CHAPTER

18

Renal toxicity

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INTRODUCTION

The kidney plays a vital role in maintaining homeostasis through the elimination of waste products, conservation of fluid and electrolyte balance, maintenance of acid–base balance, secretion of hormones and regulatory peptides, and metabolism and excretion of both endogenous compounds and xenobiotics. Although the kidney comprises roughly 0.5% of bodily mass, it receives up to 20–25% of cardiac output which can expose renal tissue to relatively high levels of blood-borne toxicants. The kidney may also be exposed to toxicants through the metabolic activation of xenobiotics by enzyme systems within the renal tubular epithelium, and through the process of urine concentration, the kidney can be exposed to higher concentrations of toxicants than other tissues. Injury to the kidney can lead to widespread systemic derangements, and due to limited regenerative ability, long-term renal insufficiency may result from exposure to nephrotoxic agents.

FUNCTIONAL ANATOMY

Kidneys are paired organs residing ventrolaterally to the lumbar vertebrae in mammals. Mammalian kidneys are bean to horseshoe shaped with uniform exterior surfaces, although some species (e.g., bears, ox, whales) have multilobulated surfaces. Kidneys can be unipyramidal (e.g., horses, dogs, cats) or multipyramidal (e.g., pigs, ox) depending on the number of renal papillae into which renal lobes empty. Mammalian kidneys are of equal size and are roughly the equivalent of three vertebrae in length. The surface of the kidney is covered by a fibrous capsule, and is brown-red in color in most species; in the cat, normal high fat content within the tubules results in a kidney that is a pale, yellow-gray color. Viewed on sagittal section, the kidneys have a medial indented hilar region from which renal artery, renal vein, lymphatics, nerves and ureter emerge. Viewing the cut surface of the sagitally incised kidney, the renal interior can be divided into two distinct sections, the cortex and medulla. The renal cortex in mammals comprises approximately 80% of the renal mass, and the normal cortex to medulla ratio is 1:2 to 1:3 in most species (Maxie and Newman, 2007). The medulla is divided into ray-shaped sections known as renal pyramids, which have their bases at the corticomedullary junction and apices that empty into the renal calyx (cats, ox) or pelvis (dogs, horses). From the hilar region, the ureter directs urine to the distal urinary bladder.

The functional unit of the kidney is the nephron, which is comprised of the renal corpuscle (Bowman's capsule and the glomerulus), proximal tubule, loop of Henle and distal tubule. The number of nephrons per kidney ranges from 200,000 in cats and 400,000 in dogs to 1,000,000 in humans. The ultimate number of nephrons is fixed at birth, although kidneys of altricial offspring of some species (e.g., dog, cat, pig) undergo nephrogenesis for several weeks after birth (Maxie and Newman, 2007). Renal blood flow originates from the renal arteries which are direct branches from the aorta. The kidneys receive 20–25% of cadiac output, allowing the entire plasma volume to be filtered approximately 100 times daily. Renal arteries progressively branch to form interlobar arteries, arcuate arteries, interlobular

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arteries and afferent arterioles, which feed blood to the glomerulus. The high hydrostatic pressure from afferent arterioles provides the force for ultrafiltration of plasma by the glomerulus, a tuft of branching and anastomosing capillaries. The glomerular "sieve" consists of the capillary endothelium, basement membrane and epithelial *podocytes* that anchor foot processes (*pedicels*) within the lamina rara of the glomerular basement membrane (GBM). These pedicels are separated by filtration slits covered by slit diaphragms containing 6–9 nanometer diameter pores through which plasma is filtered, permitting filtration of compounds up to approximately 60 kilodaltons in size. The glomerular mesangium provides the supporting framework for the glomerular capillaries, and is composed of an extracellular matrix, contractile stellate cells which respond to vasoactive hormones and phagocytic cells which are involved in local immune reactions (Khan and Alden, 2002). The distal ends of glomerular capillaries merge to form efferent arterioles that progress further down the nephron and form the peritubular capillary network that surrounds the renal tubules and helps to drive the countercurrent absorption mechanisms responsible for concentration of the urine and regulation of electrolyte balance. The majority of renal blood flow and oxygen is expended in the cortex, making the medulla a relatively hypoxic area of the kidney.

Fluid filtered by the glomerulus enters Bowman's capsule and flows into the proximal renal tubule. The proximal tubule is divided into three segments that differ anatomically and functionally. The most proximal segment, S_1, consists of the convoluted portion of the proximal tubule and possesses epithelial cells with tall brush borders, well-developed lysosome systems and numerous basally located mitochondria. The S_2 segment extends from the end of the convoluted segment to the beginning of the straight segment and constitutes a transition segment. S_2 segment epithelia have shorter brush borders, fewer mitochondria and fewer lysosomes than cells in the S_1 segment. The S_3 segment encompasses the remaining distal portion of the proximal tubule and extends into the outer reaches of the medulla. Oxygen consumption, Na^+/K^+ ATPase activity and gluconeogenic capacity are greatest in the first two segments, while the S_3 segment has higher transport capabilities for some compounds, such as ascorbic acid (Castro *et al.*, 2008). The S_3 segment is also the site for metabolic activation of some toxicants.

In the proximal tubule, passive reabsorption of water and active reabsorption (via Na^+/K^+ ATPases) of sodium occurs. Other solutes reabsorbed by the proximal tubule include potassium, calcium, phosphorus, bicarbonate, glucose, amino acids and proteins, and various xenobiotics, with each segment having a different range of and capacity for reabsorption. For instance, the S_1 segment is primarily responsible for the reabsorption of bicarbonate, glucose, amino acids and low molecular weight proteins. The proximal tubule ultimately reabsorbs 60–80% of solute and water filtered by the glomerulus. Excretory functions of the proximal tubule include the active secretion of weak organic anions and cations. The proximal tubular epithelium possesses cytochrome P450-dependent mixed function oxidases capable of metabolizing a variety of endogenous compounds and xenobiotics. Agents that are biotransformed to toxic metabolites (e.g., acetaminophen) can induce proximal renal tubular injury.

Filtrate passes from the proximal tubule into the loop of Henle, which has a thin-walled descending limb and a thick-walled ascending limb that extend to the level of the outer medullary region. In some nephrons, termed long-looped nephrons, the loop dips deeply into the inner medulla; in these nephrons, the proximal aspect of the ascending limb is thin-walled, becoming thick-walled as the tubule reaches the level of the outer medulla. Countercurrent exchange mechanisms within the loop result in the reabsorption of approximately 20% of filtered water and 25% of filtered sodium and potassium (Schnellmann, 2008). In the thin descending limb, water and interstitial solutes such as urea and electrolytes are able to freely pass into the tubule. At the level of the thin ascending limb, the tubule becomes impermeable to water and urea, and chloride and sodium ions are actively transported via Na^+/K^+ ATPases. Because the loop of Henle resides largely within the poorly oxygenated renal medulla, the high oxygen demand of the Na^+/K^+ ATPases make this segment especially susceptible to hypoxic injury (Brezis *et al.*, 1984).

The macula densa is composed of specialized cells located between the end of the thick ascending limb of the loop of Henle and the most proximal aspect of the distal tubule. This area is in close proximity to afferent arterioles, allowing for communication between the macula densa and afferent arteriole of the same nephron. An increase in intratubular solute concentration at the macula densa results in a feedback signal to the afferent arteriole, resulting in vasoconstriction and reduction of glomerular filtration rate (GFR). This feedback mechanism helps prevent massive loss of fluid and solute in the face of impaired renal tubular absorption. The proximal-most aspect of the renal distal tubule is responsible for reabsorption of most of the remaining intraluminal electrolytes such as sodium and potassium. The remaining segment of the distal tubule and collecting duct absorb remaining sodium, eliminate excessive potassium and hydrogen ions, and absorb additional water (influenced by antidiuretic hormone) as needed to regulate the volume and composition of the urine. Agents that disrupt the osmotic gradient of the medullary region (e.g., by increasing medullary blood flow) can disrupt

the ability of the kidney to concentrate urine. Collecting ducts progressively intersect and anastomose toward the renal papilla and ultimately empty into the renal calyx, renal pelvis, or ureter, depending on species. Peristaltic action of the ureter propels urine toward the urinary bladder for temporary storage and elimination.

In addition to its role in regulation of waste excretion and water/electrolyte balance, the kidney secretes a variety of hormones and regulatory peptides vital for normal systemic homeostasis. Secretion of erythropoietin by renal peritubular interstitial cells promotes red blood cell formation; significant chronic renal disease is often associated with anemia due to decreases in erythropoietin secretion. Renin secreted from the juxtaglomerular cells increases systemic and renal blood pressure and aldosterone release. Prostaglandins and prostacyclin are produced by a variety of renal cells and aid in regulation of renal vascular tone, mesangial contractility and processing of water and electrolytes by the renal tubules. The kidney also plays an important role in the xenobiotic clearance and/or metabolism.

TOXIC EFFECTS ON THE KIDNEY

Acute renal failure

Acute renal failure is defined as an abrupt decrease in renal function leading to retention of nitrogenous wastes (Langston, 2010), and is one of the most common manifestations of nephrotoxic injury (Schnellmann, 2008). The term *acute renal failure* is sometimes used interchangeably with *acute renal insufficiency* or *acute renal injury (AKI)*. The latter term has been suggested as the proper term to use in order to encompass the entire spectrum of renal injury, from minor elevations of serum chemistry values (i.e., blood urea nitrogen and creatinine) to anuric renal failure.

The primary manifestation of AKI is a decrease in GFR leading to an excess of nitrogenous wastes in the blood (azotemia). Decreases in GFR may result from prerenal, renal or postrenal causes. Prerenal causes of decreased GFR include hypovolemia, renal vasoconstriction and poor cardiac output. Postrenal factors include obstruction of the ureters, bladder or urethra (e.g., bladder stones). Primary renal factors that can result in AKI leading to decreased GFR include tubular injury, glomerular injury, interstitial disease and renal vascular compromise. In humans, prerenal factors are said to account from 20 to 80% of cases of AKI, while renal factors account for 10 to 45% and postrenal factors account for 5 to 15% (Langston, 2010). Of causes of primary renal injury, ischemia/reperfusion and nephrotoxicosis are considered to account for over 90% of AKI cases (Schnellmann, 2008). Nephrotoxicants damage the kidneys by a variety of different mechanisms including: (1) direct injury to renal tubular epithelium, leading to epithelial cell necrosis, sloughing and obstruction of tubules by cellular debris (tubular casts), (2) detachment of lethally injured cells from the basement membrane, resulting in backleakage of filtrate across the exposed basement membrane and adherence of detached cells to sub-lethally injured cells still attached to the basement membrane causing lumen obstruction, (3) renal vasoconstriction, resulting in hypoxia and ischemic necrosis of renal structures, (4) damage to the glomerular filtration barrier, and (5) impairment of renal healing and repair (Counts *et al.*, 1995). Most nephrotoxicants exert their damage at the level of the renal tubules, with many toxicants targeting specific segments of the tubules. For instance, aminoglycoside antibiotics cause damage primarily to the S_1 and S_2 segments of the proximal tubule, while mercuric chloride-induced injury is restricted to the S_3 segment at low doses, extending into the S_2 and S_1 segments only at higher doses (Diamond and Zalups, 1998).

The clinical signs of acute renal injury and/or failure can include polydipsia, nausea or vomiting, lethargy, anorexia, weakness, dehydration and polyuria/oliguria/anuria. More severe cases may have halitosis, oral ulceration, abdominal (renal) pain, palpably enlarged kidneys and cardiac arrhythmias. Clinical laboratory abnormalities indicative of AKI include elevations in blood urea nitrogen and serum creatinine (azotemia), hyperphosphatemia, hyper- or hypokalemia and metabolic acidosis. *Uremia* is the term used when azotemia is accompanied by typical clinical signs of AKI. Advanced cases of uremia may present with gastrointestinal ulceration, anemia, peripheral neuropathy, encephalopathy and cardiac dysfunction.

The ability of the kidney to heal following an acute toxic insult is dependent upon several factors including the dose and type of toxicant, the amount of functional kidney remaining, the presence and severity of secondary uremic conditions (e.g., soft tissue mineralization) and the degree of medical intervention and supportive care provided during the acute crisis. Mild to moderate renal tubular injury with retention of tubular basement membranes have a reasonable prognosis for tubular regeneration provided that supportive care is administered until tubules have had a chance to recover. In uncomplicated acute tubular injuries, regeneration of epithelial cells generally begins after about 7–10 days following the renal insult; in mild cases, full recovery of architecture may occur within 2–3 weeks, with longer recovery periods being required for more severe renal injury (Maxie and Newman, 2007). In situations where nephrons have been fully obstructed by cellular debris or crystals, or if basement membrane integrity is lost, regeneration may be incomplete, resulting in

long-term renal insufficiency and/or progression to chronic renal failure.

Chronic renal failure

Chronic renal failure (CRF) is most commonly the result of long-term exposure to toxicants, and many of the alterations seen in CRF are related to the secondary compensatory changes triggered by the initial injury. Upon loss of nephrons (and thus decrease in overall renal GFR), hemodynamic alterations occur that increase the blood flow and pressure to surviving nephrons in an attempt to reestablish normal whole-kidney GFR. Although changes such as increased glomerular pressures can help to maintain overall GFR, these increased pressures may contribute to glomerular sclerosis, tubular atrophy and interstitial fibrosis, thus furthering the progression of renal injury (Brenner *et al.*, 1982). Increased pressure within glomerular capillaries results in an increase in volume of the glomerular tuft, glomerular hypertrophy and intraglomerular hypertension. Consequences of these changes include hyaline accumulation within glomerular capillary walls, mesangial dysfunction associated with matrix accumulation and microaneurysm formation, and thrombosis due to endothelial injury (Polzin, 2010). As the glomerulus expands, podocytes are unable to maintain the integrity of slit diaphragms and focal denudation of GBM occurs, allowing leakage of larger proteins into the glomerular filtrate (proteinuria). In addition to hemodynamically induced progression of CRF, there is evidence to suggest that T-lymphocytes and interleukin-6 contribute to the ongoing interstitial fibrosis in dogs with chronic progressive kidney disease (Yhee *et al.*, 2008).

Clinical effects associated with CRF include uremia, gastrointestinal disorders (uremic gastritis, uremic enterocolitis), polyuria, polydipsia, nocturia, dehydration, atrial hypertension, peripheral neuropathy, uremic encephalopathy, myopathy, anemia, platelet dysfunction, renal secondary hyperparathyroidism, cachexia and hypokalemia (especially in cats) (Polzin, 2010). Immunosuppression is a potential complication of CRF in humans, and studies of dogs with CRF have shown impaired immunological function as well (Kravola *et al.*, 2010). Animals with CRF may show few outward signs of illness until late in the course of their disease; in some instances acute decompensation may occur during periods of physical or emotional stress (Hosseininejad and Hosseini, 2008). Lesions found in animals with CRF include kidneys that are small and irregular in shape, with uneven capsular surfaces. On cut section, pale streaks (fibrosis) may be seen within the interstitium and the parenchyma may be gritty upon cutting due to mineralization and/or crystal deposition.

Patterns of toxic renal injury

Identification of the target site of action of nephrotoxicants can assist in determining the functional impact and potential mechanism of toxicity (Figure 18.1). Toxicants that are directly toxic to cells may cause injury to the glomerulus or the S_1 segment of the proximal tubule as

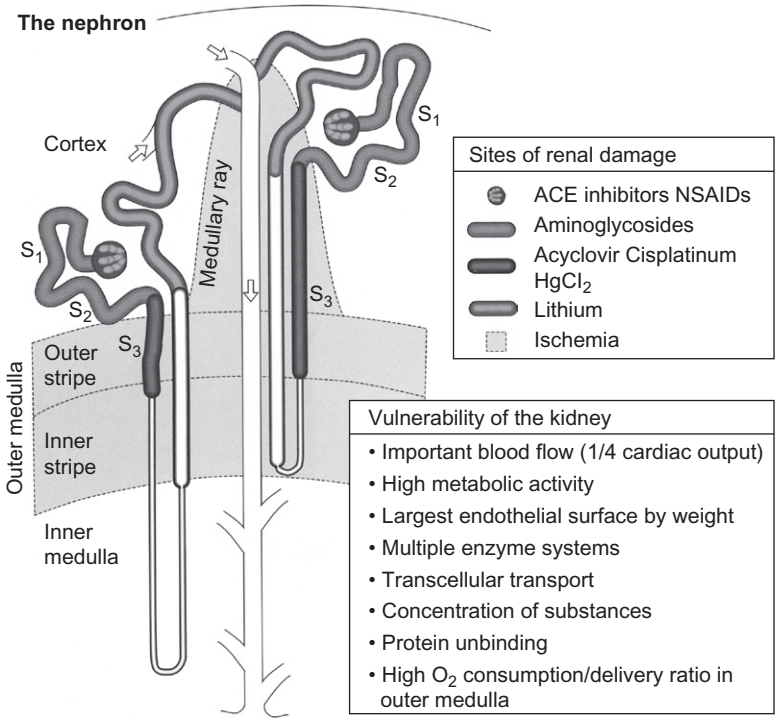

FIGURE 18.1 Sites of renal damage, including factors that contribute to the kidney's susceptibility to damage. ACE: angiotensin converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs; $HgCl_2$: mercuric chloride. (Adapted from Berl T and Bonaventure JV (1998) *Atlas of Diseases of Kidney*, Schrier RW (ed.). Blackwell Publishing, Philadelphia, with permission.)

they first enter the nephron. Conversely, direct-acting toxicants may be dilute in the initial ultrafiltrate, and may not cause injury until they reach the more distant nephron, where they may reach toxic concentrations as water is gradually reabsorbed and/or the pH changes. Some toxicants require bioactivation in order to exert their toxic effects, so they may cause site-specific injury to the S_3 segment of the proximal tubule, where bioactivation processes are most active. A list of nephrotoxicants and their primary sites of action can be seen in Table 18.1.

TABLE 18.1 Urinary tract toxicants listed by site of injury

Toxicant	Species	Lesion	Comment
Glomerular injury			
Bacterial endotoxin (hemolytic-uremia syndrome)	All	Mesangiolysis	Intravascular fibrin deposition of glomerular capillaries (Schwartzman reaction)
Crotalid snake venom	All	Mesangiolysis	Also tubular degeneration
Cyclosporine	Dogs, cats	Thrombotic microangiopathy	
Gold salts	Dogs	Membranous glomerulonephritis	Also acute tubular necrosis, vasculopathy, interstitial fibrosis
Mercury	Ox	Membranous glomerulonephritis; proximal tubule degeneration and necrosis	Affects S_1 segment of proximal tubule
Proximal tubular injury			
Acer rubrum (red maple)	Horses	Acute tubular degeneration and necrosis; hemoglobin casts in tubules	
Acetaminophen	All	Acute tubular degeneration and necrosis	Metabolic activation results in damage to S_3; hepatotoxicity more common
Amaranthus spp.	Herbivores, especially pigs, calves	Acute tubular degeneration and necrosis; perirenal edema	See text for more information
Aminoglycoside antibiotics	All	Acute tubular degeneration and necrosis	Predominantly S_1 and S_2 segments; see text for more information
Amphotericin B	Dogs, cats	Acute tubular degeneration and necrosis; tubular dilatation; glomerular and interstitial mineralization	Arteriolar vasoconstriction results in decrease in GFR
Arsenic	All	Acute tubular degeneration and necrosis, cortical necrosis (dogs)	All segments
Cadmium	All	Acute tubular degeneration and necrosis	Glomerular injury reported in seals[a]
Cantharadin (blister beetle, *Epicuata* spp.)	Herbivores, especially horses	Acute tubular degeneration and necrosis; renal cortical hemorrhages; hyperemia and hemorrhage of mucosa of renal crest, ureter, bladder, urethra	Vesicant effect on mucosa of alimentary tract, cardiac lesions
Carbon tetrachloride	All	Tubular degeneration and necrosis	Hepatic injury most prominent
Cephalosporin antibiotics (and other β-lactam antibiotics)	All	Tubular degeneration and necrosis	High intracellular concentrations in S_3 segment due to action of organic ion transporter result in cell injury
Cholecalciferol (1,25-dihydroxy cholecalciferol, vitamin D_3), calcitriol, calcipotriene, *Cestrum diurnum*, *Solanum* spp., *Trisetum* spp.	All	Tubular degeneration and necrosis; mineralization	Renal ischemia due to vasoconstriction and mitochondrial calcification secondary to hypercalcemia[b]
Cisplatin	Dog	Tubular degeneration and necrosis	Primary effect on S_3 segment due to metabolic activation
Citrinin	All species, pigs most common	Tubular degeneration and necrosis	Primary effect on S_2 segment, thick ascending limb, distal convoluted tubule and collecting ducts; see text for more information
Copper	Sheep, other ruminants less common	Tubular degeneration and necrosis; hemoglobinuric and bile nephrosis (gunmetal kidney)	Non-ruminants develop liver injury without hemolysis
Ethylene glycol	All, dogs and cats most common	Tubular degeneration and necrosis; intratubular calcium oxalate crystals	Oxalate crystals may be found in vessels of meninges, heart, liver, intestinal mucosa; see text for more information

(*Continued*)

TABLE 18.1 (Continued)

Toxicant	Species	Lesion	Comment
Lantana spp.	All grazing animals except horses	Tubular degeneration and necrosis	Lesions primarily in liver; secondary photosensitization; cardiac lesions
Lead	All	Tubular degeneration and necrosis; intranuclear inclusion bodies; karyomegaly of tubular epithelium	
Lilium spp.	Cats only	Tubular degeneration and necrosis; vascular fibrinoid necrosis	See text for more information
NSAIDs (see distal tubule section for phenylbutazone and flunixinmeglumine)	Dogs, cats, vultures, other species likely susceptible	Tubular degeneration and necrosis; occasionally papillary necrosis in dogs	See text for more information
OchratoxinA	All, pigs most commonly affected	Tubular degeneration and necrosis; cystic tubular dilatation; interstitial fibrosis; renal edema in chickens	Primary effect on S_3 segment due to bioactivation;[c] carcinogen; see text for more information
Oosporein	Chickens	Tubular degeneration and necrosis; interstitial pyogranulomatous inflammation and fibrosis	Periodic-acid-Schiff-positive granules in macula densa[d]
Oxalic acid, soluble oxalates (*Halogetonglomeratus*, *Sarcobatusverniculatus*, *Rheum rhaponicum*, *Rumex* spp., *Chenopodium*spp.)	All, ruminants and pigs most common	Tubular degeneration and necrosis; intratubular calcium oxalate crystals	Precipitation of soluble oxalates with serum calcium; hypocalcemic tetany possible
Paraquat	All	Tubular degeneration and necrosis	Pulmonary lesions most common effect (progressive pulmonary fibrosis); corrosive lesions in GI tract
Pine oil	Cats	Tubular degeneration and necrosis	Hepatic lesions more prominent
Pyrrolizidine alkaloids (*Amsinckia*, *Crotolaria*, *Cynoglossum*, *Echium*, *Heliotropium*, *Senecio* spp.)	All, predominantly horses, cattle, pigs	Tubular degeneration and necrosis; megalocytosis of tubular and glomerular cells	Hepatic lesions more prominent; secondary photosensitization, hepatic encephalopathy
Quercus spp. (Oaks)	Grazing animals, cattle most common	Tubular degeneration and necrosis; perirenal edema	See text for more information
Sulfonamide antibiotics	Ruminants	Tubular degeneration; grossly visible intratubular crystals	
Vitis spp. (grapes, raisins, Zante currants)	Dogs	Tubular degeneration and necrosis	See text for more information
Zinc	All	Tubular degeneration and necrosis; hemoglobinuricnephrosis	
Distal tubular/collecting duct injury			
Fluoride	All	Distal tubular degeneration and necrosis	
Melamine:cyanuric acid	Dogs, cats, raccoon dogs, pigs, rats, fish; others likely susceptible	Distal tubular degeneration and necrosis; crystals in distal tubules and collecting ducts	See text for more information
Interstitial injury			
Vicia spp. (vetch)	Grazing animals, primarily cattle	Eosinophilic granulomatous nephritis	Lesions can occur in any organ
Lower urinary tract injury			
Cyclophosphamide	Dogs	Hemorrhage and necrosis of urinary bladder	Bioactivation and concentration of toxic metabolites in urine
Ptaquiloside (*Pteridium* spp., bracken fern)	Cattle	Necrosis and hemorrhage of urinary bladder; urinary bladder neoplasia	Enzootic hematuria
Ptaquiloside (*Sorghum* spp.)	Horses	Necrosis and hemorrhage of urinary bladder	Equine cystitis ataxia syndrome

[a]Sonne-Hansen C, Dietz R, Lieffson PS, Hyldstrup L, Riget FF (2002) Cadmium toxicity to ringed seals (*Phocahispida*): an epidemiological study of possible cadmium-induced nephropathy and osteodystrophy in ringed seals (*Phocahispida*) from Qaanaaq in Northwest Greenland. *Sci Total Environ* **295:** 167–181.
[b]Haschek WM, Rousseaux CG, Wallig MA (2007) Kidney and lower urinary tract. In *Fundamentals of Toxicologic Pathology*, 2nd edn. Academic Press, San Diego, pp. 221–238.
[c]Boorman GA, McDonald MR, Imoto S, Persing R (1992) Renal lesions induced by ochratoxin A exposure in the F344 rat. *Toxicol Pathol* **20**: 236–245.
[d]Brown TP, Fletcher OJ, Osuna O, Wyatt RD (1987) Microscopic and ultrastructural renal pathology of oosporein-induced toxicosis in broiler chicks. *Avian Dis* **31:** 868–877.

Glomerular injury

The glomerular capillaries are the first component of the nephron to be exposed to blood-borne toxicants. The glomerular cells, matrix and mesangium are susceptible to toxic injury by several different mechanisms including direct injury to cellular components, formation of oxygen-derived free radicals, disruption of extracellular substrates (e.g., basement membranes), immune-mediated injury and disruption of renal hemodynamics (Khan and Alden, 2002). Direct injury or injury secondary to reactive oxygen intermediates can result in endothelial loss, glomerular podocyte injury and necrosis of mesangial cells and substrate (mesangiolysis). Further damage may occur secondary to cytokines released by inflammatory cells responding to the site of injury. Alterations in the GBM secondary to cellular injury can result in disruption of the glomerular filtration barrier, leading to proteinuria. Deposition of and immune-mediated reaction to various toxicants (e.g., mercurial, gold salts) can result in thickening of the GBM, disrupting the glomerular filtration barrier and leading to membranous glomerulonephropathy.

Proximal tubular injury

Tubular injury is the most common pattern of renal injury induced by toxicants and the proximal tubule is most frequently affected by nephrotoxicants (Schnellmann, 2008). Damage to the proximal tubule may occur due to direct damage from toxicants, metabolic activation of toxicants, ischemia-reperfusion or physical or chemical disruption of endothelium and/or basement membrane. The S_1 segment is the most vulnerable to injury from toxicants that exert direct injury as the epithelium in this area is exposed to the toxicant first. The proximal convoluted tubule epithelium is actively involved in endocytosis of various compounds that bind to the brush border, sequestering the compounds in phagolysosomes. When this process is overwhelmed by the presence of certain toxicants (e.g., aminoglycoside antibiotics), loss of phagolysosome membrane integrity occurs, resulting in lysosomal leakage and cell injury or necrosis (Khan and Alden, 2002). This type of injury is most commonly associated with the S_1 and S_2 segments of the proximal tubule. In contrast, the straight segment (S_3) is most susceptible to injury by metabolic activation, transporter-associated accumulation and ischemia reperfusion.

Distal nephron/renal papillary injury

Toxic injury to the distal nephron is relatively uncommon, and injury to this area generally manifests as decreased urine concentration ability or defects in acid secretion. Injury to the renal papilla is most commonly seen with chronic consumption of non-steroidal anti-inflammatory drugs (NSAIDs), although use of NSAIDs in hypovolemic animals or in conjunction with other nephrotoxicants (e.g., aminoglycoside antibiotics) has also been associated with the development of renal papillary necrosis (Talcott, 2006).

NEPHROTOXIC AGENTS

Mycotoxins

Ochratoxins

Ochratoxins are produced by various species of the fungi *Aspergillus* and *Penicillium* and are produced on a variety of cereal grains, cottonseed, nuts, dried beans and coffee beans (Haschek *et al.*, 2002). OchratoxinA (OTA) is the most common and most toxic of the ochratoxins that have been identified to date. The co-production of penicillic acid by *Penicillium ochraeus* or citrinin by *Aspergillus* spp. or *Penicillium* spp. greatly enhances the toxicity of OTA (Haschek *et al.*, 2002; Kumar *et al.*, 2007). OTA is thought to be the causative factor in endemic Balkan nephropathy of humans (Maxie and Newman, 2008). Ochratoxin toxicosis has been reported in a variety of animal species including swine, ducklings, horses, chickens, rabbits, turkeys, dogs and fish (Kitchen *et al.*, 1977; Hascheck *et al.*, 2002; Kumar *et al.*, 2007; El-Sayed *et al.*, 2009). Cattle are thought to be resistant due to degradation of ochratoxins within the rumen, although pre-ruminant calves are susceptible (Haschek *et al.*, 2002). In domestic animals, ochratoxicosis is most commonly reported in pigs and chickens as a subchronic to chronic disease affecting growth and production (Maxie and Newman, 2008; Sakthivelan and Sudhakar Rao, 2010). Pigs are considered to be the most sensitive species, with chronic toxicosis occurring following ingestion of diets containing 0.2–4 ppm OTA, while broiler chickens develop toxicosis at 2 ppm OTA (Haschek *et al.*, 2002). The renal lesions in pigs consist of proximal tubular degeneration and atrophy with interstitial fibrosis and infiltration by mononuclear cells. Cystic dilatation of degenerated tubules occurs, which can lend a pitted, irregular appearance to the renal capsule, and glomerular hyalinization has been reported in severe cases. In acute cases, perirenal edema may occur (Maxie and Newman, 2008). Additional lesions of OTA toxicosis in pigs include multifocal necrotizing enteritis, fatty degeneration of the liver and lymphoid necrosis (Szczech *et al.*, 1973). In broilers, OTA causes renal edema and renal tubular necrosis (Huff *et al.*, 1975). OTA is teratogenic,

mutagenic and carcinogenic, inducing renal tumors in rats (Haschek *et al.*, 2002).

Citrinin

Citrinin is produced by toxic strains of several *Penicillium*, *Aspergillus* and *Monascus* spp. (Bennett and Klich, 2003), and has been associated with rice, wheat, oats, rye, corn, barley, vegetarian foods colored with red *Monascus* pigments and naturally fermented sausages from Italy. Citrinin is often found in association with OTA and is less toxic than OTA (Kitabatake *et al.*, 1993). Dogs receiving citrinin at dosages of 80 micromoles/kg intravenously or 10 mg/kg orally developed proteinuria and glucosuria and ultrastructural changes in the epithelium of the S_2 segment, thick ascending limb, distal convoluted tubule and collecting ducts (Kitchen *et al.*, 1977; Krejci *et al.*, 1996). Dogs given oral 10 mg/kg citrinin twice at 24 hour intervals developed similar lesions and developed glucosuria, proteinuria and granular casts in the urine; glucosuria was the earliest abnormality noted and persisted for 5 days, as did proteinuria (Kogika *et al.*, 1993). Cylindruria persisted from days 1 to 15, and renal values (BUN, creatinine) were elevated from days 2 to 5. Clinical signs in dogs administered 10 mg/kg citrinin per day for 14 days included anorexia, retching, tenesmus, weight loss, prostration and death. Citrinin is teratogenic, embryotoxic and a putative carcinogen.

Drugs

Aminoglycoside antibiotics

Aminoglycoside antibiotics exert their nephrotoxic effects through induction of apoptosis and necrosis within the renal tubular epithelial cells of the proximal convoluted tubule as well as the distal tubules and collecting ducts (Lopez-Novoa *et al.*, 2011). Within these cells, aminoglycosides internalized though endocytosis accumulate in lysosomes, Golgi apparatus and endoplasmic reticulum. As the aminoglycoside concentration increases beyond a threshold level, the endosomal membranes become disrupted and the drug leaks into the cytosol where it activates the intrinsic apoptotic pathway, increases production of reactive oxygen intermediates, and interacts with mitochondria to interrupt the respiratory chain. Interaction with endoplasmic reticulum and Golgi apparatus result in dysfunction in protein synthesis and packaging. In sub-lethally affected cells, aminoglycosides interfere with cell membrane transporter systems, altering tubular reabsorption and threatening epithelial cell viability. Cellular necrosis and apoptosis result in the accumulation of cellular residues in the tubular lumen, causing obstruction which increases the intratubular hydrostatic pressure. This back-pressure results in leakage of ultrafiltrate into the interstitium and peritubular capillaries and reduces the glomerular filtration pressure gradient, resulting in decrease in GFR. Aminoglycosides also have some direct glomerular effects including mesangial contraction, mesangial cell proliferation and alteration of filtration barrier selectivity. Toxicosis from aminoglycosides results in loss of urine concentration ability, polyuria, proteinuria, hematuria, cylindruria, azotemia and acute renal failure. In spite of the significant renal injury that may develop due to aminoglycoside exposure, the renal effects are generally considered reversible once the drug is withdrawn (Maxie and Newman, 2008). Additional adverse effects of aminoglycoside antibiotics include ototoxicity and induction of neuromuscular blockade.

NSAIDs

Non-steroidal anti-inflammatory drugs are the most widely used analgesics in veterinary medicine and are the most common drugs involved in accidental overdoses in companion animals (Sebastian *et al.*, 2007; Gwaltney-Brant, 2007). In both therapeutic and overdose situations, the potential of most NSAIDs to have deleterious effects on the kidney must be considered. The adverse effects of NSAIDs on the kidney result from the inhibition of cyclooxygenases (COX) which results in decreased synthesis of prostaglandins (PGs). COX has two distinct isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues through the body while COX-2 is normally expressed in tissues at low levels, but can be induced in the presence of pro-inflammatory mediators that are expressed in sites of inflammation, pain or injury (Radi, 2009). COX-1 is the most abundant isoform expressed in the kidneys, and is located in the renal vasculature, collecting ducts and papillary interstitial cells. COX-2 is minimally expressed in the kidney and its localization within the different areas and impact on production of PGs in the kidney is species and maturation dependent. The kidney is a major site of PG synthesis, and PGs exert a variety of diverse functions within the kidney, including modulation of renal blood flow and GFR, regulation of sodium excretion and influencing renin release. PGs produced through the action of COX-1 are considered "protective," as inhibition of these PGs is associated with the majority of adverse effects from NSAIDs. NSAIDs such as ibuprofen are non-selective inhibitors of both COX isoforms, while newer NSAIDs may target COX-2, sparing COX-1 and resulting in fewer gastrointestinal and renal adverse effects (Khan and Alden, 2002). However, COX selectivity can be lost in overdose situations. The primary impact of COX-induced inhibition of PG synthesis in the kidney is reduction of renal blood flow, resulting in ischemia. The medulla and renal papillae

are at increased risk for NSAID-induced hypoxic injury due to their low oxygenation and relatively slow blood flow that predisposes to accumulation of toxic substances (Radi, 2009). Dogs, rats, mice and pigs are thought to be most sensitive to NSAID-induced papillary necrosis (Khan and Alden, 2002). Clinical effects of NSAID-induced renal injury include polyuria, polydipsia, dehydration, electrolyte imbalances and azotemia. Acute renal failure, interstitial nephritis and nephrotic syndrome have also been reported. Non-renal effects of NSAIDs include gastrointestinal ulceration.

Metals

Cadmium

The primary sources of exposure to cadmium are due to contamination of food, water and air. Cadmium in soil can be taken up by plants, and cadmium in water can bioaccumulate in shellfish. Inhalation exposure to cadmium can occur through exposure to industrial exhaust, fossil fuel combustion products and cigarette smoke; the latter is one of the major non-occupational sources of inhaled cadmium in humans (Gwaltney-Brant, 2002). Acute cadmium toxicosis primarily manifests as pulmonary injury, while nephrotoxicity resulting from cadmium is most commonly due to chronic exposure. Cadmium is poorly absorbed via the gastrointestinal tract, with less than 5% of ingested cadmium being absorbed; however, inhaled cadmium is more readily absorbed into the blood, where it binds to metallothionein, a 6800 dalton, cysteine-rich protein. Metallothionein transports cadmium primarily to the kidney and liver, with lesser amounts accumulating in bone and testicle. The cadmium–metallothionein complex is filtered through the glomerulus and reabsorbed from the filtrate into the proximal renal tubules by endocytosis (Khan and Alden, 2002). Within the phagolysosome, metallothionein is hydrolyzed, which releases the cadmium; the free cadmium triggers the *de novo* synthesis of additional metallothionein. Once the level of intracellular cadmium exceeds a species-specific threshold of tolerance (10–200 mcg/g wet weight), cellular injury progresses. Cadmium-injured cells have decreased reabsorptive capacity and decreased ability to concentrate urine (Gwaltney-Brant, 2002). Low molecular weight proteinuria (particularly β_2-microglobulinuria), amino aciduria, calciuria and glucosuria develop. Renal lesions include proximal tubular cell degeneration and necrosis, granular casts, hyaline casts, tubular atrophy, interstitial inflammation and interstitial fibrosis. Additional chronic renal lesions include fatty degeneration of pars recta tubular epithelium, nephrocalcinosis and glomerular disease resembling immune complex glomerulonephritis. Extra-renal effects of cadmium include osteoporosis and osteopenia, hepatocellular necrosis, myocardial injury and testicular injury. Cadmium is a mutagen and putative carcinogen.

Lead

The incidence of lead toxicosis has declined in the United States since the banning of lead-based paints in residential domiciles in 1977 and leaded gasoline in 1996 (with significant reductions in use of leaded gasoline for the prior 20 years). However, lead is still present in the paint of many older homes as well as common household items such as toys, artists' paints, linoleum, lead weights, lead fishing sinkers and ornaments. Additionally, despite bans on the use of lead shot for hunting waterfowl lead ammunition is still widely used on upland game, and lead toxicosis is still a significant cause of death among scavengers such as eagles and condors (Hunt *et al.*, 2009; Stauber *et al.*, 2010). Birds with lead toxicosis frequently present with emaciation and evidence of renal tubular degeneration (Pattee *et al.*, 2006). Acute lead toxicosis is most commonly associated with neurological signs in mammals, while chronic lead toxicosis can result in dysfunction of a variety of organ systems including gastrointestinal, neuromuscular, central nervous, hematological and renal (Gwaltney-Brant, 2002). Degeneration and necrosis of proximal renal tubules results in oliguria, amino aciduria, glucosuria and altered tubular ion transport. Acute renal failure may occur following exposure to lead, but chronic renal failure is more common. Dense, homogeneous, eosinophilic intranuclear inclusion bodies may be visualized in affected renal tubular cells; although suggestive for lead toxicosis, these inclusions are not pathognomonic as they can occur following exposure to other metals such as bismuth.

Plants

Amaranthus spp.

The pigweed family includes several different species capable of producing toxicosis, but *Amaranthus retroflexus* is the species most commonly associated with disease in domestic animals (Burrows and Tyrl, 2001). Renal injury from pigweed has been reported in pigs, cattle and sheep. Other herbivorous species are likely susceptible, although the disease was not able to be reproduced in rabbits fed *A. retroflexus* (Schamber and Misek, 1985). The toxic principle is not known. Although pigweeds do contain some oxalates, the levels are low and the clinical syndrome and lesions caused by pigweed toxicosis are not consistent with those seen in oxalate nephrosis (Burrows and Tyrl, 2001). Clinical signs generally begin

following several days of ingesting the plant, although renal lesions have been identified within 24 hours of ingestion. Clinical signs include weakness, ataxia, knuckling of pasterns, recumbency, paralysis and coma; death occurs within 1–2 days of onset of signs. Gross lesions of pigweed toxicosis include widespread edema, most prominently around the kidneys, rectum and omentum. Kidneys are pale and normal to swollen in size. Histopathologic changes within the kidney include interstitial edema, scattered hemorrhages and proximal tubular degeneration and necrosis. Dilated tubules and tubules filled with necrotic debris are often present and interstitial fibrosis may be present in chronic cases. Extra-renal lesions include edema and ulceration of the digestive tract.

Lilium spp. and Hemerocallis spp.

Ingestion of some species of the genera *Lilium* and *Hemerocallis* (Table 18.1) by cats has resulted in a potentially fatal renal dysfunction that has not been successfully reproduced in other species including dogs, rats and rabbits (Rumbeiha *et al.*, 2004). Although the toxic principle remains unknown, Rumbeiha *et al.* were able to demonstrate that the toxic effects originated from an aqueous floral extract of the Easter lily. All parts of the plant, including pollen, are toxic, and even small ingestions can result in significant renal injury (Fitzgerald, 2010). Prevention of serious renal injury can often be achieved if aggressive intravenous fluid therapy is instituted within the first 18 hours following exposure. Clinical effects include vomiting, depression, polyuria, polydipsia, azotemia, glucosuria, proteinuria and isosthenuria. Serum creatinine levels tend to elevate disproportionately to blood urea nitrogen. Histopathologic lesions include proximal convoluted tubule degeneration and necrosis with denudation of basement membrane and filling of tubular lumens with cellular debris (Rumbeiha *et al.*, 2004). Extra-renal lesions include vacuolar degeneration of pancreatic acinar cells.

Quercus spp.

Oak foliage and acorns provide forage to a variety of wildlife and livestock, but when oak is the primary source of feed for more than a few days, toxicosis can develop (Burrows and Tyrl, 2001). Oak buds, acorns and young leaves are involved in the majority of reported livestock poisonings and most oak species have, at one time or another, been implicated in animal poisonings. Cattle are most commonly affected, and reports in other species such as horses, goats and sheep are rare. The primary toxic principles in oak are tannins, phenolic and polyphenolic compounds such as ellagic and gallic acids, and tannin metabolites such as pyrogallol. At toxic doses, oak tannins precipitate proteins in the digestive tract, causing erosions and ulcerations as well as altering mucosal absorption barriers. Increased absorption of polyphenolic tannins via injured mucosa results in damage to the liver and kidney; in rats, gallic acid was identified as the compound responsible for renal tubular necrosis (Harris *et al.*, 1966). Clinical signs begin 2 days to a week or longer after animals have been consuming large amounts of oak. Affected cattle initially develop anorexia, depression, rumen stasis and constipation which are followed by diarrhea (+/− blood), dehydration, colic, polyuria and subcutaneous edema of ventral areas such as neck, brisket, abdomen and perineum (Panciera, 1978). Clinical pathologic evaluation of serum reveals metabolic acidosis, elevations in BUN and serum creatinine, and electrolyte abnormalities (e.g., hyperkalemia). Cattle with severe renal injury become weak and die, while less severely affected animals may survive, although many will become chronically debilitated due to persistent renal insufficiency (Burrows and Tyrl, 2001). The disease progression is similar in other species, though sheep and goats do not develop appreciable edema and horses tend to have more severe diarrhea (+/− blood), colic and tensmus. Gross findings include fluid accumulations within body cavities, subcutaneous edema, mesenteric edema and retroperitoneal edema (especially perirenal). Kidneys are swollen, pale and may have petechiae within the cortex; chronic cases may have shrunken, irregular and fibrotic kidneys. Extra-renal lesions include edema, congestion, erosions and ulcerations of the alimentary tract mucosa and some cases may have hepatocellular degeneration.

Vitis spp.

Ingestion of members of *Vitis* spp., including grapes, raisins and Zante currants, has been associated with acute renal failure in dogs (Morrow *et al.*, 2005) and, anecdotally, cats and ferrets (ASPCA Animal Poison Control Center, unpublished data). The toxic principle is unknown, but attempts to identify known nephrotoxins such as mycotoxins, pesticides, vitamin D_3 and heavy metals have been unsuccessful. Affected dogs generally demonstrate vomiting and/or diarrhea within 12 hours of ingestion of grapes or raisins, accompanied by anorexia, lethargy and abdominal discomfort in some cases (Morrow *et al.*, 2005). Severely affected dogs rapidly progress to anuria, and death or euthanasia occurs within 23–289 hours. Histopathological changes in the kidney include renal tubular degeneration and necrosis, primarily in the proximal tubules. Extensive sloughing of proximal tubule epithelium results in extensive necrotic debris within tubular lumens. Extra-renal lesions consist of centrilobular hepatic degeneration or necrosis, myocardial necrosis, soft tissue mineralization and fibrinous arteritis in colon, myocardium and aorta.

Miscellaneous

Ethylene glycol

The most common cause of ethylene glycol toxicosis in domestic animals is via the consumption of automotive antifreeze, and dogs and cats are the most commonly affected species, although all mammals are susceptible to toxicosis. Ethylene glycol intoxication has three distinct stages: (1) initial CNS depression and derangement due to an alcohol-like effect on the brain, (2) profound metabolic acidosis with significant cardiorespiratory effects due to formation of acidic metabolites of ethylene glycol and (3) acute renal failure due to renal tubular injury (Thrall *et al.*, 2006). Renal tubular injury is due to direct action of the nephrotoxic metabolites glycoaldehyde and glyoxylate on the renal tubules as well as mechanical injury and obstruction by calcium oxalate crystals (Thrall *et al.*, 2006; Maxie and Newman, 2007). Calcium oxalate crystalluria is considered by some to be a hallmark of ethylene glycol, but crystalluria is present in less than half of all intoxications. Therefore, the absence of oxalate crystals does not eliminate ethylene glycol as a potential toxicant. Renal changes associated with ethylene glycol intoxication include pale, swollen kidneys, which may be gritty when cut. Microscopically, proximal tubular degeneration and necrosis is associated with the deposition of birefringent, light yellow crystals arranged in sheaves, rosettes or prisms (Maxie and Newman, 2007). Oxalate crystals may also be found within tubular lumens, within renal tubular epithelial cells and within the interstitium (Figure 18.2). Animals surviving more than a few days may show areas of tubular regeneration and/or interstitial fibrosis. Extra-renal lesions may include deposition of oxalate crystals within small vessels of the brain, heart, liver and intestinal mucosa.

Melamine:cyanuric acid

In North America in 2007, the discovery of renal injury in dogs and cats ingesting commercial pet foods led to the recall of over 60 million cans and pouches of "cuts and gravy"-style pet food contaminated with melamine and cyanuric acid. The contamination was found to have originated in wheat gluten from China, where the melamine had been added to artificially inflate the apparent protein level of the product. Cyanuric acid is a hydrolysis product of melamine that may also have either been intentionally added or coincidentally present as a melamine by-product (Puschner *et al.*, 2007). Subsequent to the pet food recall of 2007, the contamination of various food sources by melamine has been identified in several countries around the world including Italy, China, Spain, Korea, Taiwan and other Asian countries (Brown *et al.*, 2007; Gonzalez *et al.*, 2009; Yhee *et al.*, 2009; Brown and Brown, 2010; Cocch *et al.*, 2010). By themselves, melamine and cyanuric acid are of low toxicity, but in combination these compounds precipitate in acidic environments to form melamine cyanurate crystals (MCA) (Puschner *et al.*, 2007). In animals ingesting feed containing melamine and cyanuric acid, precipitation of MCA in the renal tubules has been associated with tubular injury, interstitial edema and renal failure. The exact mechanism of renal injury is not known, although mechanical injury from deposition of the large crystals is likely contributory. In cats, acute renal failure was induced within 48 hours following oral administration of 32 mg/kg

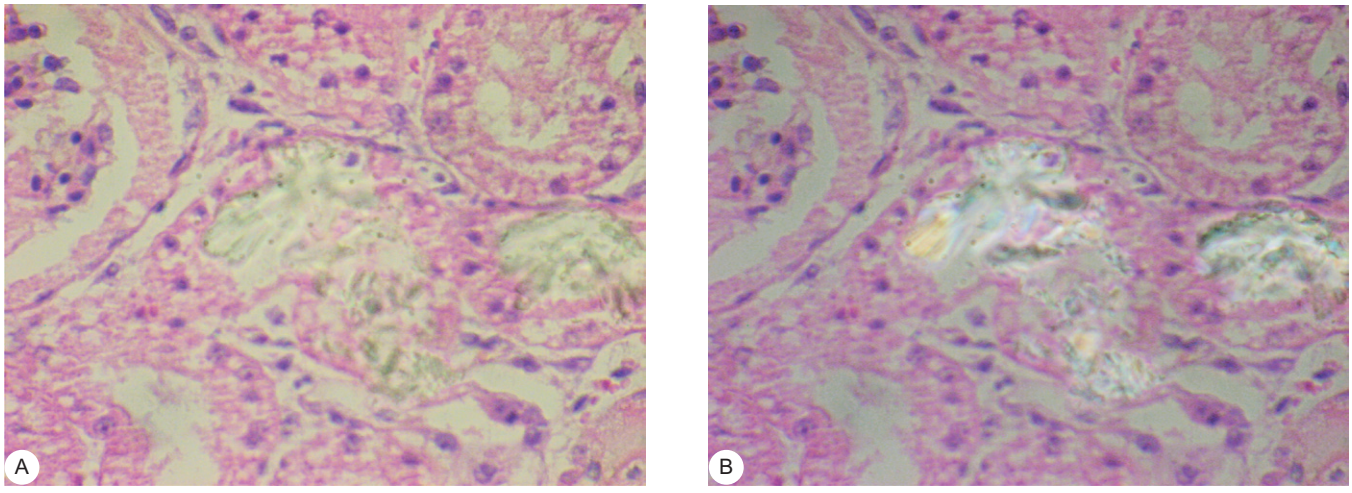

FIGURE 18.2 Ethylene glycol poisoning, canine kidney. A. Tubules are lined by degenerate and attenuated epithelium and contain crystalline material consistent with calcium oxalate crystals. H&E stain, 100 × . (Photo courtesy Thomas Brant, Mahomet, IL.) B. Tubules contain birefringent crystalline material consistent with calcium oxalate crystals. H&E stain, 100 ×, utilizing polarized light. (Courtesy Thomas Brant, Mahomet, IL.).

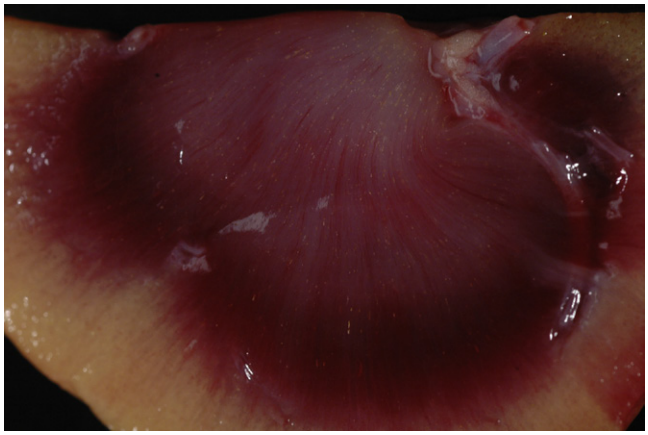

FIGURE 18.3 Melamine:cyanurate crystals, feline kidney. The corticomedullary junction is obscured by a broad, dark red band of hemorrhage. Fine dots of 0.1 cm long threads of an opaque, variably white to yellow substance (i.e., crystals) are observed. These crystals extend from the papilla of the medulla into the obscured corticomedullary junction and are in parallel with the medullary rays. They are most concentrated at the renal crest. (Courtesy of Drs. Patricia Pesavento and Birgit Puschner, Univerity of California, Davis.).

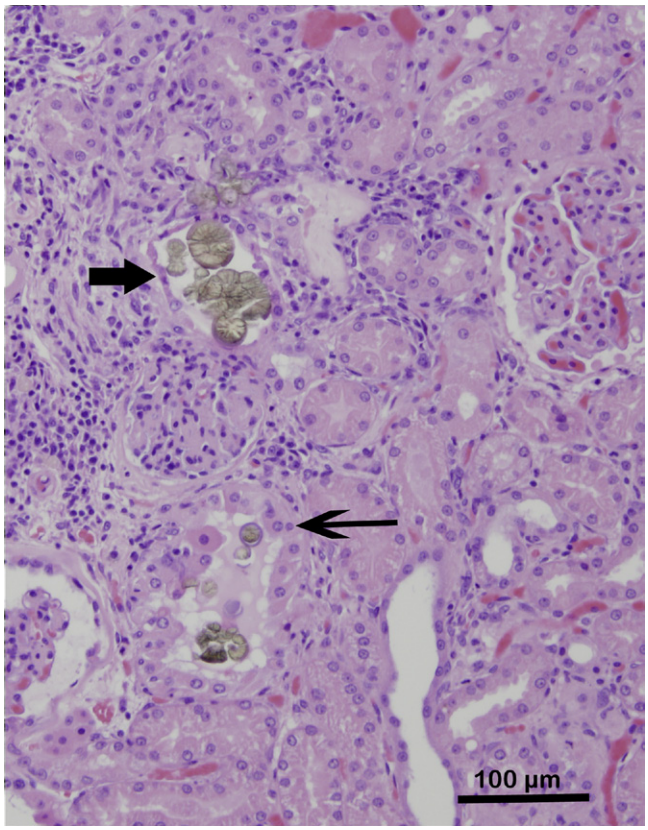

FIGURE 18.4 Melamine:cyanurate crystals, canine kidney. Renal tubular epithelium is attenuated and the lumen is expanded by variably sized, fan-shaped to starburst, gray-brown crystals (thick arrow). Another tubule has attenuated epithelium and detached and necrotic cells, proteinaceous fluid and smaller crystals within the lumen (thin arrow). Inflammatory cells are present within the adjacent interstitium. H&E, Bar = 100 µm. (Courtesy of University of California, Davis Anatomic Pathology.).

of melamine and cyanuric acid. MCA-induced nephropathy has been documented in humans, pigs, dogs, cats, fish, raccoon dogs and rats (Reimschuessel *et al.*, 2008; Bhalla *et al.*, 2009; Gonzalez *et al.*, 2009; Yhee *et al.*, 2009; Brown and Brown, 2010), although most species are likely susceptible. Affected animals develop clinical signs typical of renal injury: vomiting, anorexia, lethargy, polyuria/oliguria and dehydration. Renal lesions include hemorrhage and edema of the interstitium, predominantly in the medullary region (Figure 18.3). Degeneration and necrosis of the distal straight tubules is associated with the presence of large, translucent, pale yellow to brown, fan-shaped to starburst to globular crystals (Figure 18.4) (Puschner *et al.*, 2007). Crystals are also present in collecting ducts. The presence of these crystals in the more distal tubules, in addition to their morphology, can help to distinguish MCA from calcium oxalate crystals, which are found in the proximal tubules and tend to be smaller with variable shapes and sizes.

CONCLUSIONS

The vital role that the kidney plays in maintaining homeostasis makes renal injury due to nephrotoxic agents a serious and potentially life-threatening problem. In many instances, prevention of renal injury can be achieved through proper gastrointestinal decontamination and implementation of aggressive intravenous fluid therapy following exposure to nephrotoxicants. Once renal injury has developed, veterinary intervention is essential in order to support the patient through the acute crisis and to allow time for regeneration and repair of injured renal tissues. Depending on the extent of injury and degree of regeneration, the patient may fully recover, may be left with residual renal insufficiency or may progress to chronic renal failure.

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