The harmful effects of toxic substances because of exposures in the work place causing disease and death among workers have been known for centuries, however, only around the turn of this century major efforts began to be directed towards the recognition, measurement, evaluation and control of work place environmental health stresses in the prevention of occupational diseases.

Heavy metals like lead, cadmium and mercury have played a very important role in the life of man ever since their discovery and it can be said that every part of our life have been benefitted by the use of metals but at the same time it is necessary to ensure that our own existence is not endangered by their uncontrolled and over expended use as these metals are extremely toxic.

The increased industrialization of our society during the past few decades has promoted a great increase in the mining and processing of metallic elements and further applications are continually being realized. Though there has been a considerable increase in public awareness towards environmental pollution and occupational exposure, several incidents of major concern involving environmental contamination have taken place like the Itai-Itai disease caused by cadmium (Cd) contamination, Minamata disease because of Hg contamination [1] and also with other elements like arsenic [2], molybdenum [3] and lead [4] in several countries. During the absorption, transport, distribution, biotransformation and excretion, metals may exert their toxicity by interfering with some sensitive cellular targets either directly or indirectly.

Cadmium was recognized to be a highly toxic element but it is only during the past few decades that concern has begun to be expressed over the possible effects on human health because of long term exposure to low concentration of this element. Cadmium dust, fumes and mists pollute the atmosphere in zinc, copper, lead and cadmium refinery processes. Cadmium pollution from a mining and smelting complex, resulted in the contamination of food and drinking water and caused 'Itai-Itai' disease in Japan. 'Itai-Itai byo' disease, was encountered mostly in women aged 45-70 years and the disease was characterized by severe pain in the bones associated with osteomalacia, a waddling
gait, amino aciduria, and glycosuria [5]. Cadmium is present in natural ecosystems and is an ubiquitous element in all living organisms. In unpolluted soils the main sources of variation of cadmium content are due to the variations in the inherent composition of the soil, parent material, and the inputs of metals from fertilizers, agricultural chemicals and general atmospheric pollution [2]. Recently Mørtsvedt [6] observed that in most agricultural soils in the USA Cd is added to soils as a contaminant in phosphate fertilizers ranging from 0.32 to 1.2 g Cd ha\(^{-1}\) though it does not appear to result in increased cadmium levels in plants. Higher amounts of cadmium impurities in the superphosphate accumulate in the soil and can substantially increase the amount of cadmium available for plant uptake [4]. Cadmium concentration in plants were reported to be less than 1 \(\mu g/g\) (dry weight) [7] though the actual cadmium concentration differs with the plant species, soil type and accuracy of the analytical method. Cadmium is present in significant amounts in the aquasphere and the greatest concentration range was found in whelks, limpets, sea skaters, oysters, scallops and squids [8]. Recently Ray and Jerome [9] found very high concentration of cadmium in scallops from Geages Bank Canada and still higher in those from Browns Bank Canada far away from any source of anthropogenic input which suggests a natural source for the metal.

Thus, it is extremely difficult to avoid the transmission of cadmium through food chains to animals and man. Cigarette-smoke inhalation is another source of exposure as tobacco contains a high concentration of cadmium which is inhaled in the smoke [10].

Cadmium is becoming an ever more widely used metal in industry. The largest use of Cd is in electroplating followed by the use of Cd in Cd-bearing alloys. Cadmium electroplated items are used in automobile engine parts, aircraft parts, radio and television parts, and nuts and bolts. Cd bearing alloys are used in telephone wires, and solders. Cd-Ni batteries are extensively used in electronic equipment [11]. Cadmium oxide is used in semi-conductors, phosphors and ceramic glazes, cadmium chloride and bromide in photography, lithography, calico printing and dyeing and cadmium tungstate is used
Industrial exposures to Cd may occur from fumes emitted in smelting of impure Zn and in the distillation of Cd sponge. The most common cases of accidental industrial exposure to Cd occur in remelting scrap not suspected to contain Cd. Welding Cd plated stock and heating Cd plated rivets have also led to Cd poisoning. Accumulation of Cd-containing scraps such as batteries, alloys and paints may contaminate water supplies and the air [12]. Cadmium intoxication has been reported as a result of contamination of water with cadmium from solders in water pipes, taps or refrigeration devices [13].

The complex circumstances which may be involved in the manifestation of toxicity by humans exposed to metals either in the general environment or in the occupational atmosphere are being more fully realized and it is therefore of utmost importance to design appropriate experimental models. Improved availability of data on human subjects will lead to a better understanding of the biochemical action of heavy metals and will also be of considerable help in the assessment of potential health hazards for man, and the identification of early indicators of toxicity and treatment.

**ABSORPTION**

The main routes of cadmium intake in man are the lungs and the gastrointestinal tract [14]. Though the principal source of cadmium in the normal human diet appears to be from food rather than from air or water [15]. The chemical form of ambient air borne cadmium is not known. Although measurements of air borne cadmium concentrations have been made in many countries, the concentrations are not strictly comparable because of different sampling times and different analytical methods. Size distributions of particles containing cadmium are rarely determined. Hence only rough estimates of lung deposition rates can be made [15]. On the basis of limited cadmium containing particle size distribution data and the application of a standard lung model, about 25% of cadmium inhaled in ambient air would be deposited in the lower respiratory tract [15]. Using this deposition fraction and
an assumed average daily inhalation of 20 m$^3$, the amount of cadmium deposited in the lower respiratory tract has been estimated - rural areas: 0.005 - 0.215 μg/day; urban areas: 0.01 - 3.5 μg/day; industrialized areas with cadmium emissions: 0.05 - 25 μg/day. The highest level of 25 μg/day is probably found only in the vicinity of an operation such as a smelter [16]. The rate of absorption through the lungs is a function of the chemical form and size distribution of the inhaled particles, and various rates have been reported. In the general environment 13-19% of the cadmium inhaled is absorbed [16]. Smokers inhale a considerably greater quantity of cadmium as tobacco contains a high concentration of cadmium which is inhaled in the smoke. Ellis et al. [10] studied the cadmium content of the liver and left kidney of 20 male volunteers by partial body neutron activation technique and found the organ cadmium levels of smokers to be significantly higher than non-smokers. One pack of 20 cigarettes can contain 50 μg of cadmium of which 2-4 μg can be inhaled [17-19].

For workers exposed to excessive concentration of cadmium dust and fume a lethal exposure is possible without warning as there is only slight discomfort at the time of exposure. The estimated lethal concentration of cadmium oxide fume for human being is approximately 5 mg/m$^3$ for an 8 h exposure [19]. The threshold effect level of cadmium oxide fume and acid soluble cadmium dust on the lungs has been estimated between 20 and 50 μg/m$^3$ [20].

Food is an important source of cadmium exposure and absorption of cadmium from food takes place by the gastrointestinal tract. Tap water which is not particularly contaminated contains <2 μg/ℓ cadmium which corresponds to an intake of 2-4 μg/day [14]. But cadmium is present in significant amounts in sea foods like whelks, limpets, sea skaters, oyster, scallops and squids; the concentration range being 0.03 to 1160 ppm dry weight [8, 21]. Thus, the transmission of cadmium through food chains to animals and man can not be avoided.

Analyses of the diets characteristics of several countries show that adult cadmium intake from food ranges from 4 to 84 μg/day [18]. Dietary
data from Japan constitute a special case where the daily intake of cadmium via food, in the endemic area was calculated at 600 μg by assuming an average cadmium concentration in rice of 1 μg/g and a cadmium concentration in other food stuffs of about 10 times the value for Japan as a whole [19]. The human gastrointestinal absorption rate ranges between 4.7 and 7% and was estimated through experiments on 5 human volunteers (19-50 years old) who were given labeled Cd orally. Animal studies show that diets low in calcium, iron and protein can stimulate cadmium absorption by a factor of about 2. The rate of gastrointestinal absorption of cadmium has been found to be higher in young mice than adults [16].

**BODY BURDEN**

Body burden of cadmium ranges from <1 μg in the human new born (indicating that the placenta is an effective barrier to cadmium) to 15-30 μg in the normal adult [19]. Cadmium is about 50% lower in newborn vs maternal blood [22]. For the normal adult about 50% of the body burden is in liver and kidneys and about one-third in the kidney alone. In normal persons, the highest concentration of cadmium is found in the kidney, followed by the liver and other organs. In some cases the concentration of cadmium in the liver has exceeded the kidney level [16, 23, 24]. The pancreas has also been observed to contain high concentration of cadmium [16, 25]. Deposition of cadmium in the renal cortex has been observed to be cumulative with age up to 50 years when mean renal cortex concentrations range between 11 and 50 μg/g wet weight [17]. Elinder et al. determined cadmium concentrations in the kidney cortex, liver, and pancreas from 292 Swedish autopsies and presented them as a function of age [17]. From a comparison of the cadmium concentrations in the renal cortex by industrially exposed workers who did or did not present signs of kidney damage. Friberg et al. [19] observed that 200 μg Cd/g wet weight in renal cortex may be the critical concentration at which renal disfunction appears.

Several studies have demonstrated significantly higher kidney, liver
and lung cadmium levels in smokers as compared to those in non-smokers
[26-30]. Cadmium accumulation in smokers is related to the number
of pack-years smoked [27]. These studies indicate that cigarettes
are a major source of cadmium and can double a smoker's vs non-
smoker's kidney burden of cadmium [17, 26, 28].

METABOLISM

Information on the metabolism of cadmium and its compounds is based
on experimental animal studies, studies on human populations and
studies of autopsy materials.

Barrett et al. [12] studied respiratory deposition of cadmium aerosols
in mice, guinea pigs, rabbits and monkeys and observed that the
average fume deposition in the lung was about the same for all the
species. Cadmium, determined in the livers, kidneys, spleen and
lung of rats and monkeys showed no detectable decrease over periods
of several weeks, indicating very slow clearance of cadmium oxide
(CdO) and Cd blood levels in the exposed animals showed no differences
from unexposed animals by these methods. The subcellular deposition
in the lungs and kidneys of young male rats exposed to CdO aerosol
daily for 6 weeks at 150 μg Cd/m³ was 68 and 55 percent of the
cadmium in their respective soluble supernates [12]. The amount of
Cd retained in each organ was calculated to be a maximum of 10 percent
for the lungs and 2 percent for the kidneys. Lewis and Moorman [12]
studied the distribution and excretion of cadmium fume in three animal
species exposed daily by inhalation. Rats, guinea pigs, and monkeys
were exposed daily for 3 months (rats and guinea pigs) or 6 months
(monkeys) at a time weighted averaged concentration of 1 mg Cd/m³.
The percent retention at 3 months was 11 percent in rats and 36 percent
in guinea pigs. For monkeys, the 6 month body burden was 35 percent
of the estimated exposure dose.

The metabolic fate of Cd by routes other than inhalation have been
also studied in detail. Decker et al. [12] studied the distribution
of Cd in the rat administered CdCl₂ in the water for 1 year at six
levels from 0.1 to 50 ppm Cd, found less than 1 µg/g in the bone at the highest level, but levels of 50 µg/g or greater in the kidney and 40 µg/g in the liver. About 0.17 percent Cd was found to be retained by the kidneys at all levels from 2.5 to 50 ppm Cd and 0.3% Cd retention was found for the 0.1 ppm Cd level. For the liver, the percentage retention of Cd increased with the dose, being of the order of 0.4 percent at 50 ppm and about half this value at 0.1 ppm level.

Studies have been made using Cd with carrier in rats orally, intravenously and subcutaneously [25, 31-33] and in rabbits after subcutaneous injection [34]. Following ingestion in rats 88 percent of the Cd was fecally excreted and about 1 percent was in the kidney and in the liver each. Intravenously administered cadmium initially goes to the livers and relatively small amounts to the kidney. The pancreas accumulated large amounts in uniform distribution. The spleen contained small amounts of Cd concentrated at the capsular or subcapsular regions [32, 35]. Following a single intravenous dose maximum blood level i.e. about 50-60 percent of the injected cadmium is found in the blood at 0.5 min. The metal ion is cleared rapidly with half of it leaving the circulation in the next 2-4 min [36]. In blood cells the cadmium concentration decreases between 4 and 24 h followed by a rise during 24-96 h post-injection [37]. During the early 4 h period cadmium in blood is found mainly in the high molecular weight fraction, whereas at later times (48 h) a substantial amount of cadmium was localized in a low molecular weight fraction, possibly metallothionein [37]. Cadmium in the blood was found to be localized predominantly in erythrocytes when repeated injections were given to experimental animals [38]. About 40 percent of erythrocyte cadmium is dialysable through polyvinyl tubing, the non-dialysable part apparently being bound to haemoglobin.

Induction of metallothionein production by cadmium:

The important factor involved in the absorption, distribution and retention of cadmium that emerged, is the low molecular weight (10,000)
protein thionein, which has the capacity to bind metals like cadmium and zinc to form metallothionein [12]. Metallothionein was first isolated from horse kidney cortex and later isolated from human sources. The purified human metallothionein contains 8.1 percent sulfur, 4.2 percent cadmium, 2.6 percent zinc, 0.5 percent mercury and 0.3 percent copper and a molecular weight of 10,500 [12]. It has been detected in human kidney, liver, pancreas, spleen, testis, heart, brain and skin epithelial cells [12, 14] and most of the cadmium in tissues is probably bound to metallothionein [16]. Cadmium and zinc appear to be the only metals which can induce the synthesis of this protein [39, 40]. The bioavailability of cadmium is mainly influenced by binding to metallothionein which contains a high percent of cysteine residues [41, 42]. It has been concluded that thionein represents a family of low molecular weight proteins that contain large amounts of cysteine sulfur and that bind certain divalent metals like cadmium [12] indicating its role in metabolism as a detoxifying mechanism. The induction of biosynthesis of thionein by administration of low initial levels of Cd illustrates its crucial role in Cd toxicology [12]. Metallothionein synthesis is increased as body levels of Cd decrease. Metallothionein has been found to play a protective role in cadmium toxicity in isolated rat hepatocytes [43]. Resistance to Cd induced toxicity has been found to be related to metallothionein levels. Recently several workers have also pointed out the protective role of metallothionein against cadmium toxicity [44-46]. Disappearance of toxic symptoms of Cd some days after Cd ingestion, restoration of normal renal functioning after cadmium intoxication, formation of cadmium binding protein and increase in liver metallothionein suggest that animals detoxify Cd by sequestering it in a relatively harmless and unavailable form in the liver and kidney. The poor and slow excretion of Cd supports this suggestion. Cadmium treatment has been found to result in amplification of the metallothionein-I gene in liver [47] and thus various workers have reported the induction of metallothionein synthesis in various tissues following cadmium treatment [48, 49].

EXCRETION

Friberg et al. [19] observed that the excretion rate of cadmium is
in the order of 0.005 percent or less. Normal urinary levels of cadmium increase with age and are < 2 \( \mu g/\text{day} \). This increase is probably a function of the increase in kidney burden with age. Urinary cadmium is a poor index of body burden or kidney burden and may remain within normal limits for some time during occupational exposure. A dramatic increase in cadmium excretion may occur in the cases of renal tubular dysfunction [16]. Except for the period right after exposure, fecal excretion is low and insignificant amounts may be excreted via hair, sweat, breast milk and saliva [19]. Very small amounts of Cd (0.01-1.13 \( \mu g/l \)) have been found in human milk as well [50].

In high Cd exposures however, urinary excretion of Cd increases markedly with onset of proteinuria [12] and this finding has been found to be consistent with animal data. The magnitude of the increase may be more than 100 times normal, and probably represents mobilization of Cd from the kidney, because renal Cd in workers with renal damage is less than in those who do not have renal damage [19]. In industrially exposed populations the urinary route of excretion has been found to be of much greater importance than the gastrointestinal route [12]. Other studies [12] also indicate that the daily urinary excretion in the adult population approximates 1 to 2 \( \mu g \). If fecal excretion attained the same value, the total daily excretion would be less than the daily assimilation from food, cigarette smoke, water (and air) as evidenced by the finding that Cd accumulates in at least three organs of the body until mid life i.e. 50 to 59 years [34]. No relation has yet been established between blood levels of cadmium and body burden or kidney burden [16, 21]. In recently exposed workers cadmium in blood has been known to increase without a corresponding change in urinary cadmium output. It has been suggested that cadmium in blood is probably a reflection of current exposure and not body burden. After cessation of exposure blood cadmium levels decrease slowly. Normal concentrations of cadmium in blood are < 1 \( \mu g/100 \, \text{ml whole blood} \) [16, 21]. Blood cadmium level of exposed workers may range between 1 and 10 \( \mu g/100 \, \text{ml whole blood} \). Recently, hair cadmium levels have been found to differ in occupational and non-occupational exposures [12, 51].
TOXICITY

Acute toxicity:

Oral ingestion of as little as 14.5 mg of Cd in man is followed by nausea, vomiting, diarrhoea, abdominal cramps, headache and salivation [20]. Catarrhal and ulcerative gastroenteritis, congestion pulmonary infarcts and subdural hemorrhages are found at necropsy. As little as thirteen to fifteen ppm Cd in popsicles has sickened children, as has 67 ppm in punch and 530 ppm in gelatin [52]. A single oral dose of 3 mg to man has no effect whereas doses ranging from 350 to 8900 mg were found to be fatal [20]. No gastrointestinal changes have been reported in man repeatedly exposed to low levels of cadmium either by oral route (e.g. Itai-Itai patients) or by the pulmonary route (industrial exposure). When injected subcutaneously, Cd salts induce inflammation and coagulation necrosis at the site of injection. The most serious acute effects from Cd occur from exposure to Cd (oxide) fume during industrial operations [53, 54]. As there is usually no or only slight discomfort at the time of exposure, a lethal exposure is possible without warning. These appear 4 to 10 hours later when dyspnea, cough and tightness in the chest develop. With lesser exposures symptoms resolve within a week but in larger exposure dyspnea may be progressive and the delayed onset of pulmonary oedema is responsible for the fatal outcome. Rarely liver or kidney necrosis develops [55]. The estimated lethal concentration of cadmium oxide fume for human beings is approximately 5 mg/m$^3$ for an 8 h exposure [19]. The threshold effect level of cadmium oxide fume and acid soluble cadmium dust on the lungs has been estimated between 20 and 50 µg/m$^3$ (respirable dust) [20].

Chronic toxicity:

Cadmium has a high toxicological potential and has been found to be toxic to all systems studied in man and animals, exhibiting a variety of toxic effects [56]. The toxic effect of cadmium is enhanced by its accumulation in mammalian tissues owing to a very poor homeostatic mechanism.
Effect of cadmium on the kidney: Renal damage is the classic syndrome of chronic cadmium intoxication in humans [57]. Kidney is the organ which exhibits the first adverse effect following long-term excessive exposure to cadmium by inhalation or ingestion [58]. Exposure to cadmium concentrations ranging from 118 to 270 μg/m³ for 5-24 years causes proteinuria [59-64]. Characteristic findings in kidney damage from chronic occupational exposure to cadmium are raised kidney excretion of proteins like beta-2-microglobulin or a retinal binding protein and the alterations appear to be irreversible ever after discontinuation of occupational exposure [65]. Although proteinuria is considered to be the earliest sign of renal tubular dysfunctions, other reported evidence of renal dysfunctions are amino aciduria [12], glycosuria [66], decreased urine concentrating capacity [12, 67] and abnormalities in renal handling of uric acid, calcium and phosphorous [12]. Electron microscopic studies of renal changes in Cd intoxication show an increased size and number of lysosomes with mitochondrial enlargement from swelling, proportional to the Cd concentration. This suggests a stimulation of detoxification processes and a derangement of energy metabolism [68]. Cadmium has been observed to affect the reabsorption of low molecular weight proteins by the proximal tubule and the mechanisms that regulate in the glomerulus or in the tubule, the excretion of high molecular weight protein. The glomerular damage was indicated by an increased excretion of albumin, transferrin, and IgG and an increased plasma level of β₂ microglobulin and creatinine. The excretion of immunoglobulin light chains in the cadmium poisoning shows that cadmium interferes with the catabolism of the light chain of the immunoglobulin [69]. The increased β-galactoside by the kidney suggested that cadmium can damage some epithelial cells [70, 71]. Cd has been found to cause a number of toxic effects in animal. Cd has also been found to inhibit the amino acid transport in rabbit kidney. Intraperitoneally injected cadmium has been found to affect the gluconeogenic enzymes in rat kidney [72]. Cadmium has been found to stimulate the specific activities of some renal brush border enzymes as well as changes in renal protein synthesis in experimental animals at a dose of 0.1 to 0.3 mg Cd²⁺/100 gm body weight [73-78]. Cd in acute doses in experimental animals have also been found to alter
the kidney function [79]. Cadmium has been observed to stimulate the cyclic AMP production in chick renal tissue [80] and induce changes in avian renal morphology [81]. Several workers have proposed a role of Cd metallothionein in nephrotoxicity [82-85], but the exact mechanism of Cd induced nephrotoxicity is yet to be confirmed.

Effect of cadmium on the liver: Abnormal liver function tests are also associated with long term cadmium exposure [86] though the renal effects are more pronounced and frequent. However Cd administration in experimental animals has shown to result in a number of alterations in liver ultrastructure and functions [87-93]. Waker et al. [94] observed acceleration of rat liver phospholipid metabolism after long term cadmium administration while Oziernski et al. [95] showed that continuous administration of cadmium affects the cytochrome P-450 dependent enzymes in the liver and kidney of male rats. Cadmium has also been found to have an effect on nucleic acid in rat liver [96] and inhibit protein secretion [97]. Using isolated perfused rat liver, Lupo et al. observed that exposure to CdCl₂ at concentrations of 50-200 μM results in change of bile flow, urea synthesis and leakage of alanine amino transferase in the perfusate [98].

Recently Hussain et al. [99] observed that intraperitoneal administration of cadmium acetate (0.4 mg/kg body weight) to rats daily for 30 days was found to inhibit the activity of superoxide dismutase, to increase the endogenous levels of lipid peroxides and lipid peroxidation. Addition of varying concentrations of Cd²⁺ (10-100 μM) in vitro also inhibited superoxide dismutase in both the tissues. They suggested a possibility of involvement of free radical damage to the membrane structures in cadmium toxicity. Shukla et al. [100] observed an alteration of glutathione metabolism in liver, kidney and testes of rats exposed to cadmium.

In experimental animals, the organs which accumulate the largest quantities of cadmium are the liver and the kidneys [101]. Between 50 and 75 percent of the cation is usually found in the liver and kidneys after a single or repeated exposure at nontoxic levels [101-103].
Plasma glutamic oxaloacetic transaminase is elevated 3 h after administration of cadmium [104].

In mice a significant reduction occurs in mixed function oxidase activity in the liver four days after a single intraperitoneal injection of Cd(NO₃)₂ in doses above 7.5 µmol/kg [105]. The activity of heme oxygenase is increased and the content of cytochrome P-450 and cytochrome b₅ are decreased at 72 h.

Effect of cadmium on the lungs: Both acute and chronic exposure to excessive concentration of cadmium dust and fume may impair lung functions. Chronic inhalation of CdO dust has been reported to cause pulmonary emphysema in industrial workers [54, 106-108].

Cd has been found to exert marked effects upon phosphatase reactions in various tissues. Intravenous (i.v.) administration of Cd salt solution to rats has been found to elevate the activity of acid phosphatase in lung homogenates [109] and a fall in pulmonary alkaline phosphatase is also observable following multiple i.v. treatment with Cd salts [110]. Another interesting observation is the \textit{in vitro} depression of Mg²⁺ and Na⁺-K⁺-ATPase systems of lung alveolar macrophages by Cd ions [111]. Enzymes like monoamine oxidase requires an essential sulphhydryl group and is thus sensitive to the action of SH inhibitors like cadmium. Pulmonary changes have been noted from subchronic exposure to CdCl₂ aerosol [112]. Recently Elaine et al. [113] studied the comparative effects of inhaled CdCl₂ and CdO on rats and rabbits exposed to aerosols of CdCl₂ and CdO and both were found to cause multifocal, interstitial pneumonitis and the activities of pulmonary enzymes involved in glutathione linked detoxification systems like GSH reductase, glutathione-S-transferase, glutathione peroxidase and glucose-6-phosphate dehydrogenase were found to be inhibited immediately after exposure.

However, it is still a matter of controversy whether chronic occupational exposure to cadmium produces emphysema [14, 114, 115].
Effect of cadmium on the bones: The bone changes involved in cadmium intoxication are very similar to that of osteomalacia but intense pain and spontaneous bone fracture leading to bone deformation are more frequent in Itai-Itai patients than in osteomalacia [116]. Serum alkaline phosphatase is markedly increased and serum inorganic phosphorus is decreased in Itai-Itai patients [58]. It has been proposed that long term abnormal calcium metabolism as indicated by hypercalciuria, nephrocalcinosis, and hyperphosphaturia may result in osteomalacia found in cadmium exposed workers [117]. Studies carried out in experimental animals have shown that cadmium interferes with the final activation of vitamin D₃ to 1,25 - dihydroxycholecalciferol in the renal tubules and this may also be a factor contributing to cadmium induced bone mineralization.

Carcinogenic and mutagenic effects of cadmium: The cancer risk of cadmium to man was first reported by Pott [64], Kipling and Waterhouse [118] while surveying 248 workers exposed to CdO for a minimum of 1 year they found a high incidence of prostatic carcinoma. Subsequently several other investigators have also reported carcinoma in workers exposed to cadmium [119, 120]. Kolonel [121] showed a significant association of renal cancer with exposure to cadmium and a synergistic effect between occupational exposure and smoking. In a 1976 review published by International Agency for Research on Cancer on role of cadmium as carcinogen, it was concluded that the occupational exposure to cadmium in some forms increases the risk of prostatic cancer in man. In addition one of these studies suggested an increased risk of respiratory tract cancer [122]. Cadmium has been found to be carcinogenic to animals when given subcutaneously or intramuscularly as metal powder CdSO₄, CdCl₂, CdO or CdS [123]. Heath et al. [124] observed rhabdomyosarcoma at the site of injection. Subcutaneous injections of cadmium has been found to induce pleomorphic sarcoma at the injection site and interstitial tumors of the testes in rats, which metastases in regional lymph nodes, lungs and on the surface of the spleen, stomach and pancreas [125, 126]. Cadmium has also been found to exert a carcinogenic effect on the prostate of the rat [127].
The mutagenic action of cadmium is not well established. Shirashi et al. [128] have reported an increased frequency of chromosome abnormalities in the lymphocytes of 12 Itai-Itai patients while Bui et al. [129] could not confirm it. Chromosome abnormalities have been observed by Deknudt and Leonard [130] in the leukocytes of workers exposed to fumes and dust of cadmium and lead. The available evidence suggests a complex situation in which cadmium is mutagenic under certain conditions.

Miscellaneous effects of cadmium: Cadmium has been found to exert a number of other effects in man like anosmia [86, 131], ulcerations of the nasal mucosa [131], yellowing of dental necks [131, 132], gonadal [12] and olfactory [64, 133] damage. Acute gastrointestinal disturbances have also been found to be induced by ingestion of food or beverages which have been contaminated with cadmium [13, 19].

In experimental animals as well cadmium has been found to induce a number of toxic effects like testicular damage [134-136], teratogenicity [137], alterations of intestinal membrane enzymes [138, 139], damage of the central nervous system [140] and immunological alterations [141-145]. Cadmium exposure has also been found to induce ultrastructural changes in the cerebellum of weaned and adult rats [146], alteration of the lipid metabolism of weanling rat brain [147] and affect the social behaviour of juvenile rats [148].

Effects of cadmium on the cardiovascular system and blood components: The role of cadmium in the development of cardiovascular diseases is not clear, although several studies have suggested that cadmium exhibits a slight hypertensive action. Cadmium contributes to the high prevalence of hypertension in the USA [149]. Hypertensive persons have also been found to exhibit a significantly higher concentration of cadmium in their body fluids and tissues [150-153]. Several studies have shown that humans who have died from hypertensive complications had increased renal cadmium concentrations [154]. It has been speculated that the increase of deaths from ischaemic heart disease observed in recent years in Scandinavian countries could be brought about by
increased industrialization and mainly high pollution with cadmium, which is accumulated by shellfish and other marine animals and is eventually ingested by humans [155]. But several other workers have failed to establish an association between cadmium exposure and hypertension [156]. Hypertension is not a common feature among either Itai-Itai patients or in workers exposed to cadmium [157, 158]. Perry and Erlanger [159] suggested that at low doses cadmium exhibits a pressor action while at higher doses it decreases systolic blood pressure. Animal experiments have also implicated low concentrations of cadmium as a possible factor in hypertension and arteriosclerotic heart disease [160, 162]. Studies using rats have shown that cadmium administered in drinking water at levels in the range of 0.1-20 ppm can produce elevated systolic and diastolic blood pressures and increase mortality [163-166] while water concentrations above this range are toxic or decrease blood pressure [162, 163, 165]. Jamall et al. observed that cadmium affects some of the components of the antioxidant defence system in the rat heart [167]. Studies [168] on the effects of cadmium on the tension of isolated rat aorta showed that low concentrations of cadmium produced contractions and high concentrations produced relaxations. Cadmium induced contractions depended on external calcium and they were produced by direct stimulation of the cell membrane, low concentrations of cadmium appeared to accelerate calcium availability while high concentrations inhibited it. From animal studies, it is clear that the pressor action of cadmium is dependent on the extent of exposure. Platelets and the vascular endothelium also play an important role in the development of cardiovascular diseases. Normal functioning of both the blood platelet and the vascular endothelial cells are essential for the maintenance of vascular integrity [169]. It has been observed that a homeostatic mechanism exists, in which there is a balance between the products of the arachidonate metabolism like thromboxane A₂ and the antiaggregating prostacyclin PGI₂ [170, 171]. In experimental animals cadmium toxicity has been found to decrease the vascular endothelial production of the platelet inhibiting substance prostacyclin along with an elevation in the serum thromboxane B₂ levels indicating the stimulation of the arachidonate metabolism in platelets [172] but the effects of cadmium on the platelet release
reactions have not yet been studied though cadmium has been found to alter the platelets response to aggregating agents [173] in vivo. Recently Blache et al. [174] found that cadmium at a mM concentration in vitro inhibits human platelet aggregation and acts as a calcium agonist. Platelet aggregation followed by the platelet release reactions are the two main functions of platelets [175].

Heavy metals like mercury, lead, and cadmium are known to produce an oxidative stress by the generation of free radicals and alter the antioxidant protection mechanism of cells [176, 177]. An alteration of the antioxidant defence system of the cell would involve the accumulation of reactive oxygen species within the cells which may result in altered platelet function [178, 179]. As yet little work has been done on the effect of heavy metals on the antioxidant protection mechanism of platelets. The effects of cadmium on the antioxidant defence mechanism in platelets thus presents an interesting field for study.

Anaemia has been associated in workers exposed chronically (5 to 30 years) to CdO dust and fume [62, 180]. Piscator and Axelsson [181] found a significant correlation between high cadmium and low hemoglobin concentrations in blood.

Anaemia has also been a common condition in cadmium administered animals [182-184]. In rats anaemia has been found to develop at dietary cadmium levels as low as 31 ppm [185]. The exact mechanism of the development of anaemia is not known. Several workers [186, 187] have stated that cadmium alters the absorption of dietary iron which in turn produces iron deficiency anaemia. Although total distribution of cadmium in blood is small, cadmium absorption from ingested food into blood is continuous and the blood serves as a transport function for delivery of cadmium to target tissues [184]. Reduction of the life span of erythrocytes has been associated with cadmium poisoning [188]. Functional parameters expressive of the integrity of the erythrocyte membrane, such as the osmotic resistance and mechanical fragility are also affected by heavy metals [189]. Alteration of the
osmotic parameters is detectable after exposure to cadmium [190]. Defects in membrane permeability such as derangement of the normal monovalent cation exchange are clearly evident in the actions of cadmium [191, 192]. Cadmium has been found to induce vesicle release from rat erythrocytes [193]. Kunimoto et al. [194] have shown that administration of cadmium to rats resulted in an increase in erythrocytes with higher density in blood followed by an enhanced clearance of erythrocytes from the circulation. They have also confirmed that in \textit{in vitro} experiments cadmium accelerated age related changes of erythrocytes such as density increments, shape changes, decreased deformability and shortened \textit{in vivo} survival [195]. Changes in membrane properties of rat red blood cells have been found to be induced by cadmium accumulating in the membrane fraction [196, 197]. Recently [198] cadmium has been reported to affect the membrane associated enzymes and the antioxidant status in the rat, but data on the effect of cadmium on human erythrocytes are very scanty.
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