17

Urinary System

DIFFERENTIAL DIAGNOSIS

Konnie H. Plumlee

Most toxic effects in the urinary system involve the kidney. Very few poisons affect the lower urinary tract. Clinical signs are similar regardless of the type of poison (Table 17-1).

TOXIC RESPONSE OF THE URINARY TRACT

Scott D. Fitzgerald and Wilson K. Rumbeiha

KIDNEY

Susceptibility

The kidney is susceptible to toxicants because of its high relative blood flow—approximately 25% of total cardiac output—compared with its low percentage of total body weight (approximately 0.5% in mammals, approaching 1% in some birds).[1,2] The renal cortex receives nearly 90% of the total renal blood flow, whereas the medulla receives 6% to 10% of the blood flow, and the papilla receives approximately 2%.[3] Therefore, blood-borne toxicants tend to be delivered at highest rates to cortical tissues, whereas the medullary and papillary regions are exposed to the highest luminal concentrations of toxicants and for longer periods of time.

The kidney also has high metabolic demands, accounting for approximately 10% of the body's total oxygen consumption.[1] The kidney serves vital roles, including excretion of metabolic wastes, metabolism and excretion of xenobiotics, regulation of extracellular fluid volume, maintenance of electrolyte composition, and regulation of acid-base balance. Many of these functions rely on active transport mechanisms, which can be inhibited by toxicants. Given the diversity of kidney functions, toxicant damage to renal tissues results in a variety of systemic abnormalities.

Different portions of the kidney vary in their susceptibility to toxicant damage. The functional unit of the kidney is the nephron, which is composed of the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct. The proximal tubule is highly involved in active transport of substances and is the most sensitive portion of the nephron to both hypoxia and toxicosis. The principal function of the proximal tubule includes resorption of water, electrolytes, glucose, amino acids, and small peptides. Active resorption of solutes such as glucose, amino acids, and organic acids is dependent on Na/K-adenosine triphosphatase within tubular epithelial cells.[3] Enzymes important in the metabolism of xenobiotics, including mixed function oxidases, are present in high concentrations in the proximal tubule epithelium. Prostaglandins are produced in highest concentrations in medullary collecting ducts, predisposing the inner medullary and papillary regions to nonsteroidal antiinflammatory drug damage as a result of their inhibitory effect on prostaglandins.[3]

The glomerulus contains a tuft of specialized capillaries. The fenestrated endothelium, the glomerular basement membrane, and the visceral epithelial cell foot processes are the three components constituting the glomerular filtration membrane (GFM). Twenty percent to 40% of the blood volume flowing to the glomeruli is filtered through the GFM, which forms the ultrafiltrate.[3]

Despite the kidney's susceptibility to numerous toxicants, it also possesses enzymes for detoxification, some ability to regenerate, and considerable reserve capacity before developing clinical renal failure. Cytochrome P-450s and other enzymes that metabolize xenobiotics are found in highest concentrations in the proximal convoluted tubular epithelium. Even though glomeruli are not capable of regeneration, renal tubules may regenerate if their basement membranes remain intact following injury. In regard to reserve capacity, between 50% and 70% of nephrons must be damaged before elevations in serum renal markers (blood urea nitrogen [BUN], creatinine) occur.[3]

Mechanisms of action

Even though the list of nephrotoxicants is long, the response of the kidney is limited to only five categories (four in the

TABLE 17-1 **Poisons that Affect the Urinary System**

Source	Toxicant	Species
Plants	Calcinogenic glycosides	Livestock
	Lily	Cats
	Oak	Cattle, sheep
	Oxalates	Livestock
	Pigweed	Swine, cattle
	Ptaquiloside	Primarily cattle, but also other ruminants
Mycotoxins	Citrinin	All
	Ochratoxin	All
	Oosporein	Chicks, turkeys
Other toxins	Blister beetles	Primarily horses, but also cattle
	Cortinarius spp. (mushrooms)	All
	Pit vipers	All
Metals	Arsenic	All
	Mercurial salts	All
Pesticides	3-chloro-p-toluidine hydrochloride	Birds
	Cholecalciferol rodenticide	All
	Diquat	All
	Paraquat	All
Household and industrial	Ethylene glycol	All
	Phenols	Cats most susceptible
	Pine oil	Cats most susceptible
	Toluene	All
Pharmaceuticals	Alkylating antineoplastics	All
	Aminoglycosides	All
	Amphotericin B	All
	Cisplatin	All
	NSAIDs	All
	Sulfonamides	All
	Tetracyclines	All
	Vitamin D	All
	Vitamin K_3	Horses

kidney, the fifth affecting predominantly the lower urinary tract) based on anatomic site and reaction (Box 17-1).

Glomerular lesions. Glomerular lesions are among the most common renal lesions reported in animals. These lesions are primarily associated with immune complex deposition in glomerular basement membranes and are caused by a variety of infectious and immune-mediated diseases. However, toxic injury of the glomeruli is infrequently recognized in veterinary medicine. The single, well-recognized, toxicant-induced syndrome with direct glomerular effects is caused by snake venom. Envenomation by poisonous snakes results in a variety of toxic effects, including local reactions at the site of the wound, systemic effects such as shock, disseminated intravascular coagulopathy (DIC), and specific organ effects.[4] Venom from viperid snakes, such as Russell's vipers, and crotalid snakes, such as rattlesnakes, may cause renal lesions. Both glomeruli and the renal tubules are affected by snake envenomation. Renal tubular necrosis is thought to be caused by a combination of factors, including myoglobinuria from muscle breakdown, ischemia caused by shock, and DIC, and only partly caused by direct toxic effects of venom components. The glomerular lesions result from toxin damage directed toward the glomerular capillary endothelium and the supporting mesangial structures.[5,6] The specific venom components involved and their specific mode of action on glomerular tissues remain an active area of research.

Nephrosis. Acute tubular necrosis, also called tubular nephrosis, is by far the most commonly recognized form of toxicant-induced renal damage.[3] Toxicosis produced by a wide range of xenobiotics manifests itself by this lesion, including antimicrobial drugs, antineoplastic drugs, herbi-

BOX 17-1 PRINCIPAL ANATOMIC SITES AFFECTED BY AND REACTIONS TO NEPHROTOXINS

I. KIDNEY

Glomerulus (mesangiolysis)
- Snake venoms

Renal tubules (acute tubular necrosis)
- Antimicrobials
- Antineoplastic drugs
- Anesthetics
- Chlorinated hydrocarbons
- Herbicides
- Immunosuppressants
- Solvents
- Metals
- Mycotoxins
- Plants: Oxalate-containing and other toxins
- Endogenous nephrotoxins

Renal mineralization
- Vitamin D
- Cholecalciferol-type rodenticides
- Plants with vitamin D–like activity

Renal papilla and crest necrosis
- Antiinflammatory drugs

II. RENAL PELVIS AND LOWER URINARY TRACT

Contact irritant
- Cantharidin

Hemorrhage and neoplasia
- Bracken fern *(Pteridium aquilinum)*

Hemorrhage secondary to other causes
- Vitamin D
- Anticoagulant rodenticides

cides, heavy metals, and several classes of plant-related toxins (see Box 17-1). As previously mentioned, the proximal tubule is the portion of the nephron most severely affected by tubular necrosis for most compounds; however, the exact mechanism varies with the xenobiotic. Individual mechanisms for the various compounds are described in greater detail elsewhere in this book; only examples are cited here.

Aminoglycoside antibacterials are water-soluble, low-molecular-weight compounds and are eliminated unmetabolized, primarily by glomerular filtration. They are present in high concentrations in the renal tubules and are reabsorbed by proximal tubule epithelium cells. Aminoglycosides produce renal nephrosis by inhibiting phospholipases, leading to lysosomal dysfunction and eventually lysis.[1,3]

Oxalate toxicants, originating as metabolites from ingested ethylene glycol or directly from ingestion of oxalate-containing plants, produce tubular necrosis by chelating calcium and forming calcium oxalate crystals within renal tubules. The calcium oxalate crystals cause mechanical obstruction of the tubules as well as tubular epithelial necrosis.[1]

Inorganic mercury is a heavy metal that produces tubular necrosis. Mercury binds to various enzyme systems, partly because of its affinity for protein sulfhydryl groups, subsequently resulting in mitochondrial dysfunction.[3] Mercury also produces oxidative stress through lipid peroxidation.

Mineralization. A third type of nephrotoxic response is renal mineralization or nephrocalcinosis. Sources for this type of toxicant include excessive supplementation of vitamin D_3, ingestion of plants containing vitamin D_2, or exposure to the recently developed cholecalciferol-type of rodenticides. Cholecalciferol is metabolized in the liver to a monohydroxy metabolite that is subsequently metabolized by the renal tubular epithelial cells to the dihydroxy metabolites including calcitriol, which is the most active metabolite.[7] Calcitriol then results in increased blood calcium by stimulating calcium absorption in the gut and resorption of calcium from bones, resulting in dystrophic mineralization and damage to renal tubules, glomeruli, and blood vessels.

Papillary necrosis. The fourth type of nephrotoxic response is ischemic necrosis of the inner portion of the renal medulla, the renal papilla, or the renal crest, depending on the host species. Drugs such as acetaminophen and nonsteroidal antiinflammatories (aspirin, ibuprofen, indomethacin, phenylbutazone) produce their therapeutic effects through inhibition of prostaglandin synthesis.[3] The renal papilla receives relatively small amounts of the total renal blood flow, and so when locally produced prostaglandins, which act as vasodilators, in the papillary region are suppressed, the result is even lower local blood flow and ischemia. Although single exposure frequently produces a reversible lesion, repeated exposures result in irreversible necrosis of the medullary loops of Henle and the capillaries, with subsequent papillary fibrosis.

Organ response to injury

The three basic clinicopathologic manifestations of renal injury caused by toxicant damage are discussed in the following paragraphs.

Minimal alterations. The kidney may continue to function using its reserve capacity with only minimal alterations being found on urinalysis, such as inability to concentrate urine (isosthenuria) and increased protein leakage (proteinuria). These abnormalities are indications of mild damage and may be completely reversible.

Acute renal failure. Acute renal failure is a more severe consequence of nephrotoxicity, and is characterized by significant decrease in glomerular filtration rate and elevations in BUN and creatinine (azotemia). Acute renal failure results in marked decrease in urine production (oliguria) or anuria, proteinuria, aminoaciduria, and glucosuria. Common systemic sequelae include dehydration, metabolic acidosis, and hyperphosphatemia.[1] With proper therapy, acute renal failure can be reversed in many cases.

Chronic renal failure. Chronic renal failure is a result of prolonged renal damage and is manifested after the reserve capacity is exhausted. It represents a progression of renal damage toward end-stage kidneys and is frequently irreversible. Chronic renal failure is characterized by polyuria, isosthenuria, and elevations in BUN and creatinine. Progressive renal failure is not dependent on continued or repeated toxicant exposure. The kidneys react with compensatory mechanisms, following even a single toxicant exposure, and these compensatory mechanisms themselves may lead to continued and progressive renal damage.

Gross lesions

Mild cases of nephrotoxicosis are generally not associated with gross lesions. Kidneys suffering from more severe acute toxicoses, resulting in acute renal failure, are swollen and excessively moist on cut section. The renal parenchyma may be paler than normal and striations normally visible in the renal tissue become less clearly defined. Cases associated with diffuse vascular congestion or with pigments such as hemoglobin may present with a diffusely dark or reddened kidney. Linear pale streaks in the cortex or medulla are often grossly visible in cases associated with tubule crystal deposition or parenchymal mineralization. Papillary necrosis may present grossly as a zone of pale ischemic tissue within the inner papilla and crest; however, in chronic cases the entire papilla and crest may appear as a sharply delineated mass of dry, dark necrotic tissue.

Chronic renal failure generally results in more obvious gross lesions. End-stage kidneys are often smaller than normal, exhibiting asymmetry of size and shape between the two kidneys. The subcapsular surface tends to be pitted and irregular, and it is difficult to peel off the renal capsule as a result of multifocal fibrous adhesions. The kidney may be difficult to section because of increased interstitial fibrosis, and it may be gritty because of partial mineralization of tissues. On cut section, the end-stage kidney may have marked variation in cortical and medullary tissue thickness, single or multiple renal cysts, and radiating pale streaks within the cortex representing interstitial fibrosis (Fig. 17-1).

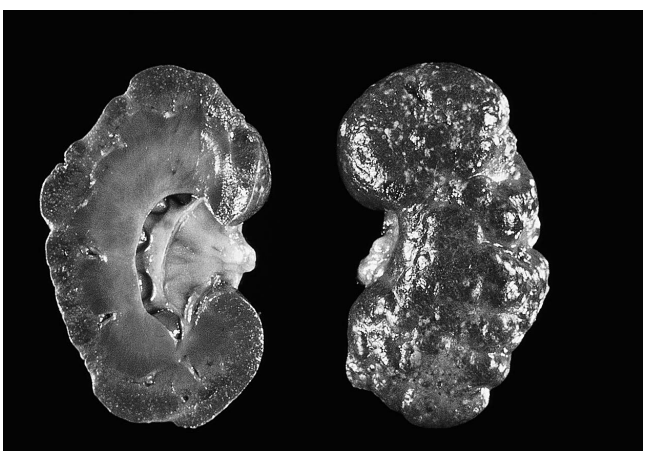

Fig. 17-1 Gross appearance of end-stage kidney from a dog exhibiting chronic renal failure. The capsular surface is pitted and irregular *(left)*. The cut section shows the uneven thickness of the cortical tissue *(right)*.

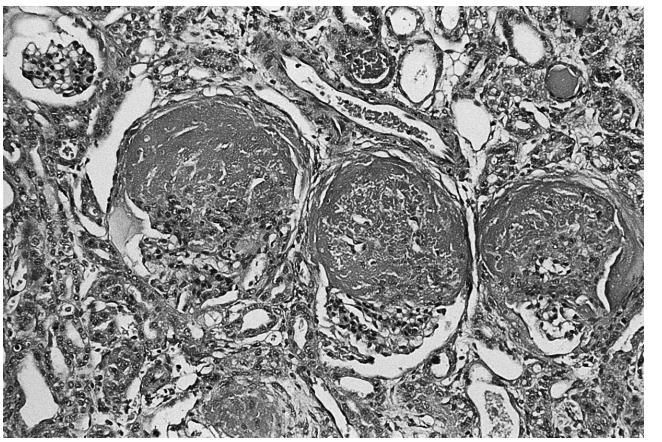

Fig. 17-2 Photomicrograph of canine renal tissue after exposure to snake venom. Three glomeruli have varying degrees of hemorrhage and necrosis (mesangiolysis). (10×)

Histopathology

As previously stated, despite the long list of toxicants that have primary renal effects, nephrotoxicants can be divided into five basic categories based on anatomic site and reaction (see Box 17-1).

Mesangiolysis. One of the least frequently reported forms of nephrotoxicosis in veterinary species is mesangiolysis, which involves necrosis and destruction of the glomerulus. Envenomation by poisonous snakes, including viperidae and crotalidae, results in a variety of toxic renal effects. In the kidney, glomerular alterations include damage to the endothelium, formation of hemorrhagic cysts, and destruction of the mesangial matrix, hence the term *mesangiolysis* (Fig. 17-2).[5,6] These changes vary from mild to severe, and the more mildly affected individuals that survive may develop mesangial proliferative glomerulonephritis. In addition, tubular necrosis in snake envenomation cases is frequent, which is believed to be caused by a combination of direct toxic tubular effects of venom fractions, as well as myoglobinuria and ischemia caused by systemic effects of the toxins.

Nephrosis. By far the most common form of toxic nephropathy is acute tubular necrosis, also referred to as nephrosis. Microscopically, this tends to affect the proximal tubules most severely, and is characterized by degeneration and necrosis of the proximal convoluted tubular epithelium (Fig. 17-3). Epithelial cells swell, developing intracytoplasmic vacuolation or hypereosinophilia. The nuclei become pyknotic and then lyse (karyolysis). Eventually, entire cells slough and undergo lysis, and the cytoplasmic remnants accumulate within the dilated tubular lumens forming granular or cellular casts.

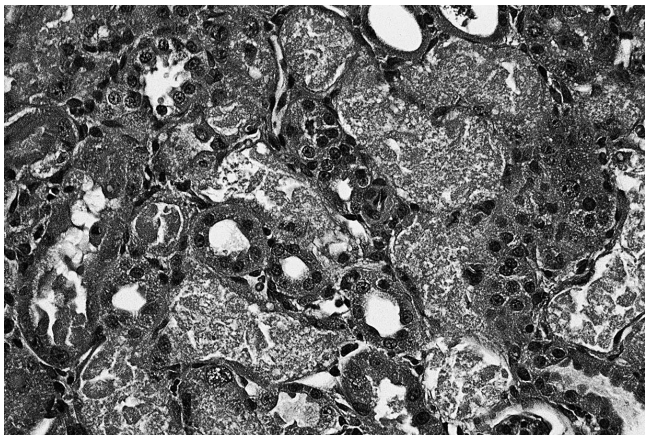

Fig. 17-3 Photomicrograph of renal tissue from a rat experimentally dosed with mercuric chloride. Multiple proximal tubules exhibit acute tubular necrosis characterized by loss of nuclei, and lumens filled with hypereosinophilic cellular debris. Admixed are relatively normal appearing distal tubules and collecting ducts. (40×)

Differentiation between acute tubular necrosis as a result of poisons or ischemia is sometimes possible, particularly in acutely affected individuals. Ischemia tends to cause a patchy epithelial necrosis as compared with the more extensive necrosis associated with toxicants.[1] Ischemia also produces a more severe necrosis that disrupts the tubular basement membrane, whereas poisons usually leave the basement membrane intact (at least until tubular swelling results in secondary localized ischemia). Through the use of either periodic acid-Schiff reaction or one of the many silver stains available, basement membranes can be evaluated microscopically to attempt differentiation between toxic and ischemic-induced tubular necrosis.

Mineralization. Renal mineralization or nephrocalcinosis may occur as a result of a variety of toxicants or as a secondary feature of renal failure. Deposits of calcium salts in the kidney tend to occur along basement membranes first, such as those lining the renal tubules, blood vessels, and glomerular tuft and capsule (Fig. 17-4). Histologically, mineral appears as thin basophilic, slightly refractile material with routine hematoxylin and eosin staining. Special stains for calcium, such as Von Kossa's stain, can be used to confirm the microscopic diagnosis. As mineralization progresses, the tubular epithelial lining becomes mineralized and degenerates, until cells exfoliate and result in tubular obstruction. Because mineral is harder than the surrounding soft tissues, the microtome blade tends to cause a shattering effect, resulting in sharp and angular bits of basophilic material, lending a distinctive microscopic appearance to mineral.

Papillary necrosis. The final category for toxicant-induced change in the kidney is necrosis of the renal papilla or crest. This portion of the kidney receives the least blood flow, and agents that tend to further restrict blood flow locally result in this type of damage. The entire inner portion of the renal medulla becomes ischemic, resulting in poorly stained necrotic tubules, whereas the surrounding area maintains normal staining affinity and may show varying degrees of vascular congestion (Fig. 17-5). Subsequently, the ischemic tissue may undergo complete coagulative necrosis and may become partially mineralized as well.

LOWER URINARY TRACT

Susceptibility

The lower urinary tract, consisting of the ureters, urinary bladder, and urethra, is more resistant to toxic-induced injury than the kidney. Perhaps this reduced susceptibility is because urinary wastes travel through this portion of the tract relatively rapidly, and the transitional epithelium lining these regions is less metabolically active than renal tissues. For this discussion, the renal pelvis is also considered part of

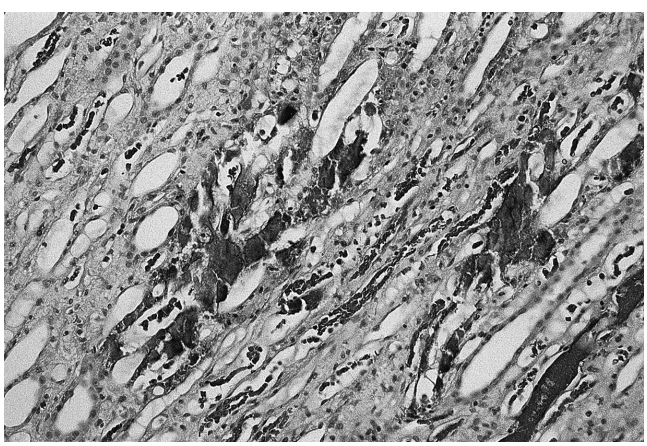

Fig. 17-4 Photomicrograph of renal tissue from a dog experimentally dosed with cholecalciferol. Multiple renal tubules contain partially mineralized epithelium which appears dark and angular (nephrocalcinosis). (20×)

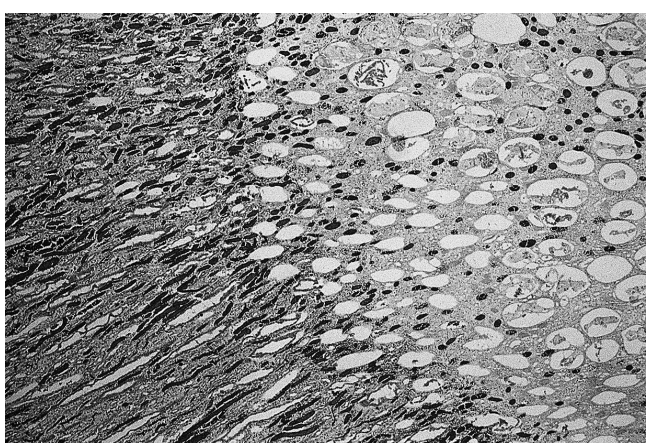

Fig. 17-5 Photomicrograph of renal tissue from a horse overdosed with a nonsteroidal antiinflammatory agent. Note the clear line of demarcation between the normal congested portion of the proximal papilla (*left*), and the pale-stained necrotic tubules in the distal papilla (*right*). (4×)

the lower urinary tract. It is anatomically part of the kidney, but its transitional lining and toxic responses are similar to those of the lower urinary tract. The portion of the lower urinary tract that is most commonly affected by toxicants is the urinary bladder because it acts as the holding chamber for urinary wastes between voidings. If toxicants are present in the urine, they have more prolonged exposure to the bladder lining.

Mechanisms of action

Hemorrhage of the lower tract is the most frequently seen response to toxic injury. Several poisons act systemically and damage blood vessels or interfere with blood clotting, so the resulting hemorrhages found in the urinary bladder are nonspecific, as with vitamin D toxicosis and anticoagulant rodenticides. On the other hand, the mechanism of action of cantharidin from ingestion of hay contaminated with blister beetles *(Epicauta* sp.) is that of a contact irritant. Even though all levels of the urinary tract, from the renal pelvis down through the urethra, can hemorrhage, the risk of hemorrhage is generally most severe in the urinary bladder.[1]

The mechanisms involved in enzootic hematuria, caused by ingestion of bracken ferns *(Pteridium aquilinum)* by ruminants, are more complicated. Toxins present in bracken ferns include a thiaminase, an unidentified bleeding factor, and multiple carcinogens (quercetin, shikimic acid, prunasin, ptaquiloside, aquilide A).[1] Although hemorrhages may be present throughout the lower urinary tract, they are most easily seen in the bladder mucosa. These hemorrhages are caused by the acute effect of the toxin on bone marrow, causing a pancytopenia and thrombocytopenia. With more prolonged ingestion, the chronic activity of the carcinogens results in multiple epithelial or mesenchymal neoplasms in the bladder, which frequently ulcerate and bleed into the bladder lumen.

Organ response to injury

Toxicants within the urine cause damage to the transitional epithelium lining the lower urinary tract. The responses of the transitional epithelium are limited, and include multifocal hemorrhage, ulceration, inflammation (ureteritis, cystitis, urethritis), squamous metaplasia, and neoplastic transformation into a variety of epithelial tumors.

Gross lesions

The most common gross lesions in urinary bladders in response to toxicants are multifocal petechial, ecchymotic, or suffusive hemorrhages. Large patches of the urinary bladder lining may become diffusely reddened and roughened in response to contact irritants. In response to chronic bracken fern ingestion, single or multiple polypoid tumors arise from the bladder wall and protrude into the lumen. These bladder tumors resulting from exposure to carcinogens within the urine most frequently develop in the trigone area, or along the ventral and lateral fundic bladder walls, because these sites have the most prolonged contact with urine.[8]

Histopathology

Microscopic alterations in the urinary bladder are consistent with the organ responses previously described. Hemorrhages within the mucosa are commonly seen. Cystitis varies from acute with associated ulcerations of the epithelium and variable leukocyte infiltrates, to chronic with subepithelial fibrosis. Transitional epithelium, when chronically irritated, tends to become initially hyperplastic and then undergoes metaplasia to squamous epithelium. Following neoplastic transformation, the epithelium may give rise to papillomas, transitional cell carcinomas, or squamous cell carcinomas, The underlying mesenchymal tissues may give rise to fibromas, fibrosarcomas, hemangiomas, hemangiosarcomas, leiomyomas, or leiomyosarcomas.[1,8]

REFERENCES

1. Maxie GM: The urinary system. In Jubb KVF et al, editors: *Pathology of domestic animals*, ed 4, San Diego, 1993, Academic Press.
2. King AS, McLelland J: Urinary system. In *Birds, their structure and function*, ed 2, London, 1984, Bailliere Tindall.
3. Goldstein RS, Schnellmann RG: Toxic responses of the kidney. In Klaassen CD, editor: *Casarett & Doull's toxicology: the basic science of poisons*, ed 5, New York, 1996, McGraw-Hill.
4. Sitprija V, Chaiyabutr N: Nephrotoxicity in snake envenomation. *J Nat Toxins* 8:271, 1999.
5. Swe TN et al: Russell's viper venom fractions and nephrotoxicity. *Southeast Asian J Trop Med Public Health* 28:657, 1997.
6. Morita T et al: Mesangiolysis: an update. *Am J Kid Dis* 31:559, 1998.
7. Tepperman J, Tepperman HM: Hormonal regulation of calcium homeostasis. In *Metabolic and endocrine physiology*, ed 5, Chicago, 1987, Year Book Medical Publishers.
8. Nielsen SW, Moulton JE: Tumors of the urinary system. In Moulton JE, editor: *Tumors in domestic animals*, ed 3, Berkeley, 1990, University of California Press.