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Original Article

Effect of Cadmium on the Renal Cortex of Adult Albino Rat and the Possible Protective Role of α- lipoic Acid

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ABSTRACT

Background: Cadmium (Cd) toxicity is related to the tissue oxidative stress due to reactive oxygen species. Alpha-lipoic acid (α-LA) has been identified as an ideal antioxidant capable of regenerating endogenous antioxidants in the body.

Aim of the Work: This study was conducted to elucidate the effect of administration of cadmium on the structure of the renal cortex of the albino rat and to find out the possible protective role of concomitant administration of α–LA.

Material and Methods: This study was carried out on 60 male adult albino rats divided into four groups. Group I (normal control group), 10 rats. Group II (sham control group), 30 rats, they were divided into 3 equal subgroups IIa, IIb & IIc received saline, saline with NaOH solution and α-LA respectively. Group III, 10 rats, received Cd intraperitoneally. Group IV, 10 rats, received Cd and α-LA intraperitoneally. The animals of all groups were sacrificed after one and four weeks of the experiment and renal cortical specimens were subjected to light and electron microscopic studies.

Results: After Cd administration, there were many changes in the renal cortex which were in line with the period of administration. The glomeruli appeared with congested blood capillaries, shrunken or severely degenerated. The glomerular capillary basement membrane was thickened and degenerated or disrupted in many areas. The major processes of some podocytes were degenerated with loss of minor processes. The Bowman's space was obliterated, widened, or contained hemorrhage or tissue debris. The proximal convoluted tubules (PCT) appeared with widened lumen with casts or debris. Some cells of the PCT showed disrupted brush border with few or absent microvilli. Other cells were of degenerated or vacuolated cytoplasm with few mitochondria or absence of organelles. The nuclei became pyknotic in some cells. The distal convoluted tubules (DCT) were less affected. Few of them showed tissue debris, casts or desquamated cells in their lumen. The cytoplasm of some cells of DCT was vacuolated. Concomitant administration of α–LA with Cd greatly minimized these changes.

Conclusions: Cd administration resulted in marked degeneration in the renal cortex. These effects were in line with the period of exposure and that α –LA had a protective role against Cd induced toxicity.

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Key Words: Cadmium; alpha-lipoic acid; renal cortex; antioxidants.

INTRODUCTION

Cadmium (Cd) is ranked seventh in the "Top 20 Hazardous Substances Priority List" delineated by the Agency for Toxic Substances and Disease Registry and the U.S. Environmental Protection Agency *(Wang et al., 2007)*. Heavy Cd usage began in the 1940s with large-scale applications in industry, mining and the burning of fossil fuels. Principal uses nowadays include nickel-cadmium batteries, pigments, and plastic stabilizers *(Fay & Mumtaz, 1996)*.

Major occupational exposures to Cd occur in nonferrous metal melting, production and processing of Cd alloys and compounds

and, increasingly, in the recycling of electronics *(Bernard, 2008)*.

Cigarette smoke is, by far, the greatest source of Cd exposure *(Zalups & Ahmad, 2003)*. Each cigarette contains 1–2 µg of Cd. About 40–60% of Cd in the inhaled smoke enters the systemic circulation *(Elinder et al., 1983)*. For nonsmokers, the major source (besides passive smoking) is ingestion of Cd-contaminated food as shellfish, liver, kidney and grain and cereal products *(Bernard, 2008)*.

Once absorbed, Cd irreversibly accumulates in the human body particularly in kidneys and other vital organs including lung, pancreas, testis, placenta and bone. However, the kidney and liver are the two primary target organs *(Zalups & Ahmad, 2003)*. In addition to its extraordinary cumulative properties, Cd is also a highly toxic metal that can disrupt a number of biological systems, usually at doses that are much lower than most toxic metals *(Jarup et al., 1998; Bernard, 2004; Nordberg et al., 2007)*.

Although the acute toxicity of Cd was discovered early in the 19th century, its chronic effects in humans was recognized much later in the late 1930s as pulmonary, bone and renal lesions among industrial workers *(Brzoska et al., 2003; Prozialeck & Edwards, 2007; Lee et al., 2007)*.

As a consequence of its unique filtration, secretory and reabsorptive capabilities, the kidney is often exposed to higher levels of toxic substances than most organs. Thus, chronic exposure to low-Cd doses accumulates primarily in the kidney and it is the first organ to display signs of toxicity *(Bernard & Lauwerys, 1986)*. Industrial workers are exposed to Cd nephropathy mainly by inhalation while the general population is affected via contaminated foods. The Cd induced renal toxicity is dose-dependent. The adverse effects occur only when the Cd concentration in kidney cortex reaches a critical threshold. This threshold has been estimated as 150-200 part per million (150-200 µg/g weight of renal cortex) both in human and in experimental animals *(Bernard et al., 1992)*. Cd is eliminated very slowly with a half-life of 15–20 years *(Jarup, 2002)*.

It has been established that the proximal convoluted tubule (PCT) is the main site of Cd reabsorption as more than 90% of the filtrated Cd is reabsorbed along this segment *(Barbier et al., 2004)*. Renal dysfunction induced by Cd may be due to proximal tubular damage affecting the passive paracellular pathway *(Robinson et al., 1993; Jacquillet et al., 2007)* or decrease in active trans-cellular ion transport *(Thevenod, 2003)*.

Several mechanisms have been proposed to explain the toxic effect of Cd on renal cells. Cd may cause nephrotoxicity by generating free radicals *(Hassoun & Stohs, 1996; Reyes et al., 2002)*, by inducing necrosis *(Dally & Hartwig, 1997)* or apoptosis *(Jacquillet et al., 2006)*.

Biological compounds with antioxidant properties contribute to the protection of cells and tissues against deleterious effects of reactive oxygen species and other free radicals. Alpha-lipoic acid (α -LA) has been identified as an ideal antioxidant found naturally in our diets, but appears to have increased functional capacity when given as a supplement. This metabolic antioxidant can scavenge a number of free radicals both in hydrophilic and lipophilic environments *(Bustamante et al., 1998; Moini et al., 2002)*. Therefore, it has been proposed that α -LA is a therapeutic agent in the prevention or treatment of pathological conditions mediated via oxidative stress *(Bliska & Wlodek, 2005)*.

Pretreatment of rats with α -LA protected markedly against hepatotoxicity and nephrotoxicity induced by an acute oral toxic dose of acetaminophen as assessed by biochemical measurements and by histological examination *(Abdel-Zaher et al., 2008)*.

Although the kidney is the primary organ affected by the Cd toxicity, only few studies have described its effect on the structure of the kidney. Furthermore, no previous study has mentioned the use of α –LA as a protective measure against Cd nephrotoxicity. Therefore, the aim of the current study was to clarify the effect of administration of Cd on the structure of the renal cortex and to find out the possible protective role of concomitant administration of α –LA.

MATERIAL AND METHODS

Drugs and chemicals

- Cadmium chloride (LOBA Chemie PVT. LTD, India) and Alpha-lipoic acid (Fluka Bio-Chemika, Switzerland) were purchased from El-Gomhoryea Company for chemicals, Cairo, Egypt.

- All other chemicals were of analytical grade.

Animals and treatments

This study was carried out on 60 male adult albino rats, weighing 190-250 g. They were obtained from the Animal House, Faculty of Medicine, Cairo University. Rats were housed in stainless steel cages under a normal hygienic conditions and allowed water and food (laboratory chow) ad libitum throughout the study. They were divided into four groups:

- **Group I** (normal control group): 10 rats raised under normal conditions. Five of them were sacrificed with subgroups IIIa & IVa and the other five were sacrificed with subgroups IIIb & IVb.

- **Group II** (sham control group): 30 rats that were divided into 3 subgroups:

  Subgroup IIa (saline-treated group): 10 rats that received daily intraperitoneal (IP) injection of ½ ml saline. They were further divided into 2 subgroups (5 rats each): subgroup IIa1 treated for 1 week & subgroup IIa2 treated for 4 weeks.

  Subgroup IIb (saline and Na OH treated group): 10 rats that received IP injection of ½ ml saline and Na OH solution (0.05 mol NaOH dissolved in one liter saline) daily *(Abdel-Zaher et al., 2008)*. The rats were divided into 2 subgroups (5 rats each): subgroup IIb1 treated for 1 week and subgroup IIb2 treated for 4 weeks.

  Subgroup IIc (α-LA treated group): 10 rats that received daily IP injection of 100 mg/kg α-LA dissolved in ½ ml of saline and Na OH solution *(Peth et al., 2000)*. The rats were divided into 2 subgroups (5 rats each): subgroup IIc1 treated for 1 week & subgroup IIc2 treated for 4 weeks.

- **Group III** (Cd treated group): 10 rats that received daily IP injection of cadmium chloride 500 µg/kg dissolved in ½ ml saline. The rats were divided into 2 subgroups (5 rats each): subgroup IIIa treated for 1 week *(Karabulut-Bulan et al., 2008)* and subgroup IIIb treated for 4 weeks *(Jacquillet et al., 2007)*.

- **Group IV** (Cd and α-LA treated group): 10 rats that received daily IP injection of 500 µg/kg cadmium chloride and 100 mg/kg α-LA dissolved in ½ ml of saline and Na OH solution. The rats were subdivided into 2 subgroups (5 rats each): subgroup IVa treated for 1 week and subgroup IVb treated for 4 weeks.

Procedure

Sacrifice was done on the due date for each group by decapitation. The anterior abdominal wall was opened by a midline incision. The kidneys were carefully dissected and their cortices were taken off. A small specimen was selected for electron microscopy and the rest of the cortex was dehydrated and embedded in paraffin. Sections of 5µm-thickness were cut, subjected to Hematoxylin & Eosin technique and examined by light microscopy *(Drury & Wallington, 1976)*. The specimen selected for electron microscopy was fixed in fresh 3% glutaraldehyde at 4°C for four hours, washed in 0.15 M phosphate buffer, pH 7.4, for two hours (two changes), postfixed in 1% osmium tetroxide for one hour at 4°C, dehydrated and embedded in epoxy resin. Serial semithin sections were cut at 1µm-thickness by Seo UMTP-6M ultramicrotome, stained with 1% toluidine blue and examined by light microscope. For electron microscopy, ultrathin sections (0.1 µm thick) were prepared using the same ultramicrotome and stained with uranyl acetate and lead citrate *(Hayat, 2000)*. The sections were examined by Seo TEM and photographed under different magnifications.

RESULTS

Light Microscopy

Sections of both group I (control group) and group II (sham control group) revealed the normal

histological structure of the renal cortex. The Malpighian renal corpuscles appeared normal with normal Bowman's spaces and normal glomeruli. The blood capillaries of the glomeruli were normal; some of them contained red blood corpuscles. The proximal convoluted tubules (PCT) were normal with narrow lumina. They were lined by a single layer of few pyramidal cells with basal rounded nuclei and indistinct cell boundaries. Their apical surfaces showed a well-defined brush border. The distal convoluted tubules appeared normal with wide lumina. They were lined by a single layer of cuboidal cells with central rounded nuclei and ill-distinct cell boundaries. Their apical surfaces revealed an ill-defined brush border. All tubules rested on clear tubular basement membrane (Figs. 1, 2).

Cadmium administration (group III) resulted in many alterations in the renal cortex. Those of group III a showed some normal Malpighian corpuscles with normal glomeruli and normal Bowman's space (Figs. 3-a, b). The capillaries of some glomeruli were congested (Figs. 3-c, 4-a) with obliteration of the Bowman's space (Fig. 4-a). Few Malpighian corpuscles showed capsular hemorrhage partially obliterating the Bowman's space (Fig.3-d). The proximal and distal convoluted tubules appeared normal in some areas (Figs. 3- b, d) while in other areas there were casts in their lumina (Fig. 3-c). The cells of some PCT showed vacuolations in their cytoplasm (Figs.4-a, b), few of them showed apical nuclei (Fig. 4-a) while others showed an incomplete brush border (Fig. 4-b). Few distal convoluted tubules showed vacuolations in their cytoplasm with debris and desquamated cells in their lumina (Fig.4-b). Interstitial tissue showed mild (Fig. 3-c) to moderate (Fig. 3-a) congestion of the blood vessels and mononuclear cell infiltration (Fig.3-b).

In group III b, many Malpighian corpuscles appeared with shrunken glomeruli (Figs. 5-a, b, 6-a). Many other Malpighian corpuscles showed severe degeneration of their glomeruli (Fig. 5-a) or with remnants of their desquamated cells and tissue debris in the Bowman's space (Fig. 6-b). There were some normal Malpighian corpuscles with normal glomeruli and normal Bowman's space (Fig. 5-b). Few PCT appeared normal (Fig. 5-a), while many tubules appeared with vacuolated cytoplasm of their cells (Figs. 5-a, 6-a, b). There were many areas of severely degenerated tubules, either hyaline degeneration (Fig. 5-b) or with pyknotic nuclei (Figs.6-a, c) and rarefied cytoplasm (Fig. 6-c). Some PCT showed tissue debris in their lumina (Fig. 6-c). Some DCT appeared with separation of the lining epithelium from the basement membrane (Fig. 5-a) or with severe hyaline degeneration (Fig. 5-b). Other DCT were with vacuolated cytoplasm (Figs. 6-a, b) while few tubules showed tissue debris in the lumen (Fig. 6-b).

No histological changes were observed in group IVa (with concomitant administration of α-LA with Cd for one week) apart from mild congestion of the glomerular (Figs. 7, 8-a) and interstitial blood capillaries (Figs. 7, 8-a). The Bowman's space is obliterated in few Malpighian corpuscles (Fig. 8-a). Both proximal and distal convoluted tubules appeared normal (Figs. 7, 8-a, b).

Malipighian corpuscles of group IVb appeared with shrunken glomeruli and widened Bowman's space (Figs. 9, 10). Tissue debris was observed in dilated Bowman's space of some Malipighian corpuscles (Fig. 10). Some PCT appeared normal or with casts in their widened lumina (Fig. 9) while other tubules showed cytoplasmic vacuolations of their cells with disrupted brush border (Fig. 10). Most of DCT appeared normal (Fig. 9) while hyaline casts could be observed in few tubules (Fig. 9). Congestion appeared marked (Fig. 9) or mild (Fig. 10) in the interstitial capillaries.

Electron Microscopy

Electron microscopic study of groups I and II revealed the normal structure of the renal cortex. The Malpighian corpuscles showed normal glomeruli. The glomerular blood capillaries appeared with normal trilamellar glomerular capillary basement membrane. The leucocytes and red blood corpuscles (RBCs) were observed in the capillary lumen. The podocytes appeared normal with their major and minor processes which rested on the capillary basement membrane. Normal Bowman's space could be seen. The tubules appeared with basal nuclei, many longitudinally-arranged mitochondria. The tubular basement membrane appeared with normal thickness and exhibited basal infoldings closely related to mitochondria (Figs. 11, 12). The luminar surface of the PCT cells showed numerous microvilli projecting in the tubular lumen (Fig. 13).

Cadmium administration (group III) resulted in many electron microscopic changes in the renal cortex. The intensity of these changes was proportionate to the period of exposure.

Renal cortices of group IIIa showed mild congestion of the glomerular capillaries with areas of thickened degenerated (loss of trilamellar structure) basement membrane. Mononuclear cell infiltration was observed in the interstitium between the glomerular blood capillaries (Fig. 14). Some of the cells of the proximal convoluted tubules showed loss of microvilli, while others showed few ones. Tissue debris was observed in the lumen of some PCT (Fig.15). No obvious changes were detected in the DCT.

In group IIIb, the capillary basement membrane of many glomeruli was thickened and degenerated with areas of disruption. Many podocytes appeared with degenerated major processes and there were areas of loss of minor processes. Mononuclear cell infiltration was observed in the interstitium of the glomerular blood capillaries (Fig.16). There was patchy distribution of severely degenerated PCT with tissue debris in their lumina. The cells of the PCT showed rarefaction of the cytoplasm with absence of organelles apart from few small globular mitochondria in some cells. Extravasation of RBCs was observed in between the basement membranes of different tubules (Fig.17). The DCT were less affected than the PCT. Few DCT showed nearly normal cells beside the degenerated ones. Tissue debris was observed in the lumen of the affected tubules (Fig.18).

Sections of group IVa showed slight deviation from that of the controls. Few glomeruli appeared with areas of thickening and degeneration of the basement membrane (Fig.19). Few PCT were minimally affected with rarefied cytoplasm of their cells. The PCT cells appeared with large number of longitudinal and globular mitochondria and few microvilli. The tubular basement membrane appeared normal with preserved basal infoldings (Fig.20). No obvious changes were detected in the DCT.

Some glomeruli of group IVb showed areas of thickened degenerated glomerular capillary basement membrane (Fig.21). Some PCT were moderately affected. The cells showed moderate number of globular mitochondria and minimal rarefaction of the cytoplasm. The basement membrane of PCT appeared normal and microvilli were observed in some cells (Fig. 22). The DCT appeared within nearly normal structure (Fig.23). Congestion of the glomerular (Fig.21) and interstitial (Fig.23) capillaries was also observed.

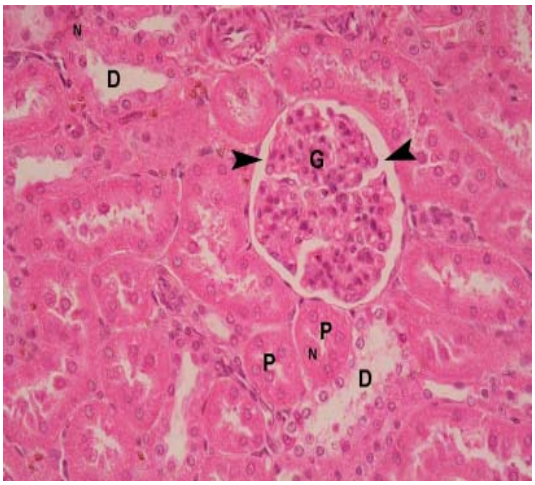

Fig. 1: A photomicrograph of a section of renal cortex of a control albino rat (group I), showing normal structure of the Malpighian renal corpuscle with normal glomerulus (G) and normal Bowman's space (arrow head). The proximal convoluted tubules (P) are normal with narrow lumina. Their cells are pyramidal with rounded basal nuclei (N) and indistinct cell boundaries. The distal convoluted tubules (D) are normal with wide lumina and lined by a single layer of cuboidal cells with rounded nuclei (N). Hx. & E.; X 400

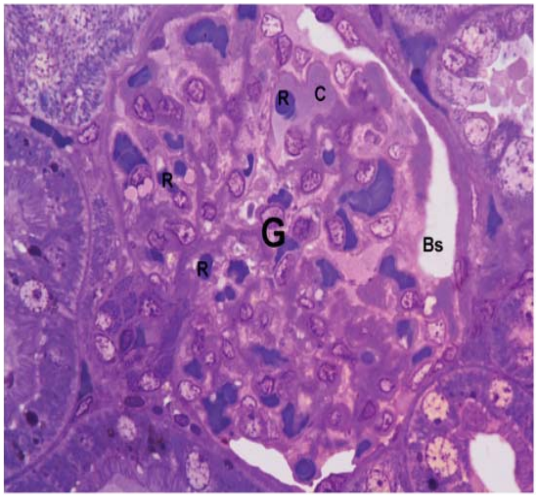

Fig. 2 A: A photomicrograph of a semithin section of renal cortex of a control albino rat (group I), showing normal structure of a Malpighian renal corpuscle with normal Bowman's space (Bs). The glomerulus (G) appears with normal capillaries (C), some of them contain red blood corpuscles (R). Toluidine blue; X 1,000

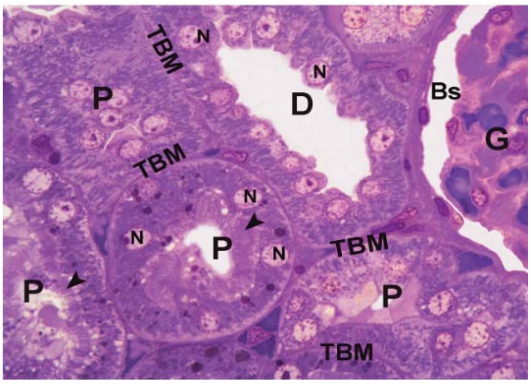

Fig. 2 B: A photomicrograph of a semithin section of renal cortex of a control albino rat (group I), showing normal proximal convoluted tubules (P) with narrow lumina. They are lined by few pyramidal cells with round basal nuclei (N), indistinct cell boundaries and well defined brush border (arrow head). A normal distal convoluted tubule (D) appears with wide lumen and is lined by a single layer of cuboidal cells with central rounded nuclei (N), indistinct luminal brush border and ill-distinct cell boundaries. All tubules rest on clear tubular basal membrane (TBM). A part of normal glomerulus (G) with normal Bowman's space (Bs) can be seen . Toluidine blue; X 1,000

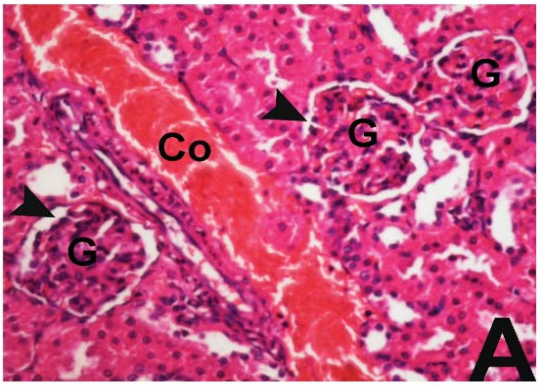

Fig. 3 A: A photomicrograph of a section of renal cortex of an albino rat from group IIIa, showing moderate congestion (Co) of a blood vessel, normal Malpighian corpuscles with normal glomeruli (G) and normal Bowman's space (arrow head). Hx. & E.; X 400

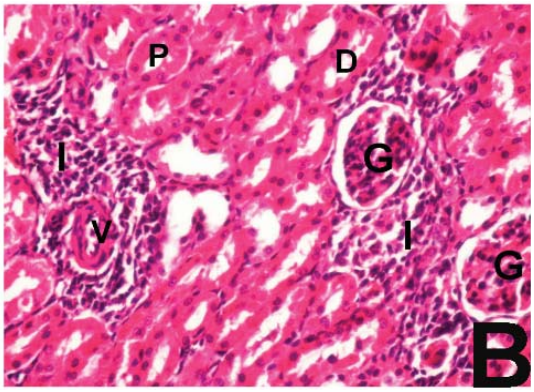

Fig. 3 B: A photomicrograph of a section of renal cortex of an albino rat from group IIIa, showing mononuclear cell infiltration (I). The glomeruli (G), proximal (P) and distal (D) convoluted tubules appear normal. A blood vessel (V) can be seen. Hx. & E.; X 400

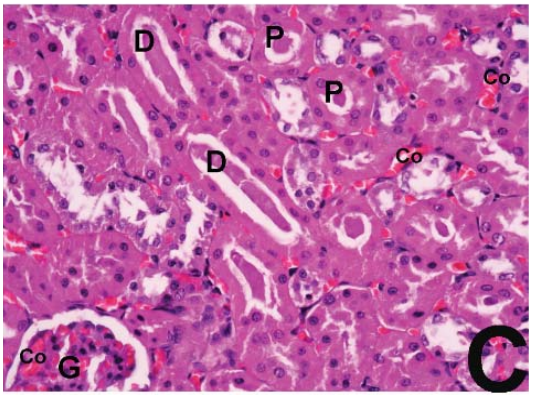

Fig. 3 C: A photomicrograph of a section of renal cortex of an albino rat from group IIIa, showing capillary congestion (Co) of both glomerulus (G) and interstitial tissue. Casts appear within proximal (P) and distal (D) convoluted tubules. Hx.& E.; X 400

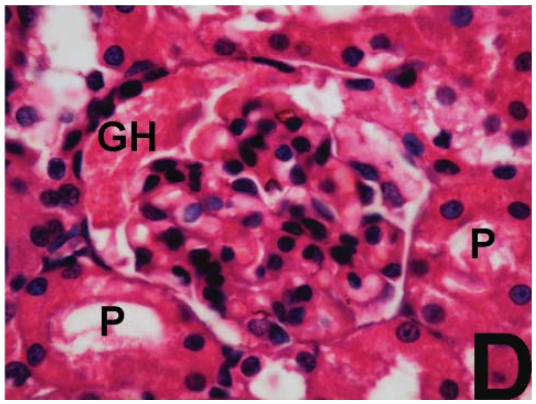

Fig. 3 D: Aphotomicrograph of a section of renal cortex of an albino rat from group IIIa, showing a Malpighian corpuscle with glomerular haemorrhage (GH) partially obliterating the Bowman's space. Proximal convoluted tubules (P) appear normal. Hx. & E.; X 1,000

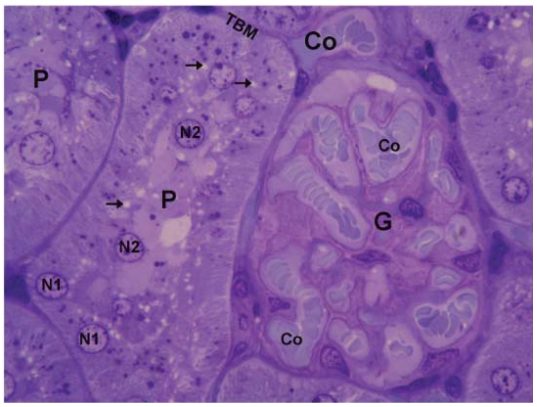

Fig. 4 A: A photomicrograph of a semithin section of renal cortex of an albino rat from group IIIa, showing a Malpighian corpuscle with moderate congestion (Co) of the glomerular (G) capillaries. Obliteration of the Bowman's space can be observed. Two proximal convoluted tubules (P) appear with normal nuclei (N1) or become apical (N2), many vacuoles (arrow) and normal tubular basement membrane (TBM). Moderate congestion (Co) of the interstitial capillaries is observed. Toluidine blue; X 1,000

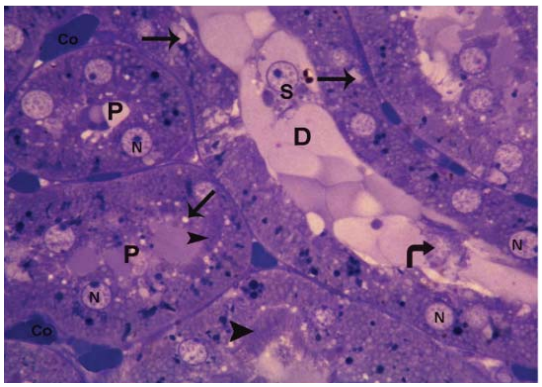

Fig. 4 B: A photomicrograph of a semithin section of renal cortex of an albino rat from group IIIa, showing a distal convoluted tubule (D) with few normal nuclei (N). A desquamated cell (S) and tissue debris (curved arrow) appear in the lumen. Few proximal convoluted tubules (P) show normal nuclei (N) and incomplete brush border (arrow head). Many vacuoles (arrow) appear in both proximal and distal tubules. Moderate congestion (Co) of the interstitial capillaries is observed. Toluidine blue; X 1,000

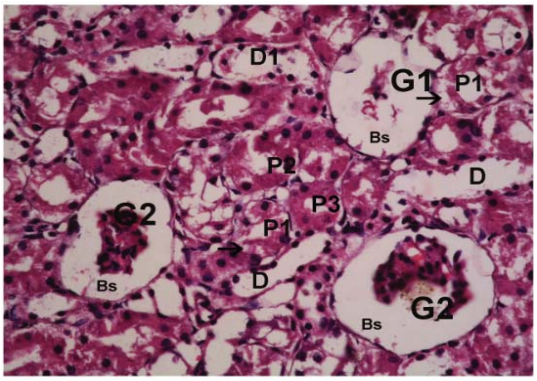

Fig. 5 A: A photomicrograph of a section of renal cortex of an albino rat from group IIIb, showing a Malpighian corpuscle with severely degenerated glomerulus (G1) and 2 less affected Malpighian corpuscles with shrunken glomeruli (G2) with excessive widening of the Bowman's space (Bs). Many proximal convoluted tubules (P1) show marked vacuolation (arrow) in their cell, others (P2) are less vaculated and few tubules appear normal (P3). The distal convoluted tubules show degeneration (D) or separation of their cells from the basement membrane (D1). Hx. & E.; X 400

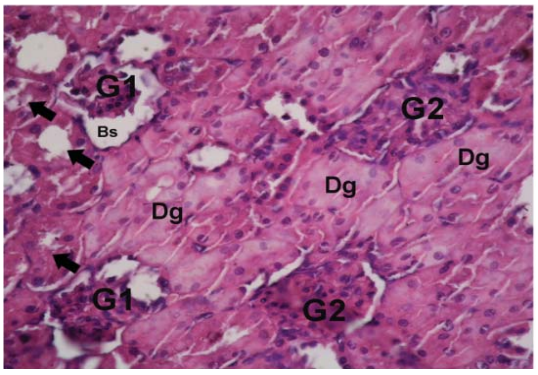

Fig. 5 B: A photomicrograph of a section of renal cortex of an albino rat from group IIIb, showing severe degeneration (Dg) affecting many tubules while some proximal tubules (arrow) appear nearly normal. Two Malpighian corpuscles show shrunken glomeruli (G1) with widening of the Bowman's space (Bs) and the other two corpuscles (G2) appear normal. Hx. & E.; X 400

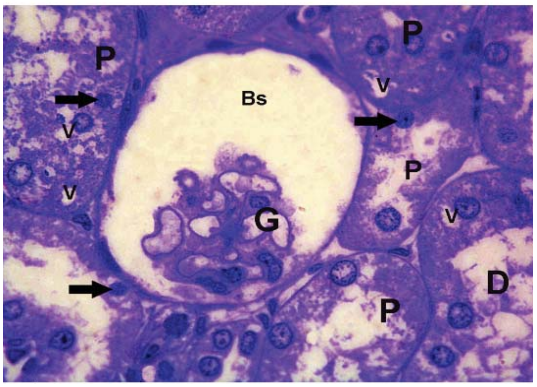

Fig. 6 A: A photomicrograph of a semithin section of renal cortex of an albino rat from group IIIb, showing a Malpighian corpuscle with shrunken glomerulus (G) and marked widening of the Bowman's capsule (Bs). Proximal (P) & distal (D) convoluted tubules show cytoplasmic vacuolations (V) of their cells. Some proximal convoluted tubules show cells with darkly stained (pyknotic) nuclei (arrow). Toluidine blue; X 1,000

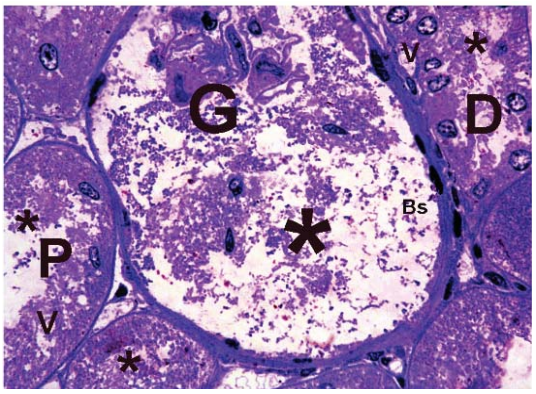

Fig. 6 B: A photomicrograph of a semithin section of renal cortex of an albino rat from group IIIb, showing a Malpighian corpuscle with shrunken glomerulus (G) and sloughing of some degenerated glomerular cells and tissue debris (*) in the widened Bowman's space (Bs). The proximal (P) & distal (D) convoluted tubules appear with vacuoles (V) in their cells and tissue debris (*) in their lumen. Toluidine blue; X 1,000

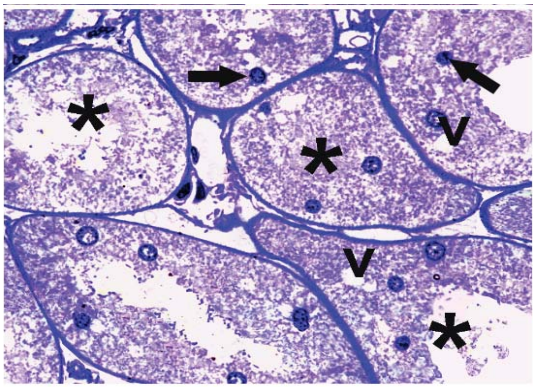

Fig. 6 C: A photomicrograph of a semithin section of renal cortex of an albino rat from group IIIb, showing tubules with (pyknotic) nuclei (arrow) and vacuoles (V) within rarefied cytoplasm. Tissue debris (*) is observed in the tubular lumen. Toluidine blue; X 1,000

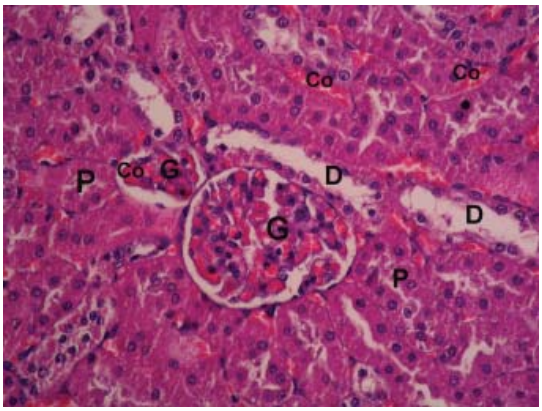

Fig. 7: A photomicrograph of a section of renal cortex of an albino rat from group IVa, showing mild congestion (Co) of the glomerular (G) and interstitial capillaries. The proximal convoluted tubules (P) and distal convoluted tubules (D) appear normal. Hx. & E.; X 400

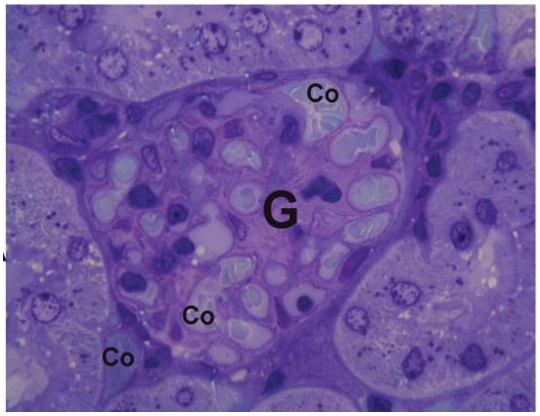

Fig. 8 A: A photomicrograph of a semithin section of renal cortex of an albino rat from group IVa, showing a Malpighian corpuscle with mild congestion (Co) of the blood capillaries of the glomerulus (G). Obliteration of the Bowman's space can be observed. The surrounding tubules appear normal. Mild congestion (Co) of the interstitial capillaries appears within the cortex. Toluidine blue; X1,000

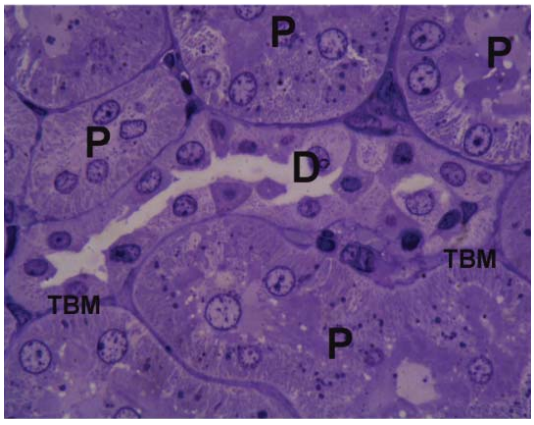

Fig. 8 B: A photomicrograph of a semithin section of renal cortex of an albino rat from group IVa, showing one distal (D) and few proximal (P) convoluted which appear normal. The tubules rest on clear basement membrane (TBM). Toluidine blue; X 1,000

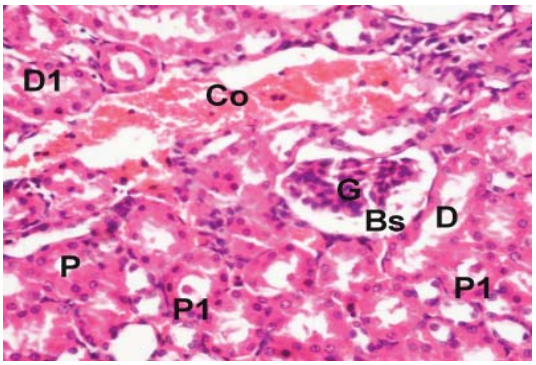

Fig. 9: A photomicrograph of a section of renal cortex of an albino rat from group IVb, showing a Malpighian corpuscle with shrunken glomerulus (G) and widened Bowman's space (Bs). Proximal convoluted tubules appear normal (P) or with casts in their widened lumina (P1). Distal convoluted tubules appear normal (D) or with casts in their lumina (D1). Marked congestion (Co) in a blood vessel can be observed. Hx. & E.; X 400

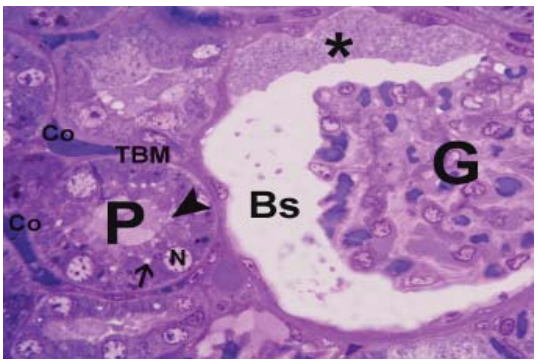

Fig. 10: A photomicrograph of a semithin section of renal cortex of an albino rat from group IVb showing: a Malpighian corpuscle with shrunken glomerulus (G) and widening of the Bowman's space (Bs) which contains tissue debris (*). The proximal (P) convoluted tubules appear with normal nuclei (N), many vacuoles (arrow) and disrupted brush border (arrow head). Mild congestion (Co) of the interstitial capillaries appears within the cortex. The tubules rest on normal basement membrane (TBM). Toluidine blue; X 1,000

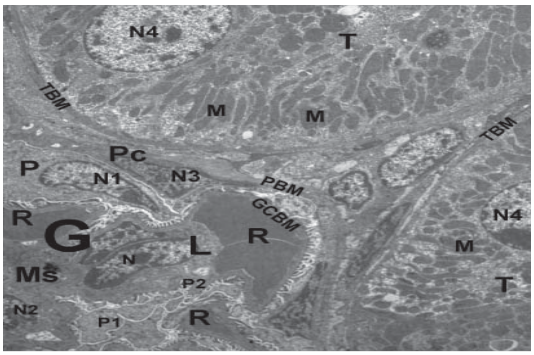

Fig. 11: An electron micrograph of renal cortex of a control albino rat (group I), showing a part of a glomerulus (G) with a leucocyte (L) and its nucleus (N) and red blood corpuscles (R) in its capillaries. A podocyte (P) appears with a nucleus (N1) surrounded with cytoplasm. Major processes (P1) of the podocyte appear with many minor processes (P2) resting on normal trilamellar glomerular capillary basement membrane (GCBM). Part of a mesangial cell (Ms) appears with its nucleus (N2). Parietal endothelial cell (Pc) appears with its nucleus (N3) resting on parietal basal membrane (PBM). Parts of 2 cells of 2 different tubules (T) appear with basal nuclei (N4), many longitudinal mitochondria (M) and tubular basal membrane (TBM) of normal thickness. X 2,500

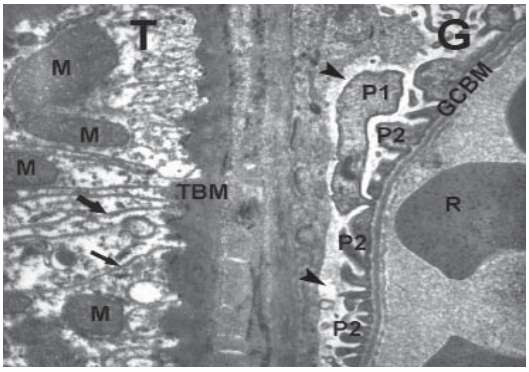

Fig. 12: An electron micrograph of renal cortex of a control albino rat (group I), showing a part of a cell of proximal convoluted tubule (T) with normal trilamellar basement membrane (TBM) which exhibits basal infoldings (arrows) closely related to mitochondria (M). A part of a normal glomerulus (G) with normal podocyte with normal major processes (P1) and minor processes (P2) which rest on the glomerular capillary basement membrane (GCBM) which exhibits normal trilamellar structure. A red blood corpuscle (R) appears inside the capillary. Normal Bowman's space (arrow head) can be seen. X10,000

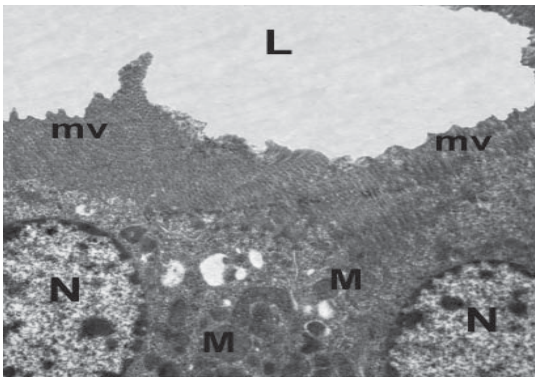

Fig. 13: An electron micrograph of renal cortex of a control albino rat (group I), showing parts of two cells of proximal convoluted tubule with normal nuclei (N), mitochondria (M) and apical numerous microvilli (mv) projecting in the lumen (L). X6,000

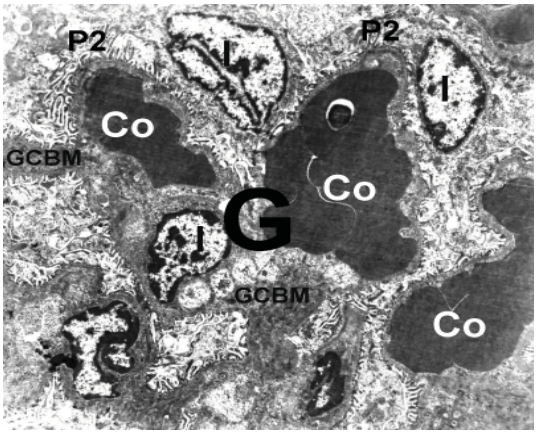

Fig. 14: An electron micrograph of renal cortex of an albino rat from group IIIa, showing part of a glomerulus (G) with mild congestion (Co) of its capillaries. The glomerular capillary basement membrane (GCBM) appears thickened with minor processes (P2) of the podocytes resting on it. Mononuclear cell infiltration (I) can be observed. X3,000

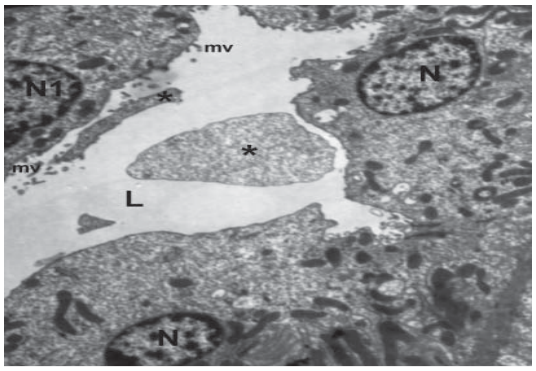

Fig. 15: An electron micrograph of renal cortex of an albino rat from group IIIa, showing a part of a proximal convoluted tubule. There is loss of microvilli of 2 cells (N) and there are few microvilli (mv) in one cell (N1). Tissue debris (*) is observed in the lumen (L). X4,000

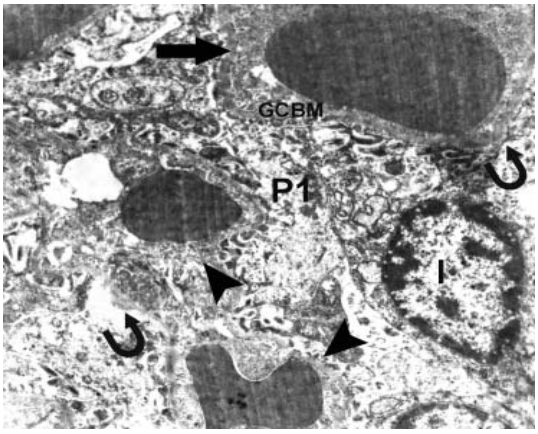

Fig. 16: An electron micrograph of renal cortex of an albino rat from group IIIb, showing part of the glomerulus with degenerated basement membrane (GCBM) of blood capillaries which is thickened (arrow) or disrupted (arrow head). There is a degenerated major process (P1) of a podocyte. There are areas of loss of minor processes (curved arrow). Mononuclear cell (I) is observed in the interstitium. X6,300

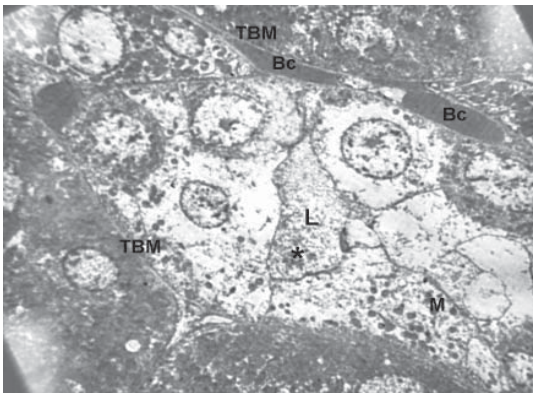

Fig. 17: An electron micrograph of renal cortex of an albino rat from group IIIb, showing a severely affected proximal convoluted tubule with tissue debris (*) in its lumen (L). The cells of the affected tubule show rarefied cytoplasm with absence of organelles apart of few small globular mitochondria (M). Their luminar surfaces show no microvilli. The affected tubule is surrounded by relatively less affected tubules with moderate number of organelles. Blood cells (BC) appear between the basement membrane (TBM) of the different tubules. X 1,500

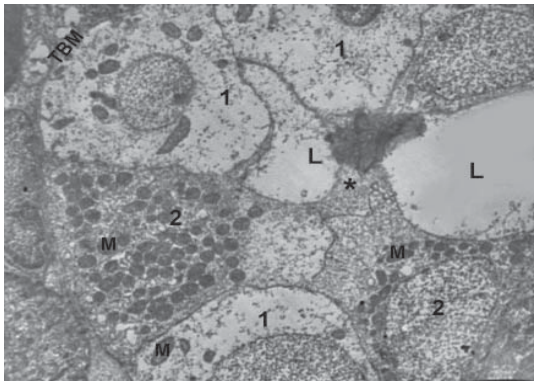

Fig. 18: An electron micrograph of renal cortex of an albino rat from group IIIb, showing a distal convoluted tubule with severely degenerated cells (1) and other cells with nearly normal appearance (2) with many mitochondria (M). The luminar surfaces show no microvilli. There is debris (*) in the lumen (L). The tubular basement membrane (TBM) is normal. X 3,000

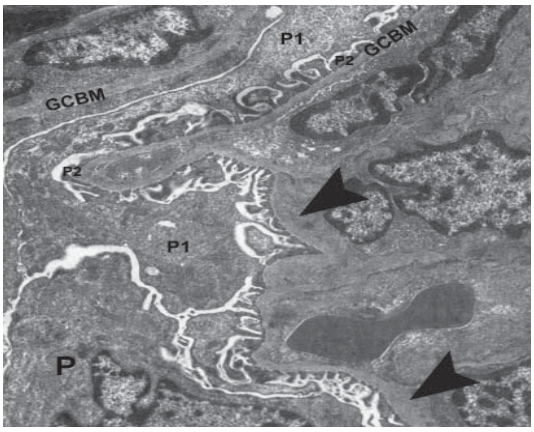

Fig. 19: An electron micrograph of renal cortex of an albino rat from group IVa, showing a part of a glomerulus. The glomerular capillary basement membrane (GCBM) is degenerated with loss of its trilamellar structure and thickened in some areas (arrow head). A podocyte (P) appears normal. The major (P1) and minor (P2) processes of the podocytes are normal. X 5,000

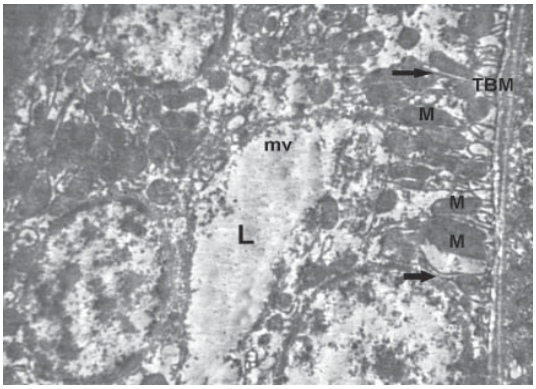

Fig. 20: An electron micrograph of renal cortex of an albino rat from group IVa, showing a minimally affected proximal convoluted tubule with basal infoldings (arrows) closely related to columns of large number of longitudinal and globular mitochondria (M). The cells are partially affected with minimal rarefaction in the cytoplasm. Their luminar surfaces show few irregular microvilli (mv) projecting in the lumen (L). The basement membrane (TBM) is normal. X 4,000

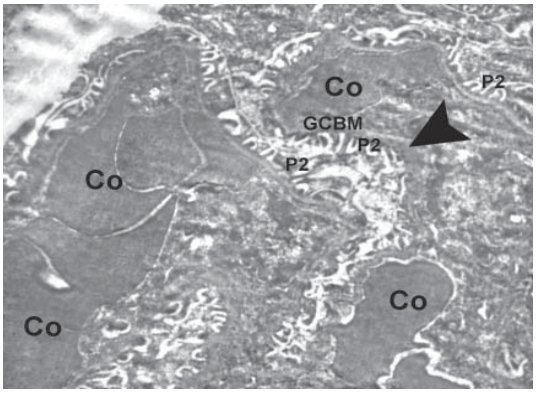

Fig. 21: An electron micrograph of renal cortex of an albino rat from group IVb, showing part of a glomerulus with congested (Co) capillaries. The minor processes (P2) rest on the capillary basement membrane (GCBM). Part of the membrane appears thickened and degenerated (arrow head). X 4,000

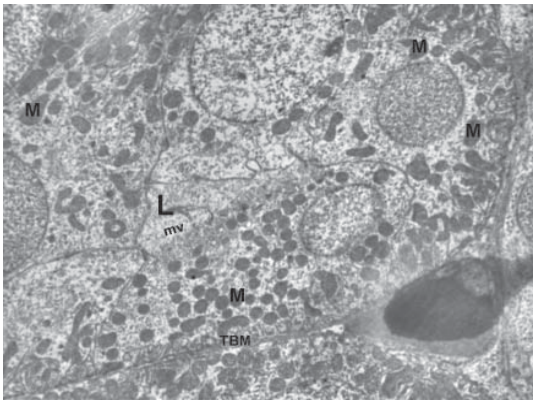

Fig. 22: An electron micrograph of renal cortex of an albino rat from group IVb, showing minimally affected proximal convoluted tubule. Its cells show minimal rarefaction of the cytoplasm with moderate number of globular mitochondria (M) and few microvilli (mv) projecting in the lumen (L). The tubular basal membrane (TBM) is of normal thickness. X 3,000

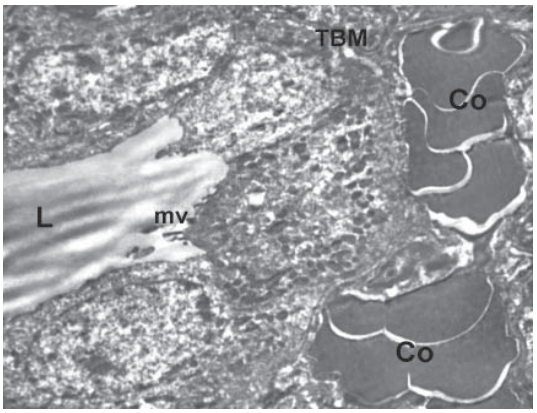

Fig. 23: An electron micrograph of renal cortex of an albino rat from group IVb, showing part of a distal convoluted tubule with nearly normal structure. The cells of the tubule show few microvilli (mv) projecting in the lumen (L). The tubular basement membrane (TBM) is normal. Two congested (Co) interstitial capillaries are observed. X 3,000

DISCUSSION

Cadmium (Cd) is typically the metal of the 20th century. It is widely used in many industries *(Fay & Mumtaz, 1996)*. Cigarette smoke is, by far, the greatest source of Cd exposure for smokers and nonsmokers *(Zalups & Ahmad, 2003)*. Exposure to Cd is inevitable for most population, especially in developing countries, due to its environmental pollution. Cd dispersed in the environment can persist in soils and sediments for decades. When it is taken up by plants, Cd concentrates along the food chain and ultimately accumulates in the body of people eating the contaminated food. The most salient toxicological property of Cd is its exceptionally long half-life in the human body *(Bernard, 2008)*.

The renal cortex was used in this work as it is responsible for 83.8% of renal function, the main site of excretion of Cd and its metabolites as well as it is the first site of damage by Cd toxicity *(Nordberg et al., 2007)*. It was also found, after Cd exposure, that the renal cortex showed the highest Cd concentration *(Nagamine et al., 2007 ; Nakazato et al., 2008)*.

The results of the present study revealed that cortical changes induced by Cd were patchy in distribution. This finding was previously observed by *Brzoska et al. (2003)*. In the present study, Cd administration (group III) resulted in changes in Malpighian renal corpuscles of all tested renal cortices, especially after prolonged Cd administration. Shrinkage and degeneration of the glomeruli which were obvious in the present work were in correspondence with those reported by *Rodriguez-Barbero et al. (2000), L'Azou et al. (2002) and Hirano et al. (2005)*. The later authors reported that glomerular contraction resulted in decrease of glomerular filtration which might lead to renal impairment. *Apostolova et al. (2006)* and *L'Azou et al. (2007)* attributed the glomerular shrinkage to the disruption of the cytoskeleton of the mesangial cells and their contraction. Moreover, *Thijssen et al. (2007a)* found an increase in the collagen 1 and fibronectin in the extracellular matrix of the glomeruli which was dose related. They added that this increase might lead to glomerular fibrosis and degeneration.

In the present work, some glomeruli appeared with congested capillaries or with capsular hemorrhage and thickened degenerated capillary basement membrane. Thus, the Bowman's space appeared partially or completely obliterated. These findings were in agreement with those of *Brzoska et al. (2003)* who attributed the hemorrhage to the thickening of the capillary vessels and widening of the endothelial spaces. However, *Stoev et al. (2003)* reported that the increase in glomerular size was due to glomerular endothelial proliferation. The debris found in Bowman's space in the present work could be explained by desquamation of the proliferated degenerated endothelial cells. Prolonged Cd administration in the current study resulted in degeneration of the major processes of the podocytes with loss of minor processes in many areas which is in agreement with findings obtained by *Asar et al. (2004)*. Mononuclear cellular infiltration was evident in some glomeruli which were also recorded by *Brzoska et al. (2003)*. On the other hand, *Kukner et al. (2007)* recorded that there were no significant changes affecting the Malpighian renal corpuscles after intake of Cd for one week.

It could be suggested that degeneration of the capillary basement membrane was due to the affection of mesangial cells and podocytes which are responsible for the integrity and renewal of the basement membrane. Furthermore, the mononuclear cell infiltration was to remove the tissue debris and the degenerated endothelial cells.

The current study revealed variable changes in the PCT following Cd administration. The degree of affection was proportional with period of administration which was also recorded by *Thijssen et al. (2007b)*. The basal infoldings of the PCT cells were diminished or lost. This finding is in agreement with that of *Sabolic et al. (2006)* and *Thijssen et al. (2007a)*. The brush border was incomplete or disrupted and the microvilli were few or absent in the cells of the affected PCT. Similar findings were reported by *Herak-Kramberger and Sabolic (2001)* and *Sabolic et al. (2006)*. In the present work, the cytoplasm appeared in some areas vacuolated, rarefied or with hyaline degeneration. These findings were reported before by *Stoev et al. (2003)* and *Thijssen et al. (2007b)*.

The mitochondria were diminished in number in the present work and appeared globular. Moreover, *Thijssen et al. (2007a)* described the mito-

chondria to be disarranged and migrated towards the lumen. *Takaki et al. (2004)* attributed the cadmium-induced nephropathy and dysfunction in PCT to mitochondrial DNA deletion. These findings are not in line with those obtained by *Asar et al. (2004)* who mentioned that the mitochondria increased in number and became larger.

In the present work, the nuclei of the cells lining PCT became pyknotic especially with extended Cd administration. The lumen became wider with appearance of casts or tissue debris within it. These findings are in agreement with the findings of *Brzoska et al. (2003)*.

The current research showed that Cd administration resulted in some changes in few DCT. These changes were in the form of cytoplasmic vacuolations, atrophy of the nuclei, mitochondrial swelling and obliteration of tubular lumen. Also, few DCT revealed apical direction of nuclei and presence of tissue debris or desquamated epithelial cells in the dilated lumen. These observations are in agreement with results of *Kukner et al. (2007)* who mentioned that Cd nephrotoxicity affected distal convoluted tubules secondary to changes in the PCT.

In addition, *Sabolic et al. (2002)* pointed that the primary effect of Cd was in the PCT due to their ability to concentrate this substance and its toxic metabolites leading to electric changes and disturbance in the tubular reabsorption active transport system.

The current study revealed mild to severe congestion of the blood vessels in the renal cortex and blood extravasation between the tubules (peritubular hemorrhage). *Asar et al. (2004)* reported that the actual causes of these changes remain obscure. However, *Kukner et al. (2007)* reported that cadmium has a direct toxic effect on the wall of small blood vessels leading to vasodilatation and extravasation of blood from their necrotic walls. The mononuclear cell infiltrations found in the present work were also observed by *Brzoska et al. (2003)*. It could be suggested that the cellular infiltration was to remove the tissue debris and degenerated and desquamated epithelial and endothelial cells.

Some reports by *Waalkes (2003)* suggested that prolonged exposure to Cd might be carcinogenic and causes malignancy in the lungs, kidney, urinary bladder or liver. Moreover, *Nawrot et al. (2006)* mentioned that Cd lowered acidity of urine and increased urinary tract bacteria which reduced urinary nitrate into nitrite with the formation of N-nitroso compounds. These compounds would be carcinogenic to the renal epithelium of many animal species and human beings. On the other hand, *Bernard (2008)* denied the occurrence of any renal cell neoplasia as a result of Cd. The current study could not detect any manifestation of hyperplasia, dysplasia or malignant transformation of the renal cells of the albino rat. A longer period of continuous Cd administration may be required to confirm such malignant changes; a point that needs further investigation.

Concomitant administration of alpha lipoic acid (α-LA) with Cd (group IV) markedly minimized the adverse effects of Cd. Some Malpighian corpuscles showed mild glomerular congestion with obliteration of the Bowman's space. Few glomeruli showed partial degeneration of the glomerular basement membrane. Some PCT demonstrated different changes in the form of wide lumen which contained tissue debris. Their cells showed vacuolated or mildly rarefied cytoplasm, few globular mitochondria or disrupted brush border and few microvilli. The DCT were minimally affected showing casts in their lumen. There were some congested interstitial blood capillaries.

Yang et al. (2009) explained the mechanism of Cd toxicity. They reported that Cd stimulated Ca+ release from the endoplasmic reticulum with consequent depolarization the mitochondrial membrane. Depolarization of the mitochondrial membrane could result in release of reactive oxygen species (ROS). This ROS will result in oxidative stress which activated both apoptosis and autophagic cell death. *Moini et al. (2002)* proved that α -LA can scavenge a number of free radicals both in hydrophilic and lipophilic environments. Moreover, *Wollin & Jones (2003)* found that α –LA was capable of regenerating endogenous antioxidants in the body including vitamin C, vitamin E and intracellular reduced glutathione. Thus, it could be suggested that α –LA by itself and by regenerating antioxidants capture the ROS and protect the renal tissue from their oxidative mitochondrial damage and their degenerating effects. This is supported by previous findings of *Nemmiche et al. (2007)* who reported that alpha-

tocopherol (vitamin E) protected the liver and brain from Cd-induced oxidative stress in Wistar rat. Also, *Karabulut-Bulan et al. (2008)* observed that vitamin C, vitamin E, and selenium had minimized the Cd -induced renal toxicity in rats. Moreover, *Jihen et al. (2008)* found that selenium and zinc administration had a protective role in rat liver and kidney against Cd-induced toxicity. Furthermore, *Kara et al. (2008)* confirmed the protective role of selenium, vitamin E and melatonin in Cd-induced oxidative damage in rat liver and kidneys.

It is concluded that Cd administration resulted in marked degeneration in the renal cortex which might predispose to renal failure. These effects were in line with the period of exposure and were greatly minimized with concomitant alpha lipoic acid administration. So, it is recommended to replace Cd with other save alloys in industries to prevent Cd contamination of air and food. If Cd exposure is inevitable, protective measures, including alpha lipoic acid administration, should be applied to exposed population. Also cigarette smoking should be prohibited. Further studies for longer periods of Cd administration should be performed to evaluate its possible carcinogenic effect.

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تأثير الكادميوم علي قشرة الكلية للفأر الأبيض البالغ والتأثير الوقائى المحتمل لحمض الألفا ليبويك

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ملخص البحث

تم تصنيف الكادميوم في المرتبة السابعة ضمن قائمة أعلى عشرين عنصرا ضارا حيث يستخدم الكادميوم على نطاق واسع فى الصناعة و التنقيب عن المعادن وينتج عن حرق الوقود ومن دخان السجائر و قد استهدفت هذه الدراسة توضيح تأثير أعطاء الكادميوم على تركيب قشرة الكلية للفأر الأبيض البالغ و استبيان الدور الواقي المحتمل لإضافة حمض الألفا ليبويك.

وقد أجريت هذه الدراسة على ستين من ذكور الفئران البيضاء البالغة تم تقسيمهم إلى أربع مجموعات : المجموعة الأولى (المجموعة الضابطة الطبيعية) تكونت من عشرة فئران و المجموعة الثانية (المجموعة الضابطة الخفية) تكونت من ثلاثين فأرا تم تقسيمهم إلى ثلاث مجموعات فرعية متساوية ٢ أ و ٢ ب و ٢ ج تم إعطاؤها محلول ملحي طبيعي و محلول الملح مع هيدروكسيد الصوديوم و حمض الألفا ليبويك على الترتيب و المجموعة الثالثة (عشرة فئران) تم اعطاؤها كادميوم فى الغشاء البيريتونى و المجموعة الرابعة (عشرة فئران) تم إعطاؤها كادميوم مع حمض الألفا ليبويك في الغشاء البيريتونى. وقد تمت التضحية بحيوانات جميع المجموعات بعد أسبوع و أربعة أسابيع من التجربة و تم فحص عينات من قشرة الكلى لكل المجموعات بواسطة المجهرين الضوئي و الألكترونى.

وقد أظهرت النتائج أن إعطاء الكادميوم قد تسبب في تغيرات كثيرة في قشرة الكلية وكانت شدة هذه التغيرات متناسبة مع فترة العلاج. فقد ظهرت الكبيبات الكلوية إما ذات احتقان في الشعيرات الدموية أو منكمشة أو متدهورة بشكل كبير و كان الغشاء القاعدي للشعيرات الدموية للكبيبات الكلوية إما سميكا ومتدهورا أو غير متصل وذلك في مناطق كثيرة. كما كان هناك تدهور في النتوءات الرئيسية و فقدان للنتوءات الثانوية للخلايا ذات الأقدام. و لوحظ أن هناك إما طمس أو اتساع لفراغ بومان أو احتواءه على نزيف أو بقايا أنسجة. وقد أظهرت القنوات الملتفة القريبة اتساعا في فجواتها التي كانت تحتوى على قوالب أو بقايا أنسجة. و ظهرت بعض خلايا القنوات الملتفة القريبة ذات اختلال في الحد الفرشى مع نقص أو عدم وجود خملات دقيقة وكانت خلايا أخرى تحتوى على سيتوبلازم متدهور أو ملئ بالفجوات مع وجود عدد قليل من الميتوكوندريا أو عدم وجود عضيات خلوية كما ظهرت أنوية بعض الخلايا صغيرة و داكنة. و كانت القنوات الملتفة البعيدة أقل تأثرا فقليل منها ظهر في فجواتها إما بقايا أنسجة أو قوالب أو خلايا متقشرة كما كان بسيتوبلازم بعض خلايا القنوات الملتفة البعيدة فجوات. ويمكن استنتاج أن إعطاء الكادميوم كان له تأثير تدهوري كبير على قشرة الكلية و كان هذا التأثير متناسبا مع فترة الإعطاء. كما وجد أن حمض الألفا ليبويك له دور واقي من السمية الناتجة عن الكادميوم.