) sarcoma cells. In intact sensitive cells fluoride had no effect on glycolysis.

Among the three constituents of glycosaminoglycans investigated, hexosamine, uronic acid and sulphate no alteration was found except for sulphate by fluoride toxicity in rabbits (Susheela and Mohan, 1981). Glycosaminoglycans isolated from fluoride-treated rabbit iliac crest showed the presence of dermatan sulphate in addition to the normal components. Presence of dermatan sulphate was suggested be one of the reasons for the newly formed bone during fluoride treatment to remain unmineralized (Mohan and Susheela, 1982).

Fluoride was found to inhibit glycolysis in rat hepatocytes by affecting some of the glycolytic enzymes (Asha et al., 1979). Fluoride was one of the first substances known to inhibit glycolysis (Lohmann and Mexenhot, 1934). One of the target enzymes of fluoride
inhibition is enolase (Warburg and Christian, 1941). Later other enzymes like phosphoglucomutase (Najjar, 1948; 1963), glucose-6-phosphatase (Nordlie, 1971), phosphoglycerolmutase (Cogwill and Pizer, 1956) and pyruvate kinase (Guminska and Sterkowicz, 1976) were found to be inhibited by fluoride in vitro.

A few studies have been conducted on the effect of fluoride on glucose metabolism in intact mammalian cells. It had been reported that the addition of sodium fluoride to erythrocytes or Ehrlich ascites tumor cells could decrease glucose oxidation by inhibiting enolase and pyruvate kinase (Guminska and Sterkowicz, 1976). Stossel et al. (1970) found that 20 mM sodium fluoride increased phosphorylase activity and decreased glycogen synthetase activity in polymorphonuclear leukocytes without any change in the level of glycogen. Suketa et al. (1980) reported renal glucose-6-phosphatase activity was significantly elevated by fluoride administration. The elevation of the enzyme activity was markedly suppressed by adrenalectomy.

The activity of phosphocreatine kinase was reported to be enhanced in the sera of rabbits treated with sodium fluoride indicating that degeneration of muscle fibres (Kaul and Susheela, 1974).
Fluoride was shown to increase the $V_{\text{max}}$ of adenylate cyclase by increasing the affinity of the enzyme for magnesium (Schmidt and Najjar, 1978; Crooke et al., 1980) and inhibit ornithine decarboxylase via inhibition of protein synthesis (Hongslo and Alfheim, 1978; Hongslo and Holland, 1979).

**AIM AND SCOPE OF THE WORK:**

Endemic fluorosis in human beings has been a public health problem in Anantapur district due to the presence of high levels of fluoride in drinking water. The earlier work covered extensively on the clinical aspects of skeletal fluorosis with a few biochemical studies like mineral composition of the bone, some blood parameters and certain biochemical changes in certain tissues. However, no systematic study has been undertaken so far to investigate the effects of fluoride toxicity on soft tissues. Fluoride toxicity, both chronic and acute, has also been induced in experimental animals either by supplementing drinking water with fluoride or by massive administration of fluoride. These experimental models have been found to be very useful in investigating the toxic effects of fluoride. As the earlier studies had not attempted a systemic
study of toxic effects of fluoride on nonskeletal tissues, the present study is a beginning to systematically study the effects of toxic amount of fluoride on soft tissues like liver, kidney and intestines and the changes in blood parameters.

In the present study the rats were given drinking water supplemented with 100 ppm of fluoride for a period of two months to induce fluoride toxicity and the effect on the growth rate, body weight and tissue weights were studied. The fate of the ingested fluoride was studied by estimating the level of fluoride in serum, liver and kidney. The kidneys play an important role in the excretion of fluoride. The importance of liver in the metabolism and also in the detoxicating processes is well known. As such these two tissues have been chosen for the present study. The biochemical changes investigated in these two tissues are total lipid and lipid fractions, proteins, inorganic phosphate (Pi), activities of acid and alkaline phosphatases. Blood bio-chemical parameters like blood glucose, serum lipid fractions and the activities of acid and alkaline phosphatases have also been determined. During the course of the work hyperglycemia has been observed in fluoride-
Hyperglycemia may result from either increased hepatic glycogenolysis, enhanced hepatic and renal gluconeogenesis, decreased peripheral utilization of glucose or by increased absorption of glucose from intestines.

To understand the effect of toxic amounts of fluoride on blood glucose level, hepatic glycogenolysis was assessed by estimating the level of glycogen and the activities of glycogen phosphorylase and glucose-6-phosphatase in the liver, and intestinal absorption of glucose was measured by the in vivo method.