GENERAL SUMMARY
CHAPTER - I

The uptake of $[^3H]-5$-HT with increasing time showed a significant inhibition in the presence of increasing CdCl$_2$ concentration. Maximum inhibition of 5-HT uptake was noted at 1 mM CdCl$_2$ concentration. Higher concentration of CdCl$_2$ did not increase the inhibition of 5-HT uptake any further. The addition of 1 mM CaCl$_2$ did not bring about any significant alteration in the CdCl$_2$ induced inhibition of 5-HT uptake.

The kinetics of $[^3H]-5$-HT uptake in the presence of CdCl$_2$ using Line-weaver-Burk plot showed that $K_m$ for the CdCl$_2$ treated platelets was higher than that for the control system. There was simultaneously a decrease in $V_{max}$ value.

Spontaneous release of $[^3H]-5$-HT was induced by CdCl$_2$ although increase in CdCl$_2$ concentrations did not significantly increase the spontaneous release any further.

The effects of 1 mM CaCl$_2$ in the presence of different doses of CdCl$_2$ (1 mM-0.001 mM) was also studied and no significant alteration from CdCl$_2$ treated platelets in the presence of $[^3H]-5$-HT release was observed.

Different CdCl$_2$ concentrations resulted in an inhibition of thrombin mediated release by $[^3H]-5$-HT from platelets as compared to normal control. The inhibition of thrombin induced release was not significantly increased with the increase in CdCl$_2$ concentrations.

The investigation leads to the concept that cadmium influences both uptake and release of 5-HT by platelets. Studies on the uptake indicate that CdCl$_2$ affects the rates of both the binding as well as transfer since $V_{max}$ is reduced by 50% and $K_m$ is increased. Thrombin-induced release of 5-HT was inhibited by cadmium at all the concentrations listed. However, cadmium alone could induce spontaneous release by 5-HT. None of these phenomena was affected in the presence of 1 mM calcium.
CHAPTER II

Platelet aggregation was studied in the presence of CdCl₂ concentrations ranging from 0.001 mM to 10 mM. Exposure to CdCl₂ concentrations of 0.001 mM, 0.01 mM and 0.1 mM did not produce any significant alteration in platelet aggregation but in the presence of 1 mM CdCl₂ there was complete inhibition of platelet aggregation. Simultaneous addition of 1 mM CaCl₂ did not bring about any alteration in the inhibition of platelet aggregation by 1 mM CdCl₂.

Cadmium chloride treatment in vitro resulted in a significant release of pyrophosphate PP₁ and brought about a slight release of antiheparin factor but cadmium chloride pretreatment inhibited the thrombin induced release of PP₁ and antiheparin factor.

Cadmium also induced a slight release of acid hydrolases from the lysosomal granules and at the same time CdCl₂ pretreatment caused a significant inhibition in the thrombin induced release of acid hydrolases.

Human platelets incubated with Cd²⁺ at 1 mM final concentration took up the cation slowly and the capacity of human platelets to accumulate Cd²⁺ was large, equivalent to 10 nmole Cd²⁺/mg protein.

In summary, human platelets took up Cd²⁺ in vitro and cadmium induced the release from different platelet granules while the thrombin induced release was inhibited by cadmium preincubation; Another interesting observation was that low concentrations of cadmium did not affect the platelet aggregation but platelet aggregation was completely inhibited in the presence of 1 mM CdCl₂.

CHAPTER III

Human platelets demonstrated an increased production of malondialdehyde (MDA) in the presence of 1 mM CdCl₂ after a lag phase of at least 15 minutes with a gradual increase thereafter. After 60 min there
was a significant increase in MDA production. The increase in platelet MDA production in the presence of cadmium was abolished by either 1 mM aspirin or 1 mM CaCl₂. Thrombin stimulated MDA production was significantly increased in cadmium pretreated platelets compared to control platelets.

Among the major cellular defence mechanisms, platelet catalase activity was decreased by 46% although the activity of glutathione peroxidase (GPx) remained the same. The levels of glutathione (GSH) and glutathione reductase (GR) activities were also decreased by 25% and 35% respectively. Significant elevations were noted in the activities of glutathione-S-transferase (GST) and glucose-6-phosphate dehydrogenase (G6PDH). The inadequacy of the H₂O₂ removing mechanism was further emphasized by the slower removal of externally added 0.22 mM H₂O₂ by cadmium treated platelet suspensions.

This study indicated that human blood platelets incubated in the presence of 1 mM CdCl₂ produced MDA via cyclooxygenase pathway. The time course of MDA formation indicated that Cd induced platelet activation resulted as a consequence of direct or indirect in the cellular effects of cadmium rather than platelet surface receptor linked mechanism. Cadmium intoxication in vitro was also found to alter the status of the cellular antioxidant defence system.

Chapter IV

Addition of cadmium chloride in vitro in non-hemolytic concentrations affects the membrane associated enzymes of human erythrocytes. The levels of acetyl cholinesterase, NADH-dehydrogenase and Mg-ATPase were significantly decreased in cadmium treated erythrocytes whereas the lipid peroxidation was increased appreciably.

Since the red cell is a readily available source to study the oxidative damage it was used to carry out investigations on the antioxidant defence cycle in erythrocytes after CdCl₂ treatment in vitro. The activity of catalase was not altered significantly but the activities
of GPx and SOD were decreased and the level of reduced GSH was also appreciably lowered thus providing suitable conditions for the development of peroxidation.

The kinetics of cadmium uptake into human red blood cells and the nature of the transport process were studied. Cadmium uptake into human red blood cells was found to be (a) biphasic, with both the phases being non-saturable, (b) independent of metabolically derived energy and (c) unaffected by zinc in the incubation medium.