In recent years the field of Immunology has attracted greater attention of scientific community in view of the growing awareness regarding the need to modulate the host’s immune system to achieve desirable effect for preventing any diseased condition rather than treating it by chemotherapy in advanced stage after appearance of the symptoms of disease. The advanced stage of toxicants results into various immunopathological, haematological and biochemical changes in the host.

The world health organization is drawing the attention of the people of the developing and the under develop countries towards health hazards and global hunger. People today have realized the merit of good health and on clean and nutritious food.

For the last three decades the problem of harmful effects of environment has taken deep root in the heart and mind of man. The immune system functions protective barriers to infectious agents, homeostasis of leucocyte maturation, immunoglobulin production and immune surveillance against arising neoplastic cells. The toxicants modulate immune system of the host for their benefit for the survival causing immune suppression resulting into hypersensitivity reactions and various disease of host.
Many heavy metals are considered to be essential for animal growth and essential trace nutrient of animals and human body. Many heavy metals are not present in the body and are highly toxic elements. These heavy metals are non essential heavy metals as-cadmium, lead, nickel, arsenic etc. These heavy metals are persistent and accumulative. These do not easily break down and not easily metabolized. Heavy metals toxicity to animals vary with animal species, specific metal concentration, chemical form and pH. There is wide spread environmental contamination with Cd level vary according to region as we get most of it from soil by our food. There may be some in water from contamination of water pipes, and cigarette smoke plus industrial burning of metals put cadmium into the air. Cadmium level in the atmosphere is much higher in industrial cities. It had been known for many years that workers exposed industrially to cadmium during dust and fumes were at risk. In addition to cigarette smoke and plastics, common sources of cadmium exposure in drinking water, fertilizer, fungicides, pesticides, soil, air pollution, refined grains, rice, coffee, tea and soft drinks.

The defence mechanisms in rats start developing early in the embryonic life. Protective immunity against atmospheric pollutants chicks can be achieved by passive and active immunization. Various mechanisms which effect the immune responses are B lymphocytes, T lymphocytes, antibodies, macrophages, natural killer cells, serum factors and other cytokine factors. Immune responses haematological and biochemical parameters are closely related in blood hence
any change in the immune responses would also induce alterations in the biochemical parameters like serum glucose, serum cholesterol, serum protein, serum urea, serum acid phosphatase and serum alkaline phosphatase. Various haematological parameters are also altered whenever immune responses and biochemical parameters undergo change because of the effects of pollutants.

The toxic metals alter the immune response of animal as well as human. In addition to the well documented and numerous toxic effects of cadmium on various target organs, number of studies shown that acute and chronic exposure to cadmium may result in impairment of immune functions in experiment system. Cadmium immunotoxicity in rodents is primarily characterized by marked thymic damage and splenomegaly. The morphological alteration in cluding thymic cortical cell depletion and an increase in red pulp with diminished white pulp in spleen were observed (Pathak et al. 2007). Previous studies have shown that in mammals, chronic exposure to Cd decrease the release of macrophagic cytokines and decrease phagocytic ativity. The cellular response could be decreased by exposure to Cd.

Previous work on a human T-cell has shown that Cd exerts its toxic effect via apoptosis, thus to further investigate the role of cadmium induced apoptosis in the immune system. The study of apoptotic effect of cadmium in three human cell lines: T-cell line, the B-cell line and lymphoblastic cell line and revealed a differential Cd^{2+} triggered apoptotic cell death in these cell lines.
The cadmium is toxic to several tissue most notably causing hepatotoxicity upon acute administration and nephrotoxicity upon chronic exposure. Histological evolution of liver injury reveals that acute toxicity comprises of hepatocellular swelling, sinusoidal congestion, Pyknosis and Karyorrhexis (Dudly et al. 1882). In a time course study of cadmium induced hepatotoxicity early cellular changes occur in through endoplasmic reticulum and nucleus (Dudly et al. 1985). These cellular changes may result in both apoptosis and neurosis (Habeebu et al. 1998).

Kupffer cells, the resident macrophages of the liver, appear to play a major role in the mechanism of Cd induced hepatotoxicity (Hoffman et. al. 2000., Rikans and Yamano 2000). Suppression of Kuffer cells significantly diminishes the hepatotoxicity of cadmium. Thus Kupffer cells are recognized as the primary source of proinflammatory cytokines within the liver, several reports have examined alteration in cytokine expression in response to Cd administration (Kayama et al. 1995., Li et al. 1994., Yamano et al. 2000., Szuster Ciesielska et al. 2000., Marth et al. 2000). However, no distinct pattern has been elucidated from Cd induced cytokine expression as a measure of Kupffer cell activation.

In mammalian species cadmium when administered as a single parental dose accumulates initially in the liver and induces the synthesis of Cd binding protein, metallothionein in the paranencymal cells. This synthesis is not immediate but preceded by a lag pha of about 3n². Once the synthetic mechanism has been induced, however, further synthesis occurs without leg in response to a
subsequent dose. The same pattern is observed in the kidney at acute exposure under condition that increase the renal uptake of Cd\textsuperscript{4+} at conditional low level exposure, Cd uptake occurs in both the liver and kidney and leads to accumulation of hepatic and renal metallothionein.

Most of the cadmium in the liver and kidney is bound to and inducible low molecular weight protein, metallothionein and the metal bound to the protein is believed to be non toxic as long as the protein remains as an intra cellular protein (Poulkes 1982., Kagi and Webb 1979). The metabolic fat of ingested cadmium can be decided in to several steps, uptake and absorption as the gastro intestinal tract transfer from the absorbed site to the liver (and other tissue) transfer from the liver to kidneys and excretion in to urine. Although some factors that may influence the metabolic rate of toxicity to cadmium had been investigated such as diatry protein and/or several essential elements (Banis et al. 1969., Cousins et al. 1977., Fowler et al. 1975., Fox 1979., Gontzea and Popescu 1978., Itokawa et al. 1974., Jokobs et al. 1977).

The intestinal epithelium is the main part of entrance for nutrient and at the same time the main barrier of absorption of other early administered compounds such as food activities, drugs and toxicants. The epithelial cell itself with it’s membrane form the barrier in the trans cellular route, while the functional complex between the cells seal the para cellular route and regulates its permeability. Several studies into the barrier functionally have shown reduced
para cellular barrier function in various epithelia as a result of exposure to cadmium for instance. Janecki et al. (1972 found reduced development of tract epithelial electrical resistance (TER) in sertoli cell monolayer when grown in presence of cadmium. Damage of the intestinal epithelium was reported to occur after exposure to high concentration Cd$^{2+}$ in mice.

Moreover, epithelial accumulation and absorption into the several compartments are increased at high concentration in vivo and caloz cells. Rossiel describe a reduction in TER and increase in trans epithelial mannitol passage in caloz monolayer after exposure to Cd$^{2+}$. It is however yet not established whether the selective effects of Cd$^{2+}$ on the para cellular barrier can account for increased absorption of cadmium in the intestinal epithelium.

Chronic exposure to cadmium can damage the renal proximal tubular dysfunction manifested by low molecular weight proteinuria, glycosuria, amino aciduria and phosphaturia (Piscator 1986) renal injury.

In the field of Agriculture, science technology and industrial development the rapidly progressing countries of the world are introducing various kinds of harmful substances in the biosphere and are thus poisoning a serious threat in the form of environmental pollutants. The tremendous growth of polluting technology and inadequate waste water treatment are chiefly responsible for the release and mixing of different kinds of chemical pollutants and are causing
deterioration in the normal condition of air, soil and water due to which life is being threatened both for man and other animals. Chronic exposure to low level pollutant in the environment, chemicals in drinking water, respiratory air and in food product are increasing risk for human health and are inducing cancer, ulcers, neurological disturbance, paralysis, heart disease and genetics diseases.

Heavy metals and their salts constitute an important group of environmental pollutant and metabolic inhibitors in aquatic and terrestrial animal. Heavy metal exerts toxic effect in the organisms at cellular, sub cellular and molecular levels. Metal cause acute, chronic, sub latent and toxiosis depending on the capability of the animals dose mode of administration and the duration of exposure. The lethal dose of a metal compound for acute, chronic and latent toxicity vary and they depend on biological and environmental variations. The inherent toxicity of a metal depends on its capacity to disturb the dynamic equilibrium in chemobiological system by combine cell organelle and macromolecules or metabolism.

Trace heavy metal may be classify into two categories – (a) Essential metals (b) Nonessential metals. Essential metals are as Manganese, Iron, Cobalt, Copper and Zinc. These metals are also present in the body of animals in a trace amount.
Non-essential metal are Mercury, Cadmium, Arsenic, Nickel and Lead. These metal are not present into the body. Cadmium (Cd) is an environmental pollutant. Cd is non-degradable at the environmental levels. It is increasing due to industrial and agricultural practices. Cd is toxic to a number of organs such as liver, kidney, testes, bone, blood, intestine, spleen and the immune system (Friberg et al. 1986; Goering et al. 1995).

Itai-Itai disease was caused by long term exposure to Cd. Patients with Itai-Itai disease show various symptoms, including nephropathy, osteomalacia, anaemia and severe pain (Friberg et al. 1986). Anaemia is a major haematotoxic effect following long term exposure to Cd in man (Noda et al. 1991; Horiguchi et al. 1994) and in laboratory animals (Lutton et al. 1984; Sakata et al. 1988; Hiratsuka et al. 1996).

Cadmium also produces immunotoxicity (Descotes, 1992). Pollutants or any environmental stress affect hematological, biochemical and immunopathological parameters.

The tendency of accumulation is reflected in the biological half life for these metal in different organism. The biological half life in man is 1460 days for lead, 280 days for arsenic, 200 days for cadmium and 70 days for mercury. The biological half-life could be an important factor in influencing the toxicity of metal. Non essential metals thus producing a cumulative effect if consumed in
small dose for a long period and produced acute toxicity in higher dose after a short period. The release of increasing quantities of heavy metal in terrestrial and aquatic environment and their accumulation in living and non living system endanger's the life by modifying various behavioural, structural and functional activities of man and animals. The heavy metals of principal toxicological concern are mercury and cadmium which shows strong affinities for ligand such as phosphate proton, purines, pyrimidines and porphyrins.

Hence these two elements can act on number of enzyme having functional sulphydril groups. On the other hand they can also induced catabolic activity in certain enzyme and hormone. They also act as preformed inhibitors or elevators of various hormones secrete by endocrine glands. Different types of pollutants also greatly affect the health of the domesticated animals such as cattle, poultry birds and man. The pollutants may be air, water and chemicals. Cadmium acetate is an environmental contaminant resulting from occupational exposure to dust, aerosol introduced during the smelting and refining the metal ores during electroplating and welding and during manufacturing the plastic stabilizers and batteries (IARC; 1993). Increase in the number of toxic substances in the atmosphere due to motarization, industrialization and urbanization constitutes a long term danger to animals and man. It was found causes like severe bone disease known as “Itai-itai” disease (Hagino and Yashiolla, 1961; Ishizalhi, 1985). Higher supply of cadmium was record to induce carcinogenic effects in mammals
Many environmental chemicals have been investigated for interference with one or other aspect of immune function. Heavy metals consisted of a group of environmental toxicant that may alter homeostasis linked to neoplastic disease and aging (Jacobson and Turner; 1980). Metal can cause cell damage by different mechanism include direct damage of cell membrane and certain organelles altering signal transduction path ways of affecting the intra cellular enzymatic system (Cheiran and Ferguson, 1997). In addition of being heavy metal, cadmium is a ubiquitous toxic metal, chronic exposure to which has been involved in a variety of pathological alteration. A number of studies have shown that kidney and liver are the major target organs of cadmium toxicity and cadmium accumulates in these two organs. While Marselt et al. 1988 reported that exposure in rats Cd$^{+2}$_ resulted in thymic damage and modified the proliferative rate of thymocyte. In addition to it accumulation in the different organ, cadmium is also detected in blood parameter, chronic exposure where it is mainly associated with nucleated cells particularly lymphocyte (Enger et al. 1983).

In eukaryotic cells numerous mode of injury can lead apoptotic or necrotic cells death with distinct and profound implication associated with each alternative mechanism. In contrast to stress induced cell death on apoptosis is a normal and strategic event with a crucial role in developmental process.
Cadmium is more readially taken up by plants that other metals such as lead (EPA, 1981). Factors contributing to soil content of water irrigating field and cadmium added with fertilizer. Respiratory absorption of cadmium is about 15 to 30 percent. Cadmium exposure is particularly hazardous where there cadmium fumes or air born cadmium. More air born cadmium is respirable. A major non-occupational source of respirable is cigrates. One cigrate contains 1 to 2 mg cadmium and 10 percent of the cadmium in a cigrate is inhaled 0.1 to 0.2 µg (Elinder et al., 1983).

Cadmium toxicity affects the immune responses and alters the host’s resistance to infectious agents and tumor. Cadmium exposure appears to inhibit the development of antibody production. The adverse affect of cadmium on humoral antibody may be due to either interference with macrophages antigen processing or antigen presentation to lymphocyte, rather than to a direct effect of cadmium on B-lymphocytes.

The present studies, therefore, have been taken up with a view to full-fill the following objectives:-

- To study immunological, haematological, biochemical and immunopathological parameters in cadmium acetate treated albino rats.

The present Ph.D. thesis comprise of the following chapters –

1. Introduction
2. Historical account
3. Materials, methods and experimental design
4. Observation
5. Discussion
6. Summary
7. References