SUMMARY

Cadmium placed in II-B group of periodic table, is closely related to zinc. The main source is zinc and lead ores, from which Cd is obtained as a by-product during refining. Cadmium and its compounds have wide industrial applications. Humans are exposed to Cd via food, water, air, cigarette-smoke, emissions from smelters and combustion of fuel and plastic waste. Grains like wheat, rice and liver and kidney of animals and shell-fish contain considerably high contents of Cd. Cadmium is highly toxic to humans. The adverse health changes induced on exposure to Cd seem essentially irreversible, because body burden of Cd hardly decreases due to its long biological half-life even long after cessation of Cd exposure. On inhalation or ingestion, Cd causes pulmonary disorders (emphysema, chronic bronchitis, bronchial carcinoma), renal dysfunction (glycosuria, aminoaciduria, hypercalcuria, renal stones), hypertension, anaemia, cardiovascular diseases, congenital defects and even cancer of prostate.
A number of factors can influence and alter the susceptibility to cadmium toxicity. Protein malnutrition is one of the important nutritional deficiency prevalent in the third world. To decipher the influence of protein deficiency on cadmium intoxication, groups of rats were maintained on normal diet containing 21% protein and low protein diet containing 5.5% protein, with or without 100 ppm Cd in diet. Animals fed different diets with or without Cd were evaluated for toxic manifestations of Cd at various intervals. The feeding of a normal diet containing Cd caused a progressive accumulation of Cd mainly in liver and kidney probably due to induced synthesis of metallothionein by Cd. However, less marked accumulation of Cd in tissues of the animals fed low protein diet containing Cd, may be due to the low availability of proteins resulting in decreased synthesis of Cd binding proteins which might also adversely affect the detoxification process. The low protein diet reduces the absorption of Zn and enhances its excretion resulting in decreased hepatic and blood Zn levels. Cadmium fed with normal diet caused an increase in hepatic and renal level of Zn and renal level of Cu. However, this effect of Cd was reduced when fed with low protein diet, indicating decreased metallothionein mediated detoxification during protein malnutrition. Low protein diet increased Fe content of liver. On the contrary, a loss of Fe from liver and kidney was observed following dietary Cd treatment. A further decrease in renal Fe level in animals
fed low protein diet containing Cd shows enhanced disturbance in absorption and metabolism of Fe due to Cd, during protein-malnutrition. The Cd induced increase in blood glucose, decrease in hepatic glycogen and increase in the activities of hepatic and renal glucose-6-phosphatase and fructose-1,6-diphosphatase may be attributed to enhanced gluconeogenesis and glycogenolysis. However, a significant decrease in the activities of hepatic and renal glucose-6-phosphatase and fructose-1,6-diphosphatase in rats fed low protein diet alone seem related to the decreased gluconeogenic activity. As the low protein diet was balanced by carbohydrates, the low availability of proteins and excess carbohydrates apparently resulted in impaired gluconeogenic activity. The significant inhibition in the activities of renal glutamic oxalacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) upon Cd feeding is an indication of nephrotoxicity. More marked inhibition of these renal enzymes and the Cd-induced alterations in blood glucose and hepatic glycogen in animals fed a low protein diet containing Cd as compared to those fed normal diet containing Cd suggest protein malnutrition to be one of the important factors that augments Cd hepato- and nephro-toxicity.

Cadmium interferes with absorption and the metabolism of zinc, copper, iron and calcium. Exposure to Cd is more hazardous when Fe intake is inadequate. There are interesting similarities between the symptoms of Cu deficiency and Cd
intoxication. Protein malnutrition is a public health problem and nutritional factors play a great role in individual susceptibility to toxic effects of the metal. Protein malnutrition alters the response of an organism to the toxin in a manner different to that observed in the fully nourished state of the body. The influence of dietary supplementation of Cu (40 ppm), Fe (400 ppm) or their combination on Cd intoxication (0.75 mg/kg, body wt., i.p., for 20 days) was investigated in rats maintained on 9% casein based protein. The induction of metallothionein in liver on Cd exposure may partly account for accumulation of Cd and Zn in this organ. The dietary supplementation of Cu, Fe or their combination showed no significant effect on the elevated renal Cd levels. However, the treatment markedly lowered hepatic and renal Zn concentration. An adverse effect of Cd exposure, is the decreased Fe absorption, resulting in lowering of hepatic and renal level of Fe. The trace metal supplementation restored the tissue Fe levels. The exposure to Cd significantly inhibited the activities of hepatic and renal acid- and alkaline-phosphatases, but increased tissue glutathione contents. The activity of ribonuclease, however, remained unaltered. Copper and/or Fe supplementation apparently antagonised the effect of Cd on phosphatases, however, only Cu supplementation could reduce the elevated renal level of glutathione. Increase in glutathione concentration might act as a defence mechanism for rapid biliary excretion of
Cd as Cd-glutathione conjugate. Cadmium exposure, however, did not elicit any effect on hepatic and renal ribonuclease activity in low protein fed animals.

The abusive consumption of alcoholic beverages deranges normal function of body system in various ways. Not only alcohol addiction itself but many disabling, and some fatal physical and psychological conditions can be attributed to excessive drinking. Chronic ethanol consumption increases the toxicity of a number of drugs. As ethanol is directly toxic to many tissues of the body, this effect may be potentiated by concomitant exposure to Cd. To investigate the influence of alcoholism on Cd intoxication, groups of rats were exposed to Cd (40 ppm in drinking water), ethanol (1 g/kg, body wt. for first week, 5 g/kg for second week and 10 g/kg for rest of weeks, through gastric gavage) or both for eight weeks and cadmium sensitive hepatic, renal or serum enzymes, tissue accumulation of Cd, essential trace element status and hepatic metallothionein were investigated. The Cd induced increase in the activities of hepatic and renal glucose-6-phosphatase and fructose-1,6-diphosphatase was due to the enhanced gluconeogenesis. The administration of ethanol alone also increased the activities of gluconeogenic enzymes in kidney. However, ethanol did not modify the Cd-induced increase in hepatic and renal gluconeogenesis. Cadmium elevated serum GOT
and GPT increased further upon co-exposure to Cd and ethanol which shows that ethanol augments Cd hepatotoxicity. The co-exposure to ethanol and Cd had no influence on the induction of glutathione by Cd and apparently did not affect self-protective mechanism of organism against Cd through conjugation with glutathione. Ethanol significantly enhanced the accumulation of Cd and Cd-induced increase of Zn in liver, kidney and spleen, hepatic content of metallothionein, and Cd and Zn bound to hepatic metallothionein. Additional accumulation of Cd and Zn in liver, kidney and spleen of animals simultaneously exposed to Cd and ethanol as compared to those exposed to Cd alone reflects their increased vulnerability to Cd due to ethanol.

Cadmium, having an unusually long biological half life, causes induction of hepatic and renal metallothionein, trace metal imbalance and alterations in carbohydrate metabolism including hyperglycemia. These Cd-induced manifestations are comparable to those observed in experimental diabetic rats, which may be controlled by administration of insulin. Therefore, a hypoglycemic agent, 1-((p-2-(chloro-o-anisamido)ethyl)phenyl)sulfonyl)-3-cyclohexyl urea (Glibenclamide) was evaluated for its ability to decrease Cd burden and to modulate the efficacy of calcium trisodium diethylenetriaminepentaacetate (CaNa₃DTPA), a well known antidote of Cd intoxication. The
animals were exposed to Cd (1 mg/kg, i.p., daily) for 3 weeks; thereafter, glibenclamide (1 mg/kg, orally) or CaNa₃DTPA (0.3 mM/kg, i.p.) or their combination were administered daily for 5 days. The tissue metal levels, Cd excretion and other Cd sensitive parameters were monitored after first and fifth dose. The combination of glibenclamide and CaNa₃DTPA proved to be better in comparison to either of them individually, for elimination of Cd via urine and faeces, when administered for five days. Apparently, glibenclamide potentiates the biliary excretion of Cd. Glibenclamide effectively reduced the Cd-induced increase in blood glucose and increase in the activities of hepatic and renal glucose-6-phosphatase and fructose-1,6-diphosphatase, a characteristic effect of a hypoglycemic agent. The reversal of enzyme activities was more marked after the fifth dose than after the first dose, the combination was as effective as glibenclamide alone. CaNa₃DTPA was effective in reducing both hepatic and renal concentration of Cd following first as well as fifth dose, while glibenclamide was effective in multiple doses. The compounds were also effective, individually as well as in combination, in partly restoring the Cd-induced increase in hepatic and renal Zn levels and decrease in hepatic Fe level; however, only the combination was effective in restoring the decreased renal level of Fe. The Cd-induced increase in renal Cu was partially restored by treatment with the combination. The administration of glibenclamide effectively
countered the effects of Cd on carbohydrate metabolism and trace metals. The combination therapy appears promising in Cd intoxication.

Calcium trisodium diethylenetriaminepentaacetate (CaNa$_3$DTPA), sodium-1,2-diaminocyclohexane tetraacetate (Na$_2$CDTA), triethyleneenetetramine hydrochloride (TETA.HCl) and sodium diethyldithiocarbamate (NaDDC) were investigated for their efficacy to mobilize Cd from various tissues and hepatic metallothionein in rats, 24 h after a single injection of radiolabelled cadmium chloride. All chelating agents effectively reduced hepatic Cd burden but did not elicit any influence on other tissues except that TETA.HCl lowered pancreatic Cd and NaDDC increased Cd in brain. The Cd-induced hepatic metallothionein content was lowered upon treatment with CaNa$_3$DTPA while it increased further following treatment with NaDDC. None of the chelating agents, however, could mobilize Cd from the hepatic metallothionein. The administration of chelating agents alone in normal animals showed that NaDDC induced far higher hepatic metallothionein synthesis and increased Zn content of the metallothionein fraction than by the other compounds.