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Renal Carcinogenic and Nephrotoxic Effects of the Flame Retardant Tris(2,3-dibromopropyl) Phosphate in F344 Rats and (C57BL/6N × C3H/HeN)F_1 Mice [1, 2]

G. Reznik, [3] J. M. Ward, [3] J. F. Hardisty, [4] *and* A. Russfield [5, 6, 7]

ABSTRACT—Tris(2,3-dibromopropyl) phosphate (TBP) was administered in the feed at one of two concentrations to groups of 55 male and 55 female inbred F344 rats and to 50 male and 50 female (C57BL/6N × C3H/HeN)F_1 mice. The high and low dietary concentrations of TBP administered orally were 100 and 50 ppm for the rats, respectively, and 1,000 and 500 ppm for the mice, respectively. For each rodent type, 55 animals of each sex were used as controls. In both rodent types, renal epithelial tumors developed at incidences that were significant for male and female rats and mice that received the doses. These tumors included renal tubular cell adenomas and carcinomas that developed from the proximal convoluted tubular epithelium. Among female mice and rats, hyperplasia and/or dysplasia of the proximal convoluted tubular epithelium with or without cystic dilatation of the tubules and increase in the size of cell nuclei were dose dependent and recognized as preneoplastic and/or toxic lesions. The comparative histogenesis of renal tubular neoplasms was discussed.—JNCI 63: 205-212, 1979.

The U.S. Federal regulations concerned with fabric flammability, particularly those that require all children's sleepwear to be fire retardant (*1-3*), have resulted in a greatly increased use of, and hence exposure to, chemical flame retardants. Moreover, flame retardants are used in home furnishings, building materials, and other substances. Their production is estimated to amount to several billion pounds annually (*4*). Until recently, of all flame retardants, TBP was the most popular. At present, the risk for humans who are exposed to TBP is being investigated extensively. TBP has been shown to be a mutagen in several test systems (*5, 6*) as well as a potent animal carcinogen (*7*). It is known to be absorbed from fabrics through human (*8, 9*) and rat skin (*10*) and to cause testicular atrophy and chronic interstitial nephritis in male albino rabbits (*11*). After 1 ppm of pure TBP was added to water containing goldfish, all fish were killed within 5 days (*12*). After laundered or unlaundered flame retardant-treated 100% polyester or polyester-blend fabrics used in children's sleepwear were immersed in water containing goldfish, all fish died within 24 hours (*13, 14*). In contrast, additional data concerning the acute toxicologic effects (rabbit eye and skin irritation at median lethal dose for rats) of TBP indicated that this substance had a low irritating activity and toxicity in mammals (*15*) and man (*16*). Contrary to these findings, a recent report showed that TBP altered human cellular DNA (*17*). A carcinogenesis test with TBP in mice and rats has been reported in detail (*7*). TBP was demonstrated to be carcinogenic in rats and mice by inducing tumors in the kidneys, stomach, lungs, and liver. This paper describes in detail the pathology of the kidneys in both of these rodent types after they were administered high and low doses of TBP.

MATERIALS AND METHODS

Inbred F344 rats and B6C3F_1 [(C57BL/6N × C3H/HeN)F_1] mice were supplied by the NCI Frederick Cancer Research Center (Frederick, Md.) and were all approximately 6 weeks old at the beginning of the test. The basic laboratory diet for both treated and control animals was Wayne Lab Blox (Allied Mills, Inc., Chicago, Ill.). TBP (Firemaster LV-T23P; Michigan Chemical Corp., St. Louis, Mich.) was administered as a component of the diet. The high and low dietary concentrations of TBP chronically administered were 100 and 50 ppm, respectively, for the rats, and 1,000 and 500 ppm, respectively, for the mice. Food and water were available ad libitum. Both types of rodents were supplied with treated feed for 103 weeks and then observed for 1 week. Food consumption by rodents in cages (2 cages for each rat group and 2 cages for each mouse group) was monitored for 7 consecutive days once a month for the first 9 months of the bioassay and for 3 consecutive days each month thereafter. All animals were housed by rodent types in rooms under normal laboratory conditions [for details, *see* (*7*)].

Animals were weighed immediately prior to initiation of the experiment. Body weights were recorded twice weekly for the first 12 weeks of the study and monthly thereafter.

Each animal was necropsied regardless of whether it died or was killed when moribund or at the end of the bioassay. Tissues were fixed in 10% buffered Formalin

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ABBREVIATIONS USED: DMN = dimethylnitrosamine; H & E = hematoxylin and eosin; PAS = periodic acid-Schiff; TBP = Tris(2,3-dibromopropyl) phosphate.

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and embedded in paraffin; sections were stained with H & E. From kidneys of 25 male and 25 female animals, graded or step sections were made. These were stained with the Feulgen reaction for DNA and also by the PAS method, with or without a fast green counterstain.

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (*7, 18*). These data were analyzed by use of the statistical techniques described in (*7*).

RESULTS

The effects of chronic and subchronic TBP treatment on the mean body weights were described in detail in (*7*). There was little weight depression in treated rats as compared with controls. However, treated mice had body weights 20% less than those of the controls throughout the experiment. From 65 to 80% of the treated rats or mice survived until the end of the study. The primary target organs were the kidneys in rats and mice and the forestomachs, livers, and lungs in mice (*7*).

Renal Neoplasms

Renal tubular cell adenomas were seen in TBP-treated rats, but no tumors of the renal tubular epithelium were found in either male or female control rats (table 1). Of 54 high-dose male rats, 3 (6%) had tumors classified as tubular cell adenocarcinomas (tubular cell carcinomas). Malignant neoplasms in the kidney were diagnosed when infiltration of tumor tissue into the tumor capsule, into adjacent renal parenchyma, or to the vessels could be seen.

In treated male and female mice, renal tubular cell adenomas occurred in low-dose and high-dose groups. Renal tubular cell adenocarcinomas were observed only in low-dose and high-dose males. Neither adenomas nor tubular cell adenocarcinomas were observed in any control mice of either sex, but 6 adenomas were found in treated females (table 1). In both rodent types these epithelial tumors appeared to originate from the proximal convoluted tubules. Frequently, the smallest tumors were seen in the outer medulla or inner cortex in the zone of the pars recta. They consisted of tubular or cordlike epithelial structures with little connective tissue stroma. The size of the lesions varied from a diameter of three or four normal tubules (fig. 3) to much larger tumors (10 mm). The tumors sometimes contained denuded or necrotic epithelial cells within the tubular lumen (fig. 4). Mitotic figures were observed in small as well as in large neoplasms and were not restricted to malignant tumors; however, they were also a consistent finding in adenomas. Cellular pleomorphism within the adenomas and carcinomas was rare (fig. 5). In some tumors, small extensions of neoplastic cells projected into the interstitial tissue between renal tubules, which indicated beginning invasiveness (fig. 6); however, in both rodent types no distant metastases were observed with this type of kidney neoplasm. They were very often multifocal in one kidney but seldom occurred bilaterally. Microscopically, these tumors consisted of cuboidal to columnar epithelium. The cell membranes were sometimes distinct. The nuclei were round and centrally to basally located in a cytoplasm that was pale and sometimes granular. The cell nuclei were large and contained one or two large centrally located nucleoli (fig. 7). Some cells had a vacuolated cytoplasm with an eccentric nucleus (fig. 7). The basement membranes around tumors or of adjacent tubules were thickened and seemed to be very often interrupted (fig. 8). Brush borders could not be detected within tumor tissue.

The adenocarcinomas sometimes replaced almost all the kidney tissue. They invaded the capsule (fig. 9) and in contrast to adenomas were sometimes not clearly demarcated from the remaining kidney cortex. The adenocarcinomas had a papillary (fig. 10), tubular (fig. 11), or compact (fig. 12) growth pattern, whereby the latter two types were the most frequent. In mice, these neoplasms often contained single or multiple cystlike structures that were filled with a fine flocculent, slightly red (in H & E-stained sections) material. Cells surrounding the cysts had eccentric nuclei and demonstrated pronounced cytoplasmic vacuolization. In many instances their nucleoli were markedly enlarged. Some of the renal tumors in the mice had pronounced hemorrhages that formed cavities filled with erythrocytes. Papillary extensions of the marginal tumor tissue protruded into these cavities. As compared to their benign counterparts, both rat and mouse adenocarcinomas had markedly more "giant cells" and demonstrated a pronounced increase in the nucleus:cyto-

TABLE 1.—*Toxic and neoplastic kidney lesions in F344 rats and B6C3F$_1$ mice after TBP feedings*

Rodent type	Treatment, ppm	Observation period, wk				No. of animals with lesion/No. of animals in group					
		Treated		Untreated		Dysplasia or hyperplasia		Tubular cell adenoma		Tubular cell carcinoma	
		Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
F344 rats	Control	—	—	107	107	0/53	0/52	0/53	0/52	0/53	0/52
	50	103	103	1	1	53/54	25/54	30/54	4/54	0/54	0/54
	100	103	103	1	1	39/54	46/54	27/54	13/54	3/54	0/54
B6C3F$_1$ mice	Control	—	—	105	105	0/54	0/55	0/54	0/55	0/54	0/55
	500	103	103	1	1	46/50	20/50	5/50	3/50	1/50	0/50
	1,000	103	103	1	1	49/50	40/46	12/49	3/46	5/49	0/46

plasm ratio. Invasion of adjacent tissues or metastases to other organs was not found.

Nonneoplastic Renal Lesions

Frequently in the kidneys of both mice and rats microscopic examination revealed small foci of dilated and hyperplastic or dysplastic proximal convoluted tubules (fig. 13). These lesions often occurred coincidently with adenomas or adenocarcinomas in the same kidney or same area. In female rats and mice, the dysplastic areas were dose related (table 1). Dysplasia occurred in as many as 96% of the male rats in the low-dose group and in 100% of the male mice in the high-dose group. Two or more foci were occasionally found within one kidney. The cells constituting these early lesions very often had a brush border and their cytoplasm filled the lumen of the tubule (fig. 14). In such areas the cell nuclei were frequently enlarged up to 10 times the size of normal cell nuclei. In some areas the nuclei also showed large nucleoli and dispersed chromatin (fig. 1). In other tubules these giant nuclei protruded into the lumen without showing cell cytoplasm at their luminal margins. The axis of these nuclei was rotated, thus being oriented in a different direction than those in normal cells. Such cells had lost their brush borders (fig. 1). In other lesions the cytoplasm of these cells was vacuolated and PAS-negative. The tubules containing such cells had thickened basement membranes (fig. 2). These lesions were not observed in the control groups of mice and rats. Selected acid-fast-stained kidney slides from male and female high-dose and control rats and mice showed no microscopic evidence of acid-fast intranuclear inclusions in the renal epithelial cells that suggested toxicity from lead or other heavy metal compounds.

DISCUSSION

Rats treated orally with TBP had a high percentage of neoplasms in the same region as the pathologic lesions in the kidneys of rabbits after their skins were painted with TBP (*11*). The tumors induced after the TBP feeding appeared to arise from the proximal tubular epithelium. This was also found in rats (*19–21*) and mice (*22*) after treatment with several other carcinogens. In man renal adenoma and adenocarcinoma arise from cells of the proximal convoluted tubule (*23*). Early lesions, such as necrosis of the proximal convoluted tubular cells, which preceded the proliferative and neoplastic changes in rats treated with DMN (*20*), were not observed. In TBP-treated rats and mice, multiple-layered tubular lesions closely resembling those observed in rats by Hard and Butler (*20*) and in mice by Lombard et al. (*22*) could be diagnosed. Tubular epithelial degeneration in outer-stripe tubular cells, including enlarged nuclei and tubular dilatation, has been reported for many chemicals (*24–30*), but most of the effects (mainly enlarged nuclei) were seen shortly after the start of treatment and not in a chronic study. In contrast to our study, tumors of the kidney are uncommon in carcinogen-treated mice (*29*) and have been reported briefly as a minor fraction of the overall tumor incidence resulting from treatment with various chemicals including DMN, urethan, procarbazine, basic lead acetate, and others (*29*). Spontaneous tumors of the kidney in F344 rats (*31, 32*) and $B6C3F_1$ mice (*32*) are rare. From the TBP-treated male mice in the high-dose groups, 25% of the animals had tubular cell adenomas and 10% had tubular cell carcinomas, a result within or greater than the range of other strong kidney carcinogens. Renal adenocarcinomas in humans are usually reported as occurring twice as frequently in males as in females (*33, 34*). The findings that only male rabbits sustained kidney damage (*11*) and that male rats and mice after being fed TBP have more early lesions and neoplasms in their kidneys than do females indicate that males in general might be at higher risk than females to develop kidney tumors caused by various agents.

The Consumer Product Safety Commission (*35*) notified the public that children's clothing containing the chemical flame-retardant TBP was banned from commerce beginning April 8, 1977. Tests have established that this substance (TBP) causes cancer in mice (*36*) and rats (*7*) and can enter the bodies of children by being absorbed through the skin or by being ingested by children "mouthing" their clothing. Risk for cancer in the population by the use of this compound in plastics and carpets (*4*) is still very high, especially for chemical and textile workers being exposed to these agents. Most nonpolar chemicals, including TBP and five other phosphate esters, are absorbed through human skin (*37*). Moreover, TBP can be absorbed directly from the fabric through human skin and can be detected in the urine (*8*). However, this is in contrast to an investigation by others (*10*) who could not detect TBP in the urine of a rat, a 5-year-old boy, and an adult male who wore TBP-finished fabrics up to 9 days. When the pure chemical was applied directly to the shaved skin of a rat, the hydrolysis product 2,3-dibromopropanol appeared in the urine (*10*). TBP produced pathologic lesions in rabbit kidneys after the skin was painted for 90 days and caused benign and malignant tumors of the skin, forestomach, and oral cavity (tongue and gingiva) in a statistically significant number of mice when the compound was applied to the skin three times weekly (*36*). Affected sites were primarily the corticomedullary junction and medullary ray areas (*11*). These results indicate that TBP can penetrate the skin of rabbits in sufficient quantities to produce substantial organ damage.

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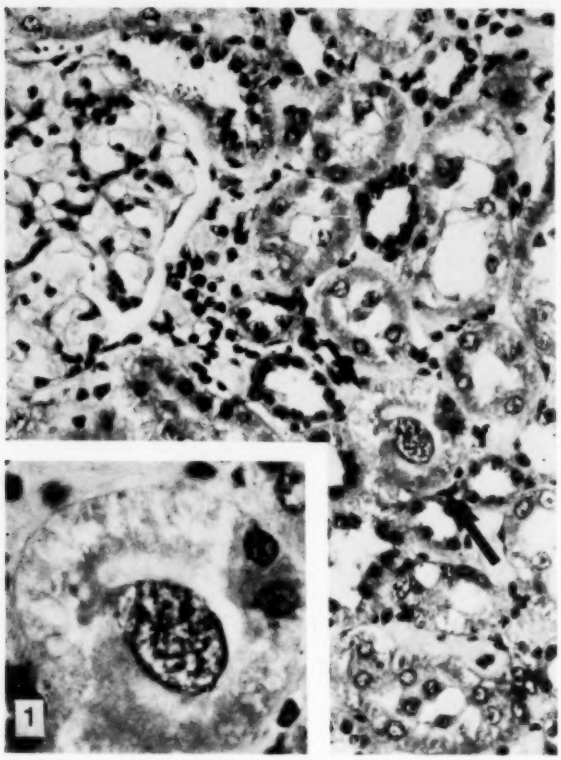


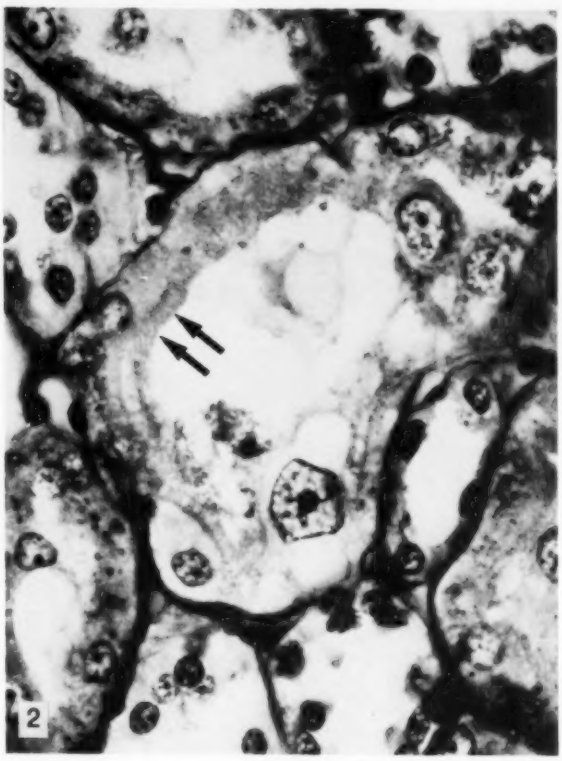


FIGURE 1.—Rotated cell nucleus in proximal tubule of kidney of high-dose male rat. Nucleus has 10 times cross-sectional area of other nuclei in same area. (*Arrows* point to area of inset.) H & E. × 330. *Inset:* Eccentrically placed nucleus, two nucleoli, and dispersed chromatin. H & E. × 880

FIGURE 2.—Vacuoles in cytoplasm of proximal tubule cells in low-dose female rat contain no PAS-positive material; brush border is partially destroyed. *Note* normal-appearing brush border (*arrows*). PAS. × 880

FIGURE 3.—Tubular cell adenoma (*large arrow*) of kidney from male rat treated with 1,000 ppm TBP. Neoplasms is not larger than glomerulus. In adjacent areas, *note* cystic dilatation of proximal tubules (*small arrows*). PAS. × 54

FIGURE 4.—Tubular cell adenoma of kidney from male rat treated with 1,000 ppm TBP. Large tumor is multilobulated with necrotic centers in different areas. Adjacent tissue is compressed. *Arrows* indicate PAS-positive material, similar to basement membrane, that extends throughout neoplasm. PAS. × 54

FIGURE 5.—Multinodular tubular cell adenoma of high-dose male rat shows small necrotic centers, compressed adjacent tissue, and polymorphy of nuclei. H & E. × 130

FIGURE 6.—Small projections of tubular cell adenoma into interstitial tissue; tumor cells show mitoses and grow in tubular pattern. PAS. × 330

FIGURE 7.—Renal tubular cell adenoma of high-dose male rat shows uniform pattern of nuclei with prominent nucleolus, sometimes with vacuolated pale-staining cytoplasm. Tumor center is cystic and filled with homogeneous stained material. PAS. × 330

FIGURE 8.—Basement membrane and basement membrane-like material within tubular cell adenoma of male high-dose rat. Membrane is thickened and partially interrupted. PAS. × 330

FIGURE 9.—Tubular cell adenocarcinoma of kidney from high-dose male mouse with several blood-filled cysts within tumor tissue. Tumor is encapsulated and infiltrates capsule (*see inset* and *arrows*). Tumor cells form tubular and cordlike structures. H & E. × 35. *Triangles* indicate *inset*. H & E. × 80

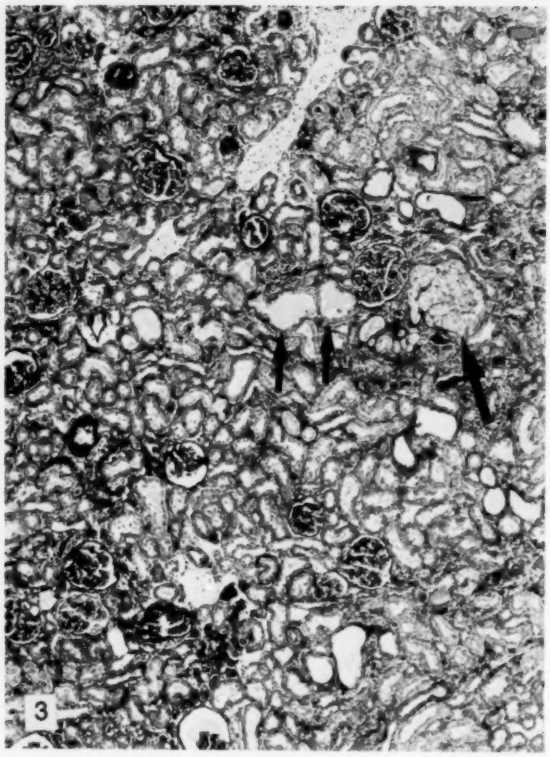
FIGURE 10.—Papillary tubular cell adenocarcinoma from high-dose male mouse with several necrotic centers. H & E. × 40

FIGURE 11.—Tubular cell adenocarcinoma of kidney from high-dose male mouse. Tumor appears pseudoencapsulated and has many empty spaces or small cysts filled with homogeneous material. H & E. × 54

FIGURE 12.—Compact tubular cell adenocarcinoma from low-dose male mouse with uniform cell nuclear pattern and slightly compressed adjacent tissue. H & E. × 80

FIGURE 13.—Three dilated proximal tubules showing hyperplasia and enlarged nuclei in low-dose female rat. H & E. × 130

FIGURE 14.—Proximal tubules of kidney from high-dose male rat; lumina are nearly obstructed by cytoplasm and enlarged nuclei with dispersed chromatin. *Note* brush border of cells (*arrow*). PAS. × 880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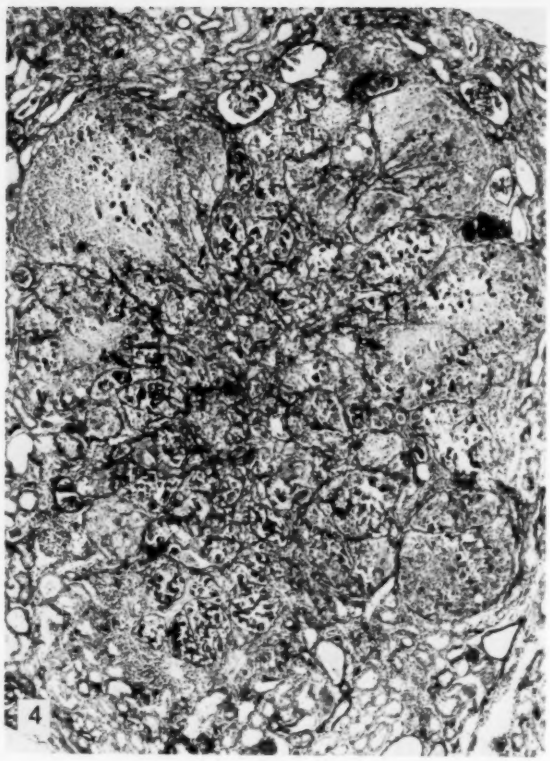
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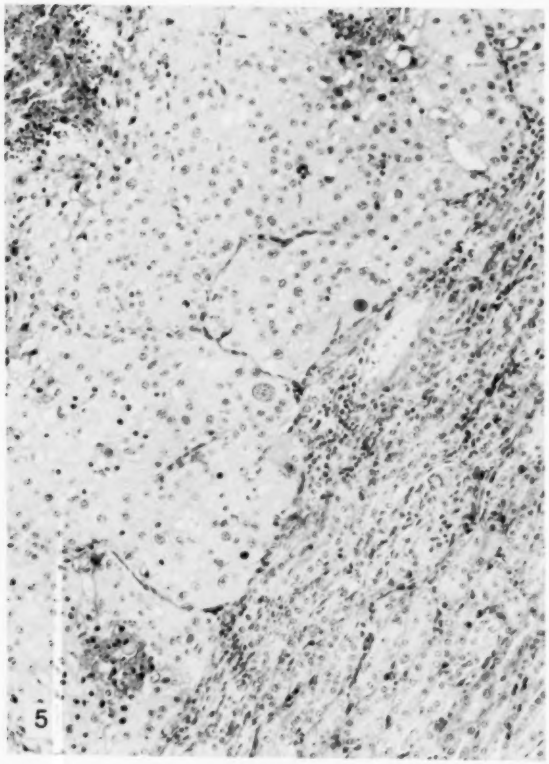
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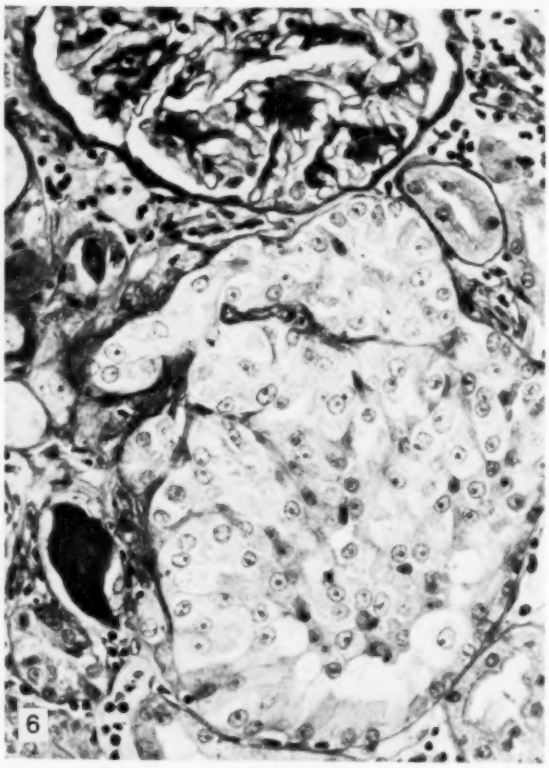
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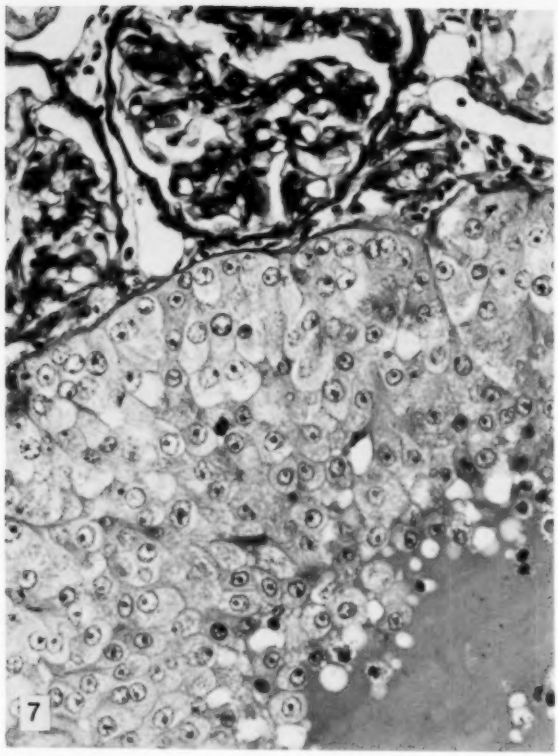

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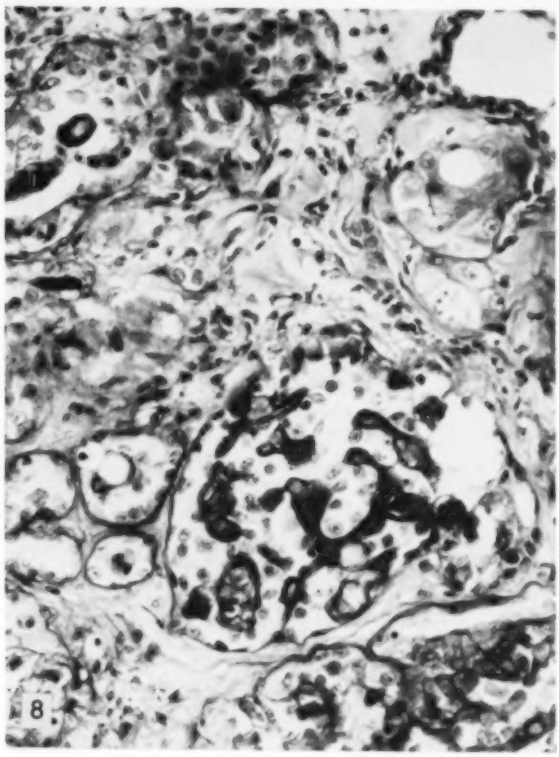

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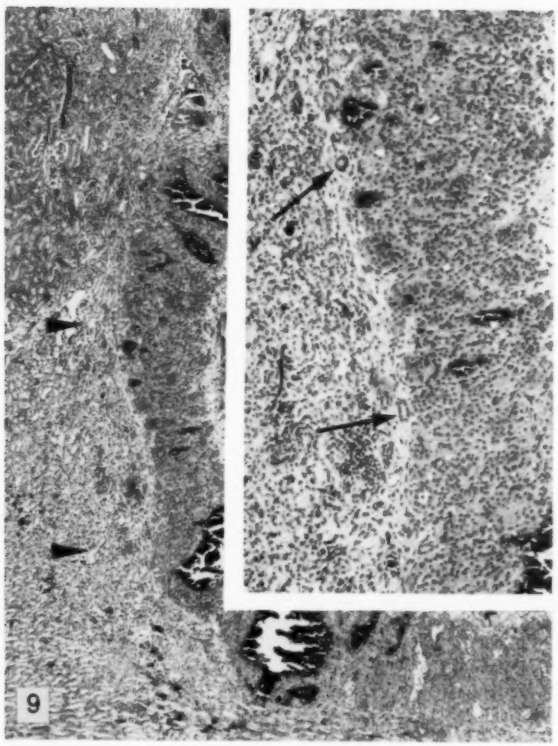

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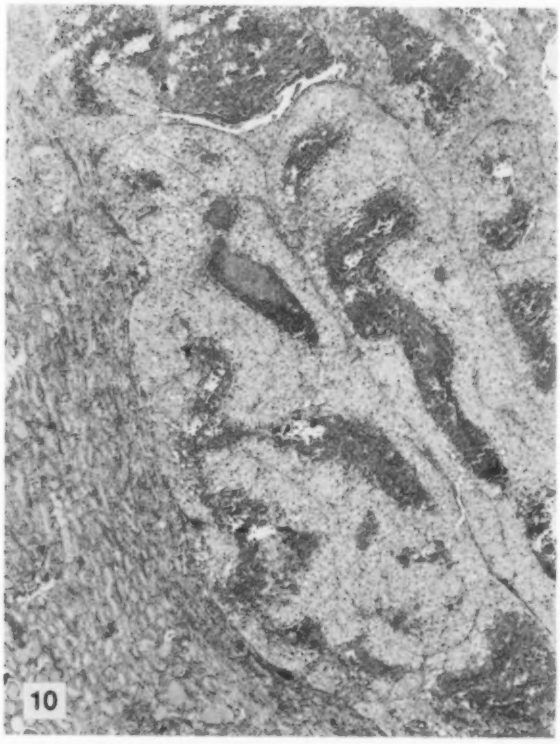

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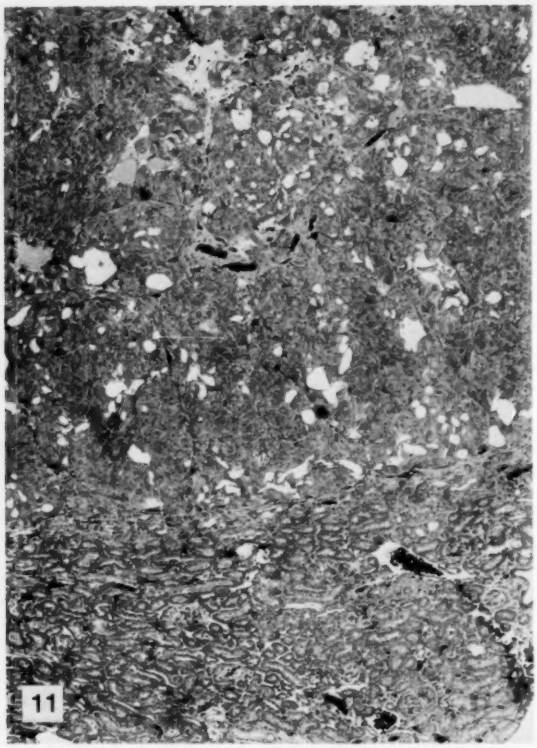
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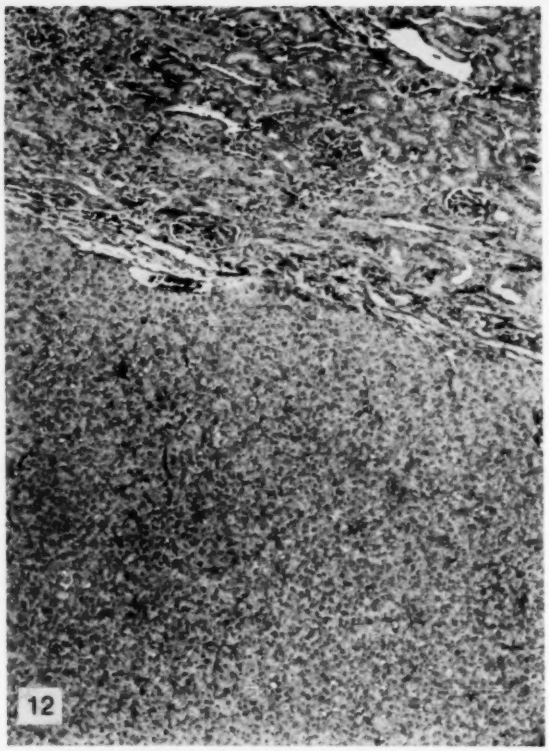
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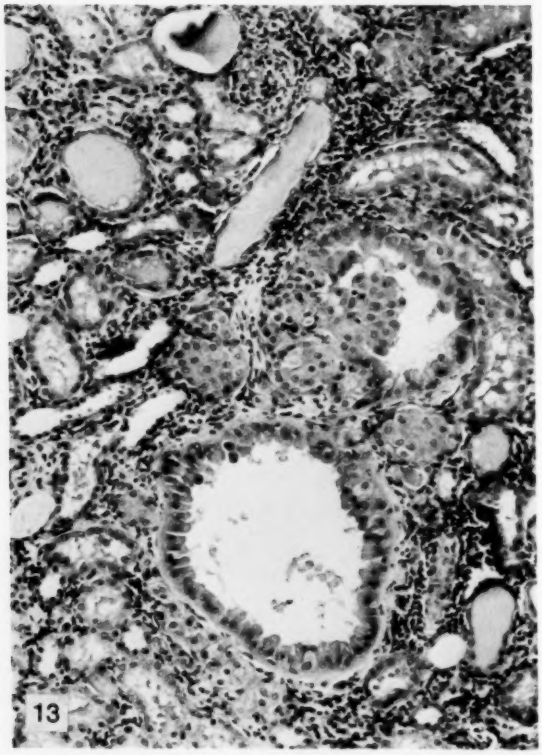
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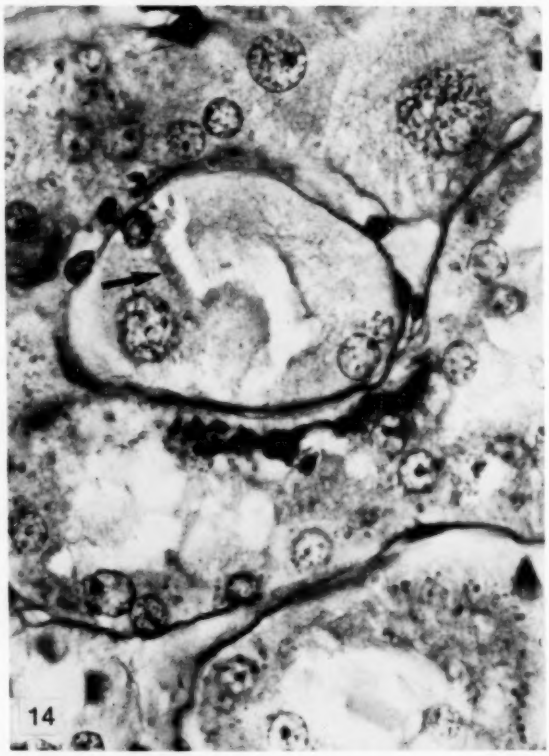
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