Cadmium is one of the important heavy metals which does not occur naturally uncombined. It is a wide spread industrial product responsible for acute and chronic poisoning in human and animals. It can contaminate air, drinking water and food by pesticides galvanized pipes, cigarette smoking, fertilization, oil and wood consumption as well as many other sources.

Cadmium has no beneficial biological functions in humans and is not normally found in body fluids and tissues. Many researchers have reported that Cd induces determinal effects on metabolism in a variety of tissues resulting in nephropathy, liver damage, bony lesions, cardiovascular diseases, emphysematous changes in the lung ..etc. On the other hand, many studies revealed that cadmium is one of the important chemical carcinogen to human as well as animals.

Hence, the present work was carried out to follow up the histopathological and histochemical changes in the liver and kidney of rats as well as the chromosomal aberrations in the bone marrow cells which might be induced as a consequence of chronic cadmium exposing. This trend aims principally to illustrate and evaluate any possible deleterious and carcinogenic effects of this heavy metal.

Furthermore, the recovery signs from the possible toxic effects of this heavy metal have been studied after its withdrawal or abstainance.

In the preliminary experiments the LD_{50} of $CdCl_2$ for subcutaneous route of administration was determined using 40 rats and it has been equal approximately 20 mg/ kg. body weight.

A total number of 90 male white rats were used in the present experiment, and the target organs comprise the liver (being the site of detoxification), the kidney (the main target organ of chronic exposure) and the bone marrow as the best tissue for studying chromosomal aberrations.

The rats used in this study were divided into (3) groups, each comprised (30) rats.

A group of rats served as a control and were given equivalent volumes of saline solution (NaCl).

The second group of rats was divided into five subgroups, four of them were injected daily subcutaneously with a dose equaling 1/8 LD50 for 10, 20, 30 and 45 days. The animals of the fifth subgroup were injected in the same way for 45 days and were left for 30 days after completion of treatment to examine the recovery signs in the studied organs.

The third group of animals were treated by the same way with 1/4 LD_{50} of $CdCl_2$ and the animals were also examined after 10, 20, 30 and 45 days as well as the fifth subgroup were left for 30 days after 45 days of treatment for studying the recovery signs due to cadmium withdrawal.

Small pieces of the liver and kidney were taken simultaneously from both nontreated and treated rats and prepared for histological and histochemical examination.

The bone marrow obtained extracted from the femora of all animals, was prepared for chromosomal aberrations studies.

The following results were obtained as a consequence of $CdCl_2$ treatment.

The liver has displayed many lesions encountering distortion of the normal architecture, cytoplasmic granularity, hydropic degeneration, invasion of the portal areas and sinusoids and disruption of the cell membranes.

Most of the portal and central veins were dilated and congested, while the sinusoids revealed a marked obliteration. In addition nuclear pyknosis and single cell necrosis were later manifested by many hepatocytes. The longer time treated groups particularly those treated with 1/4 LD_{50} of $CdCl_2$ revealed severe damage of the liver tissue which was characterized by ductal proliferation, severe karyorrhexis, karyolysis and Von Kupffer cells hyperplasia as well as large focal areas of necrosis

A mild recovery, involving incomplete restoration of the normal liver structure, was distincted by the 1/4 LD_{50} treated rats examined 30 days following cadmium withdrawal. Such recovery was more clarified in rats administered with1/8 LD_{50} and treated in the same manner.

Glycogen has undergone a gradual diminution following administration with the 1/8 and 1/4 LD_{50} doses of $CdCl_2$. These materials were approximately disappeared on the 45-th day post- treatment with the high dose.

A slight recovery of the glycogen picture was observed thirty days after Cd withdrawal in rats previously treated with 1/4 LD_{50} for 45 days, but partial restoration of this material was detected in those cases treated previously with the low dose.

DNA- containing particles displayed a mild increase in the livers of each of the 1/8 and 1/4 LD_{50} treated groups after 10 days. This picture was reversed and these inclusions gradually depleted, after 20 and 30 days from the first injection. Traces of DNA particles could be hardly detected on the 45-th day post Cd-administration, especially in the group of rats treated with 1/4 LD_{50}.

A mild recovery in the DNA inclusions was manifested in the liver of rats treated with 1/4 LD_{50} and inspected 30 days after the abstainance of $CdCl_2$. But the clarified recovery was noticed in those previously injected with the 1/8 LD_{50} dose and left for the same period of time.

RNA inclusions of the hepatocytes of the rat also underwent a slight increase in amount after 10 days of treatment with either of the 1/8 or 1/4 LD_{50} doses. This picture started to be reversed and a slight decline seemed to appear in these contents reaching the maximum depletion on the 45-th day after Cd application particularly in those treated with the 1/4 LD_{50} dose.

A partial restoration of the normal RNA levels was observed 30 days following Cd withdrawal, in the livers of rats pre-treated with 1/8 LD_{50}. But a mild recovery was apparent also after 30 days in case of treatment with 1/4 LD_{50}.

Total proteins displayed an increase in intensity in the liver cells after 10 days of 1/8 and 1/4 LD_{50} of $CdCl_2$ administration. The longer time treated groups revealed a gradual decrease in the total protein content comparing to the control group and marked diminution in this inclusion was noticed on the 45-th day post-1/4 LD_{50} of CdC_{l2} administration.

Mild restoration of the total proteins was apparent 30 days post-Cd withdrawal in the liver cells of rats treated with 1/4 LD_{50} of CdC_{l2}, whereas such recovery partially observed, after 30 days in rats administered with 1/8 LD_{50}.

The kidney :- Both of the applied doses 1/8 and 1/4 LD_{50} were found to exert marked histopathological and histochemical changes in the kidney tissues.

Histopathologically, the highly affected member of the renal tissues was the proximal convoluted tubules (PT), where their cells underwent marked deterioration in their cytoplasm and nuclei. Pyknosis, karyorrhexis, karyolysis, cytoplasmic swelling, single cell necrosis and tubular necrosis were the marked pathological alterations, which have been manifested on the 45th day post Cd-treatment with either the 1/8 and 1/4 LD_{50} doses. Other structures such as Bowman 's capsule suffered from negligible changes in those groups treated for 10 and also 20 days. The marked changes as hypercellularity of the capillary tuft and narrowing of the renal space were observed after 45 days of the first injection. The distal convoluted tubules (DT) as well as the collecting tubules underwent some necrotic changes in their epithelial cells. Fibrosis was also observed in the interstitial tissue in the longer time treated groups.

A partial recovery of the structure of the renal tissue was apparent in the epithelial cells of the proximal tubules and renal corpuscles of rats treated with 1/8 LD_{50} and inspected 30 days following Cd abstinence. Mild tissue repair was noticed after the same period in rats treated 1/4 LD_{50}.

Polysaccharides, the renal tissues manifested a slight increase in their amounts following administration of 1/8 and 1/4 LD_{50} of $CdCl_2$ for 10 days. The basement membranes and the brush borders of the proximal

convoluted tubules as well as the capillary tuft cells were noticeably had considerable amount of polysaccharides. Polysaccharides in general were later on progressively diminished being remarkably absent on the 45th day following Cd treatment, particularly with 1/4 LD_{50}.

Indications of partial polysaccharides restoration were exhibited by 1/4 LD_{50}, 30 days after Cd withdrawal. Such improvement was much more marked in those given 1/8 LD_{50} and also examined after 30 days following the last injection.

DNA- containing particles exhibited a mild increase in the nuclei of the cells of the proximal and distal convoluted tubules and mesangial cells of the capillary tuft after treatment with 1/8 and 1/4 LD_{50} doses of $CdCl_2$ for 10 days. The groups administered for longer times revealed a gradual decrease in this inclusion comparing to the normal case. This seemed to continue in a progressive manner to the extent that the nuclei appeared very feebly reactive for DNA particles on the 45th day after treatment with particularly 1/4 LD_{50}.

The recovery of the normal DNA-content was in a parallel correlation with that in the protein case, where it was partially restored in those animals treated with 1/4 LD_{50} after 30 days of Cd- abstinence. But, it was more obvious in the animals treated with 1/8 LD_{50} and left for the same period of time.

RNA particles have manifested an ascending abundance in the cytoplasm and nucleoli of most cells of the renal tissue as a result of administration of 1/8 and 1/4 LD_{50} of $CdCl_2$ for 10 days. Those inclusions later on underwent a progressive diminution, which appeared particularly prominent after 45 days of $CdCl_2$ administration.

A mild restoration of the RNA content of the epithelial cells of the proximal and distal convoluted tubules as well as the mesangial cells of the capillary tuft occurred taken place in rats previously given 1/4 LD_{50} and inspected 30 days after $CdCl_2$ withdrawal, whereas, treatment with 1/8 LD_{50} revealed a partial restoration of such inclusions after the same period of time.

Total proteins were slightly increased in the epithelial cells of the proximal convoluted tubules as well as the mesangial cells of the capillary tuft, 10 days after administration of each of the low and the high doses of $CdCl_2$. This increase followed by a progressive diminution with the weakest protein reactions remarkably distinct on the 45th day of Cd administration.

A partial recovery of protein material was observed 30 days after the end of treatment in the epithelial cells of the renal tubules of rats previously treated with 1/4 LD_{50}, while it was much more marked after 30 days in case of animals given 1/8 LD_{50} of $CdCl_2$.

DNA Image cytometry of hepatic cells demonstrated that the normal hepatocytes have a regular multiplicity of normal diploid DNA (euploid polyploidization). Chronic administration of $CdCl_2$ manifested a slight increase in the DNA- content of these cells after 10 days of treatment. This picture was progressively reversed within the groups treated for a longer time, where the maximum diminution of these inclusions (hypodiploidy) was noted on the 45th day post 1/4 LD_{50} application. The hypodiploidy has been observed through the marked increase of the Go/ G1 in those animals exposed to a long period of Cd administration.

The restoration of the normal DNA content of the hepatocytes was weakly observed in the animals inspected 30 days after 1/4 LD_{50} $CdCl_2$ abstainance. But, partial recovery was clearly appeared after the same

period (30 days) in those animals previously treated with the low dose for 45 days.

DNA image cytometry of the kidney cells manifested the same changes that observed in the liver cells except the alterations here were markedly weak. The animals examined after 10 days of administration with $CdCl_2$ revealed a mild increase in the nuclear DNA content. On the other hand, a gradual decrease was reported in the groups inspected 20 and 30 days following administration with each of the 1/8 and 1/4 LD_{50} $CdCl_2$. The marked diminution of the total DNA content of these type of cells appeared after 45 days of treatment with 1/4 LD_{50} which illustrated by increase the Go/G1 (quiescent state). Also, the DNA content of most cells was lower than the normal diploid content (2C).

Photocytometry of the last groups treated with 1/8 LD_{50} as well as 1/4 LD_{50} and left 30 days post Cd abstainance revealed a partial recovery and incomplete restoring of the normal diploid state.

Cytogenetic observations revealed incidence of structural and numerical aberrations in the bone marrow cells which appeared in different times following $CdCl_2$ administration. Centromeric attenuation as well as chromatid gaps were the early aberrations observed after 10 days of administration with the low or the high doses. All of the structural abnormalities including Centromeric attenuation chromosomal and chromatidal gaps, fragments, deletion, acentric rings, discentric fusion and beaded form were progressively observed in the following examined groups and were then markedly apparent on the 45th day of Cd injection. Hypoploidy was only the numerical aberration noticed in the longer time treated animals was known as an aneuploid state, which predicts propability of tumor incidence.

The repairing of these aberrations was slightly observed in the animals treated with 1/4 LD_{50} for 45 days and inspected 30 days following Cd abstainance, while examination of the animals treated with 1/8 LD_{50} and left for the same period of time revealed a partial recovery and an obvious repairing of the many chromosomal abnormalities. Hypoploidy was still observed.

** In general, we can say that cadmium chloride has been proved to exert many conspicuous effects on the liver and kidney of rats and many chromosomal abnormalities in the bone marrow cells, which reflect its potential carcinogenicity.*

RECOMMENDATIONS

Finally we, recommend the following,

- The industrial companies, which extract Cd or use it in different industrial processes, must take safety precautions to protect workers.

- Cigarette smoking must be prevented not only to reduce lung and other cancers, but also to reduce mortalities from cardiovascular, non-malignant respiratory diseases and liver and kidney disorders.

- Superphosphate fertilizers must be slightly used or prevented in agriculture.

- The safety precautions must be taken in consideration, when using pesticides containing Cd.

- The galvanized pipes, which are used for transferring our drinking water must be replaced by another healthy material.

- Health education and periodic check to workers and citizens exposed to Cd contamination must be done by applying the new techniques for early detection of tumor using tumor markers imaging analysis.

- Further studies have been needed to evaluate and overcome the hazardous effects of the different compounds of Cd.