The Morphologic Effects of Dieldrin and Methyl Mercuric Chloride on Pars Recta Segments of Rat Kidney Proximal Tubules

Bruce A. Fowler, PhD

This investigation was undertaken to evaluate the morphologic effects in rat kidney resulting from chronic exposure to low doses of the pesticide dieldrin, methyl mercuric chloride (CH_3HgCl) and the combination of dieldrin plus CH_3HgCl. Histologic and ultrastructural changes were confined to the proximal tubules. Alterations in these tubules were consistent and reproducible for each regimen and did not become more severe with duration of exposure. The straight segment of the proximal tubule (pars recta) was more severely affected by dieldrin and CH_3HgCl than the convoluted portion. Female rats were more markedly affected than males. Pars recta tubule cells of male and female rats exposed to dieldrin showed an increase of smooth endoplasmic reticulum (SER). Male rats displayed a greater increase in SER than females. Pars recta tubule cells of animals given CH_3HgCl also exhibited increased amounts of SER, degenerating mitochondria and cell death. Pars recta tubules of females were dilated and contained within the lumens many spherical, hematoxylin-positive staining, cytoplasmic masses, which were visible by light microscopy. These masses were characterized ultrastructurally by the presence of an SER aggregate in an area of material similar to cell matrix. In addition, cells of the pars recta of female animals contained electron-dense membranous cytosomes not present in control animals. Pars recta cells of males showed an increase in SER, but the dense membranous cytosomes observed in the pars recta cells of female rats were not seen. Rats exposed to dieldrin plus CH_3CgCl showed less morphologic alteration of the pars recta tubules than animals given methyl mercuric chloride; however, increased amounts of SER and more degeneration in tubule cells were observed in these animals when compared to control animals. The findings are discussed in relation to the conversion of CH_3HgCl to inorganic mercury *in vivo* and the known toxicity of inorganic mercury to the pars recta. Decreased tubular alteration in males and dieldrin-treated animals may be explained by sexual differences in renal enzyme levels or activities and the induction of microsomal enzyme systems by dieldrin (Am J Pathol 69:163–178, 1972).

CHLORINATED HYDROCARBON PESTICIDES and organomercury compounds are examples of environmental contaminants that can be concentrated in biologic systems and which are potentially toxic to man. Dieldrin is an extensively used chlorinated hydrocarbon pesti-

From the Department of Pathology, University of Oregon Medical School, Portland, Oregon and the Environmental Health Sciences Center, Oregan State University, Corvallis, Oregon.

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Address reprint requests to Dr. Bruce A. Fowler, National Institute of Environmental Health Sciences, Pathologic Physiology Branch, Box 12233, Research Triangle Park, NC 27709.

cide. Methyl mercury is the most common organomercurial found in the environment.

Most investigations concerning the effects of chlorinated hydrocarbons on mammalian systems have centered on the liver. A variety of such agents are known to cause a proliferation of smooth endoplasmic reticulum (SER) in hepatic cells.[1-5] Hutterer *et al* [2,3] observed an induction by dieldrin of aniline hydroxylase and cytochrome P450. In addition, these authors noted a decrease in oxidative phosphorylation from continued exposure to this agent.

Although the kidney has not been of primary concern in most investigations, several authors have reported high levels of chlorinated hydrocarbon pesticides in this organ.[6,7] Boyd *et al* [8-11] described congestion and fatty degeneration of renal tubules in rats fed with these pesticides. Treon *et al* [12] reported necrosis of the convoluted tubules in a variety of laboratory animals poisoned with endrin, another chlorinated hydrocarbon pesticide.

Studies on the toxicity of organomercury compounds in humans have been concerned with damage to the central nervous system. Individuals poisoned by the ingestion of fish containing high levels of organic mercury showed severe neurologic disorders resulting from destruction of the granule cell layer in the cerebellum.[13-15] Several other clinical investigations [16,17] have described a significant increase in proteinuria in persons occupationally exposed to organomercury compounds.

Long-term experimental laboratory studies [18-20] have shown that both organic and inorganic mercury derived from exogenous organomercury compounds is concentrated in the kidneys. Other investigators [21-23] have reported that this inorganic mercury is an *in vivo* metabolic product. Inorganic mercury is known to be highly toxic to the proximal tubules.[24,25]

The present study was undertaken to evaluate the morphologic effects of long-term exposure to dieldrin and methyl mercuric chloride on the kidney, since this organ accumulates these two environmental toxicants and their effects on renal ultrastructure have not been reported. Because living organisms are simultaneously exposed to numerous environmental toxicants, and since one toxicant may influence the toxicity of another, the combined effects of dieldrin and methyl mercuric chloride were also investigated.

Materials and Methods

A total of 84 inbred Oregon State University-Wistar rats (39 males and 45 females) were housed in sterile chambers [26] throughout the experiment. Dieldrin,

methyl mercuric chloride (CH_3HgCl) and the combination of dieldrin plus CH_3HgCl were added to the daily diet. All experimental and control animals received a stock laboratory ration described by Harr *et al.*[27] The average food intake for both control and experimental male rats was 19 g/rat/day. Both control and experimental female rats consumed an average of 15 g/food/rat/day.[28] The groups of animals were studied for the time periods indicated in Table 1.

The animals were anesthetized with ether and their right kidneys excised. For light microscopy, samples from the kidneys of all animals were fixed overnight at room temperature in 10% formalin. These were embedded in paraffin and sectioned at 5 μ. Sections of tissue from each animal were stained with hematoxylin and eosin. In addition, sections from both mercury-treated female rats and control female rats killed at 84 days were stained with the periodic acid-Schiff procedure.

For electron microscopy, tissue blocks approximately 1 cu mm in volume were cut from samples of both inner and outer cortex of all kidneys. These blocks were immersed for 3 hours in a fixative containing glutaraldehyde, 2.5%, formaldehyde, 2.0%, $CaCl_2$, 250 mg/liter and 0.085 M cacodylate buffer (pH 7.4).

In addition, in a duplicate series of experiments, the right kidneys of 4 mercury-treated female rats and 4 control female rats that had been treated for 84 days with methyl mercuric chloride were perfused via cardiac puncture with a Ringer's-procaine solution [29] followed by the above fixative containing sucrose. The kidneys were removed and small pieces were subsequently fixed by immersion for 3 hours at room temperature.

All tissues were postfixed in a solution of 1.5% osmium tetroxide in 0.1 M Sörensen's phosphate buffer (pH 7.4) for 2 hours at room temperature,[30] then dehydrated in a 50 to 100% graded series of alcohols, passed into propylene oxide and embedded in Araldite according to the method of Luft.[31] Thin sections were cut on an LKB ultratome and mounted on 300 mesh uncoated copper grids. The sections were double stained first with lead citrate [32] and then with 3% uranyl acetate and examined with either an RCA EMU 3-G or Philips EM 200 electron microscope.

Results

The histiologic and ultrastructural morphology of the normal rat kidney has been extensively described.[33,34] In this study the segmentation of the proximal tubule was determined using the criteria estab-

Table 1—Dose Level, Numbers, Duration of Exposure and Age at Death of Experimental and Control Rats

Regimen (level in diet)	No. of Rats		Days of diet	Age at death (days)
	Male	Female		
Dieldrin (5.0 ppm)	8	8	84	112
	7	6	142	170
CH_3HgCl* (2.0 ppm)	3	6	84	112
	3	4	142	170
Dieldrin (5.0 ppm) plus	2	2	84	112
CH_3HgCl (2.0 ppm)	3	4	142	170
Control	7	11	84	112
	6	4	142	170

* 2 ppm Hg as CH_3HgCl

lished by Maunsbach.[34] The histology and ultrastructure of kidneys from control rats in this study did not vary from these descriptions. In experimental animals, morphologic alterations were most marked in the pars recta segment of the proximal tubule. These changes are summarized in Table 2.

Animals Exposed to 5.0 ppm Dieldrin in the Diet

Light microscopic histology of tissue from animals of both sexes was indistinguishable from controls.

The ultrastructural changes produced by dieldrin in the pars recta of the proximal tubule were similar in both sexes. Increased amounts of SER characterized pars recta cells of dieldrin treated animals. Pars recta tubule cells from male rats showed a greater relative increase in SER aggregates than was observed in females (Figures 1 and 2).

Animals Exposed to 2.0 ppm CH_3HgCl in the Diet

Morphologic alterations of pars recta tubule cells from female rats were different from those observed in males.

Female rats

Histologic sections of kidneys from female animals displayed dilatation of the pars recta segments as a result of flattening of the pars recta epithelium and the presence of many large, hematoxylin-positive, PAS-negative spherical cytoplasmic masses in tubule lumens (Figure 3). The masses did not arise from the collapse of tubules during fixation, since they were observed in the patent lumens of pars recta segments from perfusion-fixed tubules. These cytoplasmic mas-

Table 2—The Ultrastructural Effects of Dieldrin and CH_3HgCl on the Pars Recta in Comparison to Control Animals

Changes in pars recta tubule cells	Male	Female
Dieldrin		
Dense membranous cytosomes	—	—
Increased SER	++	+
SER-containing cytoplasmic masses	—	—
CH_3HgCl		
Dense membranous cytosomes	—	+++
Increased SER	+	+++
SER-containing cytoplasmic masses	—	+++
Dieldrin plus CH_3HgCl		
Dense membranous cytosomes	—	+
Increased SER	+	±
SER-containing cytoplasmic masses	—	±

+ indicates increase; — indicates no change

ses were characterized ultrastructurally by the presence of an SER bundle and an occasional microbody (Figure 4). Rough endoplasmic reticulum profiles were sometimes observed in these masses, usually around the periphery of the SER aggregated. Other organelles were rarely observed in these masses.

Pars recta cells of treated females contained large aggregates of SER and dense membranous cytosomes (Figures 5 and 6).

Male Rats

Paraffin-embedded sections of kidneys from males given 2.0 ppm CH_3HgCl in the diet could not be distinguished from controls. In contrast to females, dilatation of the pars recta segments and the presence of cytoplasmic masses were not observed. By electron microscopy, these pars recta cells displayed more SER per thin section of tissue than controls, but less than the females. No dense membranous cytosomes were observed (Figure 7).

Animals Exposed to 5.0 ppm Dieldrin plus 2.0 ppm CH_3HgCl in the Diet

Morphologic alterations observed in kidneys of animals exposed to dieldrin plus CH_3HgCl were less extensive than those in animals given CH_3HgCl alone.

Female rats

Light microscopy of kidney sections from female rats showed moderate dilatation of the pars recta tubules, but fewer cytoplasmic masses within tubule lumens than in animals exposed only to CH_3HgCl (Figure 8; compare with Figure 3).

Cells of the pars recta, by electron microscopy, showed little if any increase in SER and fewer dense membranous cytosomes than females given CH_3HgCl alone. Their ultrastructure was similar in appearance to those of males on this regimen.

Male rats

Histologic sections of kidney from male rats fed dieldrin plus mercury in the diet showed normal morphology. Ultrastructural morphology of cells of the pars recta showed slightly more SER in comparison to controls but less than males given dieldrin or CH_3HgCl alone (Figure 9).

Discussion

Low doses of dieldrin and CH_3HgCl produced different effects in kidneys of rats exposed to either substance for long periods of time.

The severity of ultrastructural changes in cells of the pars recta was more dependent upon the sex of animals than on the duration of exposure. Administration of both compounds together did not produce an additive response but appeared to result in less cellular change than when either compound was given alone.

Increased amounts of SER were noted in animals given dieldrin. Several investigators [2,3] have associated proliferation of SER with induction of microsomal detoxification enzyme systems. Furthermore, biochemical studies [35–38] have shown dieldrin to be a potent inducer of microsomal detoxification enzymes. Therefore, the proliferation of SER in pars recta tubule cells seen in this experiment probably represents a cellular attempt to detoxify dieldrin.

The more marked effect of dieldrin on the pars recta of female rats may be explained by sexual differences in detoxification enzyme activities. Numerous investigators [36,38,39] have reported that the activity level of liver microsomal enzymes is higher in the adult male rat than in the adult female. Sexual differences have also been reported [39–42] for a number of renal enzymes. Koerner and Hellman [39] found that the activity of the microsomal enzyme 11β-hydroxysteroid dehydrogenase in kidneys of male Wistar rats was twice that of kidneys from female Wistar rats. In the present study, pars recta cells from dieldrin-treated male rats showed a greater relative increase in SER than those of dieldrin-treated females. This may suggest a greater intrinsic responsiveness by males to dieldrin, via an inducible enzyme system.

The kidneys of CH_3HgCl-treated female rats were more severely affected than those of male rats. Organomercury compounds are known to be converted to inorganic mercury in the kidney [21–23,43] where they are concentrated to high levels.[18–20,44–47] Fitzhugh *et al* [48] found the kidneys of female rats to be more sensitive to low doses of phenyl mercury and inorganic mercury. Inorganic mercury (*eg*, $HgCl_2$) is known to damage selectively the pars recta of the proximal tubule.[24,25] Swollen mitochondria and proliferation of SER and cellular necrosis characterize acute inorganic mercury poisoning.[24,25]

Mercury derived from methyl mercury has been reported to concentrate in the microsomal fraction of rat kidney and liver.[49,50] The SER is a logical site for the conversion of methyl mercury to inorganic mercury because detoxification enzyme activities including oxidative demethylation [51–53] are present in microsomes. It is not known whether the conversion of methyl mercury to inorganic mercury is an enzymatic or nonenzymatic process, but it seems likely that cleavage of the carbon-mercury bond by either mechanism could release inorganic mercury

which might then react with microsomal enzymes as a noncompetitive inhibitor. The mechanism by which the mercurials cause enzyme inhibition is through combination of mercury with sulfhydryl (SH) groups present at the active sites of many enzymes, including those found in microsomes.[54,55] The inhibition of microsomal enzymes in pars recta cells could render SER aggregates nonfunctional. This could then account for their selective extrusion in cytoplasmic masses [56] through a process of potocytosis.[33,57,58]

It has been previously suggested [56] that the loss of these masses from pars recta cells into the urine could produce a proteinuria similar to that observed in persons occupationally exposed to organomercurials.[16,17]

The more marked effect of CH_3HgCl on the pars recta cells of female rats, in comparison to males, is again probably due to sex differences in the levels or activities of renal enzymes.[39–42] The enzymes, alkaline phosphatase, acid phosphatase, β-hydroxybutyrate dehydrogenase, glucose-6-phosphatase and nonspecific esterase, all show sex differences exclusively in the pars recta segments.[40–42] Microsomal enzymes containing SH groups which interact with mercury may be less able to metabolize mercury or excrete it conjugated with cysteine,[59] allowing it to inhibit mitochondrial and other enzyme systems.

The dense membranous cytosomes found in pars recta cells of mercury-treated females may represent a means for sequestering mercury. It has been demonstrated by others [60–62] that cytosomes (lysosomes) from renal tubule cells concentrate cations and drugs *in vivo*. Mercury derived from methyl mercury also accumulates in the lysosomal fractions of rat kidney and liver.[49,50] Cytosomes in other female rats given the same level of methyl mercury in the diet have been shown to contain acid phosphatase activity,[63] thus identifying them as lysosomes. Unstained thin sections of tissue from these animals, fixed in glutaraldehyde but not OsO_4, contained dense particulate inclusion bodies in pars recta cells.[64] These observations suggest that mercury concentrated in kidney lysosomes of these animals.

The membranous appearance of the cytosomes observed in this investigation suggest a lipidic character. A number of investigators [60–62] have isolated an acidic lipoprotein component of lysosomes, which is thought to be responsible for the binding of cationic compounds. Large membranous cytosomes have been observed [65] in proximal convoluted tubule cells of mice given the cationic herbicide paraquat, and it was suggested that proliferation of acidic lipoprotein in response to paraquat resulted in their membranous appearance. An

analogous situation could exist in the pars recta cells of mercury-treated female rats if these cells were unable to detoxify completely or excrete the mercury present. The cationic mercury might stimulate production of an acidic lipoprotein component of lysosomes, thus giving rise to their membranous appearance.

Animals exposed to both dieldrin and CH_3HgCl exhibited similar but less extensive cytologic changes than animals given either compound alone. This protective effect was more easily appreciated in female rat kidneys. One possible explanation is that dieldrin may stimulate microsomal enzyme systems and increase the metabolic activity of SER aggregates also metabolizing CH_3HgCl. Chlorinated hydrocarbon pesticides are known to stimulate the microsomal metabolism and decrease tissue storage of numerous compounds.[36] Street *et al*[66,67] have reported that the administration of DDT to animals receiving dieldrin reduced tissue storage and enhanced excretion of dieldrin. A synergistic effect of one toxicant on the metabolism of another is indicated. Dieldrin induction of microsomal enzymes in the female rat kidney could enhance the metabolism of CH_3HgCl or increase the available number of SH groups so that the inhibitory effect of mercury would be reduced.

This study shows that chronic long-term exposure to low doses of these environmental toxicants produced definite morphologic alterations in kidney tubules which are detectable by electron microscopy. The extent of these changes in the pars recta cells is largely dependent on the sex of the animal and may reflect sex-based enzymic differences. The lack of increased pathologic changes in animals given dieldrin and/or CH_3HgCl for even longer periods suggests that the detoxification enzyme systems of the proximal tubule cells reach a *steady state* condition in the presence of low-level doses of these chemicals.

Biochemical studies concerning the effects of dieldrin, CH_3HgCl and dieldrin plus CH_3HgCl on microsomal, mixed-function oxidases in renal cortical parenchyma are presently underway. These investigations should elucidate the manner in which CH_3HgCl interacts with microsomal enzymes and the extent to which dieldrin influences this interaction.

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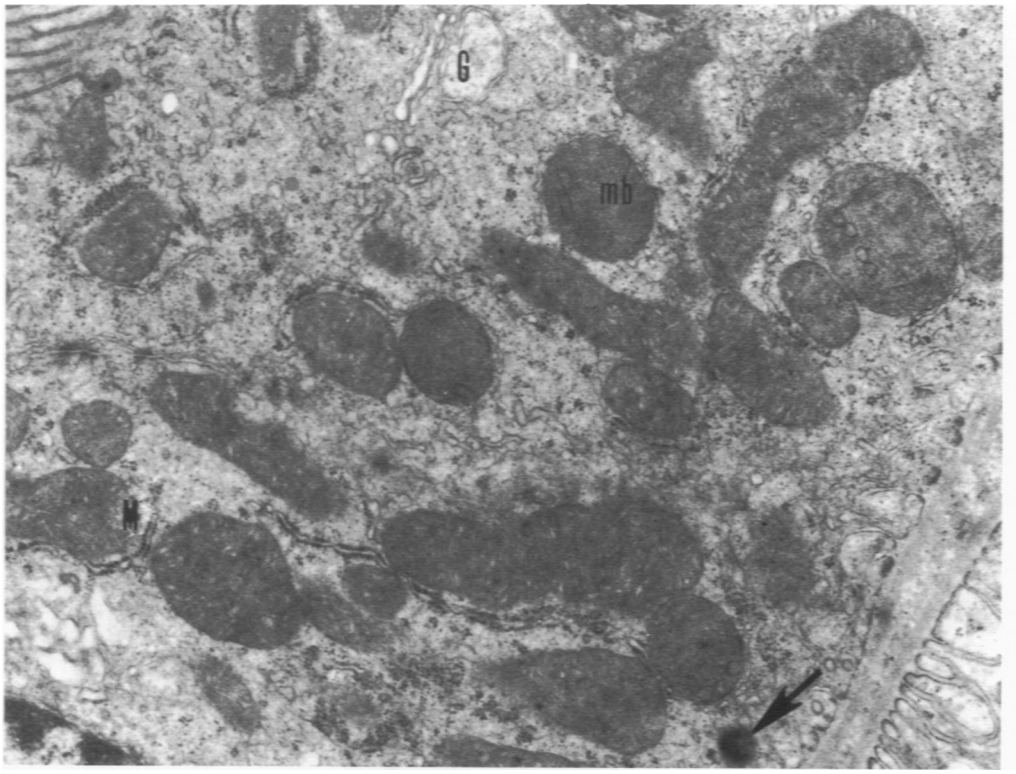
Legends for Figures

Fig 1—Pars recta cell from a normal male (control) rat showing the low profile of this cell-type, cytosome (*arrow*), Golgi (G), mitochondria (*M*), microbodies (*mb*). Similar cells in control females contained slightly more SER (× 15,960).

Fig 2—Pars recta cell from a male rat fed dieldrin for 142 days showing numerous SER aggregates (*arrows*). Compare presence of SER with Figure 1 (× 15, 960).



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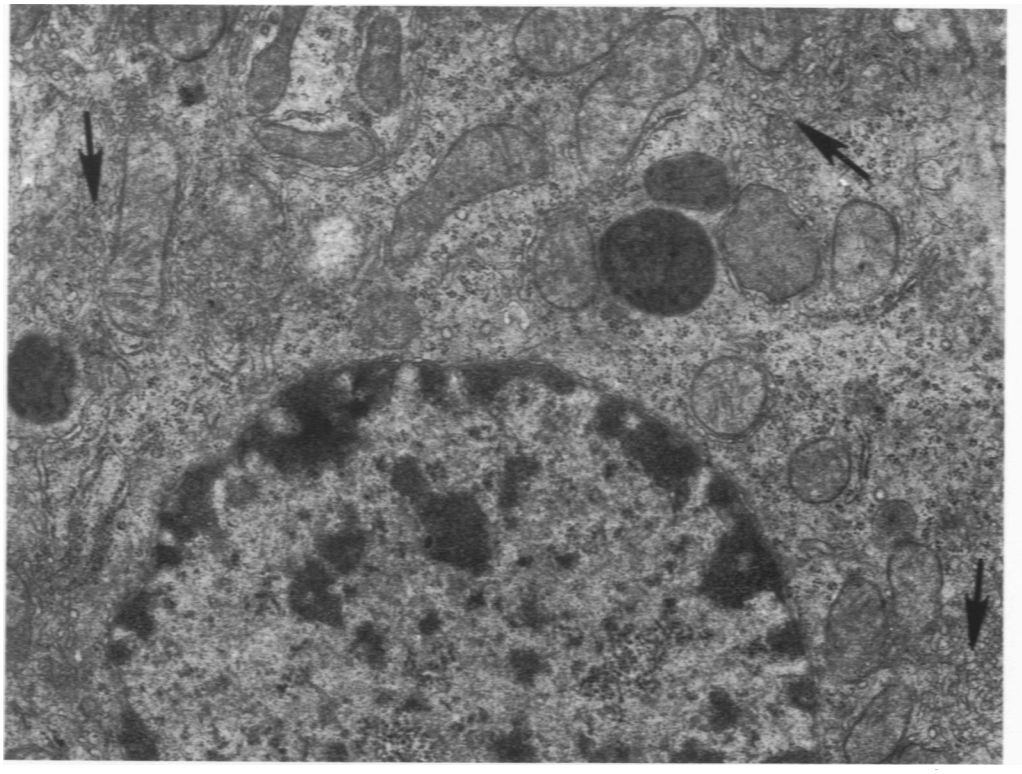

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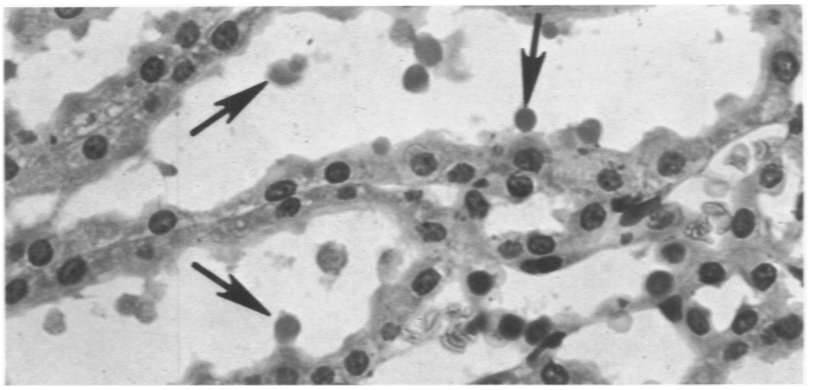


Fig 3—Light micrograph of pars recta segment from a female rat given CH_3HgCl for 84 days. Note that flattened epithelial cells line a dilated tubule lumen. Spherical cytoplasmic masses (*arrows*) are present in tubule lumen (× 610).

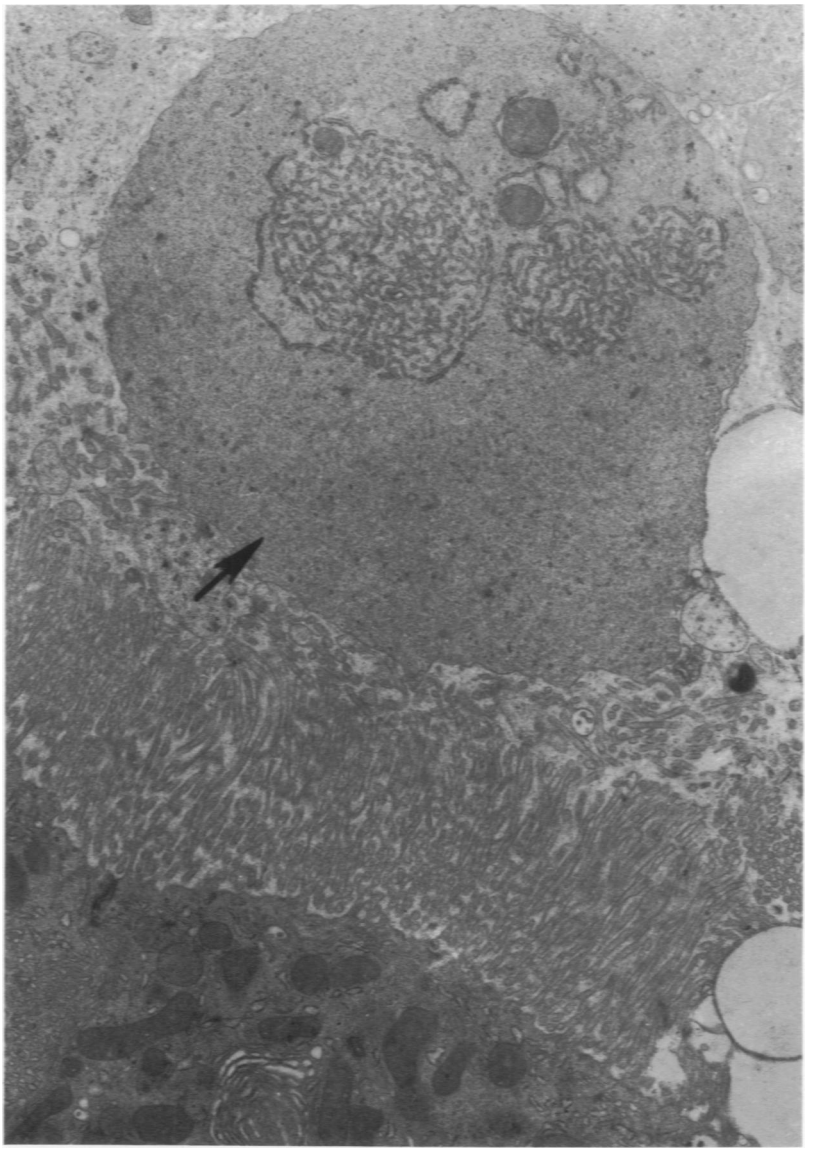
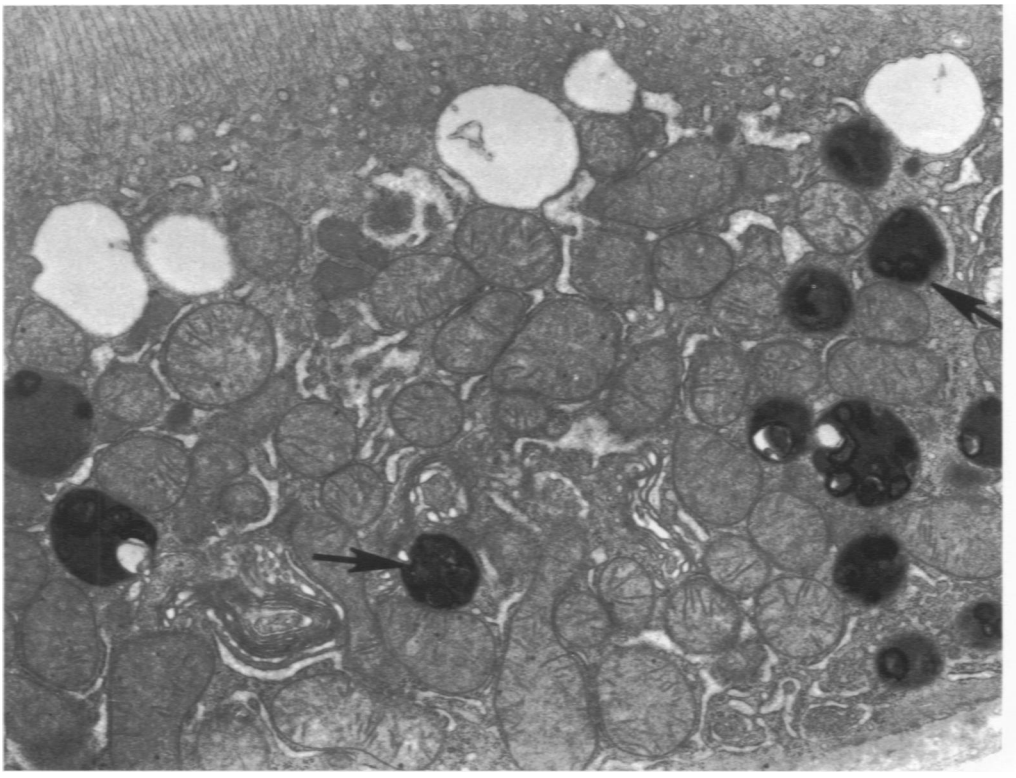


Fig 4—Tissue of the pars recta from the kidney of a female rat receiving CH_3HgCl for 84 days is shown. A spherical cytoplasmic mass (*arrow*) containing SER and a microbody is present in the patent tubule lumen. In the adjacent pars recta cell, SER, a dilated Golgi, and dilated rough endoplasmic reticulum are seen (× 10,875).



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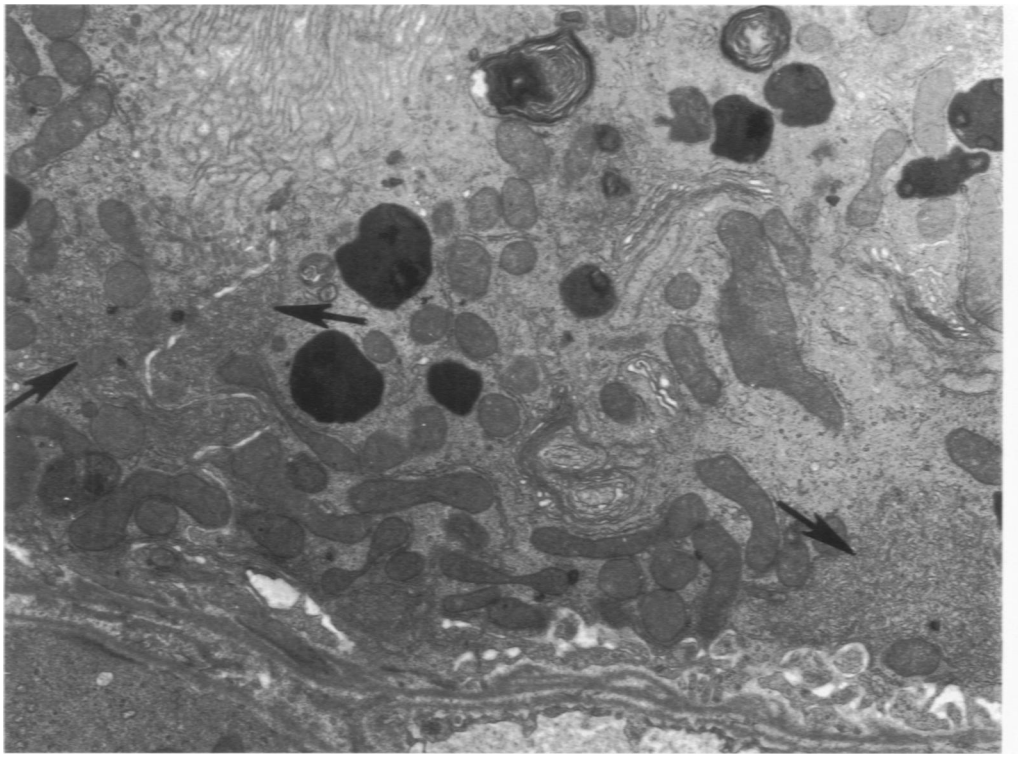
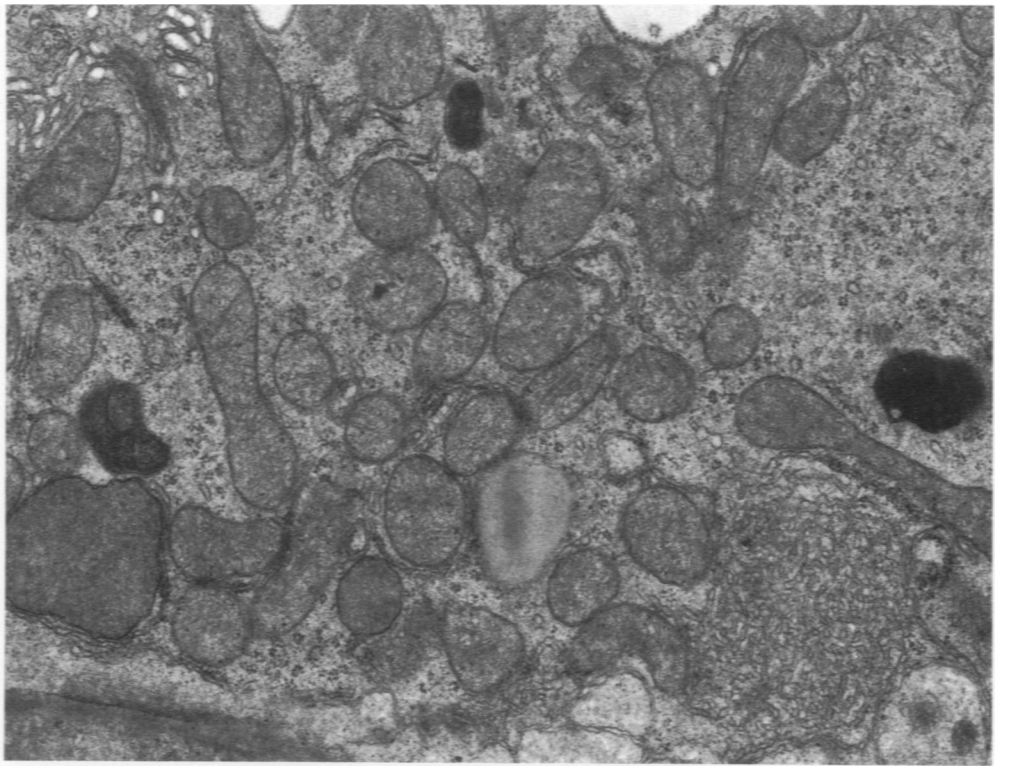
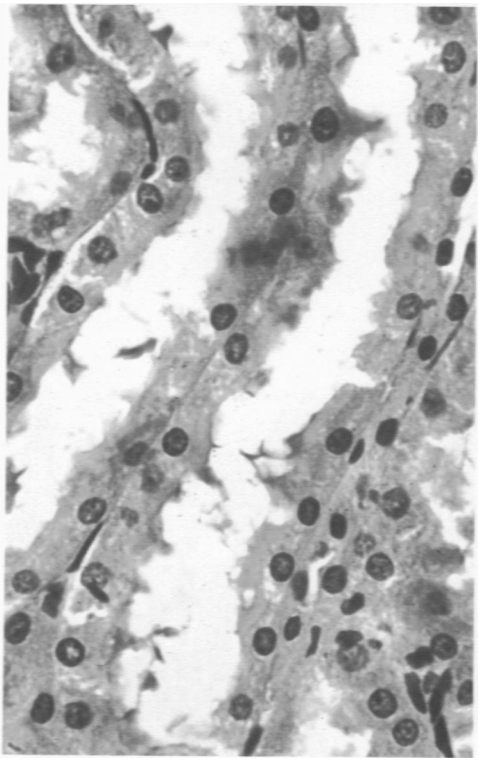


6

Fig 5—Dense membranous cytosomes (*arrows*) and somewhat swollen mitochondria in pars recta cell of a female rat exposed to CH_3HgCl for 84 days (× 13,750). **Fig 6**—Pars recta segment of a female rat given CH_3HgCl for 142 days illustrating membranous dense cytosomes and myelin-like residual bodies. SER aggregates are prominent (*arrows*) (× 11,310).





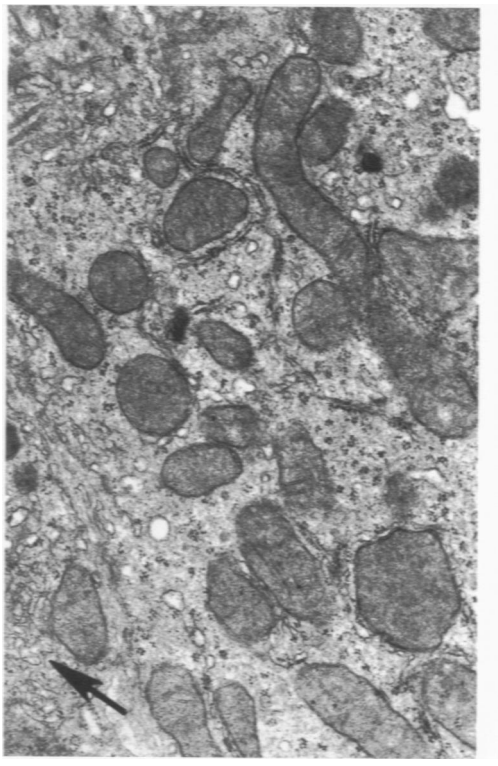


Fig 7—Pars recta cell from a male animal exposed to CH_3HgCl for 142 days showing large aggregate of SER but few cytosomes in comparison to females. Compare with Figures 5 and 6 (× 13,750). **Fig 8**—Light micrograph of pars recta segments from a female rat exposed to dieldrin plus CH_3HgCl for 142 days. Note moderate dilatation of tubules but absence of spherical cytoplasmic masses free in the lumen (× 610). **Fig 9**—Pars recta cell of a male rat receiving dieldrin plus CH_3HgCl for 142 days exhibiting small amounts of SER (*arrow*) (× 15,170).