ULTRASTRUCTURAL STUDY OF KIDNEY, LIVER AND TESTIS OF ALBINO RAT AFTER CADMIUM CHLORIDE ADMINISTRATION

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ABSTRACT

Adult male albino rats were given cadmium chloride (Cd cl_2) dissolved in H20 by intragastric intubation in a daily dose 1/5 of the LD_{50}/Kg, body weight. At the end of the 2nd and 5th month of cadmium (Cd) administration, Specimens from the kidney cortex, the liver and the testis were prepared for examination by transmission electron microscope. After two months of cadmium administration the changes in the kidney were confined to the cells of the proximal convoluted tubules which showed sparse basal infoldings of the cell membrane with rounded and randomly distributed mitochondria, increase of lysosomes and focal increase and dilation of the smooth endoplasmic reticulum (sER). After five months of cadmium administration, the proximal convoluted tubules showed lost basal infoldings of the cell membrane, rounded and degenerated mitochondria, vacuolated cytoplasm, secondary lysosomes and autophagic vacuoles; the distal convoluted tubules showed lost basal infoldings of the cell membrane and the glomeruli showed thickened glomerular basement membrane and distorted foot processes of the podocytes. After two months of cadmium administration, The hepatocytes showed dilated rough endoplasmic reticulum (rER) with loss of the attached ribosomes. After five months, there was more dilation of the (rER),matrical inclusions of the mitochondria, marked increase of the smooth endoplasmic reticulum (sER), and disintegration of the nuclei. The testis after two months of cadmium administration showed increase of lysosomes in the primary spermatocytes with degeneration of the spermatogonia and the primary

spermatocytes. After five months, there was marked disruption and desquamation of all layers of the seminiferous tubule epithelium. These results suggested strongly that cadmium has a deleterious effect on the ultrastructure of many organs and consequently on their function.

INTRODUCTION

In recent years, exposure of human beings to some metals as cadmium through polluted environment has increased with increasing industrial development (Koizumi and waalkes, 1989). Human civilization and concomitant increase in industrial activity has gradually redistributed many toxic metals from the earth to the environment and increased the possibilities of human exposure (Chowdhury and Chandra, 1987).

The usual sources of cadmium for the general population are mainly food, tobacco smoke (Hammond and Beliles,1980, and Klassen, 1985.) and drinking water as a result of leeching cadmium from galvanized copper or plastic pipes as well as from industrial or agricultural contamination (Commission of the Europian Communities, 1978).

Prolonged exposure to cadmium from the environment might constitute a hazard to health and result in long term toxic effects in animals and man (Hammond and Beliles, 1980). Several clinical observations have been reported on hepatic and renal lesions caused by prolonged exposure to cadmium and high cadmium contents have been demonstrated for the affected organs (Bracken et al., 1984). The testis also was one of the organs which showed apparent and marked response to the injurious effect of cadmium (Gunn et al., 1968). These facts have been confirmed by animal experiments (Stowe et al.,1972, steibert et al.,1984 Anderson et al., 1988 and jones et al., 1988). However, very few have investigated the ultrastructural changes of the organs which might occur when cadmium is ingested for a prolonged time. So the aim of the presesnt work is to detect early and late ultrastructural changes in rat kidney, liver and testis following oral administration of cadmium chloride for two and five months respectively.

MATERIALS AND METHODS

Thirty adult male albino rats of wistar king weighing about 150 gm each, were divided into two groups, Group A comprised (10) animals was

used as a control. Group B comprised (20) animals was given cadmium chloride ($CdC1_2$) dissolved in dist. H_2O by intragastric intubation in a daily dose 1/5 of the LD_{50}/Kg body weight as LD_{50} for $CdC1_2$ orally to rats =88 mg/kg, body weight / day (christensen et al., 1979).

All animals were kept in metal cages, given commercial laboratory chow and were observed for toxic signs and weighed once a week. At the end of the 2nd and 5th month of cadmium administration, four rats of the experimental group and two rats of the control group were killed by decapitation and small portions of the kidney cortex, the liver and the testis were cut lx 0.5mm, fixed immediately in a fixative containing 3 % glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4 at 4°C for four hours. Specimens were then washed in two changes of 0.1 M cacodylate buffer to be postfixed for two hours in 1% osmium tetroxide, dehydrated in a gradual series of ethanol, then infiltrated and embedded in a toluene-epon sequences that was later on polymerised at 60°C for one day (Luft, 1961). Thick sections (lum) were cut with an ultramicrotome (LKB-V), stained with toluidine blue and examined by the light microscope for orientation and evaluation the quality of fixation. Ultrathin sections were cut and picked on uncoated grids to be stained with uranyl acetate (5 min.) and lead citrate (2 min.) and viewed in Joel 1500 transmission electron microscope (Watson, 1958)

RESULTS

General Observations

No gross toxicological signs were noted in experimental rats rather than decreased growth weight which was more prominent in rats received cadmium for long duration (5 months).

Electron Microscopy:

The structure of the epithelial cells of proximal convoluted tubules of control rat kidney showed basal infoldings of the cell membrane, longitudinally oriented mitochondria perpendicular to the basement membrane and smooth endoplasmic reticulum (fig.l). In experimental group received cadmium for two months, the proximal convoluted tubule cells showed sparse basal infoldings of the cell membrane, rounded and randomly distributed mitochondria, focal proliferation and dilation of the smooth endoplasmic reticulum and increase of lysosomes (fig.2). However in rat received cadmium for long duration (5

months), the majority of the proximal convoluted tubular cells showed lost basal infoldings of the cell membrane, swelling and degeneration of the mitochondria, areas of cytoplasmic vacuolations, secondary lysosomes and autophagic vacuoles (fig. 3)

In the persent study, the distal convoluted tubules and the glomeruli were altered only in experimental group received cadmium for long duration (5 months). The distal convoluted tubule lining cells of control rat kidney showed prominent basal infoldings of the cell membrane and scarce free border microvilli (fig. 4), while in cadmium treated rats,some of the dital convoluted tubule lining cells showed lost basal infoldings of the cell membrane (fig. 5)

The glomeruli of control rat kidney showed the capillaries with fenestrated endothelium, the podocytes with their foot processes and the glomerular basement membrane interposed between capillary endothelium and podocyte foot processes (fig.6). However in experimental group received cadmium for five months, there was irregular thickening of the glomerular basement membrane and distorted foot processes of the podocytes (fig. 7).

The morphology observed in control rat hpatocyte was represented by abundant mitochondria and rough endoplasmic reticulum, and glycogen (fig. 8). After two months of cadmium administration, the hepatocytes showed dilation of the rough endoplasmic reticulum with decrease of the attached ribosomes (fig .9). However after five months, there was marked vesiculation of the rough endoplasmic reticulum with decrease of the attached ribosomes, matrical inclusions of the mitochondria (fig.10), marked proliferation of the smooth endoplasmic reticulum and disintegration of the nucleus (fig. 11).

Normal architecture of the control rat seminiferous tubule epithelium was shown in figs (12&13), represented by the spermatogonia, primary spermatocytes and spermatids in recesses of sertoli cells. Cadmium administration affected the majority of the seminiferous tubules of the rat testis. In animal group received cadmium for two months, there was increase of lysosomes in the primay spermatocytes with degenerative changes in the nuclei of the spermatogonia and primary spermatocytes

(fig.14). Cellular damage was more prominent in animal group received cadmium for five months where there was marked disruption and desquamation of all layers of the seminiferous tubular epithelium (fig. 15).

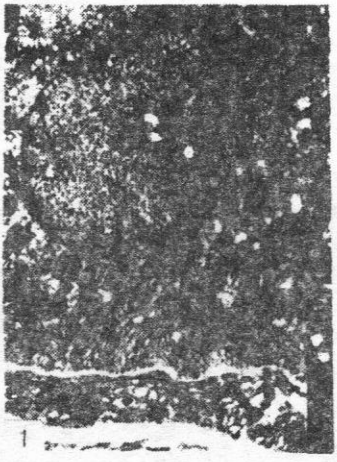

Fig. 1 : Electron micrograph of a proximal convoluted tubular cell of control rat kidney showing basal infoldings of the cell membrane (C.M), and longitudinally oriented mitochondria (M) perpendicular to the basement membrane. Note the nucleus (N) and the smooth endoplasmic reticulum (arrows). (X 7.500)

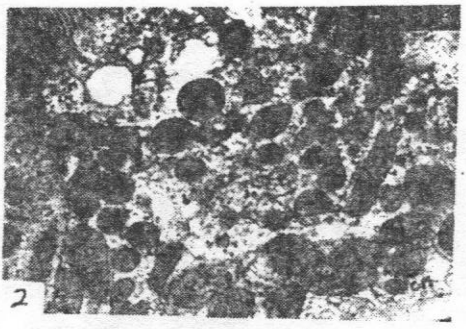

Fig. 2 : Electron micrograph of a proximal convoluted tubular cell of cadmium treated rat (2 months) showing sparse basal infoldings of the cell membrane (C.M), rounded and randomly distributed mitochondria (M), focal proliferation and dilation of the smooth endoplasmic reticulum (arrows) and increase of lysosomes (LY). Note the brush border (b.b).
(X7.500)

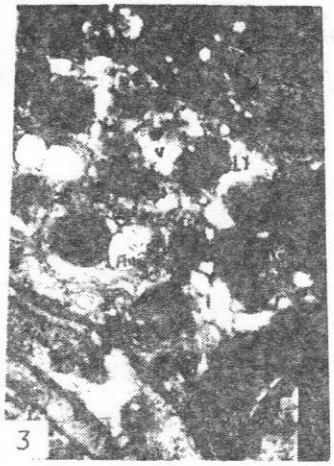

Fig 3 : Electron micrograph of a proximal convoluted tubular cell membrane, swollen and degenerated mitochondria (M), areas of cytoplasmic vacuolations (V) secondary lysosomes (ly) and autophagic vacuoles (Au). (X 13. 000)

Fig. 4 : Electron micrograph of a distal convoluted tubular cell of control rat showing the nucleus (N), basal infoldings of the cell membrane (C.M), mitochondria (M) and scarce free border microvilli (m.v) (X 7.500)

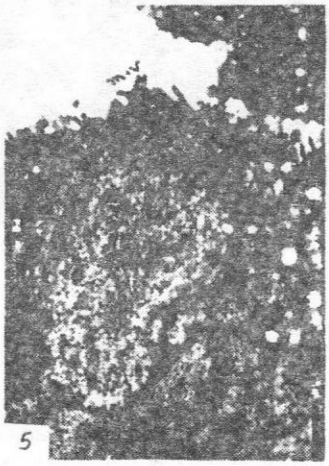

Fig. 5 : Electron micrograph of a distal convoluted tubular cell of cadmium treated rat (5 months) showing lost basal infoldings of the cell membrane. Note the nucleus (N) and free border microvilli (m.v). (X 7. 500)

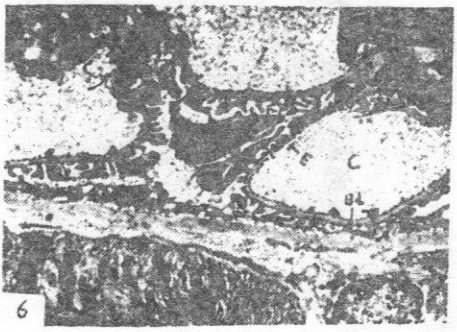

Fig. 6 : Electron micrograph of apart of a renal corpuscle of control rat showing capillaries (c) with fenestrated endothelium (E→), foot processes (F.P) of the podocytes (P), basal lamina (B.L→) interposed between the capillary endothelium and the foot processes of the podocytes (X 5. 000)

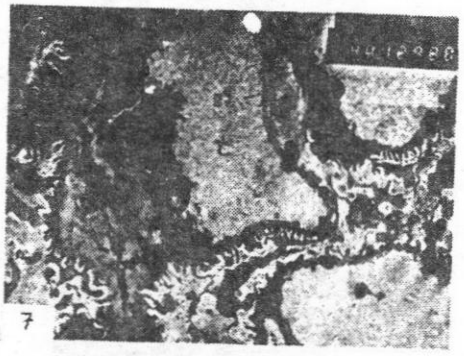

Fig. 7 : Electron micrograph of a part of a renal corpuscle of cadmium treated rat (5 months) showing capillaries (c), irregular thickening of the basal lamina (B.L→) and distorted foot processes (F.P) of the podocytes. (X 4.000)

Fig. 8 : Electron micrograph of a hepatocyte of control rat liver showing the nucleus (N), mitochondria (M), rough endoplasmic reticulum (rER) and glycogen (G). (X 10.000)

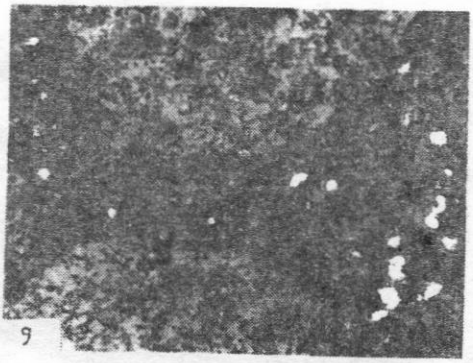

Fig 9 : Electron micrograph of a hepatocyte of cadmium treated rat (2 months) showing dilation of the rough endoplasmic reticulum (rER) with decrease of the attached ribosomes. Note the nucleus (N), lysosomes (LY), lipid (L) and glycogen (G) (X 10.000)

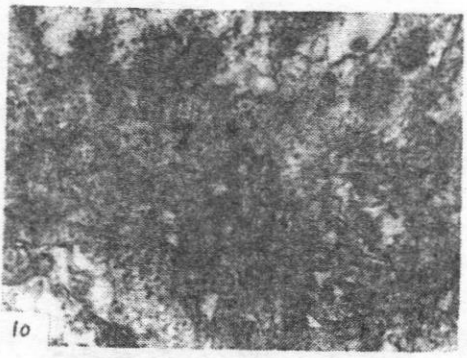

Fig 10 : Electron micrograph of a hepatocyte of cadmium treated rat (5 months) showing marked vesiculation of the rough endoplasmic reticulum (arrows) with decrease of the attached ribosomes and matrical inclusions of the mitochondria (M). (X 10. 000)

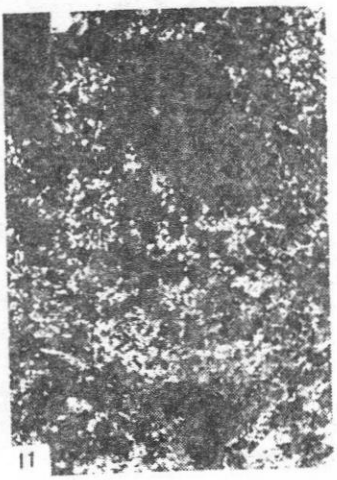

Fig. 11 : Electron micrograph of a hepatocyte of cadmium treated rat (5 months) showing marked proliferation of the smooth endoplasmic reticulum (sER). The nucleus (N) shows signs of disintegration (X 4.000)

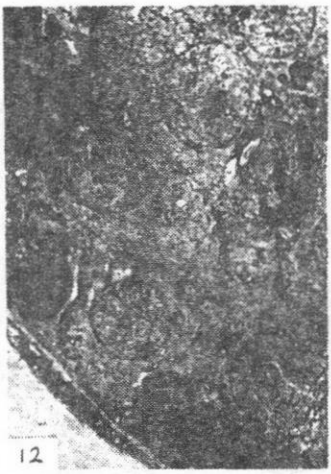

Fig. 12 : Electron micrograph of a part of seminiferous tubule epithelium of control rat testis showing spermatogonia (ST), primary spermatocytes (PS) and spermatids (SP) in recesses of sertoli cell. (X 2.500)

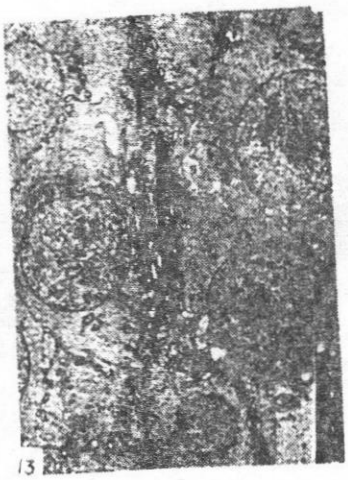

Fig. 13 : Electron micrograph of a part of seminiferous tubule epithelium of control rat testis showing, primary spermatocytes (PS) and spermatids (SP) in recesses of sertoli cell (S.C) (X 2.500)

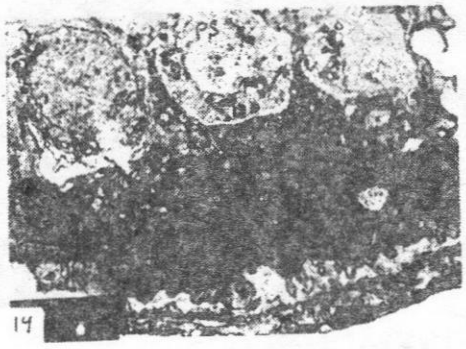

Fig. 14 : Electron micrograph of a part of seminiferous tubule epithelium of cadmium treated rat (2 months) showing increased lysosomes (LY) in the cytoplasm of the primary spermatocytes (PS). Note the degenerated spermatogonia (ST) and primary sepermatocytes . (X 3.000)

Fig. 15 : Electron micrograph of seminiferous tubule epithelium of cadmium treated rat (5 months) showing disruption and desquamation of all layers of the seminiferous tubule epithelium. (X 2.500)

DISCUSSION

The microscopic changes in chronic cadmium poisoning described by many authors have revealed the degeneration of renal tubules in man (Greeth et al., 1963 ; Kazantzis et al., 1963 ; Axlesson &piscator, 1 966 ; Hammond & Beliles, 1980 and Bracken et al., 1984), and animals (Stowe et al., 1972 ; Steibert et al., 1984 and Anderson et al., 1988)

In the present study, ultrastructural changes in renal tubular epithelium are in proportion to the duration of cadmium administration. One of the early changes we have seen in the proximal convoluted tubular cells of the rat kidney following cadmium administration was sparse of basal infoldings of the cell membrane, swelling and random distribution of the mitochondria. After longe duration of cadmium administration (5 months) the majority of the proximal convoluted tubular cells showed swelling and degeneration of the mitochondria and complete loss of basal infoldings of the cell membrane. Also some of the distal convoluted tubule lining cells showed lost basal infoldings ofthecell membrane. These findings coincide with those seen and reported by several authors (Nishizumi, 1972 ; Gatta et al., 1989 and Rehni and waalkes, 1990) . The basolateral membranes of both proximal and distal convoluted tubule cells are the sites of active processes involving Na / k^+ - ATPase activity responsible for Na reab-

sorption and K secretion and in turn control the total salt and H_2O in the body and since the prime source of energy is believed to be mitochondria, so these alterations in the cell membrane and the mitochondria are suggestive of impairment of cellular function .

Another outstanding abnormality seen in the present work is an increase in the lysosomes and autophagic vacuoles in rat kidney proximal tubule cells which became more prominent with time of cadmium administration. Functions of lysosomes are known to be concerned with the segregation and whenever possible the degradation of substance taken up by the cells from the environment as well as have the cytoplasmic constituents. At any role it is fully considered that the observed increase in this organelle was concerned with the segregation and excretion of cadmium given (Nishizumi, 1972, Gatta et al., 1989, and Matsuura et al., 1991).

In the present study, proliferation and dilation of the smooth endoplasmic reticulum (sER) was noted in rat kidney proximal convoluted tubular cells in the course of cadmium administration. This finding is similar to that described by Hazen et al. (1989) and Condron et al. (1994) in human and rat respectively. The role that this structure might play in cellular and renal function is probably related to the process of detoxification because of the presence and increase of this structure in liver and kidney when animals were intoxicated with various organic compounds (Roa, et al., 1989 and Chishti and Ratkiewicz, 1993).

As regard the renal corpuscle of the rat kidney, the glomeruli were altered only after long duration of cadmium administration (5months). There was thickening in the glomerular basement membrane and alteration of the podocytes foot processes. These results agreed with those reported by Roa et al. (1989); Hazen et al. (1989) and Chishti and Ratkiewicz. (1993). These morphological changes in the renal corpuscle revealed that cadmium has a deleterious effect on the process of renal dialysis of the blood plasma .

Based on ultrastructural changes in rat hepatocytes following cd-administration, the present study showed dilation of rough endoplasmic reticulum with a concomitant loss of membrane - bound ribosomes. Such

findings revealed the adverse action of cadmium on the process of protein synthesis (Hidalgo et al., 1976; Stoll et al., 1976 Sina and Chin, 1978 ; Gamulin et al., 1982, and Puvion & Lange, 1986) .

Another outstanding abnormalities in rat hepatocyte following cd administration were degenerative changes in the nucleus and marked proliferatoin of the smooth endoplasmic reticulum particularly after long duration. Cadmium-induced alterations in the appearance of nuclei indicate that protein synthesis may be adversely affected by action during chronic exposure (Duodely et al., 1984). The proliferation of the smooth endoplasmic reticulum in rat hepatocyte is most probably related to the process of detoxification (Chishti and Ratkiewicz, 1993)

Protein synthesis is recognised as the principal activity of the rough endoplasmic reticulum, while the smooth endoplasmic reticulum is associated with carbohydrate and lipid metabalism and with electron transport. The metabolic effect of cadmium would therefore be expected to be multiple because both types of endoplasmic reticulum of the rat hepatocyte are disturbed by cadmium (Stowe et al., 1977; Morselt et al., 1987 and Buciol et al., 1995) .

Mitochondrial inclusions observed in rat hepatocytes after five months of cadmium administratoin are similar to those reported by Hoffman et al. (1975) and Dudely et al. (1984) following cadmium intake and in response to a variety of hepatotoxins (Muscatello & pasquali, 1972 and Miyai, 1979). These inclusions also may be due to cadmium deposition on or in matrix granules in a manner similar to barium and strontium (Peachey et al., 1963) or unlikely to be accumulations of the metal itself but rather denatured matrical proteins (Miyai, 1979). Because cd- accumulation in mitochondria (Saris and Jarviscala, 1977) may inhibit the process of oxidative phosphorylatoin (Diamond and Kench, 1974), energy requirements of the cell may be impaired.

As regard the rat testis, ultrastructural alterations were observed after two months of cadmium administration. There was increase of lysosomes in the primary spermatocytes. There was also degenerative changes in the spermatogonia and the primary spermatocytes. In animal group re-

ceived cadmium for five months, cellular damage was more severe and present throughout the germinal epithelium in the form of complete disruption and desquamation. These results agreed with those reported by Stowe et al. (1972) and Jones et al. (1988). These findings also revealed that cadmium chloride caused a toxic injury to the seminiferous tubules of the rat testis and that the degree of damage was in relation to the duration of exposure. However, Gunn et al. (1988) reported that complete necrosis of the rat testis occurred within one week by s.c injection of cadmium chloride. Such rapid toxic effect of the later author experiment on the rat testis is most probably related to the difference in route of cadmium chloride administration from that used in the present work .

Conclusion

In the present study, cadmium chloride has a deleterious effect on several organs. Morphological changes appeared after five months of cadmium administration in rat kidney, liver and testis represent a progression of damage initiated after two months of cadmium administration. There is a need for an assessment of the cadmium stress on the general population and population groups at high risk such as those occupationally exposed to cadmium.

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دراسة دقيقة لكلية وكبد وخصية الفأر الأبيض بعد إعطاء كلوريد الكادميوم

د/ نـوال عـــوض

- أعطيت ذكور الفئران البالغة مادة كلوريد الكادميوم مذابة فى الماء وبواسطة أنبوبة معدية وبجرعة يومية ١/٥ الجرعة القاتلة لنصف عدد الحيوانات وذلك لكل كيلو جرام من وزن الجسم. وعند نهاية الشهر الثانى والشهر الخامس تم أخذ عينات من قشرة الكلية ومن الكبد ومن الخصية وتم تحضيرها لفحصها بالميكروسكوب الإلكترونى النافذ .

بعد شهرين من إعطاء كلوريد الكادميوم كان التأثير بالكلية مرتبط بخلايا الأنيبيبات الملتوية القريبة حيث أظهرت إتساع فى الإنثناءات القاعدية للغشاء الخلوى مع إستدارة وإنتشار عشوائى للميتوكوندريا، كما وجد زيادة فى الأجسام المحللة وزيادة وإتساع فى الشبكة الأندوبلازمية الملساء أما بعد خمسة شهور من إعطاء مادة الكادميوم أظهرت الأنيبيبات الملتوية القريبة فقد للإنثناءات القاعدية للغشاء الخلوى مع إستدارة وتنكس للميتوكوندريا، تجويفات فى السائل الخلوى، أجسام محللة ثانوية وفجوات بلعومية .

- بعض الأنيبيبات الملتوية البعيدة أوضحت إختفاء للإنثناءات القاعدية للغشاء الخلوى أما الكبيلت قد أوضحت زيادة فى سمك الغشاء القاعدى وعدم إنتظام فى زوائد أقدام الخلايا ذات الزوائد.

- بعد شهرين من إعطاء الكادميوم أظهرت الخلايا الكبدية إتساع فى الشبكة الأندوبلازمية الخشنة مع فقد للريبوسومات الملاصقة أما بعد خمسة أشهر فقد كان هناك زيادة مطردة فى إتساع الشبكة الأندوبلازمية الخشنة وظهور تكوينات بالسائل الخلوى للميتوكوندريا وزيادة مطردة فى الشبكة الاندوبلازمية الملساء وتنكس بالأنوية .

- أوضحت الخصية بعد شهرين من إعطاء الكادميوم زيادة فى عدد الأجسام المحللة فى الخلايا النفطية الأولية وأيضاً تنكس فى الخلايا النفطية المولدة والخلايا النفطية الأولية، أما بعد خمسة أشهر قد كان هناك تهتك فى كل الطبقات المبطنة للأنيبيبات الناقلة للمنى.

- توضح هذه النتائج أن للكادميوم تأثير ضار على التركيب الدقيق للعديد من الأعضاء وبالتالى على وظائفها .