SUMMARY
Acute toxicity due to ingestion of excessive amounts of fluoride is known to produce many harmful effects in humans and animals. Acute toxic effects of a single dose of a chemical are often strikingly similar to chronic effects. The wide use of fluoride supplemented medications for the treatment of some diseases, for cosmetic purpose and as insecticide have added new dimensions in exposing the population to the acute toxicity by intentional or accidental exposure to these drugs. The maintenance of stable levels of glucose is one of the most finely regulated of all the homeostatic mechanisms in which the liver, kidney, other tissues, several hormones and other factors play a part. The degree of toxicity appear to vary with the dosage and route of administration of fluoride and a characteristic response to acute fluoride toxicity is hyperglycemia. Hence, the present investigation is primarily aimed at investigating in rats: (1) The relative toxic effects in relation to the hyperglycemic response to different doses of fluoride and to the same dose of fluoride when administered by two different routes i.e., oral and intraperitoneal. (2) The role of liver and kidney in the fluoride-induced hyperglycemia.

Fluoride treatment and hyperglycemia

Acute fluoride toxicity was induced by administering different doses of fluoride (NaF dissolved in 3 ml of
water) orally (5, 10, 15, 20, 35 mg F/kg body wt.) or intraperitonially (5, 10, 15, 20 mg F/kg body wt.) to male rats fasted for 18 hours and blood samples were withdrawn at designated intervals (0, 45, 90, 180 min) and sacrificed at the end of three hours after fluoride administration. Control rats received equivalent amounts of NaCl solution and treated similarly.

The present study has demonstrated that fluoride administration irrespective of route of administration (oral/i.p) resulted in hyperglycemia at all the doses except 5 mg F/kg body wt. oral dose. Fatality was also encountered in rats that received 15 and 20 mg F/kg body wt. intraperitonially and 35 mg F/kg body wt. orally. The data also revealed that the hyperglycemic response was greater to i.p. dose of fluoride than the oral dose when the same dose of fluoride was administered. Since the persistancy and degree of hyperglycemia was marked with no fatality at 10 mg F/kg body wt., further studies were conducted using this dosage administered intraperitonially and sacrificing the rat 3 hours after treatment.

**Hepatic and renal glucose production**

The marked hyperglycemia in fluoride poisoned rats suggest either an enhanced rate of glucose production by glycogenolysis and/or gluconeogenesis.
The possibility of enhanced hepatic glycogenolysis being the cause for hyperglycemia in fluoride treated rats was tested by analysing the basal levels of glycogen of the liver in control and fluoride treated rats and changes in liver glycogen when challenged with the oral dose of glucose (200 mg/100 g body wt.) one hour prior to the treatment. This data indicated that liver glycogen may be the source for the hyperglycemic response exhibited by fluoride treatment and interference in hepatic glycogen metabolism by fluoride treatment. The enhanced activities of hepatic phosphorylase and glucose-6-phosphatase in fluoride-treated rats also pointed to enhanced hepatic glycogenolysis.

Measurement of blood levels of substrates give an indication of the mobilization and availability of the precursors (lactate, pyruvate and amino acids) and modulators (free fatty acid) of gluconeogenesis in liver and kidney. Ureagenesis can be markedly altered by variations in the levels of amino acids. The increased flow of lactate in fluoride-treated rats points to either increased operation of Cori cycle or inability of gluconeogenic tissues to utilize lactate. Hyperuremia with no change in blood amino acid levels might have resulted from renal damage by fluoride treatment.
Studies on the changes in overall gluconeogenic rate by fluoride treatment in vivo by providing gluconeogenic substrates and measuring the increments in blood glucose and liver glycogen indicated inhibition of gluconeogenesis from alanine, pyruvate, succinate and glycerol. Renal cortical slices from fluoride-treated rats also exhibited decreased capacity to synthesize glucose from glycerol, pyruvate, succinate and glutamate, the inhibition being greater with glutamate. Fluoride was also found to inhibit glucose production in vivo from pyruvate by normal fasted kidney cortex slices. The data obtained from these studies and measurement of activities of some of the gluconeogenic enzymes (glucose-6-phosphatase, fructose, 1,6-biphosphatase, phosphoenol-pyruvate carboxykinase, alanine amino-transferase, aspartate-amino-transferase and glutamate dehydrogenase) indicated derangement of hepatic and renal gluconeogenesis at PEPCK step.

Glucose utilization

Control and fluoride-treated rats were injected with [U-14C] glucose and 14C-content and also the specific radioactivity were determined in the blood taken at intervals for 3 hours. The data obtained from this study suggests a relative retardation of utilization of glucose in fluoride-treated rats.
To determine whether fluoride administration to rats could have a demonstrable effect on glycolytic pathway, the liver and kidney cortex slices from control and fluoride-treated rats were incubated with glucose under anaerobic conditions and lactate produced was measured. The present study indicated inhibition of glycolysis by fluoride treatment. Extension of these studies confirmed the earlier observations of others of demonstrable inhibition of glycolysis by fluoride in vitro when added to incubation medium containing liver and kidney cortical slices from normal rats.

The data obtained from the present study focusses the role of liver and kidney in the causation of hyperglycemia in acute fluoride poisoning. The rise in blood glucose in fluoride poisoning appears to be due to an accelerated glycogenolysis in liver and decreased peripheral utilization of glucose. Lethality at higher doses of fluoride might result from inhibition of gluconeogenesis leading to hypoglycemia.