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CHAPTER 11

The Urinary System[1]

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Key Readings Index

Kidney[2]

Structure

Mammalian kidneys are paired organs present in the retroperitoneum, ventrolateral and adjacent to the lumbar vertebral bodies and their corresponding transverse processes. These complex organs, which function in excretion, metabolism, secretion, and regulation, are susceptible to disease insults that affect the four major anatomic structures of the kidney: the glomeruli, tubules, interstitium, and vasculature. Because of the limited ways that renal tissue can respond to injury and the limited patterns of injury, in severe and prolonged disease, the endpoint will be similar—chronic renal disease and failure. Interdependence between components of the nephron also are responsible for producing a narrow range of repeatable injury patterns, which students can come to recognize on gross or histologic assessment.

Macroscopically, kidneys are organized functionally and anatomically into lobules. Each lobule represents collections of nephrons separated by the medullary rays. Renal lobules should not be confused with renal lobes. Each lobe is represented by a renal pyramid (Fig. 11-1). Among domestic animals, carnivores and horses have unilobar kidneys. Porcine and bovine kidneys are multilobar, but only bovine kidneys have external lobation (Fig. 11-2). A diffuse fibrous capsule that in normal kidneys can be easily removed from the renal surface covers the kidneys. The renal parenchyma is divided into a cortex and medulla (see Fig. 11-1). The corticomedullary ratio is usually approximately 1:2 or 1:3 in domestic animals. The ratio varies among species; for example, those adapted to the desert have a far larger medulla and thus a corticomedullary ratio that can approach 1:5. Normally the cortex is radially striated and dark red-brown except in mature cats, in which the cortex is often yellow because of the large lipid content of tubular epithelial cells. The renal medulla is pale gray to tan and has a single renal papilla, as in cats; a fused, crestlike papilla (renal medullary crest), as in dogs, sheep, and horses; or multiple renal papillae, as in pigs and cattle. The medulla generally can be subdivided into an outer zone, that portion of the medulla close to the cortex, and an inner zone, that portion closer to the pelvis. Papillae are surrounded by minor calyces that coalesce to form major calyces, which empty into the renal pelvis (Fig. 11-3), where urine collects before entry into the ureters.

Microscopically, for ease of discussion, the kidney (and nephron) can be divided into four structural units: renal corpuscle (glomerulus and Bowman's capsule), tubules, interstitium, and vasculature. The functional unit of the kidney is the nephron, which includes the renal corpuscle and renal tubules (the tubular system includes the proximal convoluted tubules, the loop of Henle, and the distal convoluted tubule). The uniniferous tubule is composed of the nephron and the collecting ducts, which are embryologically distinct from the renal tubules (Fig. 11-4). The uniniferous tubule is embedded structurally in the renal interstitium formed by a meshwork composed of stromal cells such as fibroblasts. The interstitium also contains the renal vasculature, which supplies blood first to the glomerulus and then to the renal tubules.

Glomerulus (Glomerular Tuft, Renal Corpuscle)

Macroscopically, glomeruli are difficult to detect in the normal kidney but can be accentuated by lesions that allow them to be identified on cut section as randomly distributed granular foci or as red dots throughout the cortex (Fig. 11-5). Microscopically, the glomerulus is a complex, convoluted tuft of fenestrated endothelial-lined capillaries held together by a supporting structure of cells in a glycoprotein matrix, the mesangium (see Fig. 11-5). The entire glomerulus is supported by mesangial matrix that is secreted by the mesangial cells, a type of modified pericyte. Mesangial cells are pluripotential mesenchymal cells, which are contractile and phagocytic (see E-Figs. 11-5 and 11-6) and capable of synthesizing

[1]For a glossary of abbreviations and terms used in this chapter, see E-Glossary 11-1.

[2]See E-Appendix 11-1 for methods of examining the kidney.

E-Glossary 11-1 Glossary of Abbreviations and Terms

ADH–Antidiuretic hormone
Azotemia–Excess of urea, creatinine, and other nitrogenous waste products in the blood
Bowman's capsule–Double-walled, cup-shaped dilation that surrounds the glomerulus and forms the beginning of the nephron. The inner wall is called the visceral layer, and it is composed of podocytes that closely surround the glomerular capillary tuft. The outer wall is called the parietal layer, and it forms Bowman's capsule proper, which becomes continuous with the beginning of the renal tubule.
Bowman's space–The space between the visceral and parietal layers of Bowman's capsule into which the glomerular filtrate passes before emptying into the proximal convoluted tubule. Bowman's space is also called the capsular space.
Collecting ducts–The straight terminal portion of nephrons that descend through the cortex as medullary rays and merge in the medulla to ultimately open at the tips of renal papillae, where they discharge urine into the calyces or renal pelvis
C3–Complement
DIC–Disseminated intravascular coagulation
Distal convoluted tubule–A continuation of the thick limb of the loop of Henle that is responsible for reabsorption of sodium ions
ECM–Extracellular matrix
FeLV–Feline leukemia virus
FIC–Feline idiopathic cystitis
FIP–Feline infectious peritonitis
FIV–Feline immunodeficiency virus
FLUTD–Feline lower urinary tract disease
Foot processes of podocytes–Specialized cytoplasmic processes of podocytes that interdigitate to form filtration slits through which glomerular filtrate enters Bowman's space (uriniferous space)
Glomerular basement membrane (GBM)–Also called the basal lamina, the glomerular basement membrane is the most important barrier of the renal corpuscle. It is a shared basement membrane that lies between the fenestrated endothelium of the glomerular tuft and the podocytes of the visceral layer of Bowman's membrane.
Glomerular filtrate–Fluid filtered from plasma into the urinary space (Bowman's space) after passage through the glomerular filtration barrier. It contains water, salts, ions, glucose, and albumin.
GFR–Glomerular filtration rate
Glomerulonephritis (GN)–Glomerular inflammation accompanied by secondary changes of the renal tubules and interstitium
Glomerulosclerosis–Fibrosis and scarring of glomeruli
Glomerulus–Capillary tuft that is the site of blood filtration in the kidney; together with Bowman's capsule, it constitutes a renal corpuscle
Glucosuria–The presence of glucose in the urine
Hematuria–The presence of blood, specifically red blood cells, in the urine
Hemoglobinuria–The presence of free hemoglobin in the urine, usually as a result of intravascular hemolysis
ICGN–Immune complex glomerulonephritis
Juxtaglomerular complex (juxtaglomerular apparatus)–Renal structure involved in the regulation of systemic blood pressure through the renin-angiotensin-aldosterone system. It is composed of juxtaglomerular cells, the macula densa, and the extraglomerular mesangial cells.
Loop of Henle–The distal straight segment of the proximal tubule, including the thin descending and ascending limbs and the thick ascending limb
Macula densa–Part of the juxtaglomerular apparatus that is a region of specialized epithelial cells in the distal convoluted tubule where it abuts the vascular pole of the glomerulus. Cells of the macula densa sense sodium concentration in the distal convoluted tubule and play a role in regulating systemic blood pressure.
Mesangial cells–Pluripotential modified pericytes that are contractile and phagocytic and are able to synthesize collagen and mesangial glycoprotein matrix
Mesangium–Glycoprotein matrix that is secreted by mesangial cells and supports capillary loops of glomerular tufts
Micturition–The discharge of urine from the urinary bladder; urination
Myoglobinuria–The presence of myoglobin in the urine, usually as a result of substantial muscle injury
Nephron–The functional unit of the kidney, including in the renal corpuscle and renal tubules (proximal convoluted tubule, loop of Henle, and distal convoluted tubule)
Nephritis–Inflammation of the kidney that may be focal or diffuse and involve varying combinations of glomeruli, tubules, and renal interstitium
Nephrolithiasis–The formation of calculi or stones (uroliths) within the kidney, typically within the renal pelvis
Nephropathy–Broad term indicating any disease of the kidney
Nephrosis–A form of acute tubular injury not caused by inflammation
NSAID–Nonsteroidal antiinflammatory drug
Parietal epithelium (of Bowman's capsule)–Flattened epithelial cells that line the parietal layer of Bowman's capsule proper and are continuous with epithelium lining the proximal convoluted tubule
PKD–Polycystic kidney disease
Podocytes–Specialized epithelial cells that comprise the visceral layer of Bowman's capsule. Podocytes are responsible for synthesis of the glomerular basement membrane and have foot processes that interdigitate to form filtration slits.
Proximal convoluted tubule–Longest and most convoluted segment of the renal tubule that is responsible for reabsorption of approximately 65% of ions and water of glomerular filtrate
PTH–Parathyroid hormone
Pyelonephritis–Inflammation of the kidney and renal pelvis, most often because of an ascending bacterial infection
Renal corpuscle–Structure responsible for the filtration of plasma, composed of Bowman's capsule and glomerular capillary tuft
Renal pelvis–The expansion of the upper segment of the ureter into which the renal calices open
SAA–Serum amyloid-A
Struvite–A hard crystalline mineral formed by interaction of magnesium salts and ammonium phosphate, with the final composition of magnesium ammonium phosphate hexahydrate
TNF–Tumor necrosis factor
Tubulointerstitial–Pertaining to or involving both renal tubules and renal interstitial tissues
Urachus–Fetal structure connecting the urinary bladder with the umbilicus
Uremia–Syndrome of multisystemic lesions and clinical signs that occur because of the biochemical disturbances caused by renal failure, including anorexia, vomiting, ulcerative and

E-Glossary 11-1 Glossary of Abbreviations and Terms–cont'd

necrotizing glossitis or stomatitis, ulcerative and hemorrhagic gastritis, pulmonary edema, and soft tissue mineralization

Urolithiasis–The formation of calculi or stones (mineralized aggregates) within the urinary tract, including within the renal pelvis, ureters, urinary bladder, or urethra

Uroperitoneum–The presence of urine in the peritoneal cavity, typically secondary to rupture of the urinary bladder, urachus, or ureter

Urothelium–The layer of transitional epithelium that lines the lumen of the urinary bladder, ureter, and renal pelvis

UTI–Urinary tract infection

Visceral epithelium (of Bowman's capsule)–The layer of podocytes that closely surround the capillaries of the glomerular tuft, making up part of the glomerular filtration barrier

E-Appendix 11-1 Postmortem Examination and Evaluation of the Kidney

Postmortem evaluation of the kidney has three components. First, the prosector should examine the location of the kidneys in the carcass to determine that they are of normal size and position. Second, the prosector should remove the kidneys one at a time by severing the renal artery and gently pulling the kidney outward maintaining the ureter attachment. The ureter can be examined while still attached to the kidney to determine that it is intact and of normal and uniform size and shape. With the kidney still attached, a segment or the entire length of ureter can be opened to determine whether the mucosa is normal or abnormal. Once it is determined that the ureter is normal, the kidney can be removed. Third, kidneys should be carefully examined on the capsular and cut surfaces. Longitudinal incision of each kidney from capsular surface and poles through the pelvis should be done exposing the kidney halves. The capsule can be removed from each half by grabbing the cut edge of the capsule with forceps or between the thumb and edge of the knife and stripping the capsule from the surface. Tightness with which the capsule adheres to the underlying cortex should be noted, especially if obvious fibrous adhesions attach the capsule to the subcapsular cortical surface. The cortical surface should then be examined as to contour, foci of discoloration, and smoothness or granularity. If lesions are seen, the prosector should cut the kidney at the lesion site to determine if it is merely in the capsular surface or the depth to which it extends into the kidney parenchyma. The cut surface of the sagittal section should then be examined noting the size and mucosal surface of the renal pelvis, the contour and appearance of papillae or medullary crest, the cortex to medulla ratio, color, capsular surface contour, and cortical and medullary striated appearance. Careful examination of the cortex is important, and it can be aided by using a surgery light or hand magnifier. Normal glomeruli are usually not visible except in the horse kidney, where they appear as pinpoint red dots. The prosector should note any reductions or accentuations in the cortical striations, accentuation of glomeruli, and discolored streaks or foci. For routine histopathology, a thin transverse section (approximately 0.5 cm thick) from both kidneys is removed and placed in formalin. Sections should contain capsular surface, cortex, medulla, and pelvis.

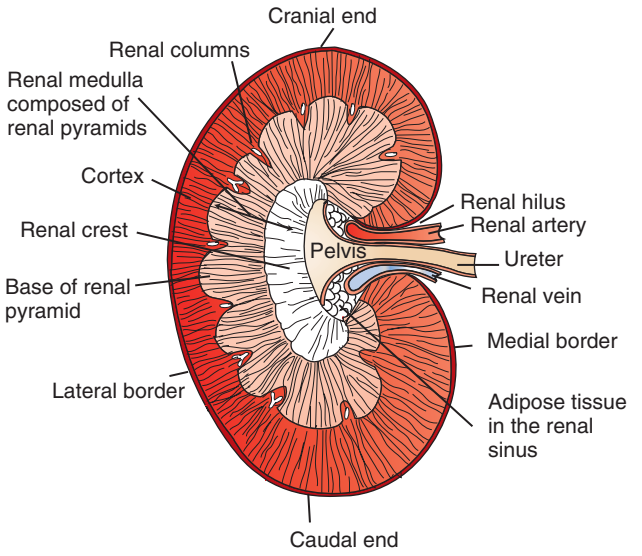


Figure 11-1 Kidney, Dorsal Section, Dog. (Based on Schaller O, Constantinescu GM, editors: *Illustrated veterinary anatomical nomenclature*, Stuttgart, Germany, 2007, Enke Verlag.)

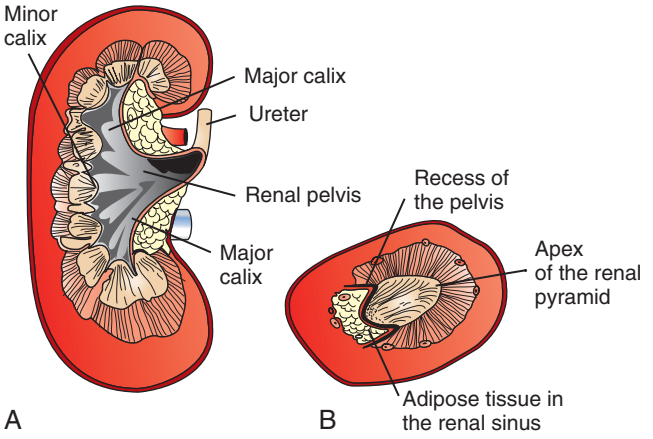


Figure 11-3 Structure of the Kidney. A, Dorsal section through hilus, pig. **B,** Transverse section through hilus, dog. (Based on Schaller O, Constantinescu GM, editors: *Illustrated veterinary anatomical nomenclature*, Stuttgart, Germany, 2007, Enke Verlag.)

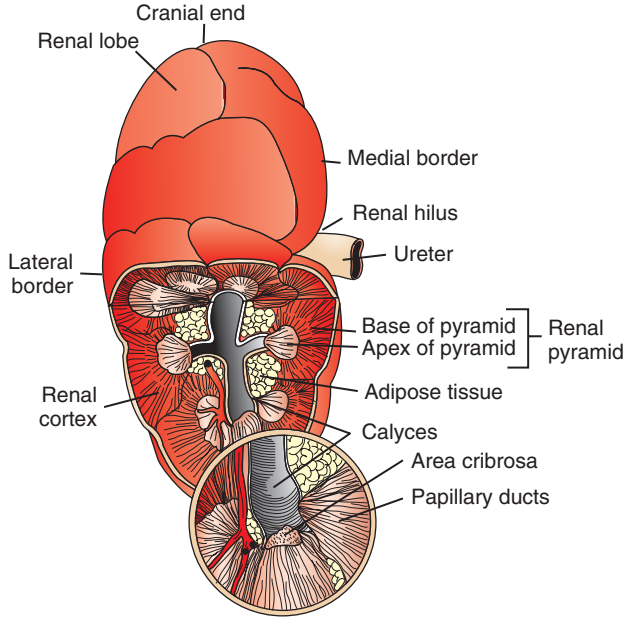


Figure 11-2 Kidney, Dorsal Surface and Partial Dorsal Section, Cow. (Based on Schaller O, Constantinescu GM, editors: *Illustrated veterinary anatomical nomenclature*, Stuttgart, Germany, 2007, Enke Verlag.)

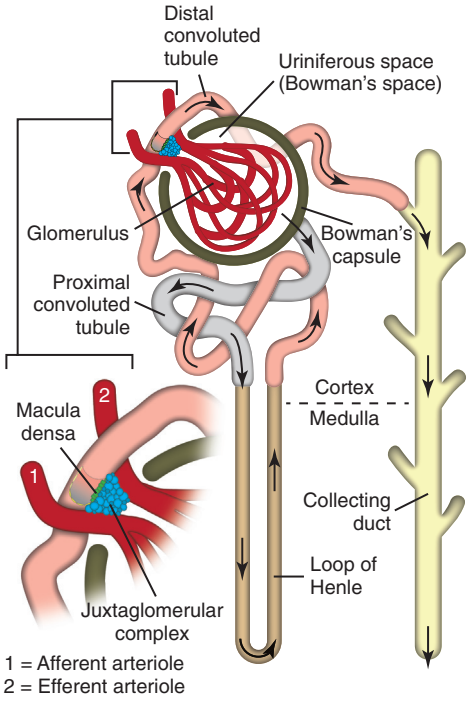


Figure 11-4 Uriniferous Tubule. A uriniferous tubule is composed of a nephron and its collecting duct. The nephron is formed by a renal corpuscle and its connecting renal tubules (proximal tubule, loop of Henle, and distal tubule). Bowman's capsule surrounds the glomerulus, and together these structures form the renal corpuscle. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

collagen and mesangial matrix, as well as secreting inflammatory mediators.

Glomerular Filtration Barrier. The glomerular filtration barrier is composed of (1) pedicles of podocytes (visceral epithelium of Bowman's capsule), (2) glomerular basement membrane (GBM) or basal lamina (produced by both endothelial and epithelial cells), and (3) the fenestrated endothelium of glomerular capillaries (Fig. 11-6).

Visceral Epithelium (Podocytes). Visceral epithelial cells (podocytes), aligned on the external surface of the basement membrane, are responsible for synthesis of basement membrane components and have special cytoplasmic processes (foot processes) that are embedded in the lamina rara externa. Negatively charged glycoproteins overlying the endothelial cells and the podocytes

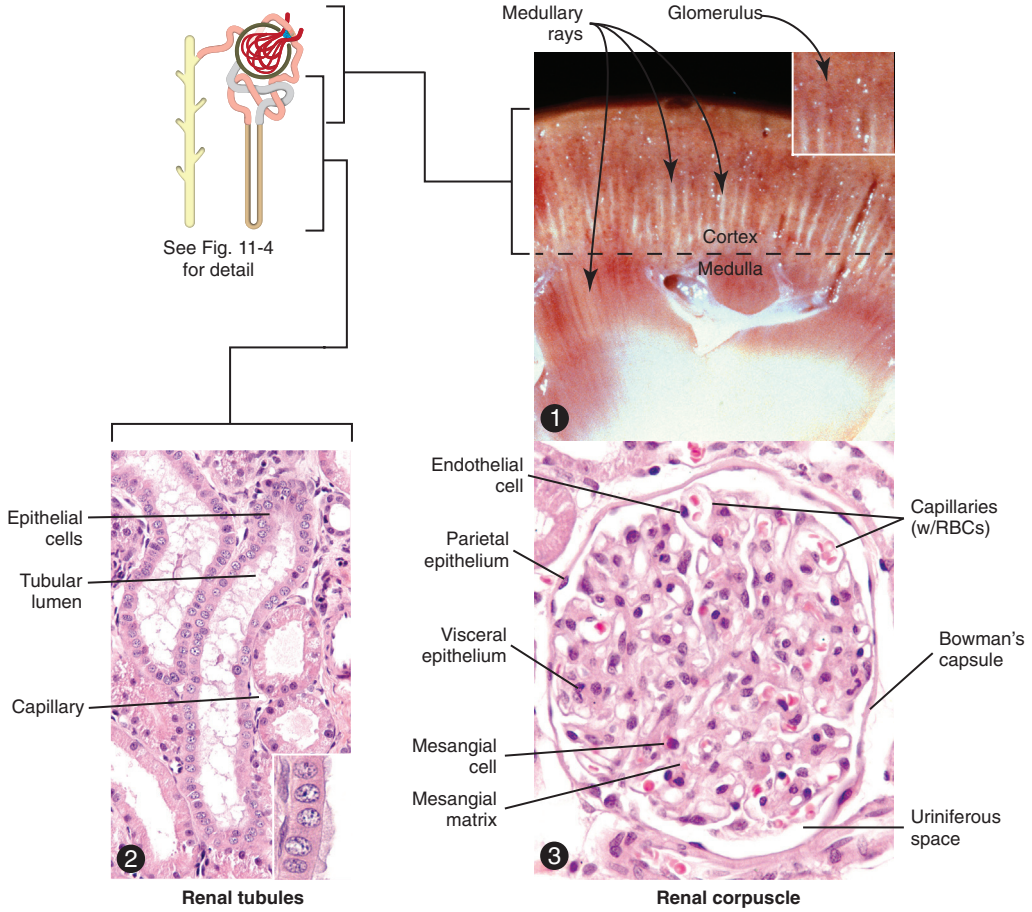


Figure 11-5 Macroscopic and Microscopic Structure of Renal Cortex, Medulla, and Corpuscle. *1,* Medullary rays are grossly visible as radial striations in the deep cortex of the kidney and are composed of collecting tubules and ducts draining nephrons located in the more superficial cortex. Glomeruli are difficult to detect grossly in the normal kidney, but they may appear as red dots (when filled with blood) or white to gray granular foci, especially when accentuated by inflammatory or reparative (healing) glomerular lesions. *2,* Renal tubules. *Inset,* Higher magnification of renal tubular epithelium. *3,* Renal corpuscle. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

contribute to the charge differential of the GBM. Foot processes from adjacent visceral epithelium interdigitate to form filtration slits between them (see Fig. 11-6). Filtration slit diaphragms are composed of nephrin, a cell adhesion molecule of the immunoglobulin superfamily, which controls slit size by its connection to podocyte actin.

Glomerular Basement Membrane (Basal Lamina). The glomerular basement membrane has a thick, dense central layer, the lamina densa, which is covered by thinner, more electron-lucent inner and outer layers, the lamina rara interna and lamina rara externa, respectively (see Fig. 11-6). The basement membrane has a network of type IV collagen, which forms a tetrameric porous infrastructure. Numerous glycoproteins, such as acidic proteoglycans and laminin, together with the collagen fibers form the complete structure of the membrane. The glomerular filtration barrier selectively filters molecules based on size (70 kDa), electrical charge (the more cationic, the more permeable), and capillary pressure. In summary, both size-dependent and charge-dependent filtration is possible because of the porous structure of capillary walls, which is a function of endothelial fenestrations, a basement membrane formed of type IV collagen, basement membrane anionic glycoproteins, and filtration slits of the visceral epithelium.

Glomerular Capillaries. The glomerular capillaries exist between the afferent and efferent arterioles and form the glomerular tuft. Glomerular capillaries interdigitate with the visceral lining of Bowman's space. The capillary endothelium is fenestrated and covered by a complete basal lamina.

Bowman's Capsule

Bowman's capsule is a cup-shaped, membranous sac at the beginning of the nephron that encloses each glomerulus and is separated from the glomerular tuft by the uriniferous space (see Fig. 11-4).

Parietal Epithelium. The capillary tuft (glomerulus) is covered by visceral epithelial cells (podocytes) and is contained within Bowman's capsule that is lined by parietal epithelial cells resembling squamous epithelium (see Figs. 11-5 and 11-6).

Tubules

The renal tubular system (in the order of flow of urine) consists of a proximal tubule, loop of Henle, and distal tubule (see Fig. 11-4). The tubules connect to the renal pelvis at the distal end of the collecting ducts, and the whole structure—including the renal corpuscle, renal tubules, and collecting ducts—is referred to as the *uriniferous tubule* (see Fig. 11-4). The proximal and distal convoluted

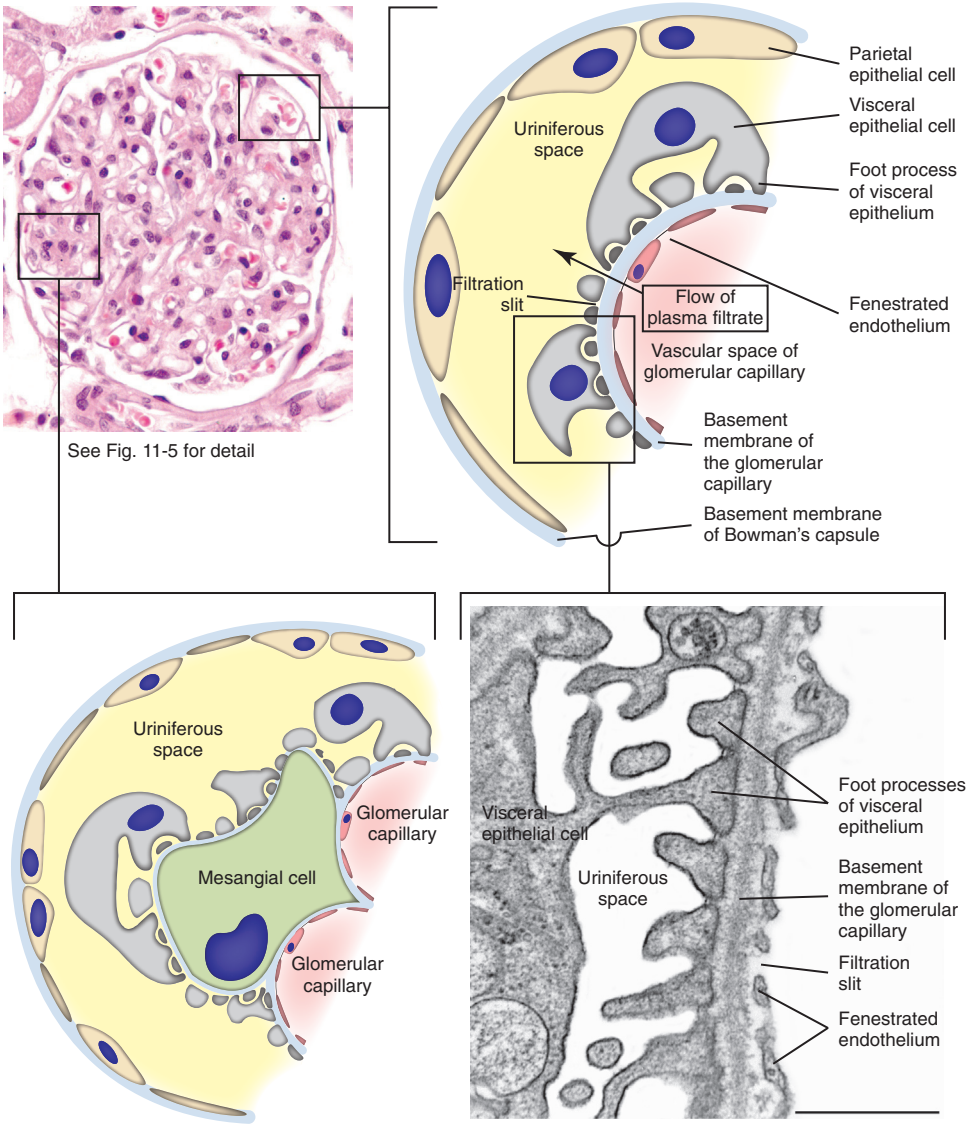


Figure 11-6 Glomerular Filtration Barrier. The glomerular filtration barrier is a layer formed by endothelial cells, basement membrane, and visceral epithelial cells (podocytes). Its main function is to filter plasma to maintain ionic and osmotic homeostasis in the blood. The filtration barrier is relatively impermeable to larger macromolecules, such as albumin and hemoglobin, and larger proteins, such as immunoglobulins. However, small and medium-sized solutes (ions), such as sodium and potassium, and other soluble moieties, such as sugar molecules, pass through the barrier as glomerular filtrate, which then travels through the renal tubules and the collecting duct to form urine. Certain molecules within the filtrate, such as sugars, can be resorbed in the tubules and returned to the plasma as needed to maintain homeostasis. In the electron micrograph, note the central electron-dense layer (lamina densa) of the glomerular basement membrane covered by lighter, more electron-lucent inner and outer layers (lamina rara interna and lamina rara externa, respectively). The small spaces visible between foot processes of visceral epithelial cells (podocytes) are filtration slits, through which plasma filtrate passes into the uriniferous space. Scale bar in the electron micrograph (lower right corner) = 500 µm in length. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois. Electron photomicrograph courtesy Dr. A.G. Armien, Diagnostic Ultrastructural Pathology Service, College of Veterinary Medicine, University of Minnesota.)

tubules are linked by the loop of Henle, which is divided into a descending and an ascending limb. The wall of the descending limb and initial portion of the ascending limb is thin (permeable), whereas the cortical portion of the ascending limb is thick (impermeable). Microscopically, the proximal tubule is lined by columnar epithelial cells that have a microvillous (brush) border. This arrangement greatly increases their absorptive surface, and their numerous intracellular mitochondria supply energy for the various secretory and absorptive functions. Distal tubules, collecting tubules, and the loop of Henle are lined by cuboidal epithelial cells that contribute to the concentration of urine by absorptive and secretory activities.

Interstitium

Macroscopically, the interstitium consists of a relatively scant fibrovascular connective tissue stroma, primarily present as a fine reticular meshwork found around and between uriniferous tubules. Microscopically, renal interstitium is composed of fibroblasts, connective tissue, and extracellular matrix that provide most of the interstitial tissue support. Glycosaminoglycans secreted as part of

the extracellular matrix (ECM) increase with age and ischemic damage. Cells in the interstitium, particularly in the medulla, are responsible for local production of prostaglandins. Blood vessels, nerves, and lymphatic vessels are present in the renal interstitium.

Vasculature

Macroscopically, knowledge of the normal renal blood supply is important in understanding the pathogenesis and distribution of various renal lesions, especially renal infarcts. Kidneys receive blood primarily through the renal artery. An interlobar artery extends along the boundary of each renal lobe (renal column) and then branches at right angles to form an arcuate artery that runs along the corticomedullary junction (Fig. 11-7). Interlobular arteries branch from the arcuate artery and extend into the cortex. They have no anastomoses, making them susceptible to focal ischemic necrosis (infarct) as in any organ with end arteries.

Microscopically, interlobular arteries have small branches that become afferent glomerular arterioles, which enter the renal corpuscle and subsequently exit at the vascular pole as efferent glomerular arterioles (see Fig. 11-7). Efferent arterioles supply the blood for the extensive network of capillaries that surround the cortical and medullary tubular system of the kidneys, known as the *peritubular capillary network*. The latter surrounds cortical segments of the tubules and then drains into the interlobular vein, arcuate vein, interlobar vein, and ultimately the renal vein. In addition, the vasa recta are formed from the deeper portions of the peritubular capillary network and descend into the medulla and around the lower portions of the loop of Henle before ascending to the cortex and emptying into venous vessels that connect to the interlobular and arcuate veins. The vasa recta parallel the descending and ascending limbs of the loop of Henle and the collecting ducts (see Fig. 11-7). Therefore the blood supply to the tubules depends on passage through the glomerular vessels.

Function

The kidney has the following five basic functions:

- Formation of urine for the purpose of elimination of metabolic wastes.
- Acid-base regulation, predominantly through reclamation of bicarbonate from the glomerular filtrate.
- Conservation of water through reabsorption by the proximal convoluted tubules, the countercurrent mechanism of the loop of Henle, antidiuretic hormone (ADH) activity in the distal tubules, and the urea gradient in the medulla. The tubular system is capable of absorbing up to 99% of the water in the glomerular filtrate.
- Maintenance of normal extracellular potassium ion concentration through passive reabsorption in the proximal tubules and tubular secretion in the distal tubules under the influence of aldosterone.
- Control of endocrine function through three hormonal axes: renin-angiotensin-aldosterone (see Fig. 12-14, A), most important, but also erythropoietin and vitamin D. Erythropoietin, produced in the kidneys in response to reduced oxygen tension, is released into the blood and stimulates bone marrow to produce erythrocytes. Vitamin D is converted in the kidneys to its most active form (1,25-dihydroxycholecalciferol [calcitriol]), which facilitates calcium absorption by the intestine.

Glomerular Basement Membrane

The GBM is structurally adept at separating substances based on size and charge. In addition, the glomerulus is equipped with its own

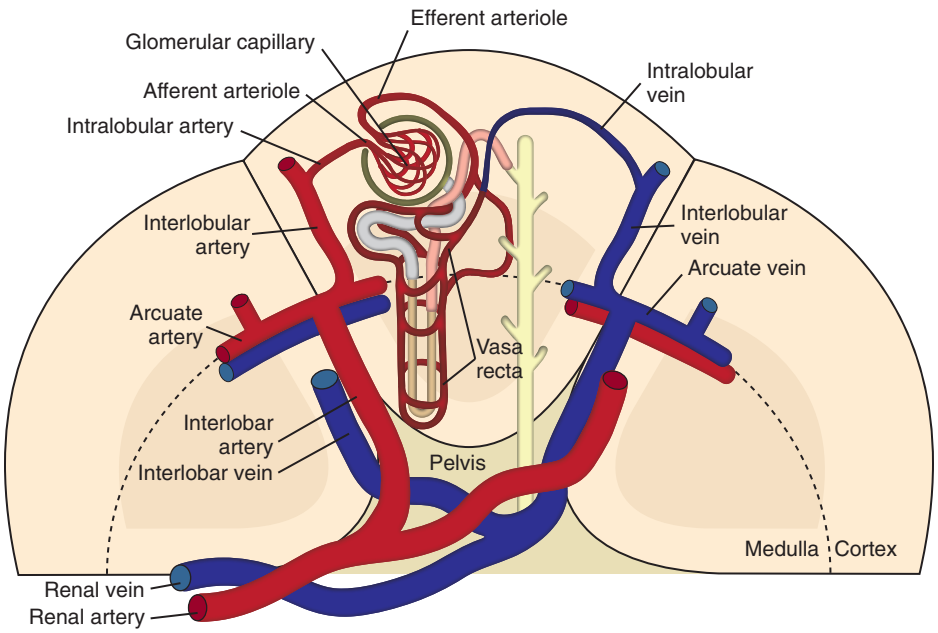


Figure 11-7 Vasculature of the Kidney. The interlobar artery branches at right angles at the corticomedullary junction to give rise to arcuate arteries that in turn branch to form interlobular arteries that extend into the cortex. Interlobular arteries give rise to smaller branches (intralobular arteries), eventually forming glomerular afferent arterioles that enter the glomerular capillary tuft and then exit at the glomerular vascular pole as efferent arterioles. The peritubular capillary network (including vasa recta) is supplied by efferent glomerular arterioles before emptying into the venous system, beginning as intralobular veins and progressing toward interlobular veins, arcuate veins, and interlobar veins before finally draining through the renal vein. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

specialized mesangial cells, a component of the monocyte-macrophage system (see Figs. 11-5 and 11-6; also see E-Figs. 11-5 and 11-6). Both size-dependent and charge-dependent filtration are possible because of the porous structure of capillary walls, which is a function of endothelial fenestrations, laminin, polyanionic proteoglycans, fibronectin, entactin and other glycoproteins, and filtration slits between adjacent visceral epithelium. Thus the normal glomerulus restricts many proteins and charged molecules from being filtered into the uriniferous (Bowman's) space and proximal tubular lumen whereby allowing permeability to water, proteins <70 kDa, and small solutes. The fluid that filters through the glomerulus into the urinary space is called *glomerular filtrate*, and it arises after passage through the glomerular filtration barrier. This ultrafiltrate of plasma (primary urine), which contains water, salts, ions, glucose, and albumin, passes into the uriniferous space and then empties into the proximal convoluted tubule at the urinary pole to traverse through and be acted on by the tubular system.

In addition to the principal glomerular function of plasma filtration, glomerular functions also include regulation of blood pressure by means of secreting vasopressor agents and/or hormones, regulation of peritubular blood flow, regulation of tubular metabolism, and removal of macromolecules from circulation by the glomerular mesangium. Integral to these functions is the juxtaglomerular apparatus, which functions in tubuloglomerular feedback by autoregulating renal blood flow and glomerular filtration rate. The juxtaglomerular apparatus is composed of four components: (1) an afferent arteriole whose smooth muscle is modified to form myoepithelial cells, which are the juxtaglomerular cells that secrete renin; (2) an efferent arteriole; (3) the macula densa; and (4) the extraglomerular mesangium. Renin, produced by cells of the juxtaglomerular apparatus, stimulates the production of angiotensin I from circulating angiotensinogen. The angiotensin-converting enzyme in the macula densa converts angiotensin I to angiotensin II, which then functions to constrict afferent renal arterioles; maintain renal blood pressure; stimulate aldosterone secretion from the adrenal gland, thus increasing sodium (Na^+) reabsorption; and stimulate ADH release (see Fig. 12-14, A). ADH principally increases the permeability of collecting tubules to water and increases the permeability of the medullary region to urea.

Proximal Tubules

A key function of the proximal tubules is to reabsorb Na^+, chloride (Cl^-), potassium (K^+), albumin, glucose, water, and bicarbonate. This is facilitated by luminal brush border, basolateral infoldings, magnesium-dependent Na^+ and K^+ pumps, and transport proteins. The proximal tubule is continuous with the loop of Henle that is in close physiologic and anatomic association with the peritubular capillary network (within the cortex) and the vasa recta (within the medulla). The loop of Henle, via a countercurrent mechanism and Na^+/K^+-adenosine phosphatase (ATPase) pumps, absorbs Na^+ and Cl^- ions, producing a hypotonic filtrate that flows into the next portion of the nephron—the distal convoluted tubule. Here, water is reabsorbed from the tubule into the interstitium because of a solute concentration gradient and by the effects of ADH. The filtrate is further concentrated in the collecting ducts by water and sodium reabsorption by a Na^+/K^+-ATPase pump and additional water reabsorption into the medullary interstitium by a urea gradient. Intercalated cells of the collecting tubule regulate acid-base balance and reabsorb potassium. Thus the final excretory product, urine, is formed.

Renal Failure (Loss of Function). Renal failure occurs when one or more of the functions previously listed are altered. When renal functional capacity is abruptly impaired approximately 75% or more, such that the kidneys fail to carry out their normal metabolic and endocrine functions, acute renal failure can ensue. It is important to remember that the glomerulus, tubules, collecting ducts, and capillary blood supply in each nephron are closely interrelated, both anatomically and functionally. Alterations in tubular structure or function influence glomerular structure and function and vice versa. For example, necrosis or atrophy of renal tubules results in loss of function of the affected nephrons and secondary atrophy of the glomerulus. In addition, because most of the capillary blood supply to tubules is through postglomerular capillaries, a reduction in glomerular blood flow consequently reduces the blood supply to the tubules.

Acute Renal Failure. Acute renal failure can be caused by (1) tubular necrosis from infectious microbes, such as bacteria (*Leptospira* spp., *Escherichia coli*, *Streptococcus* spp., *Staphylococcus* spp., and *Proteus* spp.) or viruses (infectious canine hepatitis virus and canine herpesvirus); (2) obstructive nephropathy from urolithiasis, transitional cell neoplasms of the lower urinary system, or trauma; (3) renal ischemia with tubular necrosis from occlusive vasculitis/vasculopathy caused by bacteria, bacterial toxins, or tumor emboli; (4) tubular necrosis from nephrotoxic drugs, such as aminoglycoside-based antimicrobial drugs or antineoplastic drugs; and/or (5) tubular necrosis from chemicals, such as ethylene glycol and heavy metals.

Functionally, acute renal failure can be caused by prerenal (compromised renal perfusion), intrarenal (compromised kidney function), or postrenal (obstruction of the urinary tract) factors. Prerenal factors include reduced renal blood flow, whether secondary to circulatory collapse (shock, severe hypovolemia) or local obstruction of vascular supply (thrombus or lodgment of embolus). Acute tubular necrosis, a form of intrarenal acute renal failure, induces clinical oliguria (decrease in urine production) or anuria (absence of urine production) by one or several mechanisms. These mechanisms include the following:

- Leakage of tubular ultrafiltrate from damaged tubules across disrupted basement membranes into the renal interstitium
- Intratubular obstruction resulting from sloughed necrotic epithelium

The latter mechanism is less well accepted, but both mechanisms result in decreased glomerular filtration rate.

Prerenal and intrarenal factors are most responsible for episodes of acute renal failure, with prerenal azotemia and ischemic tubular damage actually being a continuum. Postrenal obstructive diseases are discussed in the lower urinary tract section. Intrarenal disease can target tubules by the following three main mechanisms:

- Ascending disease, such as pyelonephritis
- Intraluminal toxic metabolites derived from glomerular filtrate
- Ischemia (Fig. 11-8)

Acute renal failure occurs when the kidney fails to excrete waste products and to maintain fluid and electrolyte homeostasis. The four main pathologic alterations in acute renal failure are as follows:

- Decreased ultrafiltration
- Intratubular obstruction
- Fluid back leak
- Intrarenal vasoconstriction

These alterations can occur after many insults, including the following:

- Decreased renal perfusion
- Decreased glomerular filtration
- Ischemic tubular damage
- Toxic tubular damage

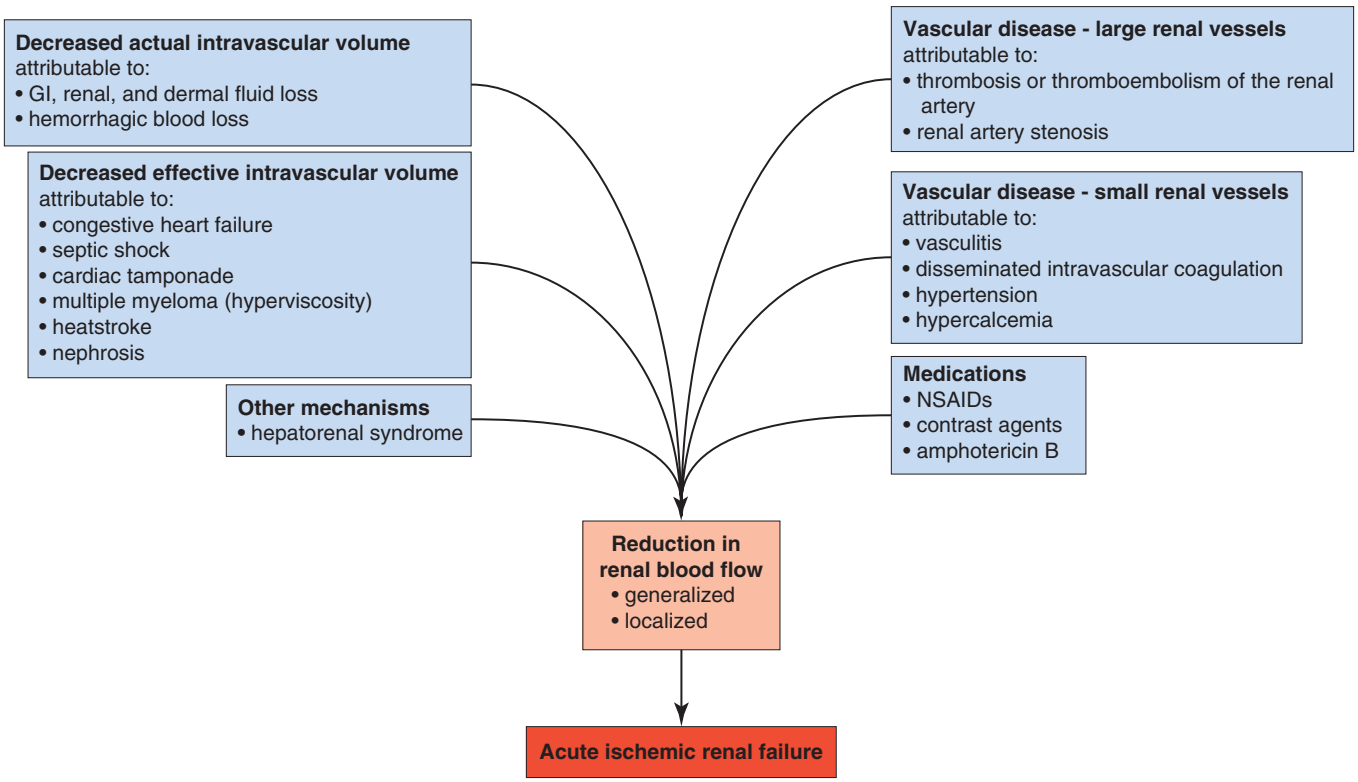


Figure 11-8 Proposed Mechanisms of Acute Ischemic Renal Failure. A wide spectrum of clinical conditions can result in a generalized or localized reduction in renal blood flow, thus increasing the likelihood of acute ischemic renal failure. Kidney ischemia and acute renal failure are often the result of a combination of factors. Decreased renal perfusion may be due to hypovolemia, decreased cardiac output, medications that alter blood flow, and vascular disease. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

- Obstructive renal tubular damage
- Tubulointerstitial inflammation, edema, or fibrosis

Animals that die of acute renal failure often do so because of the cardiotoxicity of elevated serum potassium, metabolic acidosis, and/or pulmonary edema. Hyperkalemia results from decreased filtration, decreased tubular secretion, and decreased tubular sodium transport. Cell lysis and the extracellular shift of fluid in acidic environments also contribute to the increased serum potassium concentrations. These alterations are reflected clinically by signs such as oliguria or anuria, vomiting and diarrhea, and ammoniacal-smelling breath, and an array of nonrenal lesions described later and can be detected and monitored with biochemical tests of serum, plasma, and urine for azotemia and uremia.

Azotemia and Uremia. Assays for plasma or serum concentrations of urea, creatinine, and the nitrogenous waste products of protein catabolism are routinely used as indices of diminished renal function. The intravascular increase of these nitrogenous waste products is referred to as *azotemia*. Renal failure can result in the following:

- Intravascular accumulation of other metabolic wastes such as guanidines, phenolic acids, and large-molecular-weight alcohols (e.g., myoinositol)
- Reduced blood pH (metabolic acidosis)
- Alterations in plasma ion concentrations, particularly potassium, calcium, and phosphate
- Hypertension

The result and pathologic manifestations of renal failure are a toxicosis called *uremia*. Uremia can therefore be defined as a syndrome associated with multisystemic lesions and clinical signs because of renal failure. These multisystemic lesions are discussed in greater detail in the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals.

Chronic Renal Failure. Chronic renal failure usually results from progressive renal disease with loss of nephrons and severe scarring. The pathogenesis of the underlying renal lesion can be unknown and slowly progressive or can be scarring resulting from an acute insult (see Renal Fibrosis [Scarring]). Severely scarred kidneys lack the ability to concentrate urine, resulting in polyuria and polydipsia. Anorexia with chronic progressive weight loss commonly occurs as well as other signs of uremia, such as vomiting and seizures. In the diseased kidney, production of erythropoietin, a stimulant of erythropoietic maturation, is reduced and contributes to nonregenerative anemia, as does uremia-associated increased erythrocytic fragility. Most animals in renal failure have hyperphosphatemia and low to normal calcium concentrations, although variations exist, depending on species and stage of the disease. Alterations in calcium-phosphorus metabolism in the uremic animal are a hallmark of chronic renal failure and result from a complex set of events as outlined in the following:

- When the glomerular filtration rate is chronically reduced to less than 25% of normal, phosphorus is no longer adequately secreted by the kidneys and hyperphosphatemia results.
- Because of the mass law interactions between serum calcium and phosphorus, ionized calcium concentration in serum is reduced as a result of precipitation of calcium and phosphorus.
- Reduced ionized serum calcium concentration stimulates parathyroid hormone (PTH) secretion, causing calcium release from

the readily mobilizable calcium stores in the bone and from osteoclastic bone resorption.

These changes in calcium-phosphorus metabolism are made more severe by the reduced ability of the diseased kidneys to hydroxylate 25-hydroxycholecalciferol to the more active 1,25-dihydroxycholecalciferol (calcitriol), resulting in decreased intestinal absorption of calcium. Calcitriol production is further inhibited by hyperphosphatemia. In addition, calcitriol normally suppresses PTH secretion; therefore reduced calcitriol production further increases PTH secretion. With time, these events lead to parathyroid chief cell hyperplasia (renal secondary hyperparathyroidism), fibrous osteodystrophy (renal osteodystrophy), and soft tissue calcification.

Renal secondary hyperparathyroidism is further thought to perpetuate and enhance renal disease by stimulating nephrocalcinosis (see Fig. 11-25; also see Chapter 12), the process by which renal tubular epithelium is damaged by an increase in intracellular calcium. Calcium is precipitated in mitochondria and in tubular basement membranes. Soft tissue calcification associated with uremia occurs in numerous sites and represents both dystrophic and metastatic calcification. These lesions are discussed in greater detail in the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals.

Dysfunction/Responses to Injury

The response of the urinary system to injury is the response of each of its components—kidney, ureter, bladder, and urethra—to injury. In addition, components within the kidney, such as the glomeruli, tubules, interstitium, and vasculature, have their own unique responses to injury. Responses to injury are described sequentially in this section and are summarized in Box 11-1.

Box 11-1 Renal Responses to Injury

GLOMERULI
Acute inflammation
Endothelial proliferation
Hypertrophy
Inclusion bodies
Necrosis
Mesangial cell proliferation
Amyloid deposition
Glomerular cell proliferation
Glomerular basement membrane proliferation
Increased vascular permeability
Atrophy of the glomerular tuft
Fibrosis of the glomerular tuft

TUBULES
Cell degeneration
Cell necrosis
Basement membrane rupture
Basement membrane thickening
Cell regeneration
Renal fibrosis

INTERSTITIUM
Hyperemia
Edema
Inflammation
Fibrosis

VASCULATURE
Hyperemia and congestion
Hemorrhage and thrombosis
Embolic nephritis
Infarction

Kidney

The functional unit of the kidney is the nephron, and damage to any component of the nephron (renal corpuscle and tubules) results in diminished function and progressive damage to the kidney. Renal disease can be best summarized by dividing it into general tissue responses that affect the primary anatomic components: glomeruli, tubules, interstitium, and vasculature. In the early stages of disease, specific anatomic components may be targeted by specific insults: glomeruli in immune-mediated disease and tubules in toxin-induced necrosis. However, in the more chronic stages of disease, the kidney undergoes changes related to nephron loss that are not specific to the original cause but are considered common end-stage responses to any number of inciting injurious stimuli.

Renal Corpuscle. Primary glomerular damage often occurs as a result of deposition of immune complexes, entrapment of thromboemboli and bacterial emboli, or direct viral or bacterial infection of glomerular components. Such insults are reflected morphologically by necrosis, thickening of membranes, or infiltration of leukocytes, and they are reflected functionally by reduced vascular perfusion. Continued or severe injury can result in chronic changes characterized at first by atrophy and fibrosis of the glomerular tuft (sclerosis) and secondarily by atrophy of renal tubules resulting in loss of function of the entire nephron. Similarly, chronic glomerular changes can result from reduced blood flow or chronic loss of tubular function.

Damage to the glomerular filtration barrier can result from several causes and produce a variety of clinical signs. The major clinical finding of glomerular disease is the leakage of various low-molecular-weight (small molecule size) proteins, such as albumin, into the glomerular filtrate. As a result, large quantities of albumin overload the protein reabsorption capabilities of the proximal convoluted tubular epithelium such that protein-rich glomerular filtrate accumulates in the variably dilated tubular lumina, and protein subsequently appears in the urine. Renal diseases that result in proteinuria are called *protein-losing nephropathies*. Protein-losing nephropathy is one of several causes of severe hypoproteinemia in animals. Prolonged, severe renal protein loss results in hypoproteinemia, reduced plasma colloid osmotic (oncotic) pressure, and loss of antithrombin III. These changes can lead to the *nephrotic syndrome*, which is further characterized by generalized edema, ascites, pleural effusion, and hypercholesterolemia.

The functions of the glomerulus listed in the following are affected by processes that injure it in disease:

- Plasma ultrafiltration
- Blood pressure regulation
- Peritubular blood flow regulation
- Tubular metabolism regulation
- Circulating macromolecule removal

The pathophysiologic mechanisms of glomerular injury from infectious or chemical insults have been summarized by the following three theories:

- Intact nephron hypothesis
- Hyperfiltration hypothesis
- The theory of complex deposition

The intact nephron hypothesis proposes that damage to any portion of the nephron affects the entire nephron function. This is seen when glomerular damage interferes with peritubular blood flow and results in decreased tubular resorption or secretion. Not all nephron damage is irreversible; for example, renal tubular epithelium

can regenerate but whole nephrons are not capable of regeneration. Thus the outcomes for the nephrons vary from hypertrophy to repair.

Unlike the intact nephron hypothesis, the hyperfiltration hypothesis helps explain the progressive nature of glomerular disease. Glomerular hyperfiltration is a result of increased hydrostatic pressure that damages delicate glomerular capillaries and in cases of prolonged hypertension produces a sustained deleterious effect on the glomerulus, ultimately resulting in glomerulosclerosis. Increased dietary protein can produce a transient increase in glomerular hyperfiltration and if persistent can result in glomerulosclerosis. There may be a species effect because dogs that undergo experimental hyperfiltration are much less prone to development of progressive glomerular disease than are rats.

The theory of complex deposition is derived from the fact that glomeruli are the primary site for removal of macromolecules (principally immune complex) from the circulation, even when those complexes are in small quantities and nonpathogenic. Complexes may be deposited in subepithelial, subendothelial, or mesangial locations. These immune complexes are capable of triggering a sequence of inflammatory responses including the following:

- Recruitment and localization of inflammatory cells at the site
- Release of inflammatory mediators and enzymes
- Destruction of glomerular structures such as the basement membrane
- Further compromise of nephron function
- Continuing damage by altered transglomerular hyperfiltration and perfusion shifts between nephron populations, so the less affected become overworked and succumb to the same fate

Kidney lesions differ slightly, depending on the duration of the glomerular disease. Acute disease may be identified by pallor of the parenchyma and accentuation of the glomerular tufts as fine red dots. Accompanying petechial hemorrhages may be noted. In the more chronic stage, the kidney can be shrunken and show a fine granularity to the cortical cut section. The capsule may be adherent.

Tubules

Renal tubular epithelial cells can respond to injury by undergoing degeneration, necrosis, apoptosis, and/or atrophy. The basement membrane can respond by rupturing or thickening. Tubular disease occurs as a result of tubular epithelial damage from the following:

- Blood-borne infections
- Ascending infections (intratubular pathogens)
- Direct damage from toxins (intratubular effects)
- Ischemia, infarction

When nephrons are lost because of injury, remaining tubules can undergo compensatory hypertrophy in an attempt to maintain overall renal function, but there is no regeneration of entire nephrons. In many instances of tubular epithelial cell necrosis, particularly as a response to toxins, tubular epithelium has an incredible capacity to regenerate and contribute to restoration of function, providing the tubular basement membrane scaffolding remains intact. Severe damage to or loss of tubular basement membranes, as occurs after ischemic damage, results in necrosis and loss of tubular segments, failure of functional repair, and permanent loss of function of the entire nephron, despite the potential for tubular epithelial hyperplasia.

Atrophy. Tubular atrophy can occur secondary to the following:

- External compression of tubule by a space-occupying mass, neoplasm, or abscess
- Interstitial fibrosis as the end result of ischemia
- Intratubular obstruction and backpressure
- Diminished glomerular perfusion and filtration
- Reduced oxygen tension such as with hypoxia

If the insult to the renal tubules is not lethal and is removed, some forms of acute tubular degeneration are reversible. The success of reparative regeneration is affected by several variables, including severity of degeneration.

Apoptosis. When cells undergo programmed cell death (apoptosis), they do not usually stimulate inflammatory responses. Therefore, if small numbers of tubular epithelium undergo apoptosis, a reepithelization of the tubular epithelial lining is accomplished efficiently by adjacent viable tubular epithelial cells, which by mitotic division fill the epithelial gap. The cells that are lost slough into the lumen to form cellular casts within the lumens of renal tubules.

Acute Tubular Degeneration. More severe generalized loss of tubular epithelial lining cells is repaired by proliferation of the remaining viable epithelial cells over an intact tubular basement membrane to form a low cuboidal rather than a mature columnar epithelial lining. This appears as an ectatic proximal tubule. Restitution of renal function eventually results, despite the presence of replacement low cuboidal epithelium, which is not identical to the tubular lining cell (with microvilli) present before the injury. The exact mechanism of this return to function is not entirely known. The main determinant of this regenerative ability is the viability of tubular basement membranes, which are retained more consistently after toxic rather than ischemic insults.

Tubular Regeneration. Because the regenerative process is reliant on many factors for its success, things often go awry. Examples of adverse outcomes include the following:

- Focal loss of basement membrane scaffolding allows a bulge defect to occur where the regenerative population of proliferating tubular epithelial cells coalesces to form well-differentiated syncytial cells (giant cells) at certain levels of the tubule.
- Regenerative epithelial cells fail to regain all cytoplasmic structural aspects of the original columnar epithelial cells (e.g., microvilli and luminal enzymes) because of a failure to fully differentiate, and thus function may be affected.
- If there is excessive tubular epithelial loss, the potential for regeneration is lost and repair proceeds by replacement fibrosis and scarring.
- Reperfusion is necessary for cell viability following ischemia, but reperfusion injury occurs when activated endothelial cells produce proinflammatory mediators, such as reactive oxygen species, proteolytic enzymes, and cytokines, which result in further renal injury. Evidence indicates that epidermal growth factor secreted by distal convoluted tubules mediates the tubular repair process.

The sequence of events in tubular regeneration after necrosis has been well documented in experimental model systems using mercuric chloride in mice, rats, and rabbits. In that system, morphologic evidence of regeneration of proximal convoluted tubules is seen within 3 days after a toxic dose. At this time, basement membranes are partially covered with low cuboidal to flattened and elongated epithelial cells that are more basophilic than normal because of the increased concentrations of cytoplasmic ribosomes and rough endoplasmic reticulum producing protein for repair. Nuclei are hyperchromatic and mitotic figures are present. Regenerating tubules do not function normally because they lack both a brush border and normal tubular membrane function, and this is evident clinically as polyuria. Normal-appearing tubular epithelium subsequently reappears between 7 and 14 days after toxin exposure. Normal renal

structure without residual evidence of tubular damage is restored between 21 and 56 days after exposure to the nephrotoxin. Similar periods for tubular regeneration have been described through sequential renal biopsies from human patients naturally exposed to inorganic mercury and in experimental systems using other nephrotoxins.

Acute Tubular Necrosis. Acute tubular necrosis is the single most important cause of acute renal failure. Acute tubular degeneration and necrosis, often referred to as *nephrosis*, *lower nephron nephrosis*, *tubular nephrosis*, *tubular dysfunction*, or *acute cortical necrosis*, is principally the result of nephrotoxic injury to the renal tubular epithelial cells or ischemia (Box 11-2). This was borne out by a study of cats with renal failure in which 18 of 32 cases were the result of nephrotoxin exposure and 4 of 32 cases were the result of ischemia.

Acute tubular necrosis induces clinical oliguria (decrease in urine production) or anuria (absence of urine production) by one or several mechanisms. These mechanisms include the following:

- Leakage of tubular ultrafiltrate from damaged tubules across disrupted basement membranes into the renal interstitium
- Intratubular obstruction resulting from sloughed necrotic epithelium

The latter mechanism is less well accepted, but both mechanisms result in decreased glomerular filtration rate.

Nephrotoxic Injury. Nephrotoxic injury can be caused by a large group of substances that are called *nephrotoxins*. They preferentially damage kidneys because (1) 20% to 25% of cardiac output goes to the kidney, (2) the substance is filtered into the urine by the glomerulus, and (3) the toxin or its metabolites within the renal tubular lumens are concentrated. Nephrotoxins can do the following:

- Directly damage renal epithelial cells, particularly those of the proximal convoluted tubules, after their intracellular conversion via enzyme pathways to reactive metabolites
- Produce reactive metabolites in the tubular filtrate, which can cause renal tubular epithelial necrosis after reabsorption
- Cause renal tubular epithelial necrosis after diffusion through the intertubular capillary walls and basement membranes into the tubule epithelial cell
- Indirectly stimulate vasoconstriction of the intertubular capillaries, thus causing ischemia, which further compromises renal function
- Result in nephrotoxin-associated ischemia

One of the first events in renal tubular cell damage is altered ion transport at the luminal surface (uptake). This process results in decreased sodium absorption and increased sodium ions in the lumens of the distal tubules, which stimulate the renin-angiotensin mechanism, causing vasoconstriction and reduced blood flow that result in ischemia and tubular cell damage. Nephrotoxins usually do not damage the tubular basement membranes, and if the toxin is removed, regeneration (repair) of tubules can occur in an orderly and expeditious manner. The intact basement membrane acts as a scaffold over which regenerating epithelial cells may slide. Exposure to a variety of nephrotoxins, either from the vasculature (including certain chemicals [glycolaldehyde, glycolic acid, and glyoxylic acid]) or from the tubular lumen (including certain antibiotics [aminoglycosides], pigments [hemoglobin], metals [lead], or chemicals [ethylene glycol–induced calcium oxalate crystals]), or their metabolites cause cells to undergo degeneration followed by necrosis and desquamation into the tubular lumen.

Cell death results from decreased adenosine triphosphate (ATP) production, which is central to many of the secondary metabolic derangements, including calcium ion influx, purine depletion, metabolic acidosis, and generation of oxygen radicals. Increased intracellular calcium is associated with degenerative changes in renal tubular cells, smooth muscle cells, and mesangial cells. Oxygen radicals activate phospholipase, which subsequently increases membrane permeability. Because mitochondrial respiration is disrupted, further cell membrane damage occurs.

Hypoxic or Ischemic Injury (Tubulorrhexis). Notably reduced renal perfusion from any cause can result in tubular necrosis. Severe hypotension associated with shock results in preglomerular vasoconstriction and reduced glomerular filtration. The resulting renal ischemia can produce sublethal tubular cell injury and dysfunction or

Box 11-2 Causes of Ischemic Acute Renal Failure in Small Animals

INTRAVASCULAR VOLUME DEPLETION
Dehydration
Vomiting
Diarrhea
Sequestration or shock
Thermal burns
Blood loss
Trauma
Surgery
Hypoalbuminemia
Hypoadrenocorticism
Hyponatremia (nondilutional)

DECREASED CARDIAC OUTPUT
Congestive heart failure
Low output
Restrictive pericardial disease
Tamponade
Arrhythmia
Positive-pressure ventilation
Prolonged resuscitation after cardiac arrest

INCREASED BLOOD VISCOSITY
Multiple myeloma
Polycythemia (absolute or relative)

ALTERED RENAL AND SYSTEMIC VASCULAR RESISTANCES
Renal vasoconstriction
Circulating catecholamines
Renal sympathetic nervous stimulation
Vasopressin
Angiotensin II
Hypercalcemia
Amphotericin B
Hypothermia
Myoglobinuria
Hemoglobinuria
Systemic vasodilation
Arteriolar or mixed vasodilator therapy
Anaphylaxis
Gaseous anesthesia
Sepsis
Heatstroke

INTERFERENCE WITH RENAL AUTOREGULATION DURING HYPOTENSION
Nonsteroidal antiinflammatory drugs

WARM OR COLD ISCHEMIA

Modified from Chew D, DiBartola S: Diagnosis and pathophysiology of renal disease. In Ettinger SJ, editor: *Textbook of veterinary internal medicine*, ed 7, vol 2, Philadelphia, 2010, Saunders.

cause cell death by necrosis or apoptosis. Following less severe insults and within different portions of the renal tubule, apoptosis may occur in lieu of necrosis. The apoptotic pathway can be triggered by the following:

- Binding of ligands to the tumor necrosis factor (TNF) superfamily
- Deficiency of cellular growth factors
- Imbalance between proapoptotic and antiapoptotic oncogenes
- Alteration of other mediators of apoptotic signaling pathways such as reactive oxygen metabolites, caspases, and ceramide

Proximal tubular epithelium has a microvillous border, which amplifies absorptive surface area and cellular junctional complexes that structurally polarize the cell so that membrane phospholipids and specialized proteins remain in the appropriate domains. The integrity of these cellular structures is critical to absorption and secretion. Early structural changes after ischemic insult include formation of apical blebs, loss of brush border, loss of cellular polarity, disruption of tight junctions, and sloughing of cells, which result in intratubular cast formation (E-Fig. 11-1).

Damage to the cellular cytoskeleton modifies cell polarity, cell-to-cell interactions, and cell-matrix interactions. Initially, ischemic damage modifies cell polarity by disruption of the terminal web and disassembly of the microvillar actin cores. This is followed by conversion of G actin to F actin and its redistribution from the apical cell component to form diffuse aggregates throughout the cytoplasm (E-Figs. 11-2 and 11-3). Cells are attached to each other by junctional complexes, tight junctions, and adherens junctions and to the ECM by integrins. Several mechanisms contribute to tight junction disruption, which is manifested as alteration in cellular permeability and cell polarity. The contributing mechanisms include redistribution of membrane lipids and proteins, such as Na^+/K^+-ATPase, to the apical membrane after alteration of the actin cytoskeleton and redistribution of integrins to the apical cell surface so that cell desquamation occurs. The former results in deranged sodium handling by the proximal tubular cell.

Animals with severe tubular necrosis have accompanying functional derangements of vascular, tubular, and/or glomerular origin. Vascular derangements include the following:

- Afferent arteriolar constriction
- Efferent arteriolar dilation
- Loss of autoregulation of renal blood flow

Prolonged ischemia can produce a paradoxic response of the autoregulatory system, where increased glomerular capillary resistance from tubular fluid stasis results in activation of afferent arteriolar vasoconstriction. Decreased production of or response to vasodilative factors, such as prostaglandin and atrial natriuretic peptide, also contribute. Afferent arteriole vasoconstriction, back leak of fluid, and tubular obstruction account for decreased glomerular filtration rate (GFR) (Fig. 11-9).

Tubuloglomerular feedback is the mechanism by which GFR is matched to the solute load and the solute handling characteristics of the tubules. Because of altered sodium handling, increased concentrations reach the macula densa, and activation of the renin-angiotensin system occurs. This is followed by intrarenal vasoconstriction, particularly affecting outer cortical nephrons, and results in decreased glomerular blood flow, decreased filtration, and reduced formation of urine.

Gross Lesions of Acute Tubular Necrosis. On gross examination, the recognition of acute tubular necrosis is often difficult. Nevertheless, initially the cortex is swollen, pale mahogany to beige, and with a slightly translucent smooth, thinned, capsular surface. The cut surface of the renal cortex bulges and is excessively moist; striations are muted or accentuated by radially oriented opaque, white streaks, presumably related to the stage of the necrosis, with coagulation necrosis being responsible for the white streaks. The medulla is either pale or diffusely congested.

Microscopic Lesions of Acute Tubular Necrosis. The microscopic appearance of kidneys with acute tubular necrosis varies, depending on the following:

- The extent of the tubular necrosis
- The duration of exposure to the damaging agent
- The length of time between the injury and death—in other words, the stage of necrosis or dissolution of necrotic epithelium

Initially, tubular necrosis is randomly distributed in nephrons, but the proximal convoluted tubules are most severely affected because of their high metabolic demands and first line of exposure (Fig. 11-10). Prolonged ischemia can produce necrosis of epithelium of the proximal and distal convoluted tubules, the loops of Henle, and the collecting ducts throughout the cortex and, to a lesser extent, the medulla. Glomeruli are resistant to ischemia and often remain morphologically normal, even when ischemia is prolonged. Initially, proximal tubular epithelium is swollen, and the cytoplasm is vacuolated or granular and intensely eosinophilic, all features indicative of necrosis (Fig. 11-11). In such cells, the nuclear changes are pyknosis, karyorrhexis, or karyolysis. Necrotic tubular epithelium is subsequently sloughed into tubular lumens resulting in dilated, notably hypocellular tubules that contain necrotic cellular debris and hyalinized or granular casts.

A characteristic histologic lesion of ischemic tubular necrosis is possible disruption of the tubular basement membranes, referred to as tubulorrhexis (Fig. 11-12). Tubular repair in these kidneys is imperfect because regenerating epithelial cells do not have their normal scaffolding. Tubules that remain in an affected site are less functional in resorption, can be dilated and lined by flattened epithelium, or are notably atrophic, appearing shrunken with a collapsed lumen lined by flattened epithelium and fail to heal completely by regeneration, resulting in tubular atrophy.

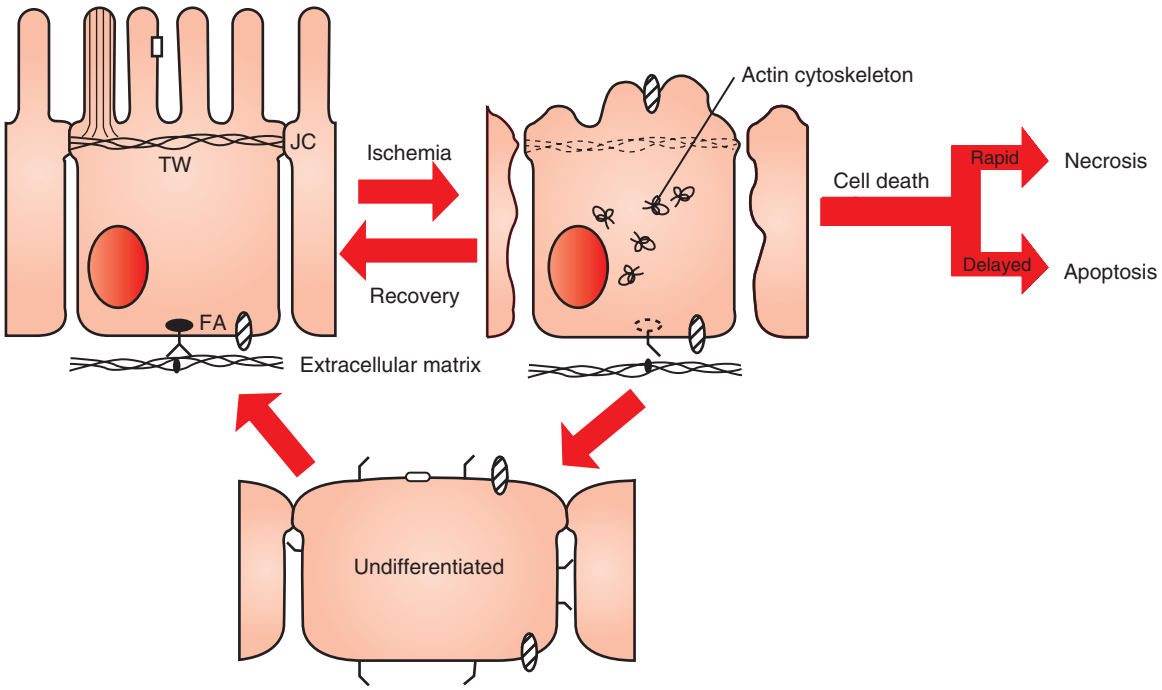
Miscellaneous Responses to Injury of Renal Tubules

Lipofuscinosis. Fine golden granules of brown iron-free pigment with the staining characteristics of lipofuscin ("wear and tear pigment") can accumulate in renal epithelial cells of old cattle and in striated muscle, resulting in lipofuscinosis. Grossly, the renal cortex can have streaks of brown discoloration, but renal function is not affected. Microscopically, the accumulations are noted most prominently within the proximal convoluted epithelial cells. The direct cause is not known, but it is suspected that accumulations result from previous cell membrane breakdown and subsequent storage of end-product in the tubular epithelial cells.

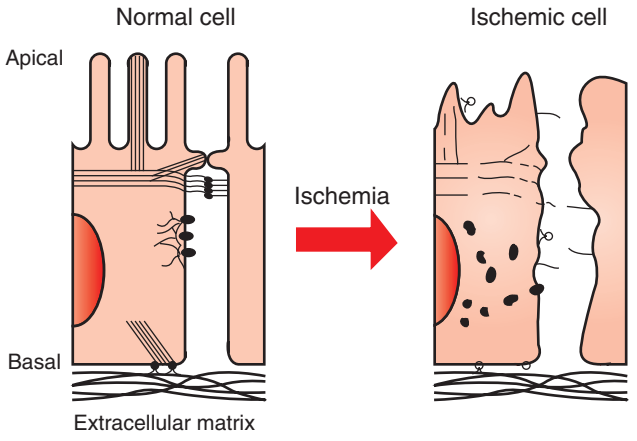
Hydropic Degeneration. Hydropic degeneration and cloudy swelling are traditional names often used to define renal tubular degenerative changes seen during the pathologic process of acute cellular swelling. Acute cellular swelling is a potentially reversible change resulting from cell membrane, sodium/potassium pump, and cell energy breakdown with increased intracellular sodium ions and water. Although rare in the kidney, a severe hydropic degeneration of the proximal convoluted tubules and the ascending loop of Henle has been observed after intravenous administration of hypertonic solutions such as dextrose.

Glycogenic Degeneration. Abundant cytoplasmic vacuolation of tubular epithelium of the outer medulla and inner cortex is seen in dogs and cats with diabetes mellitus. Glycogen can be demonstrated as the accumulating compound within the cells of the ascending limb. Treatment with insulin relieves the deposition. The change is not thought to affect renal function.

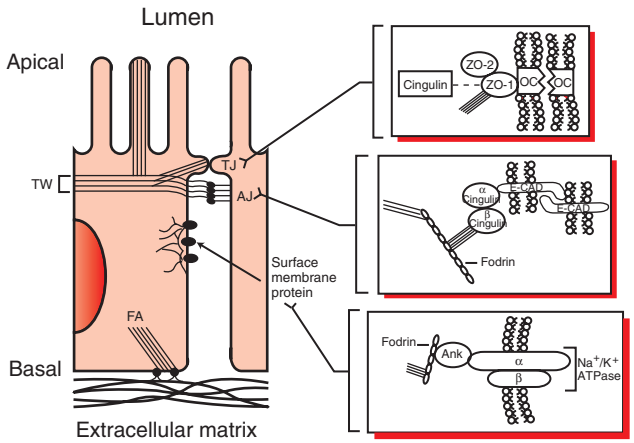
Fat. In cats, proximal tubular epithelial cell cytoplasm is usually expanded by accumulations of cytoplasmic lipid resulting in the



E-Figure 11-1 Effect of Ischemia on Cell Structure and Function. A polarized renal proximal tubule cell with a well-developed actin cortical cytoskeleton is shown on the *left*. Also shown is attachment to the extracellular matrix (ECM) via integrins. Following ischemic injury there is extensive disruption, redistribution, and aggregation of the actin cytoskeleton resulting in loss of microvilli structure, blebbing of microvilli into the lumen, detachment of cells from the ECM, and opening of junctional complexes (*JC*). Injured proximal tubule cells can undergo primary repair and recover directly into a polarized epithelial cell. Cells can also go through an undifferentiated phase followed by redifferentiation, or cells can die either rapidly via necrosis or in a much slower programmed manner known as apoptosis. The primary route of cellular repair involves direct recovery. The percentage of cells reverting to an undifferentiated state or dying depends on the severity of the injury and the location within the kidney. *FA*, Focal adhesions; *TW*, terminal web. (Redrawn from Molitoris BA, Marrs J: *Am J Med* 106:583-592, 1999.)



E-Figure 11-2 Effect of Ischemia on the Actin Cytoskeleton and the Cytoskeletal-Surface Membrane Interactions in Proximal Tubule Cells. During ischemia, alterations in the actin cytoskeleton involve disruption of the actin cytoskeleton with redistribution and aggregation of actin throughout the cytoplasm. Consequently, notable alterations occur in cytoskeletal-surface membrane interactions. Loss of cell-cell adhesion, cell-matrix adhesion, and polarity of surface membrane proteins during ischemia play a role in the diminished glomerular filtration rate that is the hallmark of ischemic acute renal failure. See Fig. 11-14 for more detail about the actin cytoskeleton and the cytoskeletal-surface membrane. (Redrawn from Sutton TA, Molitoris BA: *Sem Nephr* 18(5):490-497, 1998.)



E-Figure 11-3 Actin Cytoskeleton and the Cytoskeletal-Surface Membrane Interactions in Proximal Tubule Cells. Microvillar F-actin filaments extend into the apical actin network termed the *terminal web (TW)* and are bound together by villin and attached to the surface membrane by myosin and ezrin to form the structural core of the apical microvilli. The actin cytoskeleton associates with junctional complexes involved in cell-cell interactions, including the tight junction and the adherens junction. More detailed diagrams of the tight junction *(TJ)* and the adherens junction *(AJ)* appear to the *right* and demonstrate the interaction of F-actin filaments with TJ and AJ protein complexes. *OC* represents occludin in the diagram of the TJ, and *E-CAD* represents E-cadherin in the diagram of the AJ. The cortical actin network associates with surface membrane proteins, such as the sodium-potassium adenosinetriphosphatase, which is demonstrated by the detailed diagram to the *lower right*. *Ank* represents ankyrin in this diagram. Finally, the actin cytoskeleton associates with structures involved in cell-matrix interactions, including focal adhesions *(FA)*. F-actin filaments (stress fibers) possibly bundled together by myosin II associate with a protein complex at sites where integrins bind to the extracellular matrix. (Redrawn from Sutton TA, Molitoris BA: *Sem Nephr* 18(5):490-497, 1998.)

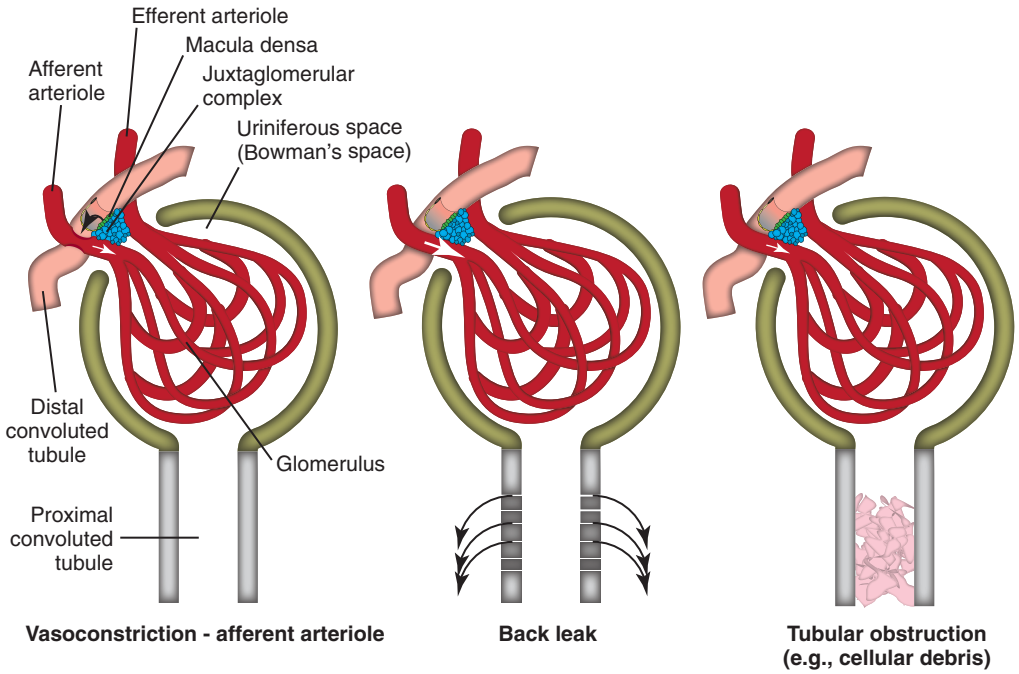


Figure 11-9 Mechanisms of Decreased Glomerular Filtration Rate (GFR) During Ischemic Acute Renal Failure. Proposed mechanisms for the decrease in GFR that occurs during ischemic acute renal failure include afferent arteriole vasoconstriction, back leak of glomerular filtrate, and tubular obstruction. All three of these mechanisms relate to ischemia-induced alterations in proximal tubule epithelial cells. Deranged proximal tubule handling of sodium leads to a high delivery of sodium to the macula densa, which in turn causes afferent arteriole vasoconstriction via tubuloglomerular feedback. Afferent arteriole vasoconstriction reduces glomerular capillary pressure and therefore GFR. Altered cell-cell adhesion results in an open tight junction that leads to increased paracellular permeability and subsequent back leak of glomerular filtrate from the tubular lumen into the extracellular space and ultimately into the bloodstream. Disrupted cell-matrix adhesion and abnormal cell-cell adhesion leads to cellular cast formation, which obstructs the tubular lumen and causes increased tubular pressure resulting in diminished or no GFR. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

usual pale, golden color of their kidneys. In dogs, tubular epithelial fat occurs, but it is much less common compared to cats and is usually restricted to the inner cortex. This site is a normal storage location and microscopically is recognized as large clearings within the renal tubular epithelial cells, most prominently in the proximal tubules. There is not thought to be any significant alteration to renal function.

Hemosiderin and Ferritin. Pigment can be present in the renal tubules. The origin of hemosiderin pigment is most likely from degradation of hemoglobin resorbed from the glomerular filtrate by proximal tubular epithelium. However, a history or concurrent lesions of a prior hemolytic crisis are often lacking. In dogs, microscopic granules of hemosiderin are frequent incidental findings in the cytoplasm of proximal convoluted tubular epithelial cells in kidneys that are otherwise normal.

Cloisonné kidneys, which occur in goats, are the result of proximal tubular basement membrane thickening as a result of deposits of ferritin and hemosiderin. Grossly, these kidneys have diffuse, intense, black or brown discoloration of the cortex (Fig. 11-13). The medulla is spared. Although this lesion is striking, renal function is normal.

Other Miscellaneous Tubular Changes. Other causes of incidental tubular changes include the following:

- Vacuolation of renal tubular epithelium in the lysosomal storage diseases, such as feline sphingomyelinosis and ovine GM1 gangliosidosis.
- Intranuclear eosinophilic crystalline pseudoinclusions (so-called crystalloids), which occur in renal tubular epithelium of old dogs. These can be round or rectangular and often greatly distort the nuclei.

Interstitium

Hyperemia. In instances of acute interstitial nephritis, especially those caused by septicemia, there can be an accompanying hyperemia of renal vasculature within the interstitium.

Edema. Similarly, in instances of acute inflammation targeting the interstitium, vascular leakage of high protein fluid (edema) can be the end result. In addition, tubular damage, especially with basement membrane breach, allows for more extensive interstitial edema accumulation.

Inflammatory Infiltrates. Interstitial inflammation is a consistent component of injury to the interstitium, whether acute or chronic, focal or generalized, or suppurative or nonsuppurative. Suppurative interstitial inflammation is typically seen in instances of hematogenous bacteremia. A variety of renal insults result in release of a wide array of cytokines and growth factors that stimulate interstitial inflammation, particularly monocyte infiltration. Fibroblasts often become activated and fibrosis ensues.

Fibrosis. Once interstitial fibroblasts become activated, fibrosis can ensue. Often, at this stage, the underlying or inciting pathogen is not present and thus its role is not determined. Recurrent bouts of fibrosis continue and set up a vicious cycle of loss and scarring so that the result is a common endpoint, known as *end-stage kidney*.

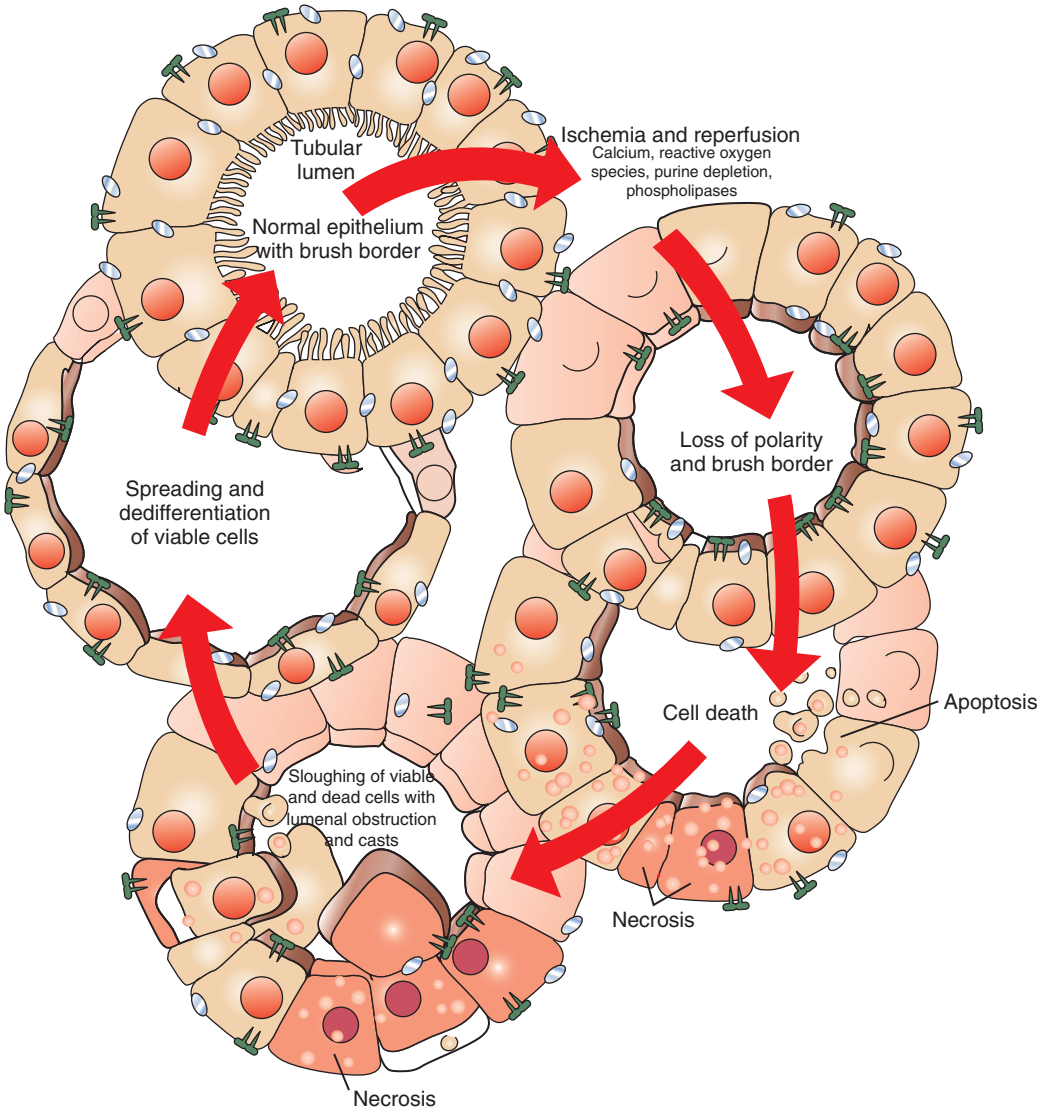


Figure 11-10 Effects of Ischemia and Reperfusion on Renal Tubules. After ischemia and reperfusion, morphologic changes occur in the proximal tubules, including loss of the brush border, loss of polarity, and redistribution of integrins and sodium-potassium adenosinetriphosphatase to the apical surface. Calcium, reactive oxygen species, purine depletion, and phospholipases probably have a role in these changes in morphology and polarity and in the subsequent cell death that occurs as a result of necrosis and apoptosis. There is a sloughing of viable and nonviable cells into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the glomerular filtration rate. The severely damaged kidney can completely restore its structure and function. Spreading and dedifferentiation of viable cells occur during recovery from ischemic acute renal failure, which duplicates aspects of normal renal development. A variety of growth factors probably contribute to the restoration of a normal tubular epithelium. (Redrawn from Thadhani R, Pascual M, Bonventre JV: *N Engl J Med* 334(22):1448-1460, 1996. Color from Molitoris BA, Finn WF, editors: *Acute renal failure: A companion to Brenner and Rector's the kidney*, Philadelphia, 2001, Saunders.)

Lymphofollicular Inflammation. Lymphofollicular inflammation is the most common response to *Leptospira* infection of the kidney. Severe multinodular lymphocytic inflammatory reaction is confined to the cortex. The reaction subsides slowly and inflammatory cells decrease in numbers and the degree of fibrosis increases. Similarly, with chronic recurrent bouts of pyelonephritis, lymphocyte-rich inflammatory infiltrates are noted within the interstitium.

Interstitial Nephritis. When interstitial inflammation, mounted against the veins, arteries, lymphatic vessels, or connective tissues of kidneys, appears to be a primary lesion, it has traditionally been called *interstitial nephritis* and may have an infectious or noninfectious cause and is acute, subacute, or chronic in its duration. Interstitial nephritis is traditionally associated with a lymphoplasmacytic infiltrate; however, other types of leukocytes can also be present. In many of these diseases, the inflammatory cell infiltrates are visible only microscopically, are not associated with renal failure, and are generally inconsequential (examples are canine ehrlichiosis and equine infectious anemia). When the renal interstitium is the site of moderate to severe, grossly visible, interstitial inflammatory cell infiltrates and fibrosis, renal failure can occur.

The renal interstitium is the fibrovascular stroma that surrounds the nephron and is significantly involved in renal diseases, whether this is of primary interstitial origin as in interstitial nephritis or

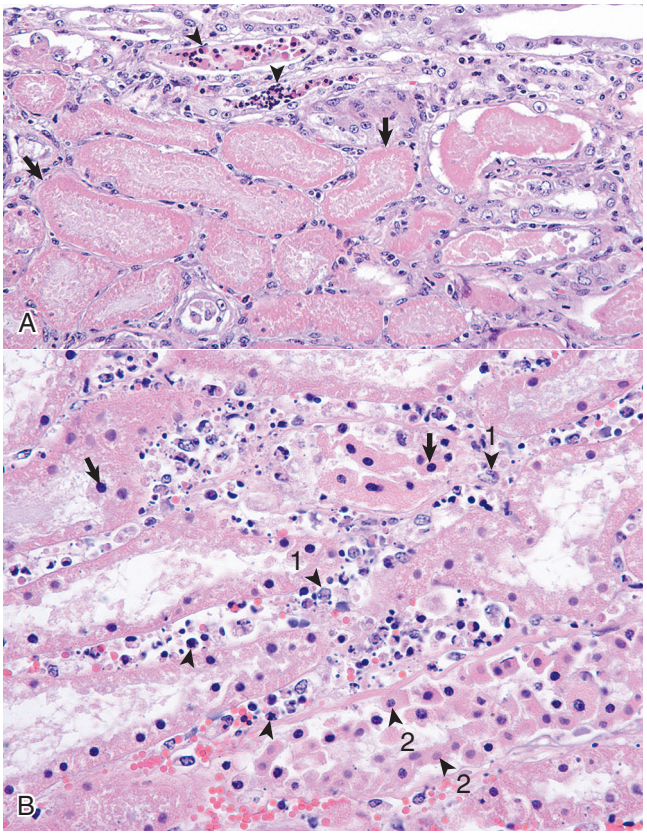


Figure 11-11 Acute Tubular Necrosis, Kidney, Proximal Tubules, Cat. A, This lesion is characterized primarily by coagulation necrosis of tubular epithelial cells *(arrows)* and nuclear pyknosis and intratubular nuclear and proteinaceous debris *(arrowheads)*. H&E stain. **B,** This lesion is characterized primarily by nuclear pyknosis *(arrows)*, karyorrhexis *(arrowheads)*, and karyolysis *(arrowheads 1)* with intratubular nuclear and proteinaceous debris and coagulation necrosis with detachment of the epithelium from the tubular basement membrane *(arrowheads 2)*. H&E stain. (Courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

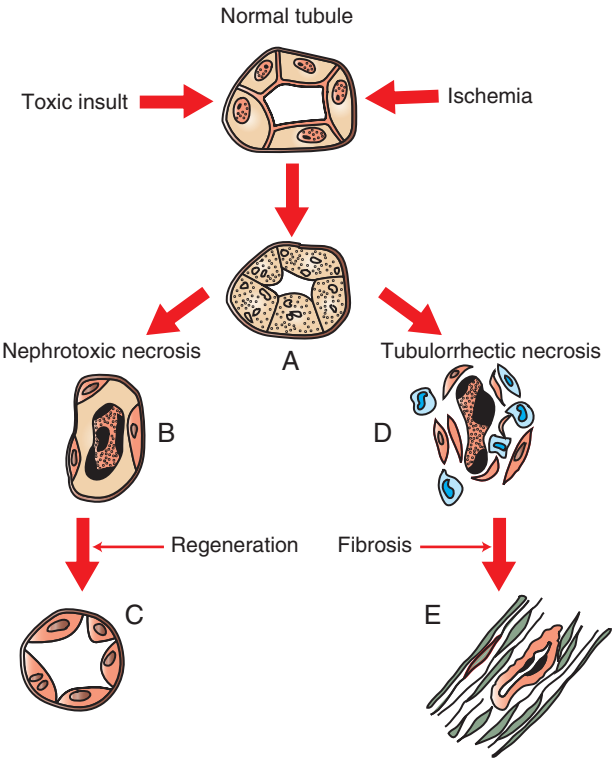


Figure 11-12 Acute Tubular Necrosis, Kidney, Proximal Tubules. Acute tubular necrosis results from a nephrotoxin or ischemia. **A,** Both insults cause acute necrosis characterized by cellular swelling, pyknosis, karyorrhexis, and karyolysis. **B,** Subsequent to nephrotoxic necrosis, there is sloughing of necrotic epithelium into the tubular lumina. The basement membranes remain intact and act as a scaffold for **(C)** tubular epithelial regeneration to occur. **D,** Ischemia may result in tubulorrhexis. Necrotic epithelial cells slough into the tubular lumen, the basement membrane is disrupted, macrophages infiltrate, and fibroblasts proliferate. **E,** Fibrosis with tubular atrophy results.

subsequent to tubular damage, when it is referred to as *tubulointerstitial disease*. Interstitial inflammation occurs as the result of ascending urinary tract infections (pyelonephritis), systemically derived infections of tubules and interstitium, toxins, or secondary to injury of tubules or glomeruli. Common acute lesions of the interstitium in response to toxins and tubular necrosis include edema, hemorrhage, and inflammation characterized by infiltration of neutrophils. As lesions become subacute to chronic, neutrophils become less prominent, and in several diseases, infiltrates of macrophages, lymphocytes, and plasma cells predominate. With chronic injury to or after atrophy of nephrons, fibrosis of the interstitium can be severe, resulting in notable reduction in nephron function and accentuation of renal disease.

Tubulointerstitial Nephritis. The term *tubulointerstitial nephritis* has been used to characterize a group of inflammatory diseases that involve the interstitium and tubules. Acute tubulointerstitial disease includes a group of processes, namely inflammation secondary to acute tubular necrosis, whereas chronic tubulointerstitial processes include the progression with time or instances in which the interstitium is the primary target.

Tubulointerstitial nephritis can result from bacterial or viral septicemias, in which these infectious microbes first infect the kidney tubules and damage them, which then incites an inflammatory response in the interstitium (Box 11-3). Acute tubulointerstitial nephritis is characterized by the presence of inflammatory cells (principally neutrophils) within the interstitium and may result from toxicoses or from acute infection with microbes such

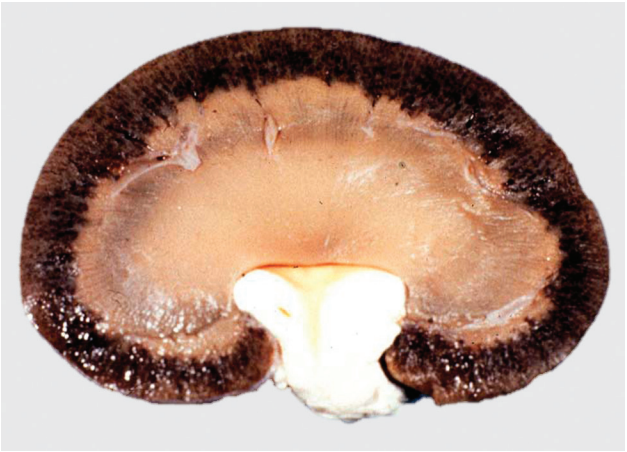


Figure 11-13 Cloisonné Kidney, Dorsal Section, Goat. The cortex is diffusely black; the medulla is unaffected. (Courtesy Dr. J. King, College of Veterinary Medicine, Cornell University.)

Box 11-3 Causes of Interstitial Nephritis

HORSES
Equine viral arteritis

CATTLE
Escherichia coli septicemia, "white-spotted kidney"
Leptospira interrogans serovar *canicola*
Malignant catarrhal fever

SHEEP
Sheeppox

PIGS
Leptospira interrogans serovar *pomona*
Porcine reproductive and respiratory syndrome

DOGS
Leptospira interrogans serovars *canicola*, *icterohaemorrhagiae*, and others
Infectious canine hepatitis virus, recovery phase
Theileria parva

as *Leptospira* (see Fig. 11-66), adenoviruses, lentiviruses, or herpesviruses. Chronic tubulointerstitial nephritis (Fig. 11-14, *A*) is a less well-characterized entity in dogs, but atrophy of tubular segments is a significant feature of this syndrome along with sparse mononuclear cell infiltration, cortical and medullary fibrosis (Fig. 11-14, *B* and *C*), variable degrees of tubular and glomerular atrophy and/or sclerosis, and compromised nephron function.

The pathogenesis of leptospirosis is discussed as an example of acute bacterial tubulointerstitial nephritis, the most well-understood causes of which include numerous serovars of *Leptospira interrogans*; however, *Leptospira kirschneri* and *Leptospira borgpetersenii* serovars are also associated with renal disease (Fig. 11-14, *D*):

- *Leptospira interrogans* serovars *canicola* and *icterohaemorrhagiae* are the most common causes of canine leptospirosis (see the section on Kidney and Lower Urinary Tract, Disorders of Dogs).
- *Leptospira interrogans* serovar *pomona* is the most common cause of the lesion in pigs and less consistently in cattle (see the section on Kidney and Lower Urinary Tract, Disorders of Ruminants (Cattle, Sheep, and Goats)).

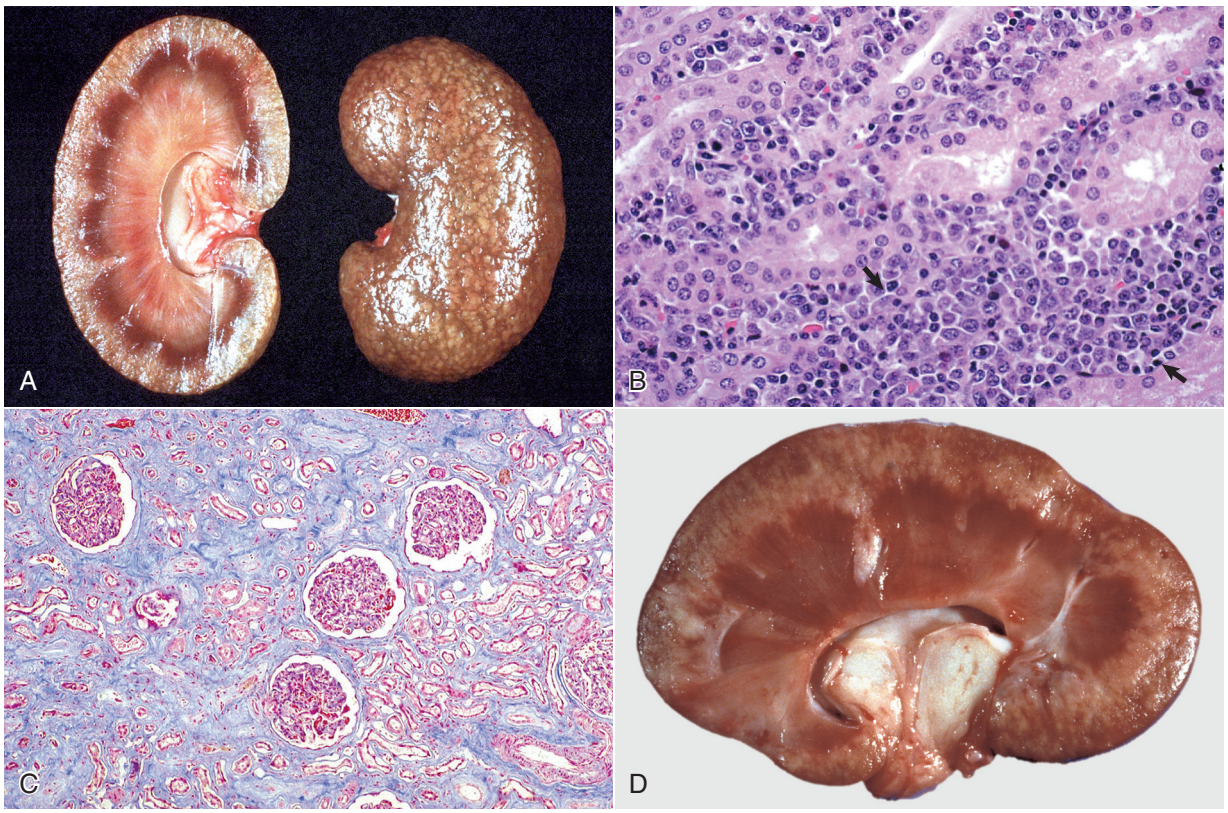


Figure 11-14 Chronic Tubulointerstitial Nephritis. A, Kidney, dorsal surface and dorsal section, dog. Note the nodularity of the capsular surface *(right)* from cortical interstitial fibrosis and the reduced width of the cortex (atrophy) *(left)*. **B,** Kidney, dog. Large numbers of lymphocytes and plasma cells expand the interstitium *(arrows)* between renal tubules. H&E stain. **C,** Kidney, exotic zoo animal. This lesion is characterized by cortical and medullary fibrosis, variable degrees of tubular atrophy, and mononuclear cell interstitial infiltrate. Masson trichrome stain. **D,** Leptospirosis, dog. The pale streaks and foci in the cortex, especially near the corticomedullary junction, are chiefly interstitial lymphoplasmacytic infiltrates accompanied by fibrosis. (**A** and **C** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy Dr. Abdy, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **D** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

- *Leptospira kirschneri* serovar *grippotyphosa* and *Leptospira borgpetersenii* serovar *bratislava* have also been associated with renal leptospirosis in several animal species.

Mechanism of Injury of Tubulointerstitial Nephritis. Three theories on the cause of chronic tubulointerstitial nephritis are (1) focal acute interstitial nephritis evolves into the chronic form, (2) it is produced as a secondary manifestation of chronic glomerulonephritis (GN) or chronic pyelonephritis, or (3) it is produced after immune-mediated damage to the renal tubules and interstitium. There are few acute tubulointerstitial diseases to account for the large number of cases of chronic tubulointerstitial nephritis seen in dogs, and thus the first theory cannot account for a high percentage of the cases. As diagnostic techniques improve, some cases of chronic tubulointerstitial nephritis may be reclassified more specifically as either chronic pyelonephritis or secondary to chronic GN.

The mechanism of injury is known in a few instances, most specifically with *Leptospira* infections. After exposure to the organism, leptospiremia occurs and then organisms do the following:

- Localize in the renal interstitial capillaries
- Migrate through vascular endothelium
- Persist in the interstitial spaces
- Migrate via the lateral intercellular junctions of tubular epithelial cells to reach renal tubular lumina
- Associate with epithelial microvilli
- Persist within phagosomes of the epithelial cells of the proximal and distal convoluted tubules
- Induce tubular epithelial cells to undergo degeneration and necrosis as a result of either direct toxic effects of the leptospires or the accompanying interstitial inflammatory reaction

Although neutrophils can be present in tubular lumina, the predominant chronic lesion is an infiltrate of monocytes, macrophages, lymphocytes, and plasma cells in the interstitium (chiefly cortical) (see Fig. 11-14, *D*). In affected dogs, interstitial plasma cells secrete *Leptospira*-specific antibodies. However, the role of those antibodies in pathogenesis or resolution of the lesion is not known.

Another well-documented mechanism for the production of tubulointerstitial nephritis is the immune response that develops secondary to canine adenoviral infection. The sequence of events includes the following:

- Localization of virus in the glomeruli (viral glomerulitis) during the viremic phase of the disease
- Production of a transient immune-complex GN
- Recovery from the acute phase of the disease
- Onset of the systemic immune response
- Disappearance of virus from the glomeruli only to reappear in tubular epithelial cells in various portions of the nephron in basophilic intranuclear viral inclusions
- Persistence of virus in tubular epithelium for weeks to months
- Production of tubular epithelial necrosis as a result of viral-induced cytolysis
- Production of chronic lymphocytic, plasmacytic, and, less commonly, histiocytic interstitial nephritis

Infection with equine arteritis virus or porcine reproductive and respiratory syndrome (PRRS) virus often results in multifocal lymphohistiocytic chronic tubulointerstitial nephritis with interstitial edema. Lesions can involve any area of the cortex but are especially intense in the medulla and at the corticomedullary junction. A severe vasculitis, characterized by fibrinoid necrosis and lymphohistiocytic infiltrates that involve the adventitial and medial layers of cortical and medullary arteries and veins, is present. Virus can be found in endothelium and in macrophages.

Deposition of immune complexes in or interactions between anti-basement membrane antibodies and tubular basement membranes can initiate immune-mediated tubulointerstitial disease in human beings and laboratory animals. Depositions of immunoglobulin (Ig) and complement have rarely been identified in renal tubular basement membranes in domestic animals, but administration of preformed complexes (bovine serum albumin and antibody) to dogs demonstrated that these complexes interacted with proximal renal tubules not glomeruli. Damaged tubules respond with epithelial cell proliferation, basement membrane thickening, and peritubular fibrosis. Currently, the role of immune-mediated mechanisms in tubulointerstitial nephritis in domestic animals is unclear.

Gross Lesions of Tubulointerstitial Nephritis. Gross lesions can be classified as acute, subacute, or chronic; chronic tubulointerstitial nephritis is discussed in more detail later (see the section on Renal Fibrosis). The distribution of lesions can be diffuse as in canine leptospirosis (see Fig. 11-66) or multifocal as in "white-spotted kidneys" of calves as the result of *Escherichia coli* septicemia (see Fig. 11-63), canine herpesvirus infection (see Fig. 11-67), malignant catarrhal fever, or porcine and bovine leptospirosis (see Fig. 11-66). In diffuse tubulointerstitial nephritis, kidneys can be swollen and pale tan with a random gray mottling of the capsular surface. The cut surface bulges; gray infiltrates of varying sizes and intensities obscure the normal radially striated cortical architecture. These renal lesions usually are manifested as coalescing gray foci that are particularly intense in the inner cortex. Focal lesions of tubulointerstitial nephritis are less extensive and composed of more discrete gray areas in the cortex and outer medulla.

Microscopic Lesions of Tubulointerstitial Nephritis. Microscopically, aggregates of lymphocytes, plasma cells, monocytes, and fewer neutrophils are randomly scattered or intensely localized throughout the edematous interstitium. Tubular epithelial cells within severely inflamed areas can be degenerate, necrotic, or both, and profound tubular loss is usually accompanied by eventual replacement fibrosis.

Renal Fibrosis (Scarring). The alternative to regeneration is irreparable damage that results in functional tubular loss when cuboidal epithelium is replaced by nonabsorptive cuboidal or squamous cells or actual physical loss of tubules so that the nephron is lost. This can occur after either an ischemic insult, tubular descruction by infectious microbes, or exposure to a limited number of nephrotoxins. The ultimate result is replacement fibrosis/scarring. This is seen most commonly if the following occur:

- The toxin is not removed.
- The basement membrane does not remain intact.
- Adequate tubular epithelium does not survive destruction by microbes or the toxic dose of a nephrotoxin to allow for complete repair.

Fibrosis with a finely granular pattern can occur subsequent to widespread necrosis of renal tubular epithelium (acute tubular necrosis). An example is oak poisoning of cattle (see Fig. 11-62), in which severe tubular necrosis extends to the level of the renal tubular basement membrane, resulting in leakage of tubular contents. The loss of the continuity of the basement membrane prevents orderly tubular epithelial cell regeneration, which can be followed by interstitial fibrosis. Experimental studies have demonstrated that after severe nephrotoxin-induced tubular epithelial cell injury, the remaining cells undergo accelerated apoptosis resulting in tubular atrophy, interstitial fibroblast proliferation, and eventual fibrosis.

Renal fibrosis is the replacement of renal parenchyma, including tubules, glomeruli, and interstitium, with mature fibrous connective tissue. It can occur as a primary event, but more frequently it is a manifestation of the healing phase of a preexisting tubular or

glomerular lesion. It is the common endpoint of all reparative stages and results when conditions are not conducive for healing of the tubular epithelium by regeneration. Regeneration of nephrons as a whole is not possible. Renal fibrosis follows many renal lesions, including primary inflammation of glomeruli (GN), tubules, or interstitial tissue (tubulointerstitial nephritis) (Fig. 11-15) and necrosis of renal tubules. Its severity usually parallels the intensity of the primary renal disease. The mechanisms by which fibrosis is induced are related to destruction and loss of nephron components by inflammatory or, less commonly, noninflammatory processes. T lymphocytes and interleukin-6 (IL-6) play important roles in renal fibrosis. Renal fibrosis is seen commonly following any number of renal insults and includes the following:

- Infarction
- Glomerulonephritis
- Tubulointerstitial disease/chronic pelvic diseases

Renal fibrosis may manifest in a multitude of grossly recognizable forms as described previously. Generally, fibrotic kidneys are recognized grossly by the pale, tan to white, shrunken, pitted, and firm consistency, along with excessive adhesions of the capsule to the underlying cortex. Fibrosis can be diffuse and finely stippled with pinpoint dimpling and granularity on the capsular surface, or it can be coarser as seen by deep and irregularly shaped depressions of the capsular surface in a diffuse, multifocal, or patchy distribution. In addition to these changes of the capsular surface, the cut surface of the cortex is thinned beneath the capsular surface depressions, and these fibrotic areas are pale tan compared with more normal parenchyma.

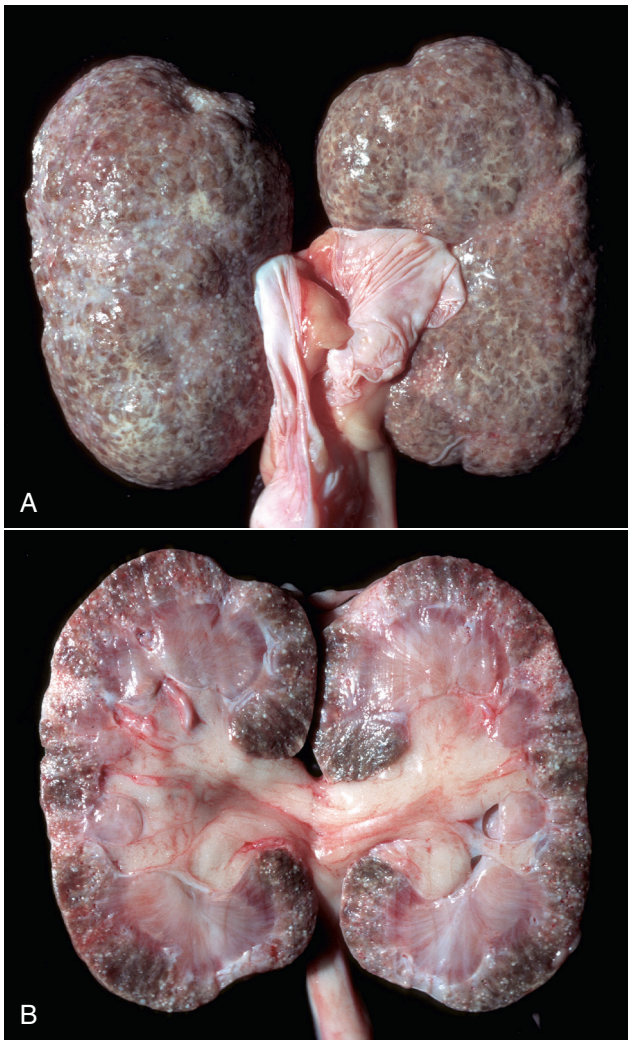


Figure 11-15 Chronic Interstitial Nephritis, Kidney, Dog. A, Diffuse interstitial fibrosis is responsible for the fine pitting of the capsular cortical surface, which is stippled red, the result of bands of fibrous tissue *(gray)* surrounding islands of renal cortex. **B,** Dorsal section. The cortex is pitted and granular because of multiple linear and focal scars, and it is also thinner than normal (atrophic). (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Microscopically, renal fibrosis is characterized by an increase in interstitial connective tissue and absence of renal tubules or by markedly atrophic nephron components (Fig. 11-16, *A*). Remaining tubules are usually atrophic and have a reduced luminal diameter or can appear ectatic because they are lined by flattened epithelium, producing an enlarged luminal diameter. A thickened hyalinized basement membrane and a lining of flattened epithelium (squamous or low cuboidal) are also characteristic. Multiple acquired, usually small, cysts can be present throughout the cortex and medulla and can be a result of either dilated Bowman's capsules and associated atrophic glomerular tufts or nephrons whose tubules have segments compressed by connective tissue (Fig. 11-16, *B*). Even in fibrotic lesions that are not the result of an infectious disease or inflammation, foci of lymphocytes and plasma cells can be seen randomly scattered throughout the interstitium (Fig. 11-16, *C*). In areas of severe interstitial fibrosis, glomerulosclerosis (as an end-stage of isolated glomeruli) is common. Calcification of vessels, tubular basement membranes, Bowman's capsules, and degenerate tubular epithelium are common in fibrotic kidneys because of alterations in calcium-phosphorus metabolism associated with chronic renal failure.

Renal fibrosis and chronic renal disease are the most frequently recognized renal pathologic processes in mature or aging domestic animals, particularly dogs and cats. When renal fibrosis and loss of nephrons are severe, these lesions can be manifested clinically as chronic renal failure and uremia. One of the most common expressions of this chronic disease is the inability of an animal to concentrate urine, resulting in frequent urination (polyuria) of dilute urine (isosthenuria). Polyuria is accompanied by dehydration and excessive water drinking (polydipsia). Hypoplastic anemia occurs as a result of the kidneys' failure to synthesize and secrete erythropoietin. Fibrous osteodystrophy can develop because of abnormal calcium-phosphorus metabolism and renal secondary hyperparathyroidism.

End-Stage Kidneys. Without careful attention to the pattern of resultant fibrosis, such kidneys are commonly called *end-stage kidneys*; however, fibrosis generally follows a pattern characteristic of the antecedent injury and is described here for tubulointerstitial disease.

A coarser pattern of diffuse renal fibrosis occurs in chronic interstitial nephritis and certain progressive juvenile nephropathies of dogs. Both cortex and medulla can be fibrotic, cortical striations are severely distorted or effaced, and the formation of multiple cortical cysts is common. End-stage kidneys are those referred to as a result of fibrosis, mineralization, sclerotic glomeruli, and foci of hyperplastic and hypertrophic tubules. Progressive interstitial fibrosis is thought to be the final common pathway to chronic renal failure.

Vasculature

Hyperemia and Congestion. Hyperemia refers to an increase in arterial blood flow, and congestion is an increase in venous blood pooling within the vasculature of the kidney. Renal hyperemia is an active process usually secondary to acute renal inflammation.

Renal congestion can be the following:

- Physiologic
- Passive

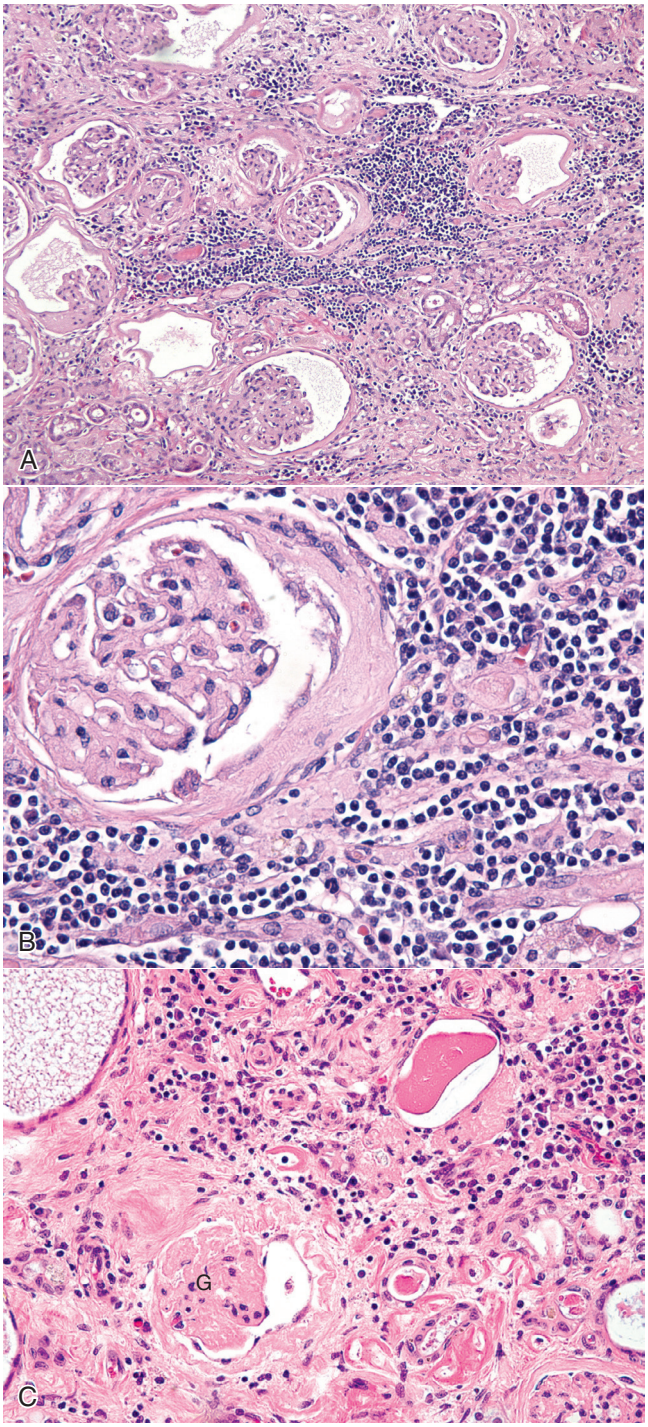


Figure 11-16 Chronic Interstitial Nephritis, Kidney, Dog. A, Dorsal section, cortex. This lesion is characterized by interstitial fibrosis, tubular atrophy, and interstitial inflammatory cell (lymphocytes and plasma cell) infiltration. The renal corpuscles have contracted glomeruli with increased volume of mesangial matrix and thickened Bowman's capsules. H&E stain. **B,** Higher magnification of **A**. H&E stain. **C,** Cortex. Higher magnification showing interstitial fibrosis, lymphocytic inflammatory infiltrates, sclerotic glomerular tufts (*G*), and ectatic tubules and Bowman's spaces. H&E stain. (**A** and **B** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois. **C** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

- Secondary to hypovolemic shock
- Secondary to cardiac insufficiency
- Hypostatic

Hyperemic kidneys are darker red than normal, can be perceptibly swollen, and ooze blood from the cut surface. Congested kidneys are dark red and ooze blood from the cut surface as the result of the accumulation of unoxygenated blood in the renal venous system. At autopsy (syn: necropsy), unilateral renal hypostatic congestion is present in animals that die in lateral recumbency, after which the force of gravity pulls the unclotted blood downward. Microscopically, the arterial and venous vessels are distended with blood, and if there has been sufficient time for the blood to clot, serum and blood cells may be present.

Hemorrhage and Thrombosis. Hemorrhage occurs when red blood cells extend beyond the vessel walls. Large intrarenal hemorrhages can result from direct trauma, renal needle biopsy, and systemic bleeding disorders, such as factor VIII deficiency. Subcapsular and renal cortical hemorrhages occur in association with septicemic diseases, vasculitis, vascular necrosis, thromboembolism, and disseminated intravascular coagulation (DIC). Perirenal hemorrhage has been noted with ovine herpesvirus arteritis (malignant catarrhal fever [MCF]) and, of course, blunt abdominal trauma or penetrating projectiles.

Petechial hemorrhages are commonly seen on the surface and throughout the cortex of kidneys from pigs that die of viremia or septicemia caused by diseases such as hog cholera (swine fever), African swine fever, erysipelas (see Fig. 11-64), streptococcal infections, salmonellosis, and other embolic bacterial diseases (e.g., *Actinobacillus* spp.). Renal cortical ecchymotic hemorrhages associated with multifocal tubular and vascular necrosis are salient and diagnostically important lesions of viremia in neonatal puppies infected with herpesvirus. Portions of thrombus that break free from affected heart valves in valvular endocarditis can lodge in the glomeruli or interstitial capillaries in any species.

When DIC causes widespread thrombosis in the glomerular capillaries (Fig. 11-17), the afferent arterioles, and, most important, the interlobular arteries, widespread cortical infarction results and is designated renal cortical necrosis. This lesion is not to be confused with ischemic acute tubular necrosis discussed in this chapter (see the section on Acute Tubular Necrosis). Partial or complete renal cortical necrosis is usually a bilateral lesion that occurs in all animal species, especially as a result of Gram-negative septicemias or endotoxemias, and is related to the following:

- Endotoxin-induced endothelial damage
- Activation of the extrinsic clotting mechanism
- Widespread capillary thrombosis

The lesion can be induced experimentally in animals by two endotoxin injections 24 hours apart and is a manifestation of the generalized Shwartzman reaction. The resulting microthrombosis of vessels throughout the renal cortex results in widespread ischemia and small and large infarcts of coagulation necrosis and hemorrhage. The renal cortex can be diffusely pale with a zone of hyperemia separating the necrotic cortex from the viable medulla, or more often the cortex is a mosaic of large, irregular hemorrhagic areas, resembling hemorrhagic infarcts interspersed with large yellow-gray areas resembling pale infarcts. The necrotic tissue can involve the full width of the cortex or only the outer portion.

Infarction. Renal infarcts are areas of coagulative necrosis that result from the local ischemia of vascular occlusion and usually are due to thromboembolism.

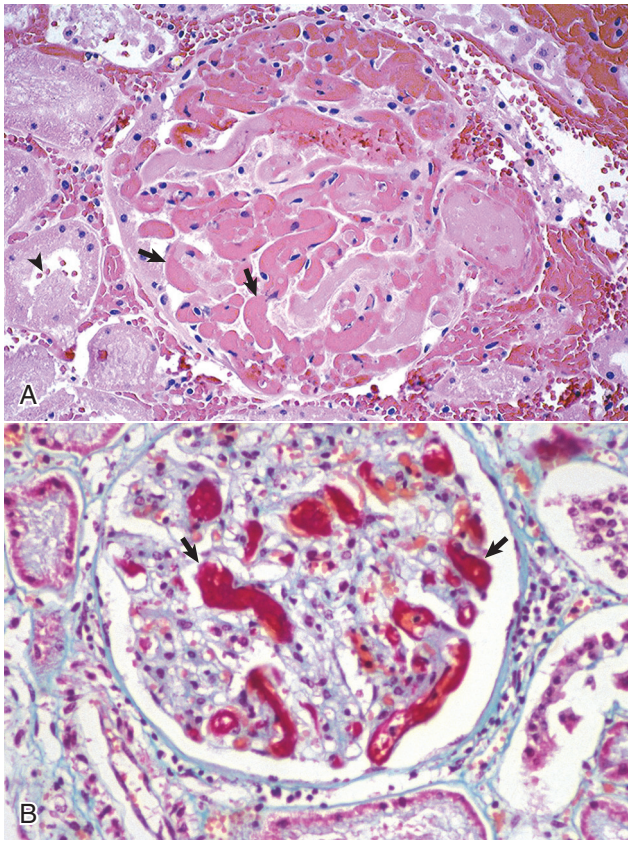


Figure 11-17 Glomerular Capillary Thrombosis, Kidney, Glomerulus, Dog. A, Microthrombi. Capillary lumens are occluded by microthrombi *(arrows)* caused by disseminated intravascular coagulation. Adjacent cortical tubular epithelial cells are undergoing coagulation necrosis with nuclei undergoing pyknosis and karyolysis *(arrowhead)*, the result of ischemia from reduced blood flow to the peritubular capillaries, which are downstream from the glomerulus. H&E stain. **B,** Fibrinous microthrombi. A glomerulus similar to the one shown in Fig. 11-23, A, stained to demonstrate fibrinous thrombi *(arrows)*. Fibrin is red. Lendrum-Fraser stain for fibrin. (**A** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy College of Veterinary Medicine, University of Illinois.)

Renal emboli are derived from the following:

- Thromboemboli
- Mural thrombi on heart valves in valvular endocarditis
- Endarteritis in parasitic diseases such as canine dirofilariasis and equine strongylosis
- Arteriosclerosis in cattle (rare)
- Neoplastic cell emboli
- Bacterial emboli
- Endotoxemia

Because of the high circulating blood volume (20% to 25% of cardiac output) through the kidney, kidneys are common sites of thromboembolism and infarction. Rarely, emboli may occlude the renal artery, causing infarction of the entire kidney. Sometimes, emboli occlude the interlobar/arcuate arteries, causing infarction of triangular (in cross section of the kidney) segments of the cortex and medulla. Most commonly, emboli obstruct smaller vessels (e.g., interlobular arteries), causing infarcts involving only the renal cortex. In general, renal infarction can occur because of thrombosis resulting from endothelial damage of glomerular capillaries associated with a vascular disease (as in Alabama rot in greyhounds; see Fig. 11-37). Renal infarcts in horses can result from emboli lodging in the renal vasculature after mural thrombosis of the aorta, from aortic wall damage caused by migrating larvae of *Strongylus vulgaris*, or from endotoxemia secondary to mucosal damage resulting from colic. Thrombosis and infarction of pulmonary, coronary, splenic, or renal arteries are common in dogs with glomerular amyloidosis, which results in loss of plasma anticoagulants, such as antithrombin III, through damaged glomeruli. Endotoxin-mediated arterial or capillary thromboemboli are a common cause of infarction in association with Gram-negative sepsis, endotoxemia, or endotoxic shock. Septic emboli, particularly those from bacterial valvular endocarditis, caused by *Trueperella pyogenes* in cattle, *Erysipelothrix rhusiopathiae* in pigs, and *Staphylococcus aureus* in small animals, can cause renal infarcts and can progress to microabscesses or granulomas, depending on the microorganism involved.

Grossly, renal infarcts appear red or pale white depending on several factors, including the interval after vascular occlusion (i.e., age of infarct) (Figs. 11-18 and 11-19). Acutely, infarcts are usually wedge-shaped in a cross section of kidney, with the base against the cortical surface and the apex pointing toward the medulla,

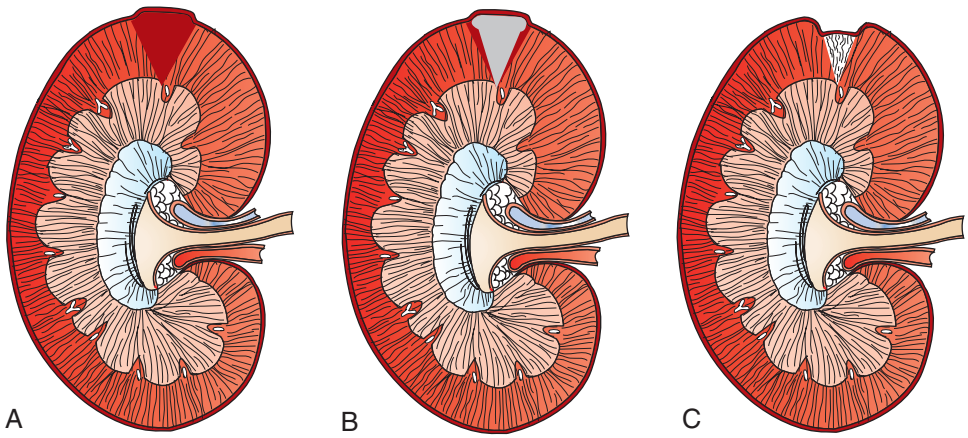


Figure 11-18 Progression of Renal Infarction. The normal progression of renal infarcts is outlined. **A** and **B,** Acute renal infarcts. Initially, renal infarcts are swollen and hemorrhagic **(A)**. In 2 to 3 days, infarcts become pale **(B)**, surrounded by a zone of hyperemia and hemorrhage. **C,** Chronic infarcts are pale, shrunken, and fibrotic, resulting in distortion and depression of the renal contour.

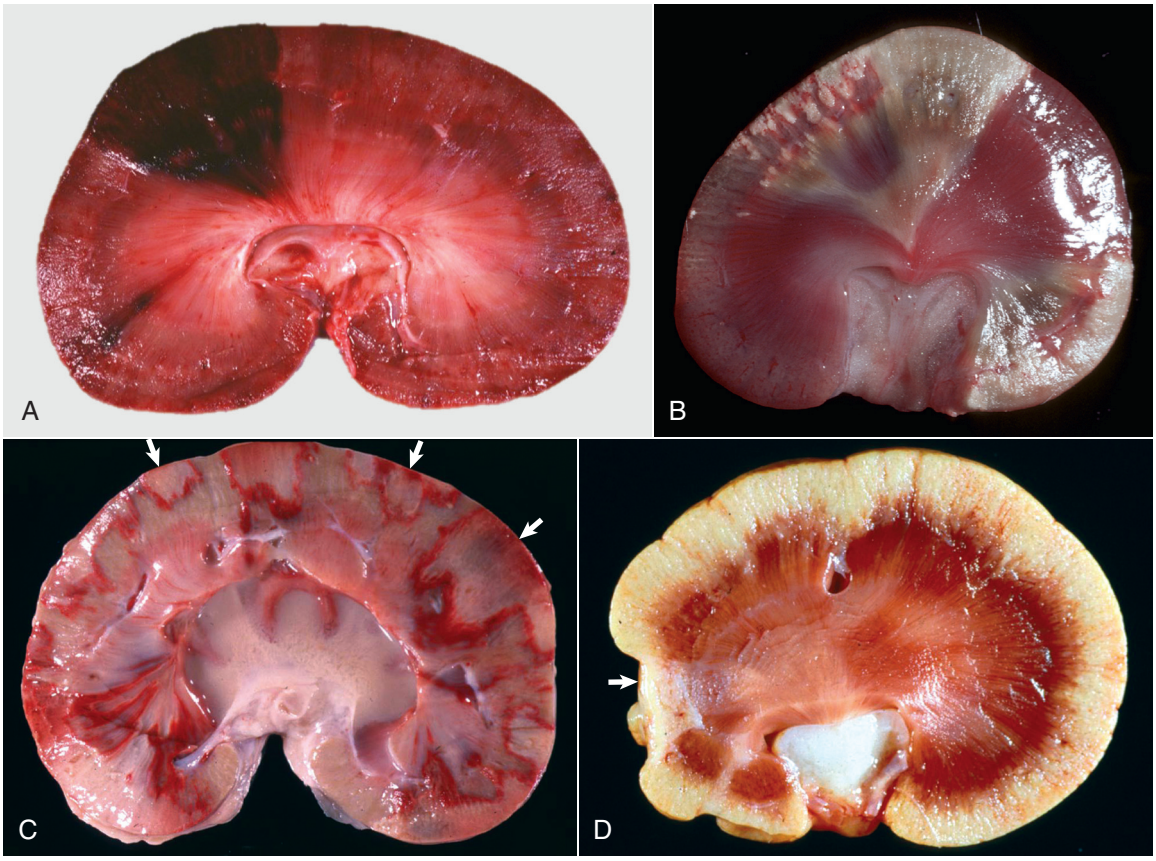


Figure 11-19 Gross Appearance of Renal Cortical Infarcts with Age, Kidney, Dorsal Sections. A, Acute (early) hemorrhagic infarct, dog. Focal wedge-shaped area of cortical necrosis. Note how the infarct bulges above the capsular surface due to cell swelling and hemorrhage. **B,** Acute pale infarcts, rabbit. There are two pale white to tan wedge-shaped infarcts *(top, lower right)*. Note how the infarct *(top)* bulges above the capsular surface, indicating cell swelling. **C,** Subacute infarcts, dog. Multiple renal cortical infarcts are pale and surrounded by a red rim of active hyperemia *(arrows)*. The cortical surface of many, but not all, of the infarcts is even with that of the adjacent unaffected cortex, indicating that cell swelling has subsided. **D,** Chronic infarct, cat. A focal pale truncated wedge-shaped scar of fibrous connective tissue has replaced the pole *(arrow)* of the renal cortex. Note that the surface of the infarct is below that of the adjacent normal kidney because of the loss of tissue, fibrosis, and contraction of the fibrous scar. (**A** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. K. Read, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **D** courtesy Dr. J. Sagartz, College of Veterinary Medicine, The Ohio State University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

conforming to a zone of cortical parenchyma supplied by the site of the obstruction. From the capsular surface, infarcts are irregular and reflect the red or pale colors of the wedge-shaped infarct seen on cut surface. Occlusion of small interlobular arteries results in infarcts that are initially slightly swollen and red because of hemorrhage (Fig. 11-19, *A*) and later develop a pale yellow-gray center of coagulation necrosis within 2 or 3 days because of lysis of erythrocytes and loss of hemoglobin (Fig. 11-19, *B*). Pale infarcts are usually surrounded by a peripheral red zone of congestion and hemorrhage along with a pale margin because of a surrounding zone of leukocytes (Fig. 11-19, *C*). Although less common, hypoxic renal necrosis as the result of venous occlusion and/or infarction is seen occasionally, and venous infarcts retain their hemorrhagic appearance longer than infarcts resulting from arterial occlusion because of the continued arterial blood flow into the area. Because of the loss of parenchyma, during healing infarcts are depressed below the cortical surface and later become pale and shrunken as a result of fibrosis (Fig. 11-19, *D*).

The scarring that follows infarction is related to several variables, including the size of the ischemic area caused by vascular compromise. Healing is by fibrosis and results in large, deeply depressed wedge-shaped (on cross section of the kidney) scars that involve primarily the cortex but can extend into the medulla. Obstruction of smaller arterioles results in smaller areas of more superficial coagulative necrosis that heal as small-diameter pits in the renal surface, which correspond to pale white, linear scars on the cut surface.

Microscopically, in an acute infarct, nephrons (including tubules, glomeruli, and interstitium) in the central zone of the infarct are necrotic (Fig. 11-20). At the periphery of the infarct, only the proximal tubules, because of their high metabolic rate, are necrotic; the glomeruli tend to be spared. After approximately 2 days, the margin of the necrotic zone contains an inflammatory infiltrate consisting largely of neutrophils and fewer macrophages and lymphocytes. Capillaries adjacent to the necrotic area are notably engorged with blood (hyperemia). Healing of the infarcted area occurs by lysis and phagocytosis of the necrotic tissue and replacement by fibrous connective tissue, which matures to a discrete scar. At autopsy (syn: necropsy), healed scarred areas are visible as pale white to gray contracted depressions from the capsular surface, and they range from linear to broad depending on the size of the acute infarct. *Septic infarcts* are initially hemorrhagic, but because of the

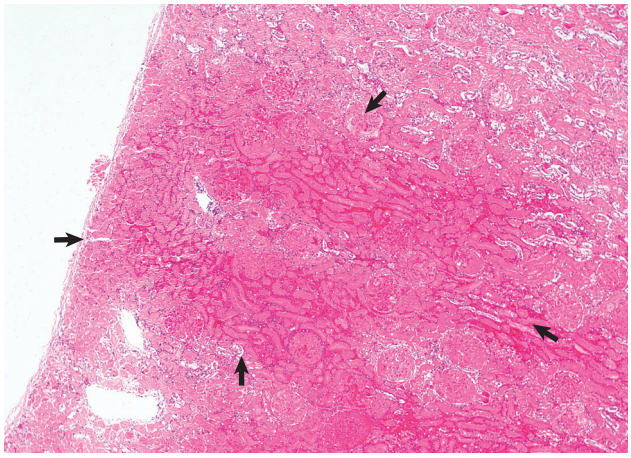


Figure 11-20 Acute Infarct, Kidney, Cortex, Dog. Note the acute infarct with a central zone of coagulation necrosis surrounded by a zone of hyperemia and hemorrhage *(arrows)*. H&E stain. (Courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

presence of pyogenic bacteria, the necrotic tissue undergoes liquefactive necrosis and the infarcts can eventually develop into abscesses and ultimately into substantial scars. Septic infarcts often fail to respect a solely cortical or medullary pattern of distribution caused by the extensive local inflammation that they generate.

Papillary (Medullary Crest) Necrosis. See the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals for a discussion of papillary necrosis.

Embolic Nephritis. Acute suppurative glomerulitis, or bacterial (embolic) nephritis, is discussed in the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals.

Aging of the Kidney

As animals age, they have increased risk of kidney disease; however, aging alone may not cause spontaneous kidney disease, but aging is associated with anatomic and physiologic changes in renal structure, function, and regenerative capacity. After maturity, there begins a slow steady reduction in the number of viable glomeruli with accompanying glomerulosclerosis, atrophic changes in tubules, increased interstitial fibrosis, basement membrane thickening, and reduced renal function. Those changes may be seen incidentally in histologic sections of aged domestic animals, especially dogs and cats. Concurrently, progressive decreased kidney weight and volume and reduced cortical thickness occur. Functionally, with age, glomerular filtration rates slowly decline, hypertension increases, urine concentrating ability declines, and vascular resistance increases. For the average animal, these changes are insidious, may not be obvious at necropsy, and may never lead to renal failure; however, current urinary or systemic disease can accelerate the process.

Portals of Entry/Pathways of Spread

Kidney as a Whole

The urinary system and especially the kidney can be exposed to injurious stimuli and microbes via a number of routes (Box 11-4), including the following:

- Hematogenous
- Ascending from ureter
- Glomerular filtrate
- Direct penetration

Box 11-4 Portals of Entry to the Kidney

ASCENDING FROM URETER

- Extension from lower urinary tract secondary to gastrointestinal content contamination (diarrhea) (females primarily)
- Extension from lower urinary tract secondary to genital tract contamination (pyometra) (females exclusively)
- Extension from lower urinary tract secondary to dermal contamination (perivulvar dermatitis)
  - Targets tubules and interstitium primarily

HEMATOGENOUS

- Localization within corticomedullary vessels
  - Septic–embolic nephritis
  - Nonseptic necrosis with infarction
- Localization within large renal vasculature
  - Massive infarction
- Localization within glomerular tufts
- Localization within interstitial vessels
  - Targets glomeruli, tubules, interstitium, and vasculature

DIRECT PENETRATION

- Activation of products in proximal tubules–necrosis
- Presence of heavy metal–mercury, cadmium
- Crystalline oversaturation
- Direct toxic action–cisplatin
  - Targets tubules

Renal Corpuscle

Hematogenous. The renal cortex has a high rate of blood flow; therefore the sustaining blood supply can provide a portal of hematogenous entry for infectious organisms, which in the kidney can lead to glomerular localization or embolic nephritis.

Tubules

Glomerular Filtrate. Substances secreted into the glomerular filtrate can produce localized trauma to tubular lining cells such as crystalline salt oversaturation (e.g., oxalate crystals). Filtered preformed toxins or metabolized substances processed by the tubular lining epithelium exert their effect principally on the proximal tubular epithelium.

Ascending Injury. Ascension from the exterior via the urethra into the urinary bladder and subsequently from the urinary bladder to the renal pelvis via the ureters (vesicoureteral reflux) can be the source of infectious diseases of the lower urinary tract and kidney. Common etiologic microbes in this process, such as bacteria, may originate from the exterior skin surface and the adjacent orifices of the intestinal or genital tracts.

Hematogenous (Interstitial Capillaries and Vasa Recta). The luminal and abluminal surfaces of epithelial cells lining renal tubules can be exposed to systemic blood-borne (hematogenous) toxins that are secreted via peritubular capillaries into the interstitial and/or luminal fluid, respectively. In addition, some infectious microbes, such as *Leptospira* sp., gain access to the tubules via the interstitial capillaries.

Interstitium

Hematogenous. The interstitium can be entered most successfully by the associated interstitial blood supply, allowing for interstitial localization of blood-borne pathogens, similar to those seen with glomerular blood-borne infections.

Ascending Injury. See previous section on Tubules.

Lymphoid Nodules. Although often present as aggregates or less commonly as nodules, lymphoid infiltrates within the interstitium are not normal; however, small aggregates or nodules are often incidental findings and of unknown cause. Previous insults typically from infectious etiologies, such as *Leptospirosis*, or as a result of ascension secondary to long-standing pyelonephritis can result in larger aggregates and nodules.

Vasculature

As in all visceral organs, the sustaining blood supply can provide a portal of hematogenous entry for infectious organisms, which in the case of the kidney principally leads to arterial localization at one of several gradated sites as follows:

- Localization within large renal vasculature: Massive infarction of the kidney is the result of large-bore renal vessel disease.
- Localization within corticomedullary vessels: In the case of associated bacterial spread, septic embolic nephritis can occur. In those examples in which the embolus is nonseptic, the result is infarctive necrosis.
- Localization within glomerular tufts: In this example, the lesions are localized to the vasculature of the small vessels within the glomerular tuft.
- Localization within interstitial vessels: In this example, the lesions are localized to necrosis of interstitial tissues and tubules.

Defense Mechanisms/Barrier Systems

Defense mechanisms unique to the renal system have evolved to counteract the routes of typical exposure to injurious agents and include those localized to the renal corpuscle, tubules, interstitium, and vasculature (Box 11-5).

Renal Corpuscle

Glomerular Basement Membrane. The most important of these barrier systems is the glomerular filtration membrane (basement membrane or basal lamina) (see Fig. 11-6). The glomerular membrane is structurally adept at separating substances based on size and charge. Both size-dependent and charge-dependent filtration occur because of the porous structure of glomerular capillary walls, which is a function of endothelial fenestrations, a basement membrane formed of type IV collagen, basement membrane anionic glycoproteins, and filtration slits of visceral epithelium. This inherent function of the glomerulus can also protect other regions of the nephron from damage by circulating inflammatory cells and their cytokines, as well as infectious microbes that are present in the systemic circulation (i.e., bacteria in bacteremia).

Glomerular Mesangium. The glomerulus is equipped with its own specialized mesangial cells, a component of the monocyte-macrophage system (see Fig. 11-6), which can remove macromolecules from circulation.

Box 11-5 Renal Defense Mechanisms against Injury and Infectious Microbes

- Barrier system—glomerular basement membrane (GBM)
- Monocyte-macrophage system—glomerular mesangium
- Immune system
  - Innate responses
  - Humoral responses
  - Cellular responses

Tubules

The most effective barrier system associated with the tubules is the tubular basement membrane. Intact basement membranes restrict intraluminal organisms, such as ascending bacteria, from gaining easy access to the interstitium. They also provide the scaffolding for reepithelialization of the tubule, which follows tubular necrosis in association with many toxic principles but not in instances of renal ischemia.

Interstitium

Innate humoral and cellular responses by the immune system contribute to protection of the kidney. Humoral antibodies may protect mucosal surfaces such as those of the renal pelvis and less commonly the tubular epithelial cell lining, especially against insults such as ascending bacterial infections or those accessing the interstitium via interstitial capillaries. Cell infiltrates are typically localized to the interstitial tissues. Lymphocytes and plasma cells within the interstitium provide cell-mediated surveillance against invasive pathogens (i.e., *Leptospira*), and in the case of plasma cells, they can locally produce antibodies.

Vasculature

Intact endothelial lining of the renal vasculature functions as a localized defense mechanism (barrier system) to prevent access by intravascular pathogens, many of which produce toxic by-products (e.g., bacterial endotoxin) that can damage endothelium and allow for localized vasculitis and bacterial colonization. The result is often embolic septic nephritis. Intact endothelium also prevents activation of the clotting cascade and thus reduction in the likelihood of thrombus formation.

Lower Urinary Tract[3]

Structure

The lower urinary tract is the conduit for transport of urinary waste from the kidney to the exterior through paired ureters, the urinary bladder, and the urethra.

Ureters

The ureters enter the bladder wall obliquely and are covered by a mucosal flap, the vesicoureteral valve, which is an important structure because it normally prevents reflux of urine from the bladder into the ureter and renal pelvis. The ureters are lined by transitional epithelium that should normally be smooth and glistening. Microscopically, the ureteral mucosa is folded longitudinally and the underlying tunica muscularis is composed of poorly defined internal and external longitudinal muscle layers with a prominent middle circular muscle layer. Externally, the ureter is surrounded by either adventitia or peritoneal serosa.

Urinary Bladder

At death, the urinary bladder can contract to such a degree that the normal bladder wall appears thick on autopsy (syn: necropsy). The normal mucosa of the urinary bladder should be smooth and glistening. Urine should be clear except in horses, in which it is cloudy because of the normal presence of mucus and crystalline material produced by the branched tubuloalveolar mucous glands in the submucosa of the renal pelvis and proximal ureter. Microscopically, as in other mucous membranes, the lamina propria has small lymphoid follicles, which, after inflammation or antigenic stimulation,

[3]See E-Appendix 11-2 for methods of examining the lower urinary tract.

E-Appendix 11-2 Postmortem Examination and Evaluation of the Lower Urinary Tract

Examination of the lower urinary tract includes ureters, urinary bladder, and urethra. Ureters are best examined prior to separation from the kidneys. Ureters should have a uniform diameter throughout their length and usually follow a direct course to the trigone on the dorsal surface of the urinary bladder. In neonates, the umbilical arteries may extend from the umbilicus, alongside the urinary bladder to the aorta. In older animals, these vessels involute to form the round ligaments of the bladder. At autopsy (syn: necropsy), the urinary bladder may have a surprisingly thick wall if it is empty and contracted. This thickening is not abnormal if the bladder can be dilated by manual stretching. Conversely, in animals with a history of prolonged recumbency, the urinary bladder is often dilated and full because of an inability to posture for urination.

If urine is present in the bladder, its color, clarity, and consistency should be noted. Urine is normally clear, but for cases in which death has preceded the autopsy (syn: necropsy) by more than a few hours, it is not unusual for urine to be made somewhat cloudy by sloughed urothelium. Horses normally have cloudy urine that may contain visible mucus and crystalline material produced by the mucous glands in the submucosa of the renal pelvis and proximal ureter. The normal mucosa of the ureters, urinary bladder, and urethra should be smooth and glistening. Following inflammation or other antigenic stimulation, lymphoid follicles in the lamina propria of the bladder mucosa may become hyperplastic and be grossly visible as 1- or 2-mm discrete, circular white foci.

In cases of suspected urethral obstruction, the entire length of the urethra may be dissected out intact after sawing through and removing a portion of the pelvis (pubic symphysis ventrally or acetabulum laterally). Thus the full length of the urethra can be carefully opened and examined for uroliths, inflammation, masses, or other abnormalities.

can be large enough to be seen grossly as discrete, circular, white foci (1 to 2 mm) in the mucosa. Histologically, the bladder is an expanded ureter, lined by pseudostratified transitional epithelium ranging from 3 to 14 cells thick, depending on the species and degree of distention. The urinary bladder wall is composed of poorly defined internal and external longitudinal muscle layers, a prominent middle circular muscle layer, and externally either adventitia or peritoneal serosa.

Urethra

During continence, the bladder is relatively flaccid and the urethra acts as a valve. Microscopically, the urethra is lined by transitional epithelium cranially and stratified squamous epithelium in the caudal segment, immediately cranial to or at the urethral orifice.

Function

Ureters

The function of the ureters is to propel urine from the kidney to the urinary bladder by peristalsis.

Urinary Bladder and Urethra

The urinary bladder stores urine and, in concert with the urethra, expels it. During micturition (urination), contraction of the detrusor muscle (the urinary bladder musculature) pumps urine through the relaxed urethra.

Dysfunction/Responses to Injury

Ureter, Urinary Bladder, and Urethra

Most diseases of the lower urinary tract are related to obstruction of flow or infection. The predominant responses of the lower tubular tract to injury include dilation and pressure necrosis caused by obstruction to the ureter or urethra and inflammation in response to exposure to infectious etiologies. In addition, concentration of excreted urinary substances, such as drug metabolites, pesticides, and other toxins, can damage the surface of the lower urinary system and predispose it to infection, secondary hyperplasia and metaplasia, or neoplastic transformation.

Portals of Entry/Pathways of Spread

Common portals of entry and pathways of spread for infection of the lower urinary tract are shown in Box 11-6.

Box 11-6 Portals of Entry into Lower Urinary System

ASCENDING

Extension from exterior secondary to contamination from the gastrointestinal tract

Extension from exterior secondary to contamination from the genital tract

Extension from exterior secondary to contamination from the skin

DESCENDING

Extension from disease processes that occur within the kidney and renal pelvis

DIRECT EXTENSION OR EXPOSURE FROM THE LUMEN

Accumulation of toxins in the urine during stasis and collection

Urinary tract calculi formation

DIRECT PENETRATION FROM THE ABDOMEN (CYSTOCENTESIS)

Ascending Infection

Extension from the exterior can occur secondary to bacterial contamination from the gastrointestinal tract, the genital tract, or severe bacterial dermatitis and result in damage due to ascension of bacteria. This represents a unique mechanism because the lower urinary tract is a blind-ended tubular system that has only one exit to the exterior (i.e., through the urethra), unlike the intestinal tract, which is a continuous tubular system. This structural arrangement predisposes to bacterial ascension and colonization, especially in females, due to their shorter, easily distensible urethra. In males, risk of ascending infection is decreased but risk of urethral obstruction is increased, due in part to the ureter's narrow diameter and increased length. Bacteria with adhesion capabilities may overcome peristalsis and periodic urine flushing and ascend the ureter to the renal pelvis via a process called vesicoureteral reflux (see Fig. 11-45). Regular and complete emptying of the urinary bladder helps minimize risks of pathologic changes, in contrast to urinary stasis, urine retention, and infrequent urinations, which predispose to ascending disease.

Descending Infection

Extension of disease processes that occur within the kidney and renal pelvis, such as pyelonephritis, may account for spread of inflammation into the lower urinary tract. Aggregates of inflammatory exudate and debris may be seen within the renal pelvis or carried distally by the flow of urine.

Direct Extension or Exposure from the Lumen

When toxic principles are excreted in the urine, they may accumulate to injurious concentrations because urine is stored in the urinary bladder for extended periods. As a result, these agents may injure the mucosa of the lower urinary tract and predispose it to infection, secondary mucosal hyperplasia, or neoplasia. In addition, the presence of a urolith anywhere within the lower urinary tract can result in trauma to the mucosa, with accompanying edema, hemorrhage, ulceration, and, in the most severe cases of obstruction, may lead to rupture caused by pressure necrosis.

Direct Penetration from the Abdomen (Cystocentesis)

Although rare as a portal of entry, it is possible for surface skin bacteria to be transmitted to the urinary bladder lumen through direct penetration of the abdomen after diagnostic procedures such as cystocentesis.

Defense Mechanisms/Barrier Systems

Defense mechanisms unique to the lower urinary system have evolved to counteract the typical forms of injury (Box 11-7). The most notable of these defense mechanisms of the lower urinary tract, which includes the ureters, urinary bladder, and urethra, are as follows:

- The flushing action of urine minimizes risks of bacterial adherence and ascension.
- Peristalsis acts to eliminate bacteria with adhesion capabilities.
- Inhospitable environment for bacterial growth controlled by urine pH and osmolarity.
- Protective urothelial mucus coating.
- Innate immune response.
- Humoral immune response.
- Cellular immune response.

Aging of the Lower Urinary Tract

Age-related changes in the lower urinary tract are not of major significance in domestic veterinary species. Acquired urinary incontinence is a common, long-term sequela of sterilization (spaying) in

Box 11-7 Urinary Tract Defense Mechanisms against Injury and Infectious Microbes

- Urine flow (flushing)
- Peristalsis
- Urine pH and osmolarity
- Urothelial cell protective mucus coat
- Immune system
  - Innate responses
  - Humoral responses
  - Cellular responses

Table 11-1 Nonrenal Lesions of Uremia

Lesion	Mechanism
Pulmonary edema	Increased vascular permeability
Fibrinous pericarditis	Increased vascular permeability
Ulcerative and hemorrhagic gastritis	Ammonia secretion and vascular necrosis
Ulcerative and necrotic stomatitis	Ammonia secretion in saliva and vascular necrosis
Atrial and aortic thrombosis	Endothelial and subendothelial damage
Hypoplastic anemia	Increased erythrocyte fragility and lack of erythropoietin production in the kidney
Soft-tissue mineralization	Altered calcium-phosphorus metabolism (stomach, lungs, pleura, kidneys)
Fibrous osteodystrophy	Altered calcium-phosphorus metabolism
Parathyroid hyperplasia	Altered calcium-phosphorus metabolism

female dogs, but it is more a result of urethral changes associated with sterilization than a result of aging. Sterilization in dogs leads to decreased smooth muscle in the urinary bladder and urethra as well as shorter urethral length, which may impair urethral sphincter function. Additional risk factors for urinary incontinence in dogs include medium to large stature, previous tail docking, and obesity.

Kidney and Lower Urinary Tract

Disorders of Domestic Animals

Nonrenal Lesions of Uremia

Nonrenal lesions of uremia identified clinically or at autopsy (syn: necropsy) are useful indicators of renal failure (Table 11-1). The severity of nonrenal lesions of uremia depends on the length of time that the animal has survived in the uremic state. Therefore, in acute renal failure, nonrenal lesions are few, whereas many lesions can be present in chronic renal failure. During renal failure, numerous so-called "uremic toxins" accumulate in the blood. These toxins fall into three classes: (1) small water-soluble compounds including urea, phosphate, creatinine, and guanidines; (2) medium-sized molecules including fibroblast growth factor-23, β_2-microglobulin, parathyroid hormone, and leptin; and (3) protein-bound compounds including a variety of phenols and indoles. Typically, nonrenal lesions can be attributed to either one of the following mechanisms:

- Endothelial degeneration and necrosis, resulting in vasculitis with secondary thrombosis and infarction in a variety of tissues (i.e., intestinal tract).

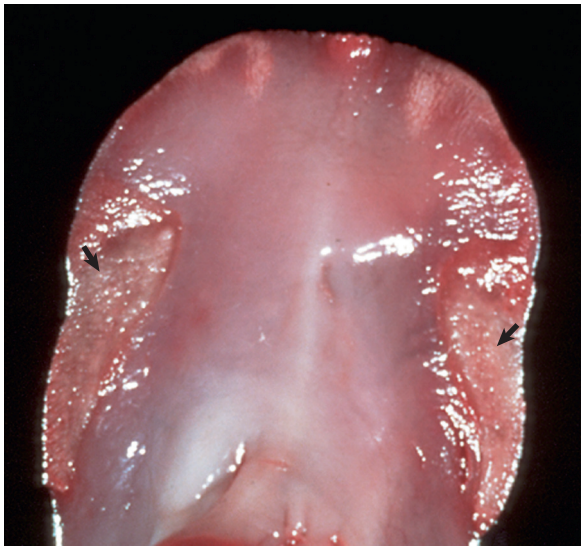


Figure 11-21 Ulcerative Glossitis, Uremia, Tongue, Ventral Surface, Cat. Bilaterally symmetrical ulcers *(arrows)* are present on the rostrolateral borders of the ventral surface of the tongue. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

- Caustic injury to epithelium of the oral cavity and stomach, which results in ulcer formation, is secondary to the production of large concentrations of ammonia after splitting of salivary or gastric urea by bacteria.
- Increased erythrocyte fragility and lack of erythropoietin production.
- Altered calcium/phosphorus metabolism (renal secondary hyperparathyroidism).

Systemic nonrenal lesions of uremia include one or more of the following:

- Ulcerative and necrotic glossitis/stomatitis characterized by a brown, foul-smelling, mucoid material adherent to the eroded and ulcerated lingual and oral mucosa. Ulcers are most commonly bilateral (symmetric) and present on the underside of the tongue (Fig. 11-21).
- Ulcerative and hemorrhagic gastritis in dogs and cats (Fig. 11-22), often with secondary midzonal mineralization (Fig. 11-23). Ulcers are not large and often are present along the rugae. The gastric wall can be gritty when cut because of calcification of the inner and middle layers of the mucosa and the submucosal arterioles. This lesion is less commonly seen in horses and cattle, in which intestinal lesions predominate.
- Ulcerative and hemorrhagic colitis in horses and cattle, in which large areas of colonic mucosa are often edematous and dark red because of hemorrhage. The gastrointestinal contents can be bloody and smell of ammonia. Microscopically, coagulative necrosis, hemorrhage, and a neutrophilic infiltrate occur in the intestinal mucosa. Degeneration, necrosis, and mineralization of the arteriolar intima and media are often present in the gastric mucosa and submucosa (Fig. 11-23, *B*).
- Intercostal mineralization/uremic mineralization is characterized, particularly in dogs, by calcification of the subpleural connective tissue of the cranial intercostal spaces (Fig. 11-24). These lesions are white-gray granular pleural thickenings with a horizontal "ladder-like" arrangement. The intercostal muscles are only superficially calcified. Patchy or diffuse pulmonary calcification of the lungs results in their failure to collapse, areas of paleness, and mild to moderate firmness and crunchiness and can

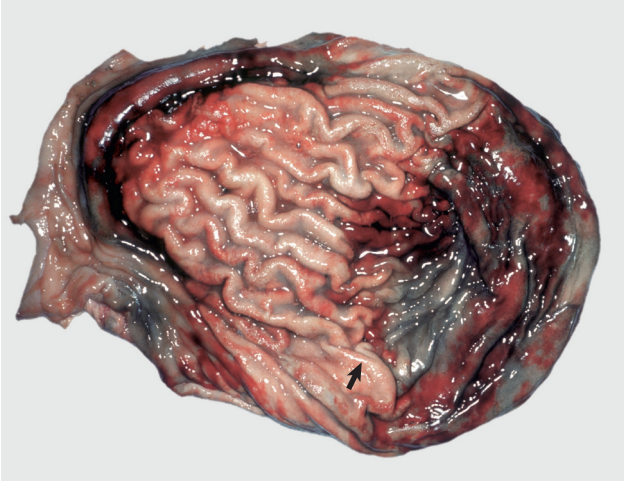


Figure 11-22 Uremic Gastritis, Stomach, Dog. Because of uremia, the stomach wall is hemorrhagic *(right)* and the stomach contents may contain blood and mucus (not shown here). Note the edematous mucosal thickening *(arrow)*. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

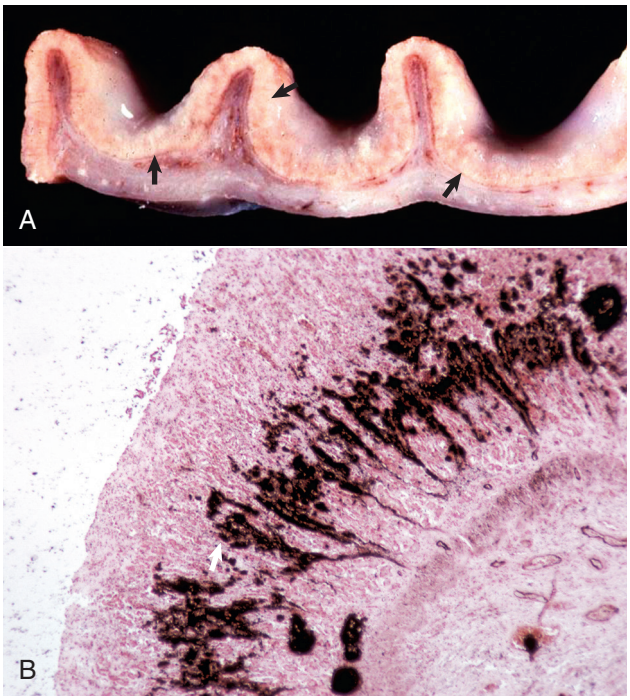


Figure 11-23 Uremic Gastritis, Stomach, Dog. A, There is accentuation of the gastric rugae and calcification in the deep mucosa *(arrows)*. **B,** The mucosa has laminar mineralization *(black color)* of gastric glands *(arrow)*, von Kossa stain. (**A** courtesy Dr. J. King, College of Veterinary Medicine, Cornell University. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Figure 11-24 Thoracic Cavity, Parietal Pleura, Cat. Horizontally oriented streaks *(arrows)* of mineral (intercostal mineralization) are present in the subpleural intercostal connective tissue as a result of chronic uremia. (Courtesy Dr. J. King, College of Veterinary Medicine, Cornell University.)

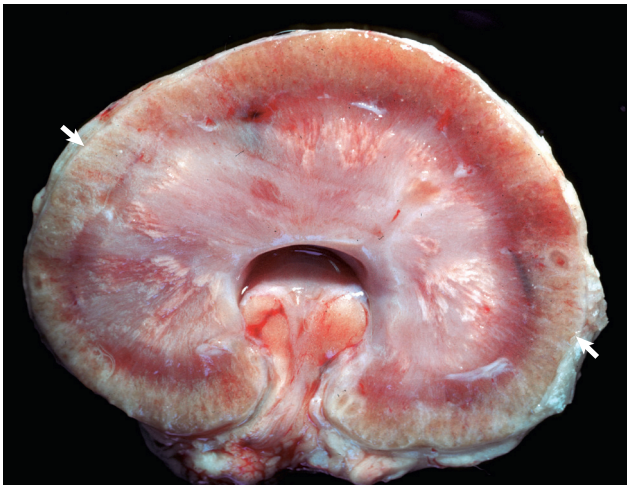


Figure 11-25 Nephrocalcinosis, Kidney, Dorsal Section, Dog. Note the white streaks *(arrows)* in the cortex and medulla attributable to mineralization of the interstitium, basement membranes, and tubules. This lesion results from diseases that increase plasma calcium concentrations (e.g., hyperparathyroidism). Renal tubular epithelium is damaged by an increase in intracellular calcium, which is initially precipitated in mitochondria and tubular basement membranes. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

occur occasionally in conjunction with the lesions of uremic pneumonitis and localized emphysema.

- Fibrinous pericarditis is characterized by fine granular deposits of calcium on the epicardium (visceral pericardium).
- Diffuse pulmonary edema is characterized by alveoli that contain fibrin-rich fluid and often a mild infiltrate of macrophages and neutrophils. This lesion is also called *uremic pneumonitis*. The underlying lesion is a vasculitis affecting the alveolar capillaries, which results in increased vascular permeability and high protein effusion.
- Arteritis is characterized macroscopically by finely granular roughened plaques within the left atrial endocardium and less frequently in the proximal aorta and pulmonary trunk. Arteritis in conjunction with loss of the anticoagulant antithrombin III by glomerular leakage is conducive to the formation of large mural thrombi at these sites.
- Nephrocalcinosis (calcification), although usually not visible at autopsy (syn: necropsy), can occur in the damaged kidneys of uremic animals, but it can also occur in vitamin D toxicosis or primary or nutritional hyperparathyroidism (Fig. 11-25). The kidneys can be gritty when cut because of calcification of tubular basement membranes, Bowman's capsules, and necrotic tubular epithelium, especially in the medulla and inner cortex.

Disorders of the Kidney

Developmental Abnormalities

Renal Aplasia, Hypoplasia, and Dysplasia. Renal aplasia (agenesis) is failure of the development of one or both kidneys such that no recognizable renal tissue is present. In these cases, the ureter may be present or absent. If present, the cranial extremity of the ureter begins as a blind pouch. A familial tendency for renal aplasia has been observed in Doberman pinscher and beagle dogs. Because life can be sustained when more than one-fourth of renal function is maintained, unilateral aplasia is compatible with life, if the other kidney is normal. Unilateral aplasia can go unnoticed during life and be recognized at autopsy (syn: necropsy). Bilateral aplasia is obviously incompatible with life and occurs sporadically.

Renal hypoplasia designates incomplete development of the kidneys in a variety of species so that fewer than normal nephrons are present at birth. Renal hypoplasia has been documented as an inherited disease of purebred or crossbred Large White pigs in New Zealand and described in foals of various breeds, as well as in dogs (Fig. 11-26, *A*) and cats (Fig. 11-26, *B*). Hypoplasia can be unilateral (Fig. 11-26, *B*) or bilateral; it is rare and difficult to diagnose subtle

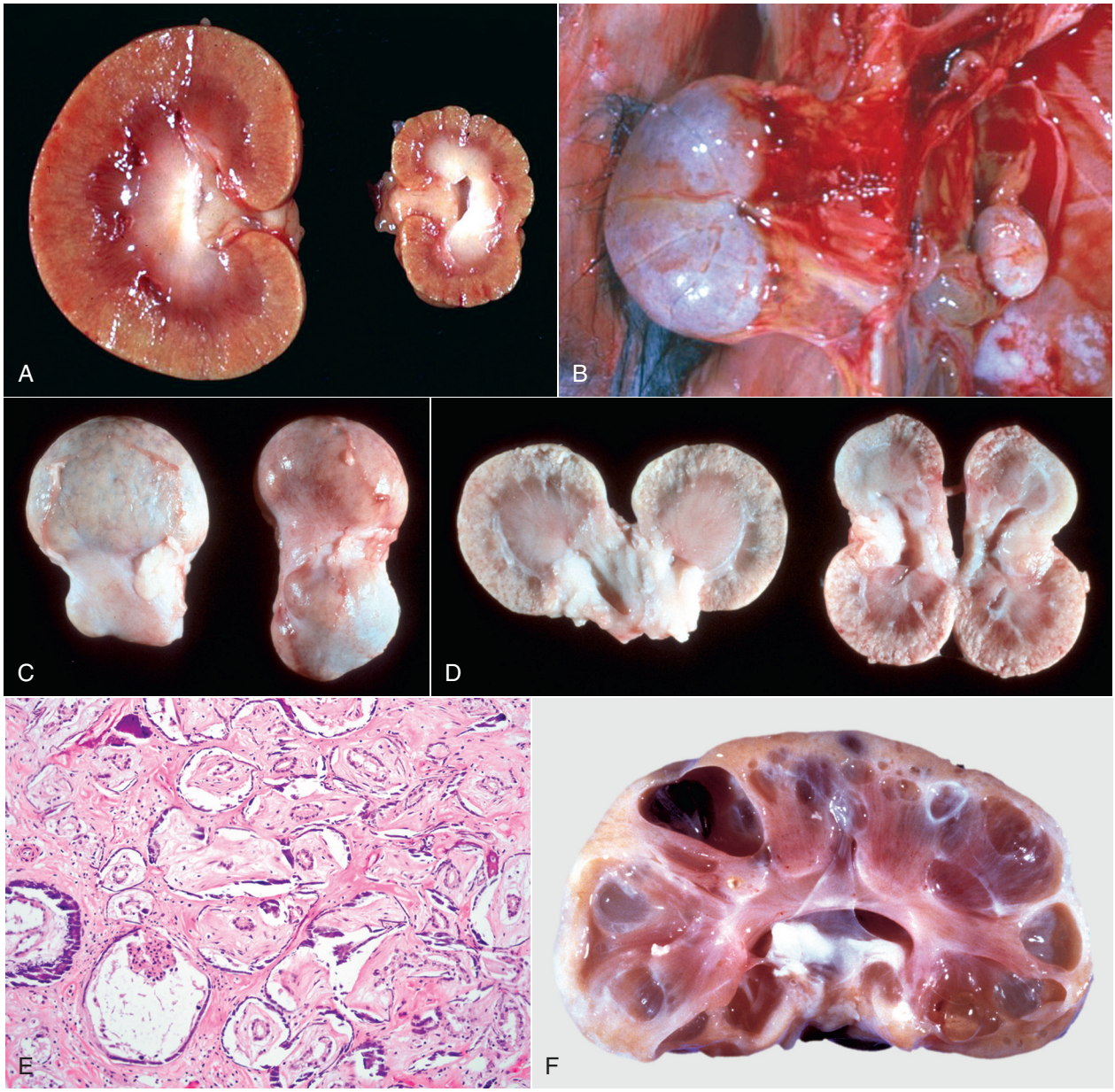


Figure 11-26 Types of Congenital Developmental Anomalies, Kidney. A and **B,** Unilateral hypoplastic kidneys, young dogs. **A,** Dorsal sections. **B,** The grossly affected right kidney is nearly identical in structure to the left kidney but smaller (hypoplasia). **C,** Juvenile progressive nephropathy, young dog. Bilateral abnormally shaped firm kidneys. **D,** Juvenile progressive nephropathy, dorsal sections, dog. Section of the kidneys from **C**. **E,** Juvenile progressive nephropathy, chronic, dog. Note the interstitial fibrosis, tubular atrophy, dilated urinary space, and mineralization. H&E stain. **F,** Polycystic disease, dorsal section, cat. Numerous variably sized tubular cysts are present in the cortex and medulla. The cysts contain clear colorless fluid. This condition is hereditary, and Persian cats are predisposed. (**A** courtesy Dr. B. Weeks, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. M. Miller, College of Veterinary Medicine, University of Missouri; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **C** and **D** courtesy College of Veterinary Medicine, University of Illinois. **E** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee. **F** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

cases grossly or microscopically. In cattle and pigs, the number of renal papillae in the hypoplastic kidney can be compared with those in a normal kidney. Hypoplastic kidneys from pigs and foals have a notable reduction in the number of glomeruli. In foals, for example, 5 to 12 glomeruli are present per low-power field in affected kidneys compared with 30 to 35 glomeruli per low-power field in normal adult kidneys. Unless significant renal mass is compromised by this condition, hypoplasia is clinically silent.

Occasionally, some bovine kidneys are found to have reduced numbers of external lobes, but these kidneys are not hypoplastic and are microscopically and functionally normal; the reduction in external lobes merely represents fusion of the lobes. The shrunken, pitted kidneys in young animals, particularly dogs, are often diagnosed as hypoplastic. However, in most of these cases, these small kidneys are due to the following:

- Renal fibrosis, resulting from renal disease developing at an early age
- Dysplasia
- Progressive juvenile nephropathy

Renal dysplasia is an abnormality of altered structural organization resulting from abnormal differentiation and the presence of structures not normally present in nephrogenesis. Cystic renal dysplasia has been described in sheep and is inherited as an autosomal dominant trait. Renal dysplasia occurs infrequently and, like renal hypoplasia, must be differentiated from renal fibrosis and, in dogs, other forms of progressive juvenile nephropathy. Dysplastic changes can be unilateral or bilateral and can involve much of an affected kidney or occur only as focal lesions. Dysplastic kidneys can be small, misshapen, or both. Microscopically, five primary features of dysplasia are described as follows:

- Asynchronous differentiation of nephrons inappropriate for the age of the animal—aggregates of small hypercellular glomeruli in the cortex
- Persistence of primitive mesenchyme so that the interstitial connective tissue has a myxomatous appearance
- Persistence of metanephric ducts
- Atypical (adenomatoid) tubular epithelium
- The presence of cartilaginous and/or osseous tissue

Interstitial fibrosis, renal cysts, and a few enlarged hypercellular glomeruli (compensatory hypertrophy) are changes seen secondarily to the primary dysplastic changes. The numbers of nephrons, lobules, and calyces are normal. Bilateral renal dysplasia characterized by persistent mesenchyme and atypical tubular development has been described in foals.

Progressive juvenile nephropathy (familial renal disease) of Lhasa apso, shih tzu, golden retriever dogs, and perhaps other canine breeds are likely examples of renal dysplasia (Fig. 11-26, C to *E*). Asynchronous differentiation is often seen and to a lesser extent several other features of dysplasia. However, until these hereditary lesions of dogs are better characterized, it is probably best to retain the general diagnostic term of progressive juvenile nephropathy (see the section on Kidney and Lower Urinary Tract, Disorders of Dogs).

Ectopic and Fused Kidneys. Ectopic kidneys are misplaced from their normal sublumbar location because of abnormal migration during fetal development. Ectopic kidneys occur most frequently in pigs and dogs and usually involve only one kidney. Ectopic locations often include the pelvic cavity or inguinal position. Although ectopic kidneys are usually structurally and functionally normal, malposition of the ureters predisposes them to obstruction, which results in secondary hydronephrosis. Fused (horseshoe) kidneys result from the fusion of the left and right cranial or left and right caudal poles of the kidneys during nephrogenesis. This fusion results in the appearance of one large kidney with two ureters. The histologic structure and function of the fused kidneys are usually normal.

Renal Cysts. Renal cysts are spherical, thin-walled, variably sized distentions principally of the cortical or medullary renal tubules and are filled with clear, watery fluid. Congenital renal cysts can occur as a primary entity or in cases of renal dysplasia. The pathogenesis of primary renal cysts is not entirely understood. Cysts are likely derived from normal or noncystic segments of the nephron, most commonly the renal tubules, the collecting ducts, and Bowman's (urinary) space. Although genetic mechanisms can be involved in the pathogenesis of renal cysts, experiments with toxic chemicals indicate that genetic predisposition is not a requirement. The following four mechanisms of renal cystic dilation are considered plausible:

- Obstruction of nephrons can cause increased luminal pressure and secondary dilation (called *cystic dilation* when it is well-developed).
- Modifications in ECM and cell-matrix interactions result in weakened tubular basement membranes allowing saccular dilation of tubules.
- Deranged function of renal tubular cilia in genetic polycystic disease resulting in tubular epithelial hyperplasia with production of new basement membranes, increased tubular secretion, and increased intratubular pressure causes development of enlarged, dilated tubules.
- Dedifferentiation of tubular epithelial cells results in loss of polarity of cells with abnormal cell arrangements in tubules, reduced tubular fluid absorption, increased intratubular pressure, and dilation of tubules.

These mechanisms are not mutually exclusive, and several mechanisms often work in concert to create renal cysts.

Cysts range in size from barely visible to several centimeters in diameter. Cysts are usually spherical, delineated by a thin fibrous connective tissue wall lined by flattened epithelium, and filled with clear, watery fluid. The sources of fluid are glomerular filtrate, transepithelial secretions, or both. When viewed from the renal surface, the cyst wall is pale gray, smooth, and translucent. Kidneys can have single or multiple cysts. Congenital solitary or a few incidental cysts can cause no alteration in renal function and are common in pigs and calves. Acquired renal cysts can occur because of renal interstitial fibrosis or other renal diseases that cause intratubular obstruction. These cysts are usually small (1 to 2 mm in diameter) and occur primarily in the cortex.

Polycystic Kidneys. Polycystic kidneys have many cysts that involve numerous nephrons. Congenital polycystic kidneys occur sporadically in many species but can be inherited as an autosomal dominant lesion in pigs and lambs and inherited along with cystic biliary disease in Cairn and West Highland white terriers. The lesion, termed *polycystic kidney disease* (PKD), is inherited as an autosomal dominant trait in families of Persian cats and bull terriers. In addition, PKD is diagnosed sporadically in numerous exotic and domestic animal species. Although less well-characterized in animals than in human beings, this autosomal dominant, high-penetrance, heritable condition is related to mutations in one or more genes (*PKD-1* and/or *PKD-2*) and altered function of the related proteins, principally polycystin-1 and polycystin-2. Manifestation of tubular cysts occurs after mutation of both alleles of these genes, the first of which is a germline mutation, and the second is somatic mutation. Polycystin-1 and polycystin-2 are transmembrane proteins important in cell-to-cell and cell-to-matrix interactions and calcium channeling. In addition, these proteins work together in renal tubular cells and are associated with renal tubular cell cytoplasmic membranes and cilia and are important in

renal tubular development, signal transduction, control of cell cycle, and migration. Although the exact mechanisms for cyst formation are not known, polycystin-1 and polycystin-2 mutations modify cilia function, cell proliferation, and migration resulting in tubular epithelial proliferation and increased fluid secretion. In addition, loss of polycystin-1 from its basolateral location may alter critical pathways controlling normal tubulogenesis, thus contributing to cyst formation. Polycystic renal disease with cysts arising from glomeruli has been described in collie puppies. The gross appearance of the cut surface of a polycystic kidney has been described as "Swiss cheese" (Fig. 11-26, *F*). As cysts enlarge, they compress the adjacent parenchyma causing atrophy. When extensive regions of renal parenchyma are polycystic, renal function can be impaired.

Diseases of the Glomerulus

Immune-Mediated Glomerulonephritis. Glomerulonephritis (GN) most often results from immune-mediated mechanisms, most notably after the deposition of soluble immune complexes within the glomeruli and less commonly after the formation of antibodies directed against antigens within the GBM. Antibodies to the basement membrane (anti-GBM disease) bind and damage the glomerulus through fixation of complement and resulting leukocyte infiltration. This mechanism of GN has been well documented in human beings and nonhuman primates but only rarely in other domestic animals. To confirm the diagnosis of anti-GBM disease, Ig and complement (C3) must be demonstrated within glomeruli. Antibodies must be eluted from the kidneys and found to bind to normal GBMs of the appropriate species.

Immune-complex GN (ICGN) occurs most commonly in dogs and cats and is the most common glomerular disease in dogs, accounting for 48% of glomerular diseases in a recent study. ICGN often occurs in association with persistent infections or other diseases that characteristically have a prolonged antigenemia that enhances the formation of soluble immune complexes. ICGN can be associated with specific chronic viral infections, such as feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV); chronic bacterial infections, such as pyometra or pyoderma; chronic parasitism, such as dirofilariasis; autoimmune diseases, such as canine systemic lupus erythematosus; and neoplasia (Box 11-8). In addition to the role of persistent infections, a familial tendency for development of ICGN has been described in a group of related Bernese mountain dogs.

ICGN is initiated by the formation of soluble immune complexes (antigen-antibody complexes) in the presence of antigen-antibody equivalency or slight antigen excess, which then do the following:

- Selectively deposit in the glomerular capillaries
- Stimulate complement fixation with formation of C3a, C5a, and C567, which are chemotactic for neutrophils
- Damage the basement membrane through neutrophil release of proteinases, arachidonic acid metabolites (e.g., thromboxane), and oxidants, particularly oxygen-derived free radicals and hydrogen peroxide
- Continue to damage the glomeruli by the release of biologically active molecules from monocyte infiltrations in the later stages of inflammation (Fig. 11-27, *A*)

Although circulating immune complexes may contribute to this process, antibody binding to endogenous glomerular antigens or entrapped nonspecific antigens is more common. Direct action of C5b to C9 on the glomerular components results in activation of both glomerular epithelial cells and mesangial cells to produce damaging mediators, such as oxidants and proteases.

Many specific factors determine the extent of deposition of soluble immune complexes in the glomerular capillary walls. These include persistence of appropriate quantities of immune complexes in the circulation, glomerular permeability, the size and molecular charge of the soluble complexes, and the strength of the bond between the antigen and antibody (avidity). Small or intermediate complexes are the most damaging because large complexes are removed from circulation through phagocytosis by cells of the monocyte-macrophage system in the liver and spleen. An increase in local glomerular vascular permeability is necessary for immune complexes to leave the microcirculation and deposit in the glomerulus. This process is usually facilitated via vasoactive amine release from mast cells, basophils, or platelets (see Fig. 11-27, *A*). Mast cells or basophils release vasoactive amines because of the interaction of the immune complexes with antigen-specific IgE on the surface of these cells, by stimulation of the mast cells or basophils by cationic proteins released from neutrophils, or by the anaphylatoxin activity of C3a and C5a. Platelet-activating factor (PAF) is released from immune complex–stimulated mast cells, basophils, or macrophages and causes platelets to release vasoactive amines.

Localization of the complexes within the various levels of the basement membrane or in subepithelial locations depends on their molecular charge and avidity. Once small, soluble immune complexes are deposited within the capillary wall, they can become greatly enlarged because of interactions of immune complexes with free antibodies, free antigens, complement components, or other immune complexes.

Box 11-8 Diseases with Immune-Complex Glomerulonephritis

HORSES
Equine infectious anemia
Streptococcus sp.

CATTLE
Bovine viral diarrhea
Trypanosomiasis

SHEEP
Hereditary hypocomplementemia in Finnish Landrace lambs

PIGS
Hog cholera
African swine fever

DOGS
Infectious canine hepatitis
Chronic hepatitis
Chronic bacterial diseases
Endometritis (pyometra)
Pyoderma
Prostatitis
Dirofilariasis
Borreliosis (Lyme disease)
Systemic lupus erythematosus
Polyarteritis
Autoimmune hemolytic anemia
Immune-mediated polyarthritis
Neoplasia–mastocytoma
Hereditary C3 deficiency

CATS
Feline leukemia virus (FeLV) infection
Feline infectious peritonitis (FIP)
Feline immunodeficiency virus (FIV)
Progressive polyarteritis
Neoplasia
Progressive membranous glomerulonephritis (GN)

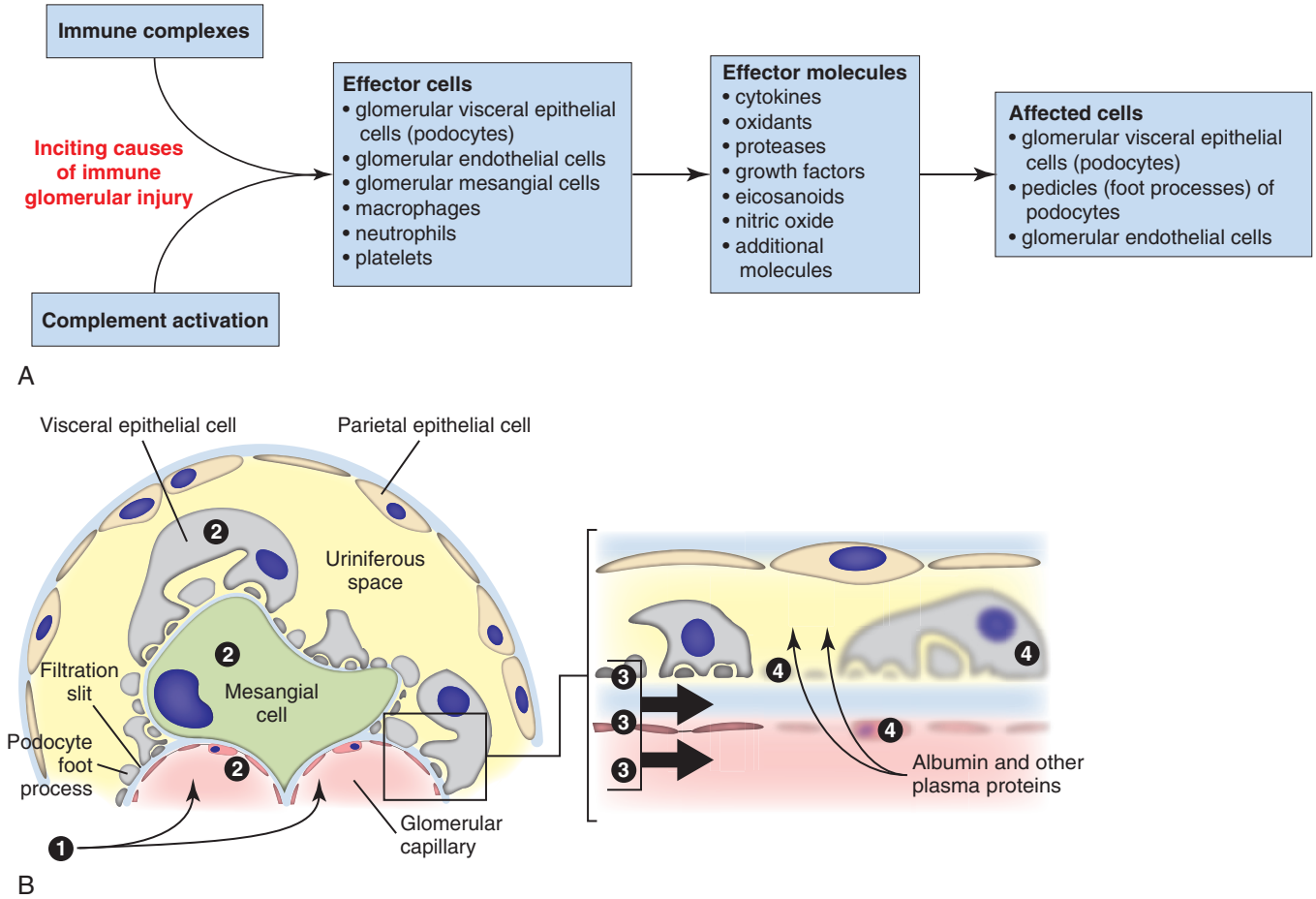


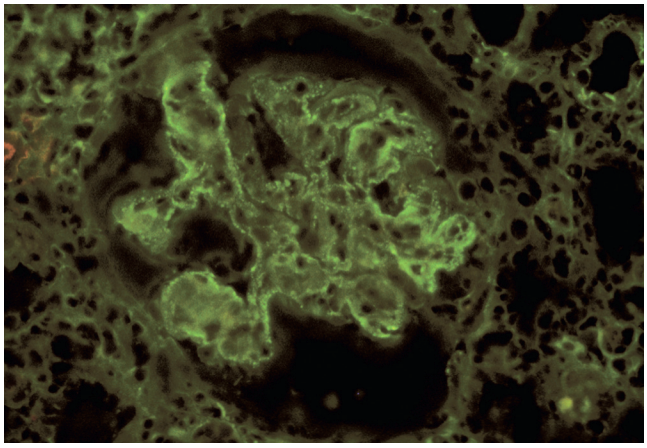
Figure 11-27 Mediators of Immune Glomerular Injury and Epithelial Cell Injury. A, Mediators of immune glomerular injury, including effector cells, molecules, and cells affected or injured. **B,** Visceral epithelial cell (podocyte) injury. The postulated sequence is a consequence of antibodies against epithelial cell antigens, arriving in the circulating blood *(1)* with subsequent activation of effector cells, including podocytes and mesangial cells *(2)*. This leads to liberation of toxins, cytokines, or other effector molecules *(3)* that cause injury of podocytes, podocyte foot processes, and endothelial cells *(4)* with subsequent cell detachment, resulting in protein leakage through the defective glomerular basement membrane and filtration slits. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

After immune-complex deposition, glomerular injury can also occur from the aggregation of platelets and activation of Hageman factor, which results in the formation of fibrin thrombi that produce glomerular ischemia. Furthermore, glomerular epithelial cell and ECM damage can result directly from the terminal membrane attack complex of the activated complement cascade (C5 to C9). This can result in epithelial detachment (causing proteinuria) and GBM thickening subsequent to upregulation of epithelial cell receptors for transforming growth factor (Fig. 11-27, *B*). Cell-mediated cytotoxic responses (from sensitized T lymphocytes) to glomerular antigens or complexes may exacerbate renal lesions. Complexes themselves may modulate the immune response through interaction with receptors on various cells.

Finally, if exposure of the glomerulus to immune complexes is short-lived, as in a transient infection such as infectious canine hepatitis, glomerular immune complexes will be phagocytosed by macrophages or mesangial cells and removed, and the glomerular lesions and clinical signs may resolve. Conversely, continual exposure of glomeruli to soluble immune complexes, such as in persistent viral infections or chronic heartworm disease, can produce progressive glomerular injury, with severe lesions and clinical manifestation of glomerular disease (Box 11-9).

Ultrastructurally, immune complexes either in the GBM or in a subepithelial location appear as electron-dense granular bodies. Complexes that are poorly soluble, fairly large, or of high avidity often enter the mesangium, where they can be phagocytosed by macrophages and appear ultrastructurally as dense granular deposits within the mesangial stroma or within macrophages. Other ultrastructural changes commonly seen are loss, effacement, or fusion of visceral epithelial cell (podocytes) foot processes, cytoplasmic vacuolation, retraction and detachment of visceral epithelium, and infiltrates of neutrophils and monocytes within the mesangium.

A diagnosis of ICGN can be made by immunofluorescent or immunohistochemical demonstration of immunoglobulin and complement components, usually C3, in glomerular tufts. To augment light microscopic findings, transmission electron microscopy can be done to demonstrate typical subepithelial and intramembrane electron-dense deposits, fusion of podocyte foot processes, and intramesangial hypercellularity. In dogs, IgG or IgM are the most common immunoglobulin isotypes demonstrated in ICGN; however, combinations of IgG, IgM, and IgA also occur in the glomeruli of some dogs. In one study, IgA was the only immunoglobulin found in three dogs with ICGN. Both Ig and C3 are usually demonstrated in a granular ("lumpy-bumpy") pattern using immunofluorescent or immunohistochemical techniques (Fig. 11-28; E-Fig. 11-4); however, in anti-GBM disease, as reported in human beings, horses, and a single dog, the antibody deposits have a linear distribution conforming to the basement membranes. It is important to remember that



E-Figure 11-4 **Immune-Complex Glomerulonephritis, Aleutian Mink Disease, Kidney, Glomerulus, Mink.** Intraglomerular immunoglobulin deposits demonstrated by immunofluorescence. Note the granular ("lumpy-bumpy") pattern of fluorescence in this case of Aleutian mink disease. Immunofluorescence microscopy. (Courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

Box 11-9 Progression of Glomerular Immune-Complex Deposition

DEPOSITION AFFECTED BY

Appropriate quantities of immune complexes in the circulation
Glomerular permeability
The size and molecular charge of the soluble complexes
Strength of the bond between antigen and antibody

GLOMERULAR PERMEABILITY AFFECTED BY

Release of vasoactive amines from mast cells, basophils, or platelets
- Immune complexes interact with antigen-specific immunoglobulin E on surface of mast cells or basophils
- Cationic proteins from neutrophils stimulate release of vasoactive amines from mast cells and basophils
- C3a and C5a cause release of vasoactive amines
- Platelets release vasoactive amines following release of platelet-activating factor from immune-complex stimulated mast cells, basophils, and macrophages

GLOMERULAR PROGRESSION AFFECTED BY

Aggregation of platelets, activation of Hageman factor, fibrin thrombi formation, and glomerular ischemia
Terminal membrane active complex of activated complement cascade damages glomerular epithelial cells and extracellular matrix (ECM) resulting in epithelial cell detachment and basement membrane thickening
Cell-mediated cytotoxic responses from T lymphocytes sensitized to glomerular antigens or complexes may exacerbate renal lesions

fluorescing deposits indicate the presence of immunoglobulin or complement but do not specifically indicate the presence of disease. In addition, immunofluorescence may be negative when all reactive binding sites are occupied, thus complicating diagnosis of this condition.

The diagnosis of preformed ICGN can be confirmed only by demonstrating that the antibodies from the immune complexes, eluted from glomeruli, do not bind to normal glomerular elements and hence represent deposition of preformed circulating complexes. Once this has been done, the ideal situation would be to identify the causative antigen present in the immune complexes. This process is accomplished by eluting antibodies from diseased glomeruli and attempting to identify their specificity for suspected antigens. For example, antibodies eluted from the glomeruli of dogs with GN associated with severe heartworm disease bind to several *Dirofilaria immitis* antigens, including the body wall of adult worms, parasitic uterine fluid, and microfilaria. In most cases of immune-complex GN, the specific causative antigen usually escapes determination. Demonstration of electron-dense deposits in mesangial, subepithelial, or subendothelial locations by electron microscopy is also supportive of the diagnosis of immune-mediated GN.

Gross lesions of acute ICGN are usually subtle. Kidneys are often slightly swollen, have a smooth capsular surface, are of normal color or slightly pale, and have glomeruli that are visible as pinpoint red dots on the cut surface of the cortex (Fig. 11-29). The normal glomeruli of horses are usually visible, so this feature of pinpoint red dots for glomeruli cannot be used for diagnosis in that species. If lesions do not resolve but become subacute to chronic, the renal cortex becomes somewhat shrunken and the capsular surface has a generalized fine granularity. On cut surface, the cortex can be thinned and its surface granular, and glomeruli can appear as pinpoint pale gray dots. With time, more severe scarring can develop throughout the cortex (see the section on Renal Fibrosis).

Microscopically, ICGN has several histopathologic forms. Although various classifications of GN have been published, the following simple classification is well understood among veterinary pathologists. Lesions in glomeruli may be described as membranous or membranoproliferative (Fig. 11-30). Glomerular lesion localization and distribution can be characterized with the following terminology:

- Focal—involving <50% of glomeruli
- Diffuse—involving >50% of glomeruli
- Segmental—involving portions of the glomerular tuft
- Global—involving all of the glomerular tuft
- Hilar—focused primarily near the vascular pole
- Tip—focused primarily near the outer portions of the tuft

Most of the lesions in ICGN are diffuse, but within an individual affected glomerulus, lesions can be either global or segmental. In the more chronic form, a variety of glomerular tuft changes will be noted, depending on whether the damage is related to mesangial proliferation, membranous proliferation, or both. Tufts may be enlarged, shrunken, or normal size depending on the amount of mesangial matrix present. Reduction in cellularity, enhancement of the capillary outlines within the tuft, proliferation of the parietal epithelial cells, expansion of Bowman's space by high protein ultrafiltrate, and variable thickening of Bowman's capsule may also be observed. *Glomerulosclerosis* (see later) is the stage in which there is a reduction in the number of functional glomeruli with replacement by abundant fibrous connective tissue and subsequent obliteration of Bowman's space due to capsular fibrosis.

In addition, in protein-losing glomerulopathies, tubules often contain abundant eosinophilic homogeneous proteinaceous material, and the proximal tubular epithelium often have microscopic eosinophilic intracytoplasmic bodies referred to as *hyaline droplets*, which represent accumulations of intracytoplasmic protein absorbed from the filtrate.

Microscopic details of each type of glomerular disease are discussed in the next sections.

Membranous Glomerulonephritis. Membranous GN is characterized by diffuse glomerular capillary basement membrane thickening without obvious increased cellularity. These thickenings are often most obvious when capillary loops at the periphery of the tuft are examined. Special stains such as periodic–acid Schiff (PAS) or Masson's trichrome can assist in membrane examination. Membrane thickening occurs because of the presence of subepithelial immunoglobulin deposits, as the predominant change (Fig. 11-31; also see Fig. 11-30, *B*). These deposits are separated by protrusions of GBM matrix that eventually encompass these deposits. After removal of the deposited material, cavities are left in the GBM and later these fill with GBM-like material, which results in sclerotic change within the glomerular tuft. This is characterized by increased deposition of positive material (periodic acid–Schiff [PAS]) and a lesser amount of fibrosis. This variation is the most common form of ICGN in cats.

Membranoproliferative Glomerulonephritis. Membranoproliferative GN (mesangioproliferative, mesangiocapillary) is characterized by hypercellularity following proliferation of glomerular endothelial cells, glomerular epithelial cells, and mesangial cells. Concurrently, there is an influx of neutrophils and other leukocytes involving capillary loops and the mesangium with thickening of the capillary basement membrane and mesangium (see Fig. 11-30, *C* and Fig. 11-31). Sometimes, the hypercellularity is more obvious than membranous thickening, and those cases have traditionally been called "proliferative" glomerulonephritis. More recent classification schemes no longer recognize the "proliferative" glomerulonephritis type, and those cases should more appropriately be considered variants of membranoproliferative GN. Membranoproliferative GN is

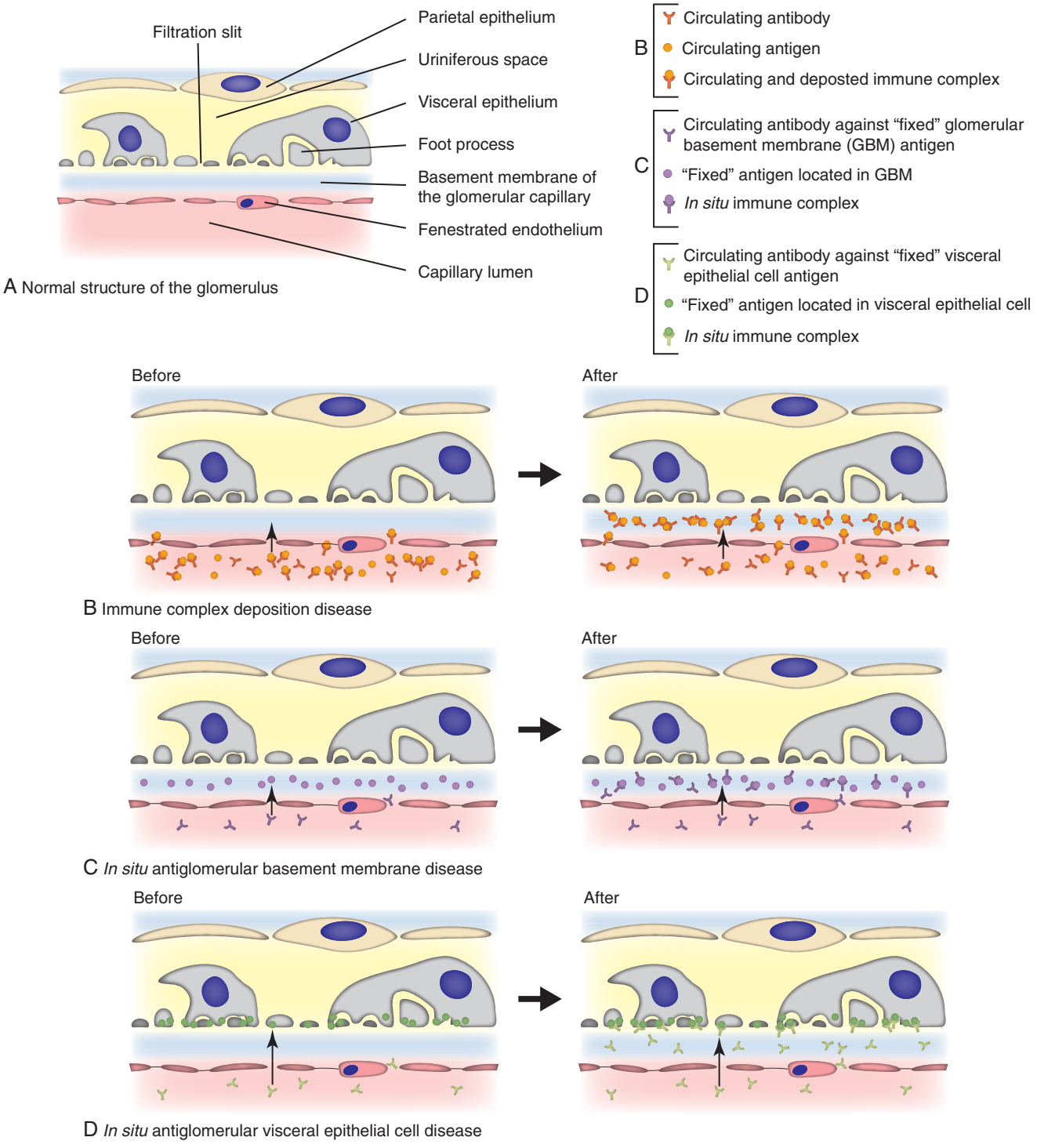


Figure 11-28 Antibody-Mediated Glomerular Injury. A, Normal structure of the glomerulus. Antibody-mediated glomerular injury can result either from the deposition of circulating immune complexes **(B)** or from formation of complexes in situ **(C** and **D)**. Using immunofluorescence microscopy (not shown here), antiglomerular basement membrane (anti-GBM) disease **(C)** and antiglomerular (visceral epithelial cell) disease **(D)** are characterized by linear patterns of immunofluorescence deposition in glomeruli, whereas deposition of circulating immune complexes in glomeruli is characterized by granular ("lumpy-bumpy") patterns (see E-Fig. 11-4). (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

the most common morphologic form of ICGN in the dog. With light microscopy, membranoproliferative GN changes are similar across cases; however, differences can be seen with immunofluorescent and electron microscopy. The latter technique has resulted in subcategorization of human being membranoproliferative GN into types I and II (see Fig. 11-31). Type I lesions, which are typical of those found in domestic animals, are characterized by the presence of subendothelial deposits and a granular pattern after deposition of C3 and lesser quantities of IgG, C1q, and C4. Type I disease appears to be secondary to deposition of circulating immune complexes. Type II is far less common in human beings than type I and is also referred to as *dense deposit disease* because electron-dense material of unknown

composition and smaller quantities of C3 form an irregular deposit within the subendothelial space and the lamina densa. Type II disease may be a form of autoimmune disease, but its pathogenesis is not clear.

Several other changes in the glomerulus and Bowman's capsule usually accompany the lesions discussed previously. These changes include adhesions between the epithelial cells of the glomerular tuft and Bowman's capsule (synechiae; singular = synechia); hypertrophy and hyperplasia of the parietal epithelium lining Bowman's capsule; deposition of fibrinogen and fibrinous thrombi in glomerular capillaries, secondary to or as a result of the glomerular damage; and dilated renal tubules filled with homogeneous proteinaceous fluid. An increase in mesangial matrix is often also present. If the damage is mild and the cause is removed, glomeruli can heal without obvious or with minimal residual lesions. However, if the lesion is severe and prolonged, subacute to chronic glomerular changes develop. Bowman's capsule can become thickened, hyalinized, and reduplicated. In severe cases, proliferation of parietal epithelium, an influx of monocytes, and deposition of fibrin can occur within Bowman's capsule, resulting in the formation of a semicircular, hypercellular, intraglomerular lesion known as a *glomerular crescent*. The glomerular crescent can also undergo fibrosis, and if Bowman's capsule ruptures, glomerular fibrosis can become continuous with interstitial fibrosis. Interstitial and periglomerular fibrosis, foci of interstitial lymphocytes, and plasma cells and glomerulosclerosis may be present in chronic GN.

Figure 11-29 Proliferative Glomerulonephritis (GN), Kidney, Dorsal Section, Dog. The small, white, round foci in the cortex are enlarged glomeruli. (Courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

Minimal Change Disease. In human beings, a common protein-losing glomerulopathy, especially in children, is one in which glomerular histologic changes are minimal or absent, hence the name minimal change disease (MCD). The lesion is characterized ultrastructurally by diffuse effacement of visceral epithelial cell (podocyte) foot processes with minimal or no basement membrane

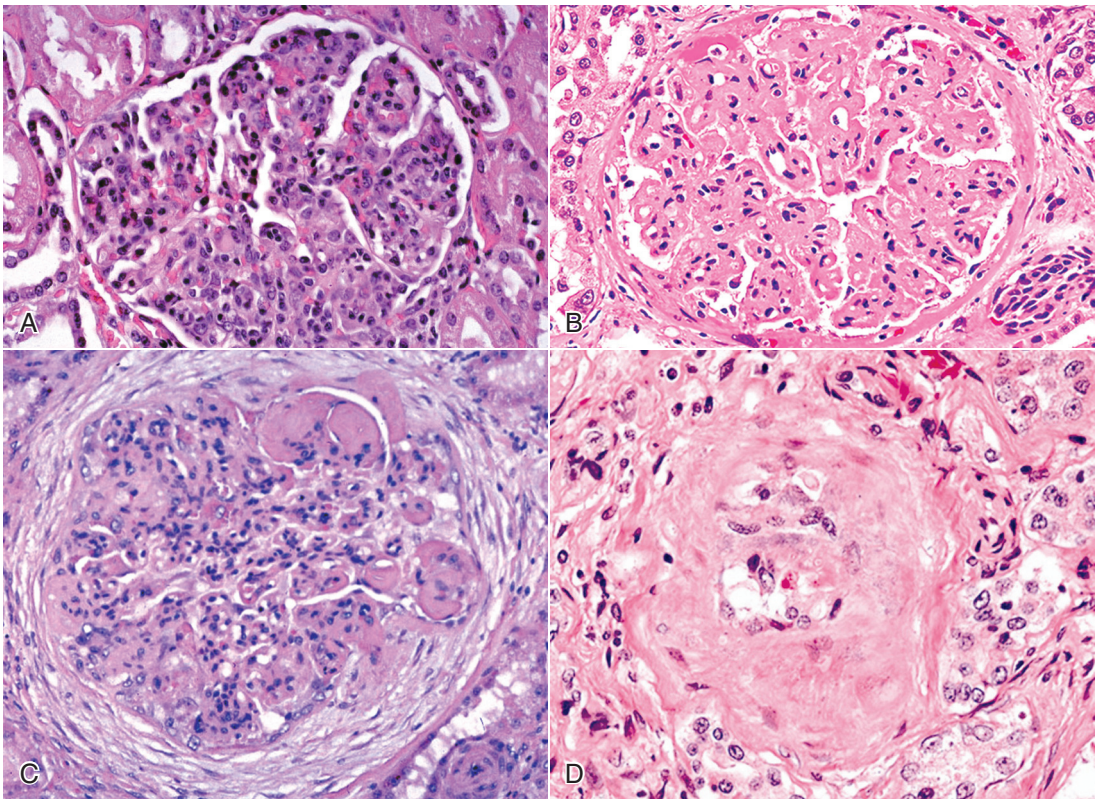


Figure 11-30 Types of Glomerulonephritis (GN). A, Proliferative GN, pig. The lesion is characterized principally by hypercellularity of the glomerulus due to increased numbers of mesangial cells. H&E stain. **B,** Membranous GN, dog. The lesion is characterized by generalized hyaline thickening of glomerular capillary basement membranes. It can occur in dogs with dirofilariasis. H&E stain. **C,** Membranoproliferative GN, horse. Membranoproliferative GN has histologic features of both proliferative GN and membranous GN. Abundant periglomerular fibrosis surrounds this hypercellular glomerulus (mesangial cells). Mesangial matrix is prominent in the top-right area of the glomerulus. H&E stain. **D,** Glomerulosclerosis, dog. Note the hypocellularity, shrinkage, and hyalinization due to an increase in fibrous connective tissue and mesangial matrix and almost complete loss of glomerular capillaries. In glomerulosclerosis (the end stage of chronic GN), glomeruli are essentially nonfunctional. H&E stain. (**A** and **C** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** and **D** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

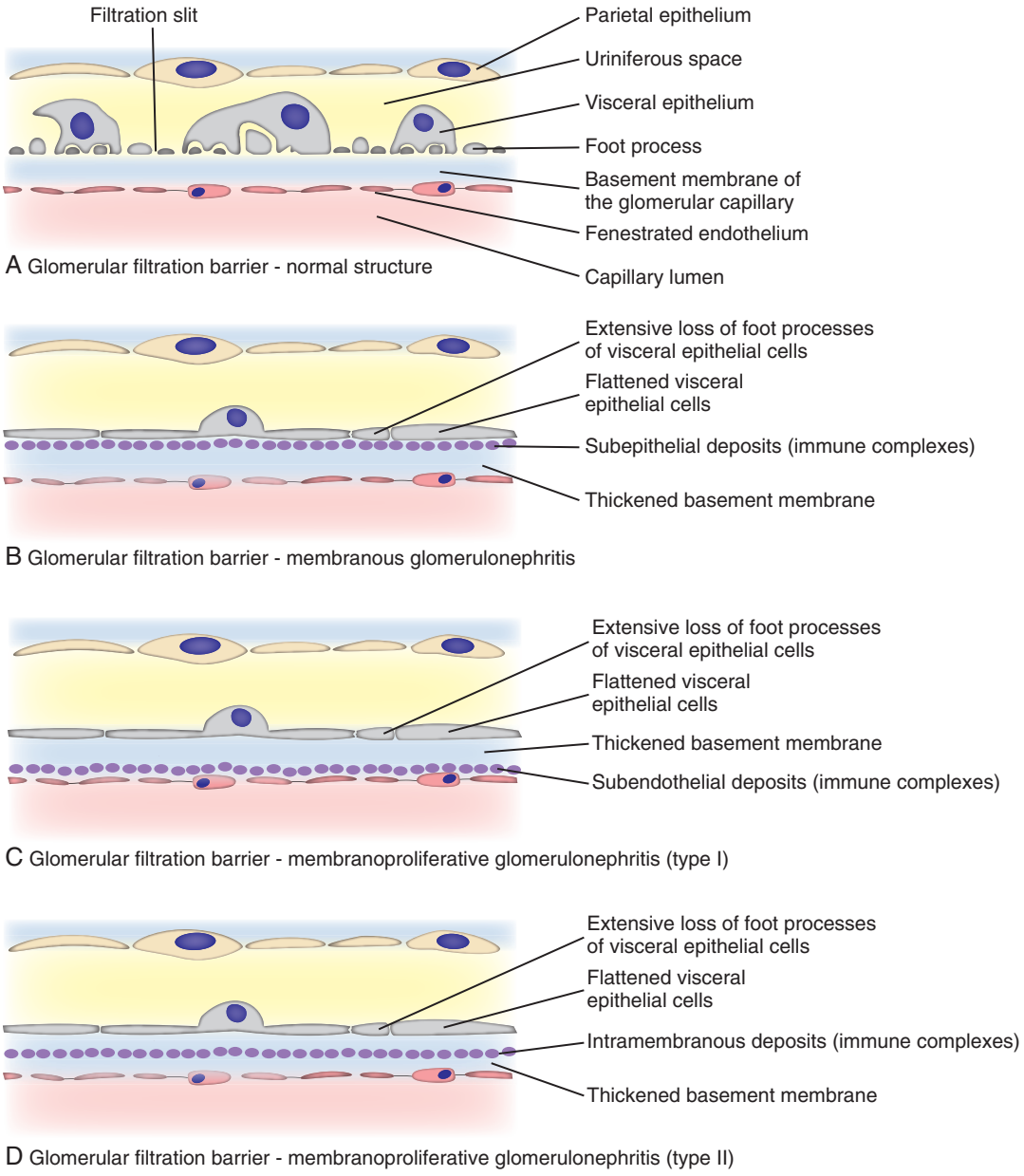


Figure 11-31 Sites of Immune Complex Deposition in the Glomerular Filtration Barrier in the Major Types Glomerulonephritis (GN). **A,** Normal structure of the glomerular filtration barrier. **B,** Membranous glomerulonephritis. Immune complexes are deposited in the basement membrane just beneath the visceral epithelium. **C,** Membranoproliferative glomerulonephritis (type I). Immune complexes are deposited in the basement membrane just beneath the vascular endothelium and lead to a granular pattern in the basement membrane. **D,** Membranoproliferative glomerulonephritis (type II). Immune complexes are deposited in the basement membrane and lead to the irregular deposition of electron-dense material within the lamina densa. Although not shown in this schematic diagram, type I and type II membranoproliferative glomerulonephritis commonly have hypertrophy and hyperplasia (proliferation) of glomerular endothelial cells, epithelial cells, and mesangial cells in response to the immune complexes and the biological processes they induce. Leukocytes (acute inflammation) may also be recruited from the microvasculature into the proliferative response. (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

deposits. The cause of MCD is not obvious, but in most cases it is considered to be an immune dysfunction causing visceral epithelial cell damage. In addition, MCD has been correlated with nonsteroidal antiinflammatory drug (NSAID) therapy or treatment with other drugs. MCD has been described in dogs treated with the antimast cell tumor drug, masitinib. Histologically, glomeruli are essentially normal; however, ultrastructurally, visceral epithelial cell foot process effacement is diffuse and severe.

Glomerulosclerosis. In chronic GN, severely affected glomeruli shrink and become hyalinized because of an increase in both fibrous connective tissue and mesangial matrix and a loss of glomerular capillaries (Fig. 11-30, *D*). In addition, there is periglomerular fibrosis. These glomeruli are hypocellular and essentially nonfunctional. This process is referred to as *glomerulosclerosis*, and affected glomeruli are sometimes referred to as *obsolescent*. Nomenclature applied to GN for describing the numbers of glomeruli involved and the location of the lesion in the glomerulus can be used to describe glomerulosclerosis. Glomerulosclerosis can be diffuse, involving all glomeruli, or multifocal. In addition, glomerulosclerosis can involve an entire glomerular tuft (global) or only portions of the tuft (segmental), thus

appearing as a nodular or segmental hyalinized thickening in affected glomeruli. Because tubules receive their blood supply from the vasa recta, derived from the glomerular efferent arteriole, glomerulosclerosis reduces the blood flow through the vasa recta, thus decreasing oxygen tension in the tubules. The ensuing hypoxia is responsible for tubular epithelial cell death via apoptosis resulting in failure to regenerate to columnar cells. Affected tubules often have reduced diameters and are lined by cuboidal or squamous cells, which lack a brush border and the functions of the normal columnar cells. In addition, chronic proteinuria often accompanies glomerulosclerosis and has been reported to promote tubular epithelial cell loss through apoptosis.

Numerous factors are associated with and accelerate glomerulosclerosis, including the following:

- Unrestricted protein in the diet
- Increased glomerular capillary pressure in the remaining functional glomeruli
- Cytokines from local GN-induced inflammation
- Platelet-derived growth factors (PDGFs)

These factors have the following effects:

- Alter cellular components of the functional glomerular tufts
- Cause hypertension and transglomerular hyperfiltration with resultant damage to endothelium
- Activate mesangial cells to proliferate
- Increase mesangial matrix production
- Accelerate visceral epithelial cell loss, which allows synechiae (i.e., adhesions between visceral and parietal epithelial cell layers in the glomerulus) to form

Glomerulosclerosis is not only the end stage of GN but also can develop in any chronic disease in which severe damage to nephrons or loss of nephron function occurs, including the loss of functional tubules. Mild multifocal glomerulosclerosis of unknown cause is often an incidental finding in aged animals. Glomerulosclerosis has been reported occasionally in animals with hypertension and diabetes mellitus. In these cases, global or nodular eosinophilic glycoprotein material (hyaline material) is deposited in the glomerular mesangium.

Glomerular Amyloidosis. Amyloid, an insoluble fibrillar protein with a β-pleated sheet conformation, is produced after incomplete proteolysis of several soluble amyloidogenic proteins. Amyloid deposits in patients with plasma cell myelomas or other B lymphocyte dyscrasias (called *AL amyloidosis*) are composed of fragments of the light (λ) chains of immunoglobulins. In domestic animals, spontaneously occurring amyloidosis is usually an example of what is called *reactive amyloidosis* (AA amyloidosis). This form of the disease is often associated with chronic inflammatory diseases; the amyloid deposits are composed of fragments of a serum acute-phase reactant protein called *serum amyloid–A* (SAA) protein. Amyloid fibrils from either source are deposited in tissue along with a glycoprotein called *amyloid P component*.

Glomeruli are the most common renal sites for deposition of amyloid in most domestic animal species, although the medullary interstitium is a common site in cats, particularly in Abyssinian breed. Renal amyloidosis commonly occurs in association with other diseases, particularly chronic inflammatory or neoplastic diseases. However, idiopathic renal amyloidosis (i.e., amyloidosis in which an associated disease process is not recognized) is also described in dogs and cats. The underlying pathogenic mechanisms of idiopathic renal amyloidosis are not known. In one study, 23% of dogs that presented with proteinuria had renal amyloidosis. A hereditary predisposition for the development of reactive amyloidosis (AA) has been found in Abyssinian cats and Chinese Shar-Pei dogs. A familial tendency is suspected in Siamese cats, English foxhounds, and beagle dogs. In cattle, renal amyloidosis is nearly always due to chronic systemic infectious disease. Glomerular amyloidosis is responsible for many cases of protein-losing nephropathy in animals that have notable proteinuria and uremia. It can, like ICGN, result in the nephrotic syndrome. Long-standing glomerular amyloidosis results in diminished renal blood flow through the glomeruli and the vasa recta. Such reduced renal vascular perfusion can lead to renal tubular atrophy, degeneration, and diffuse fibrosis and, in severe cases, renal papillary necrosis. Medullary amyloidosis is usually asymptomatic unless it results in papillary necrosis.

Kidneys affected with glomerular amyloidosis are often enlarged and pale and have a smooth to finely granular capsular surface (Fig. 11-32). Amyloid-laden glomeruli may be visible grossly as fine translucent to tan dots on the capsular surface. Similarly, the cut surface of the cortex can have a finely granular appearance with scattered glistening foci, less than 0.5 mm diameter in the cortex (see Fig. 11-32). Treatment of kidneys with an iodine solution, such as Lugol's iodine, in many cases results in red-brown staining of glomeruli, which become purple when treated with dilute sulfuric acid (Fig. 11-33). This technique provides a rapid presumptive diagnosis of renal amyloidosis. Medullary amyloidosis is usually not grossly recognizable.

Microscopically, glomerular amyloid is deposited in both the mesangium and subendothelial locations. Amyloid is relatively acellular and can accumulate segmentally within glomerular tufts; thus a portion of the normal glomerular architecture is replaced by eosinophilic, homogeneous to slightly fibrillar material (Fig. 11-34, *A*). When amyloidosis involves the entire glomerular tuft, the glomerulus is enlarged, capillary lumina become obliterated, and the tuft can appear as a large hypocellular eosinophilic hyaline sphere (Fig. 11-34, *B*). Amyloid can be present in renal tubular basement membranes, and these membranes appear hyalinized and thickened. In addition, in cases of glomerular amyloid deposition, secondary changes may be present in renal tubules, which are usually markedly dilated, have variably atrophic epithelium, and

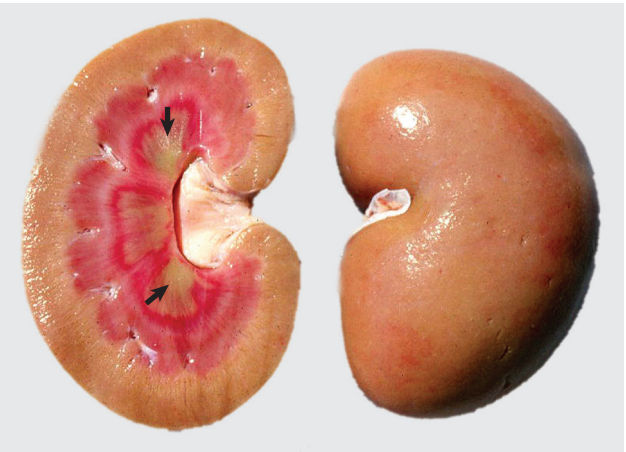


Figure 11-32 Amyloidosis, Kidney, Dog. Grossly, kidneys affected by amyloid deposition are diffusely tan, waxy (firm), and of normal size or slightly enlarged. Affected glomeruli are not grossly visible in this specimen, unlike in advanced cases of glomerular amyloidosis or chronic GN. In advanced cases of amyloidosis, glomeruli may be visible as pinpoint, glistening, round, cortical foci. In cats and Shar-Pei dogs, amyloid is deposited in the medullary interstitium, not in the glomeruli. There are also multiple foci of medullary crest necrosis (yellowish-green *[arrows]*). (Courtesy Dr. G.K. Saunders, The Virginia-Maryland Regional College of Veterinary Medicine; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

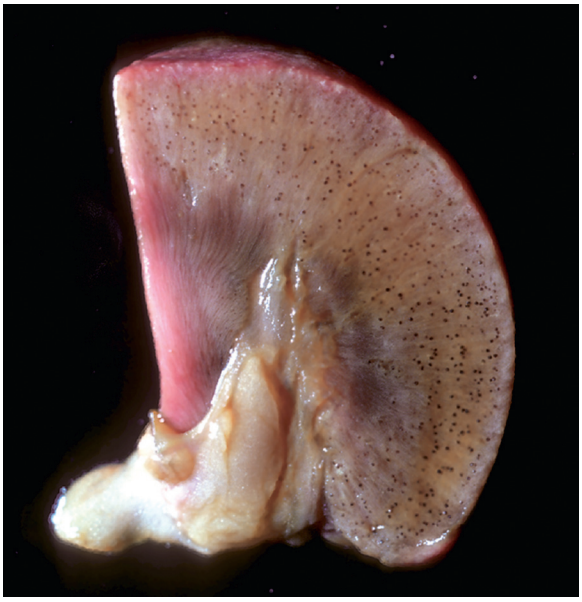


Figure 11-33 Amyloidosis, Kidney, Transverse Section, Dog. On the cut surface of fresh kidney treated with Lugol's iodine followed by dilute sulfuric acid, glomeruli containing amyloid are visible as multiple dark blue dots in the cortex. Lugol's iodine treatment. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

contain proteinaceous and cellular casts. Amyloid is confirmed microscopically by staining with Congo red stain (Fig. 11-34, *C*). When viewed with polarized light, amyloid has a green birefringence (Fig. 11-34, *D*). Loss of Congo red staining after treatment of a section of affected kidney with potassium permanganate suggests amyloid is AA (i.e., of acute-phase reactant protein origin).

Acute Suppurative Glomerulitis: Bacterial (Embolic) Nephritis. Embolic nephritis, which can also be referred to as *acute suppurative glomerulitis*, is the result of a bacteremia in which bacteria lodge in random glomerular capillaries and to a lesser extent in interstitial capillaries and arterioles causing multiple foci of inflammation (microabscesses) throughout the renal cortex. Although the glomeruli appear targeted, this is really a manifestation of renal vascular disease. A specific example of embolic nephritis is *Actinobacillosis* of foals caused by *Actinobacillus equuli* (Fig. 11-35) (see Disorders of Horses). These foals usually die within a few days of birth and have small abscesses (1 mm or less in diameter) in many visceral organs, especially the renal cortex. Embolic nephritis also occurs commonly in the bacteremia of pigs infected with *Erysipelothrix rhusiopathiae* or sheep and goats infected with *Corynebacterium pseudotuberculosis*. *Trueperella pyogenes* was the most common isolate (26/31) from cases of embolic nephritis in necropsied cattle. *Staphylococcus aureus*, *Mannheimia haemolytica*, and *Streptococcus bovis* were also represented.

Grossly, multifocal, random, raised, 1 mm or less in diameter, tan foci are seen subcapsularly and on the cut surface throughout the

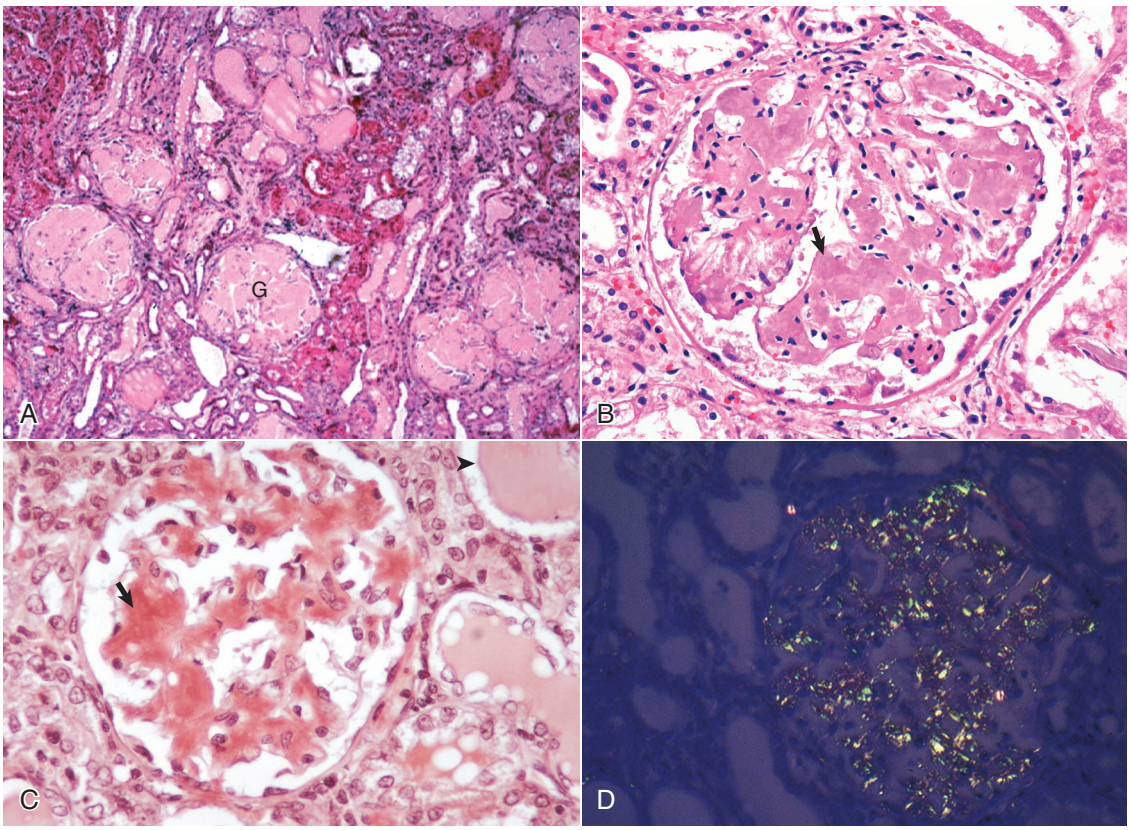


Figure 11-34 Amyloidosis, Glomerulus, Kidney, Dog. A, All glomerular tufts (*G*) are diffusely and notably expanded by amyloid (pale eosinophilic homogeneous deposits), with the result that they are relatively acellular. H&E stain. **B,** Amyloid, the pale eosinophilic homogeneous hyalinized deposits, expands the mesangium of the glomerulus *(arrow)*. H&E stain. **C,** Amyloid stains orange with Congo red staining *(arrow)*, a technique used to confirm it. Note the proteinaceous casts in tubular lumina *(arrowhead)*, a consequence of glomerular damage allowing leakage of proteins into the filtrate (protein-losing nephropathy). Congo red stain. **D,** Congo red–stained amyloid deposits. These deposits have a light-green (often called apple green) birefringence when viewed under polarized light. Polarized light microscopy. (**A** courtesy Dr. B.C. Ward, College of Veterinary Medicine, Mississippi State University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **D** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

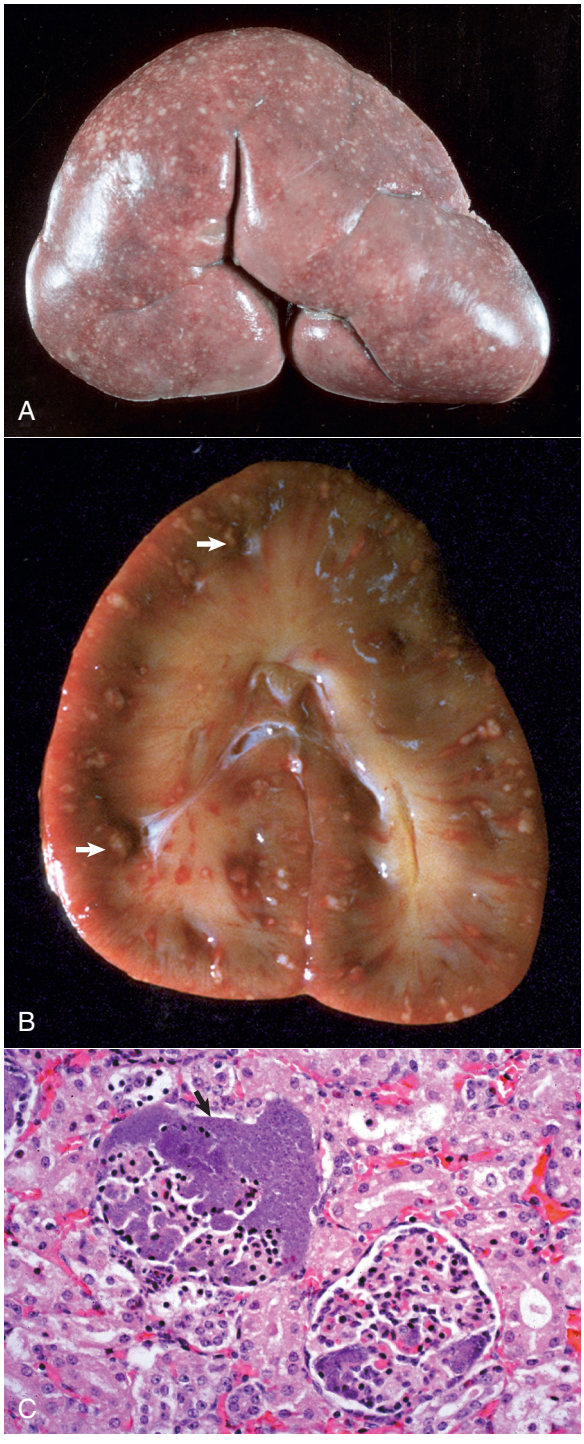


Figure 11-35 Embolic Nephritis (Suppurative Glomerulitis), Kidney, Horse. A, Multiple, small pale white necrotic foci and abscesses are present subcapsularly. **B,** Dorsal section. Variably sized abscesses are scattered throughout the cortex *(arrows)*. **C,** Causative bacteria *(arrow)* enter the kidney via the vasculature (bacteremia) and lodge in the capillaries of glomeruli, where they replicate and induce necrosis and inflammation. H&E stain. (**A** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

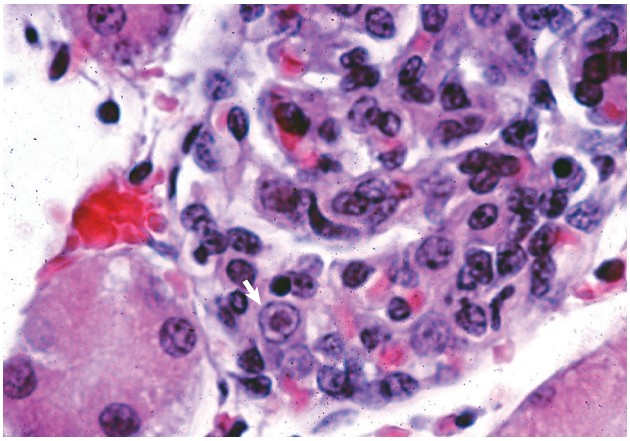


Figure 11-36 Infectious Canine Hepatitis, Kidney, Cortex, Dog. Renal glomerular endothelial cells contain intranuclear inclusion bodies *(arrow)*. H&E stain. (Courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

renal cortex. Microscopically, glomerular capillaries contain numerous bacterial colonies intermixed with necrotic debris and extensive infiltrates of neutrophils that often obliterate the glomerulus. Glomerular or interstitial hemorrhage can occur as well. As with many other inflammatory diseases, if the affected animal survives, the neutrophilic infiltrates either persist as focal residual abscesses or are progressively replaced by increasing numbers of lymphocytes, plasma cells, macrophages, and fibroblasts, ultimately forming coalescing scars.

Viral Glomerulitis. Glomerulitis, caused by a direct viral insult to the glomerulus, occurs in acute systemic viral diseases, such as acute infectious canine hepatitis (Fig. 11-36), equine arteritis virus infection, hog cholera, avian Newcastle disease, and neonatal porcine cytomegalovirus infection. The lesions are mild, usually transient, and result from viral replication in capillary endothelium. Acute viral GN produces the following gross lesions:

- Kidneys are often slightly swollen.
- Renal capsular surface is smooth.
- Kidneys are normal color or pale.
- Glomeruli are visible as pinpoint red dots on the cut surface of the cortex.

Viral-induced intranuclear inclusions are present in glomerular capillary endothelium from viremias of infectious canine hepatitis and cytomegalovirus infections. The inclusions of each disease are similar and are usually large, basophilic to magenta, and either fill the nucleus or are separated from the nuclear membrane by a clear halo. In the other diseases (equine arteritis, hog cholera, maedivisna, porcine circovirus, and avian Newcastle), viral antigens can be demonstrated in endothelium, epithelium, or mesangial cells by immunofluorescence, immunohistochemistry, or polymerase chain reaction (PCR). In cases of viral glomerulitis, lesions include endothelial hypertrophy, hemorrhages, necrosis of endothelium, and a thickened and edematous mesangium. Clinically, animals are systemically ill from the viral infection, but the glomerular signs are specifically those of a transient proteinuria.

Chemical Glomerulonephritis. Although much less common than the immune-mediated forms of GN, chemically induced glomerular disease occurs in a variety of different ways. Chemicals typically induce glomerular injury by any of the following:

- Direct injury to glomerular epithelial cells
- Direct injury to endothelial cells of the glomerulus

- Altered renal blood flow
- Induction of immunologic reactions and inflammatory responses, which may occur with any of the following:
  - Incorporation of drugs into immune complexes
  - The formation and targeted deposition of antigen-antibody complexes
  - The formation of antinuclear antibodies
  - The formation of anti-GBM antibodies within the glomerular tuft

Puromycin aminonucleoside, adriamycin, and histamine-receptor antagonists all induce proteinuria through targeted damage to glomerular epithelial cells. The immunosuppressive drug, cyclosporine A, alters renal perfusion and ultimately the glomerular filtration rate by damaging glomerular endothelial cells. Numerous foreign substances are capable of producing immune complexes including injectable hyperimmune serum, gold, and D-penicillamine. Procainamide and hydralazine result in production of antinuclear antibodies, and occupational exposure to hydrocarbon solvents can create anti-GBM antibodies. Often, drug-induced lesions lead to irreversible nephron loss and compensatory cellular and functional hypertrophy of other nephrons. The continuing physical loss of nephrons sets up a cycle for an increase in glomerular hypertension and hyperfiltration, which results in glomerulosclerosis, progressive nephron loss, and interstitial fibrosis.

Miscellaneous Glomerular Lesions

Glomerular Lipidosis. Glomerular lipidosis, characterized by small aggregates of lipid-laden, foamy macrophages in glomerular tufts, is an occasional incidental finding in dogs. A similar but more extensive glomerular lipidosis has been described in cats with inherited hyperlipoproteinemia, which is a generalized disease characterized by hyperchylomicronemia, atherosclerosis, and xanthogranulomas in numerous parenchymatous organs, including the kidneys (see the section on Granulomatous Nephritis). Microscopically, glomeruli contain foamy macrophages, characteristic of glomerular lipidosis, as well as increased mesangium and thickened Bowman's capsule.

Glomerular Vasculopathy. An idiopathic renal glomerular and cutaneous vasculopathy was originally described in greyhounds and has since been found in numerous purebred and mixed-breed dogs. The cause of this disease is unknown, but renal lesions are similar to those seen in DIC, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome in human beings. At autopsy (syn: necropsy), kidneys from affected dogs are swollen and congested and show cortical petechiae (Fig. 11-37, *A*). Microscopically, numerous glomeruli have segmental or global fibrin thrombi, hemorrhage, and necrosis (Fig. 11-37, *B*). At the glomerular vascular pole, the walls of afferent arterioles have fibrin deposits and foci of necrosis. Affected greyhounds have multifocal erythematous and ulcerated skin lesions and distal limb edema. Variable systemic signs of uremia often accompany the cutaneous lesions.

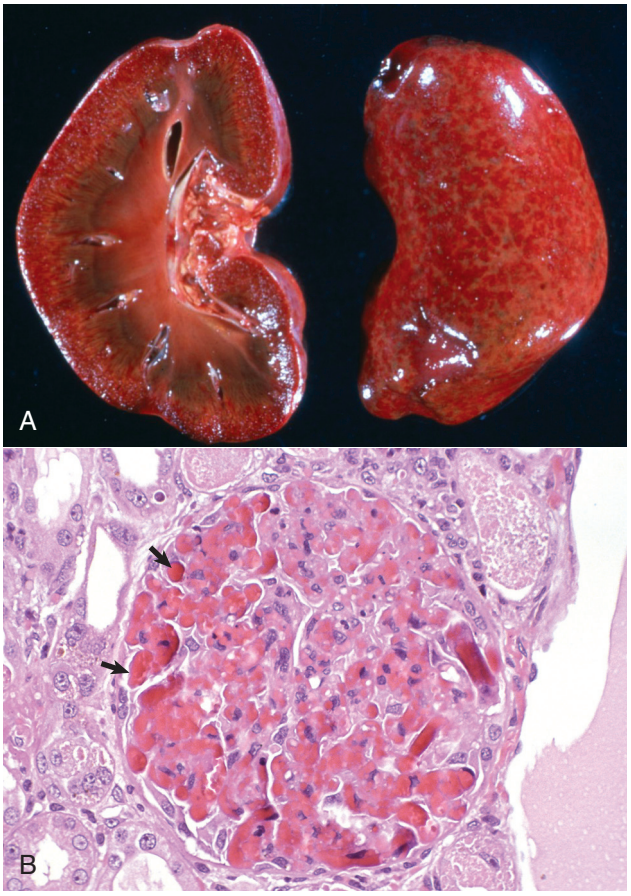


Figure 11-37 Vasculopathy, Renal (and Cutaneous) Vasculopathy Syndrome, Glomerulus, Kidney, Dog, Greyhound. A, The fine white dots in the cortex (on both the capsular and cut surfaces) are glomeruli with extensive glomerular capillary thrombosis. **B,** Necrotic glomerular endothelial cells and extensive glomerular capillary thrombosis *(arrows)* are typical of idiopathic glomerular (and cutaneous) vasculopathy syndrome in greyhound dogs. H&E stain. (**A** courtesy Dr. B. Weeks, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. B.W. Fenwick, Virginia Tech.)

Diseases of the Tubules

Inherited Abnormalities in Renal Tubular Function. Inherited abnormalities in tubular metabolism, in transport, or in reabsorption of glucose, amino acids, ions, and proteins have been described in dogs. Primary renal glucosuria, an inherited disorder in Norwegian elkhounds and sporadically occurring in other dog breeds, occurs when the capacity of tubular epithelial cells to reabsorb glucose is significantly reduced. Gross and histologic lesions are not seen, because this is a functional disorder. Glucosuria most commonly results from diabetes mellitus, acromegaly, or catecholamine release and predisposes dogs to the following:

- Bacterial infections of the lower urinary tract
- Urinary bladder emphysema, secondary to splitting of glucose molecules by bacteria (principally *Escherichia coli*, *Clostridium perfringens*, and rarely with *Candida* yeasts), with subsequent release of carbon dioxide (CO_2) into the bladder lumen and absorption of gas into the lymphatic vessels of the bladder (Fig. 11-38)

A hereditary generalized defect in tubular reabsorption similar to the Fanconi syndrome in human beings has been described in Basenji dogs. The underlying tubular defect appears to be abnormal membrane structure of the proximal tubular epithelial cell brush borders because of altered lipid content in the cell membrane. Gross lesions are not identifiable in the early stages. Histopathologic changes in the kidneys are initially minimal, consisting of irregularly sized tubular epithelial cells in the convoluted tubules and loops of Henle. With time, dogs with Fanconi syndrome develop progressive renal insufficiency and associated renal fibrosis. Aminoaciduria, glucosuria, proteinuria, increased phosphaturia, metabolic acidosis, and multiple endocrine abnormalities characterize this disease clinically. Transient acquired forms have been noted in association with copper storage hepatopathy.

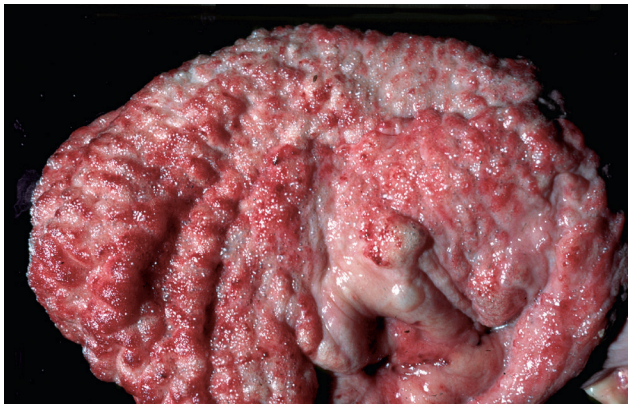


Figure 11-38 Emphysema, Urinary Bladder Mucosa, Cow. The multiple "nodules" are mucosal gas bubbles that have expanded the mucosa and are secondary to bacterial infections of the lower urinary tract (principally by *Escherichia coli*, *Clostridium perfringens*, and rarely *Candida* yeasts). Microorganisms split glucose molecules to release CO_2 into the bladder lumen, from where the gas can be absorbed into bladder lymphatic vessels. This animal was injected with calcium borogluconate as a calcium source to treat milk fever. Following intravenous injection, calcium ions readily dissociate from the parent molecule, and the resulting gluconate provides a sugar source for resident urinary bacteria. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

The excretion of large quantities of cystine in the urine (cystinuria) is a sex-linked inherited tubular dysfunction seen occasionally in purebred and mongrel male dogs. It is important because it predisposes affected dogs to calculus formation and obstruction of the lower urinary tract (see the section on Urolithiasis).

Acute Tubular Necrosis. Acute tubular necrosis, as described in the section on tubular response to injury, can be seen following exposure to any of the following nephrotoxins (Box 11-10):

- Pigments
  - Hemoglobin
  - Myoglobin
  - Bile/bilirubin
- Heavy metals
  - Lead
  - Mercury
- Pharmaceutical agents (e.g., chemotherapeutic and antimicrobial agents)
  - Cisplatin
  - Aminoglycosides (see the section on Kidney and Lower Urinary Tract, Disorders of Dogs)
  - Oxytetracycline
  - Amphotericin B
  - Sulfonamides
  - Monensin
- Nonsteroidal antiinflammatory drugs
- Fungal toxins
- Plant toxins
  - Pigweed
  - Oxalate-containing plants
  - Oak tannins
- Antifreeze (ethylene glycol)
- Vitamins and minerals
  - Vitamin D
  - Hypercalcemia
- Bacterial toxins
- Pet food contaminants (see the section on Kidney and Lower Urinary Tract, Disorders of Dogs)
  - Melamine
  - Cyanuric acid
  - Raisins

These nephrotoxins are discussed in greater detail in the next section.

Box 11-10 Common Nephrotoxins of Domestic Animals

HEAVY METALS
Mercury
Lead
Arsenic
Cadmium
Thallium

ANTIBACTERIAL AND ANTIFUNGAL AGENTS
Aminoglycosides
- Gentamicin
- Neomycin
- Kanamycin
- Streptomycin
- Tobramycin

Tetracyclines
Amphotericin B

GROWTH-PROMOTING AGENTS
Monensin

NONSTEROIDAL ANTIINFLAMMATORY DRUGS
Aspirin
Phenylbutazone
Carprofen
Flunixin meglumine
Ibuprofen
Naproxen

FOOD AND FOOD CONTAMINANTS
Grapes or raisins
Melamine
Cyanuric acid

BACTERIAL AND FUNGAL TOXINS
Clostridium perfringens epsilon toxin
Ochratoxin A
Citrinin

PLANTS
Pigweed (*Amaranthus retroflexus*)
Oaks (*Quercus* sp.)
Isotropis sp.
Yellow wood tree (*Terminalia oblongata*)
Lilies (*Zantedeschia* spp., *Lilium* spp., and *Hemerocallis* spp.)

OXALATES
Ethylene glycol (antifreeze)
Halogeton (*Halogeton glomeratus*)
Greasewood (*Sarcobatus vermiculatus*)
Rhubarb (*Rheum rhaponticum*)
Sorrel, dock (*Rumex* sp.)

VITAMIN D
Vitamin D supplements
Calciferol-containing rodenticides
Cestrum diurnum
Solanum sp.
Trisetum sp.

ANTINEOPLASTIC COMPOUNDS
Cisplatin

Nephrotoxic Pigments

Hemoglobinuric Nephrosis. A set of events leading to ischemic tubular necrosis frequently occurs in hypoperfused kidneys complicated by hemoglobinuria. Hemoglobinemia results in hemoglobinuria when the renal threshold for resorption is exceeded. Hemoglobinuria may occur in the following:

- Chronic copper toxicity in sheep
- Leptospirosis or babesiosis in cattle
- Red maple toxicity in horses
- Babesiosis or autoimmune hemolytic anemia in dogs

In these diseases, serum concentrations of hemoglobin are increased. Hemoglobin passes into the glomerular filtrate, producing greatly increased intraluminal concentrations that cause hemoglobinuric nephrosis. Normally, hemoglobin attaches to a carrier haptoglobin for plasma transportation, and the hemoglobin-haptoglobin complex is too big to pass through the glomerular filtration barrier. Hemoglobin is not excreted in the urine until supplies of the carrier molecule are depleted or exceeded and hemoglobin becomes free in the plasma. Hemoglobin is not nephrotoxic itself, and intravenous infusions of hemoglobin into healthy animals produce no recognizable lesions. However, large concentrations of hemoglobin in the glomerular filtrate can increase the tubular necrosis that occurs as a result of renal ischemia. For example, in chronic copper toxicity in sheep, renal ischemia is secondary to hypovolemic shock and severe Heinz body, hemolytic anemia. Therefore hemoglobinuria can have an additive deleterious effect on tubular epithelium already undergoing hypoxia.

At autopsy (syn: necropsy), the renal cortices in severe hemoglobinuria are diffusely stained red-brown to blue-black and have intratubular hemoglobin casts (Fig. 11-39, *A*). Hemoglobin casts appear as a red-black stippling of the capsular surface and continue into the cortex as radially oriented, dark red streaks. The medulla is diffusely dark red or has patchy red streaks. Classically, kidneys from sheep with chronic copper toxicity are diffusely, uniformly, and strikingly blue-black and described as "gunmetal blue." Microscopically, proximal tubular epithelial degeneration and necrosis are severe, and tubular lumens are filled by abundant orange-red granular refractile material, the characteristic appearance of a heme compound (Fig. 11-39, *B*).

Myoglobinuric Nephrosis. Myoglobinuria results from acute and extensive muscle necrosis and occurs in the following:

- Exertional rhabdomyolysis in horses, greyhounds, and wild or exotic animals (see the section on Kidney and Lower Urinary Tract, Disorders of Horses)
- *Cassia* spp. and *Karwinskia* spp. toxicity
- Severe direct trauma to muscle (e.g., traffic accident)

A set of events leading to ischemic tubular necrosis frequently occurs in hypoperfused kidneys complicated by myoglobinuria. In these diseases, serum concentrations of myoglobin are increased, as these products pass into the glomerular filtrate, producing greatly increased intraluminal concentrations that cause myoglobinuric nephrosis. Compared to hemoglobin, myoglobin more freely passes through the glomerular filtration barrier and is excreted in the urine because it does not use a carrier protein for plasma transport and it is a smaller molecule. Myoglobin is not nephrotoxic in itself, and intravenous infusions into healthy animals produce no recognizable lesions. However, large concentrations of myoglobin in the glomerular filtrate can increase the tubular necrosis that occurs as a result of renal ischemia. For example, in rhabdomyolysis in horses, renal ischemia is likely secondary to poor renal perfusion seen in hypovolemic shock. Therefore myoglobinuria can have an additive deleterious effect on tubular epithelium already undergoing ischemic necrosis.

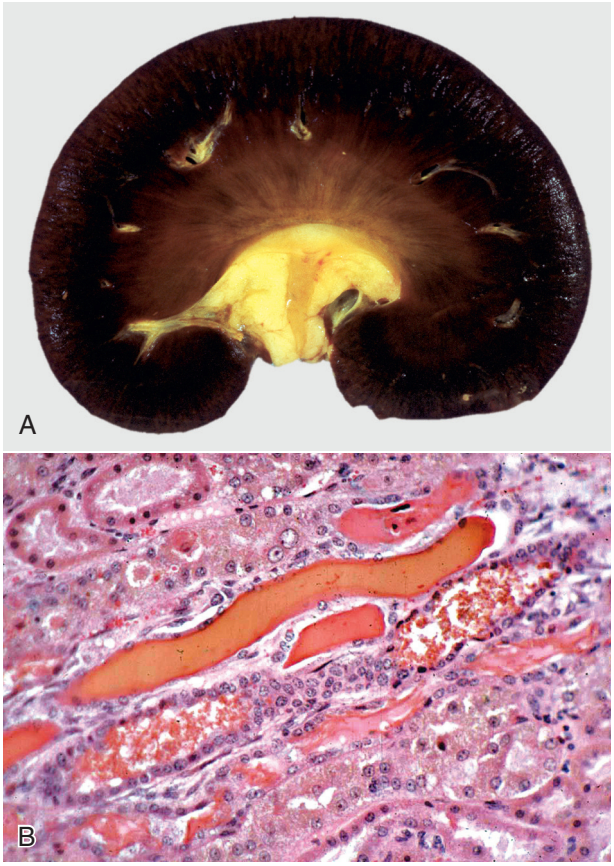


Figure 11-39 Hemoglobinuric Nephrosis, Kidney. A, Dog. Severe diffuse hemoglobin staining of the cortex and medulla is secondary to hemoglobinemia from an acute intravascular hemolytic crisis. Note the yellow staining (jaundice) of the pelvic fat and the intima of cross sections of the arcuate artery at the corticomedullary junction. **B,** Sheep. Several distal tubules contain hyaline and coarsely granular hemoglobin casts that occurred following intravascular hemolysis (hemoglobinemia) from chronic copper toxicosis. H&E stain. (**A** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy Dr. A.R. Doster, University of Nebraska; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

At necropsy, the renal cortices in myoglobinuria are diffusely stained red-brown to blue-black and have intratubular myoglobin casts, which cannot be differentiated from hemoglobin casts (Fig. 11-40).

Cholemic Nephrosis. Increased serum concentrations of bilirubin, as in young lambs, calves, and foals with immature hepatic conjugating mechanisms, can be associated with proximal tubular cellular swelling, degeneration, and yellow-brown-green pigmentation of the proximal tubular epithelial cells. The term *cholemic nephrosis* has been applied to this lesion; however, its significance is doubtful. Acute tubular necrosis, when seen in association with severe bilirubinemia, the so-called hepatorenal syndrome, probably is not caused by bile acid or bilirubin retention per se but by ischemia from prerenal causes such as constriction of renal vessels related to shock or catecholamine release.

Heavy Metals. Nephrotoxic tubular necrosis is caused by several classes of naturally occurring or synthetic compounds. Inorganic arsenic and certain heavy metals, including inorganic mercury, lead, cadmium, and thallium, are nephrotoxins. Common sources of heavy metals for oral exposure include herbicides (arsenic), old paints (lead), batteries (lead), automobile components (lead),

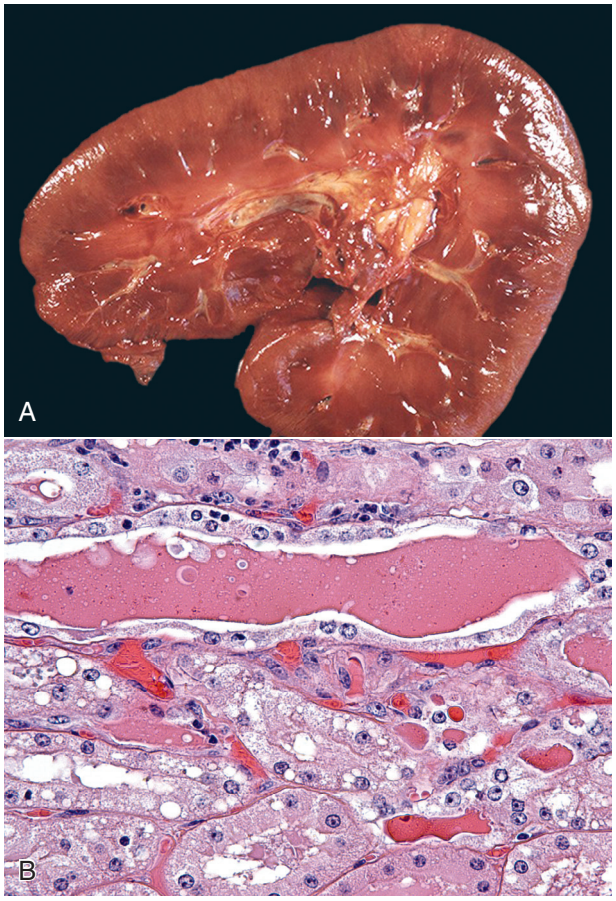


Figure 11-40 Myoglobinuric Nephrosis, Kidney, Horse. A, Diffuse myoglobin staining of the cortex and medulla (reddish-brown) is secondary to myoglobinemia from severe rhabdomyolysis. **B,** Myoglobin casts are present in dilated distal tubules, which are lined by flattened epithelial cells. H&E stain. (**A** courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **B** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

impure petroleum distillates, and other environmental contaminants. Acute tubular necrosis from mercury is caused by the following:

- Damage to membranes of proximal convoluted tubular epithelial cells.
- Mitochondrial damage produced by these toxins: Damage is often related to the interaction of these metals with protein sulfhydryl groups.

In mercury toxicosis, mercuric ions are in capillary blood and glomerular filtrate and therefore enter the proximal tubular epithelium both from the luminal side and via diffusion from the peritubular side. Mercuric ions concentrate in rough endoplasmic reticulum and cause early tubular changes that include loss of the brush border and dispersion of ribosomes. These changes are followed by mitochondrial swelling and cellular death. In addition, cadmium has been reported to cause cell death in proximal convoluted tubules by apoptosis.

The specific metal involved in toxic tubular injury cannot be identified by the renal lesions alone. The exception is lead toxicity, in which the endothelial and epithelial cells of affected glomeruli and proximal tubules, respectively, sometimes have acid-fast intranuclear inclusions composed of a lead-protein complex (Fig. 11-41).

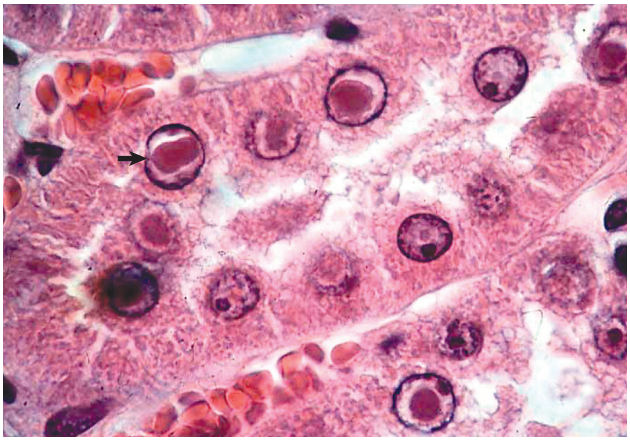


Figure 11-41 Nephrosis, Lead Toxicosis, Kidney, Cortex, Rat. Acid-fast intranuclear inclusion bodies *(arrow)* present in the proximal convoluted tubular epithelium are diagnostic of lead poisoning. Acid-fast stain with H&E counterstain. (Courtesy Dr. J. King, College of Veterinary Medicine, Cornell University.)

Pharmaceutical Agents. These agents are nephrotoxic and cause acute tubular necrosis when administered at excessive doses or too frequently. Cisplatin, a platinum-containing cancer chemotherapeutic agent, causes tubular necrosis by the following:

- Direct tubular epithelial damage
- Reducing renal blood flow via vasoconstriction mediated by the renin-angiotensin mechanism

The best-characterized group of nephrotoxic pharmaceutical agents are the aminoglycoside antibiotics (gentamycin, neomycin, etc.). Aminoglycosides concentrate in proximal tubular epithelium lysosomes, Golgi bodies, and endoplasmic reticulum. They reach a threshold, are released into the cytosol, and damage mitochondria causing apoptosis and necrosis. In addition, renal blood flow is reduced, adding a hypoxic component to the toxicity.

Oxytetracycline is occasionally nephrotoxic in cattle and dogs. The mechanism of tubular damage has not been determined, but it is known that large concentrations of tetracycline antibiotics are necessary and are thought to inhibit protein synthesis in tubular epithelial cells.

Amphotericin B, an antifungal polyene antibiotic, is nephrotoxic by vasoconstriction and/or the direct disruption of cellular membranes. This membrane damage interferes with normal cholesterol-lipid interactions and causes potassium ion loss, intracellular hydrogen ion accumulation, acute cellular swelling, and necrosis of proximal and distal tubules. These renal changes are not confined to drug overdose but, rather, can occur in animals given the recommended therapeutic dosage.

Sulfonamide-induced tubular necrosis, a common entity in years past, occurs infrequently today because the presently used sulfonamides have greater solubility than those used in the past. Sulfonamides produce tubular epithelial cell necrosis most readily in dehydrated animals. Crystals form in tubules and cause necrosis of the renal tubular epithelium by direct toxicity and by mechanical damage. Fine granular yellow crystalline deposits can be seen grossly in the medullary tubules of affected animals, but the crystalline deposits are dissolved during fixation in aqueous fixatives such as 10% buffered neutral formalin.

Monensin is an ionophore antibiotic used as a feed additive to control coccidiosis and stimulate weight gains in poultry and cattle. Horses are particularly susceptible to toxicosis with monensin.

Although necrosis of striated muscle is the major lesion, renal tubular degeneration or necrosis occurs concurrently.

Nonsteroidal Antiinflammatory Drugs. Ingestion of nonsteroidal antiinflammatory drugs (NSAIDs), such as phenylbutazone, aspirin, carprofen, flunixin meglumine, ibuprofen, and naproxen, has been associated with acute renal failure in small animals, especially dogs. In horses, NSAID toxicosis is usually associated with nonfatal renal papillary necrosis and mucosal ulceration (see the section on Papillary Necrosis). The mechanism of acute renal failure is related to NSAIDs decreasing the synthesis of renal prostaglandins. Because prostaglandins are responsible for maintaining normal renal blood flow, NSAID administration results in afferent arteriolar constriction that decreases renal perfusion, resulting in acute tubular degeneration and medullary papillary necrosis and acute renal failure. The overall incidence of NSAID-induced renal failure in small animals is low and is seen most commonly in animals that ingest excessive amounts of the drug or have a concomitant disorder such as dehydration, congestive heart failure, or chronic renal disease.

Fungal Toxins. Naturally occurring nephrotoxic mycotoxins can originate from *Aspergillus* sp. and *Penicillium* sp. (e.g., ochratoxin and citrinin). Ochratoxin A is nephrotoxic for monogastric animals, particularly pigs, in which the lesions are tubular degeneration and necrosis. In addition, long-term ingestion results in diffuse renal fibrosis presumably as the result of continual damage to the tubule epithelial cells and thus allowing no time for regeneration.

Plant Toxins. Several species of pigweed, particularly *Amaranthus retroflexus*, can be responsible for acute tubular necrosis and perirenal edema in pigs and cattle. The toxic principle is likely a group of phenolic compounds present in the leaves. Oak toxicosis (*Quercus* spp.) is seen in ruminants after consumption of new leaves or acorns. The toxic principles are tannins and their breakdown products. See the section on Kidney and Lower Urinary Tract, Disorders of Ruminants (Cattle, Sheep, and Goats), Oak Toxicity: Acute Tubular Necrosis (*Quercus* Spp.) for a discussion of tannins. Several nephrotoxic species of lilies (*Lilium* spp., *Zantedeschesia* spp., and *Hemerocallis* spp.) have been associated with acute tubular necrosis in small animals, especially cats. The toxic principle is not known.

Oxalate-induced tubular necrosis occurs in sheep and cattle after ingestion of toxic quantities of oxalates that accumulate in plants of various genera, such as *Halogeton*, *Sarcobatus*, *Rheum*, and *Rumex*. After absorption from the intestine, calcium oxalates precipitate in either vessel lumens or walls or within renal tubules, where they cause obstruction and epithelial cell necrosis. Illness in oxalate poisoning occurs not only because of renal disease but also because of neuromuscular dysfunction, the result of the hypocalcemia produced by chelation of serum calcium by oxalates. An oxalate-induced nephrosis has been described in Tibetan spaniels with an inherited hyperoxaluria. A chronic oxalate nephrosis in ragdoll cats of unknown inheritance and etiology is also reported.

Chemicals

Antifreeze. See the section on Kidney and Lower Urinary Tract, Disorders of Dogs, Ethylene Glycol Intoxication for a discussion of antifreeze as a nephrotoxin.

Vitamins and Minerals

Vitamin D. Vitamin D given as multiple excessive doses (vitamin D intoxication [vitamin D nephropathy]) or by accidental ingestion of calciferol-containing rodenticides can cause nephrosis in dogs and cats. In livestock, chronic ingestion of plants, such as *Cestrum diurnum* in the southern United States or *Solanum* sp. or *Trisetum* sp. in other countries, each of which contains a chemical with vitamin D–like biologic activity, can also cause nephrosis. Ingestion of excessive amounts of vitamin D can induce hypercalcemia. Hypercalcemia results in decreased cAMP formation, which impairs sodium resorption and interferes with ADH receptors. In addition, if the hypercalcemia persists, progressive mineralization of tubular and GBMs occurs (see Fig. 11-25). Development of lesions depends on the length of time between exposure to rodenticides and death or the duration of continued exposure to vitamin D. In acute cases, the kidneys have a smooth capsular surface. Microscopically, tubular epithelium is necrotic and atrophic with a few calcified deposits in the tubules scattered randomly throughout the cortex. In more chronic cases, the surface of the kidney is finely granular as a result of fibrosis. White, chalky deposits can be seen within the cortex. Interstitial fibrosis, tubular dilation, glomerular atrophy, and extensive calcification of tubular basement membranes are seen microscopically.

Interstitial Calcification (Hypercalcemic Nephropathy). Hypercalcemia from a variety of causes results in inactivation of adenyl cyclase with decreased AMP so that sodium transport is impaired in the ascending limb of the loop of Henle, distal tubule, and collecting ducts. Hypercalcemia interferes with ADH receptors in the collecting ducts, resulting in renal diabetes insipidus. Mineralization of the basement membrane and epithelium initially in the outer zone of the medulla and then involving the interstitium, vessels, and glomeruli is seen when hypercalcemia persists. The leading cause of hypercalcemia in dogs and cats is hypercalcemia of malignancy, a paraneoplastic syndrome. PTH-related peptide (PTHrp), a peptide that resembles PTH, results in bone resorption. It is produced most commonly by lymphomas or carcinomas of the apocrine glands of the anal sac. In addition, excess vitamin D either from rodenticides or excess dietary sources (toxic plants) can result in a similar syndrome. Less common causes of hypercalcemia include primary hyperparathyroidism and secondary renal hyperparathyroidism.

Bacterial Toxins. Bacterial toxins, such as the epsilon exotoxin, produced after marked enteric proliferation by *Clostridium perfringens* type D in small ruminants, can result in grossly recognizable bilateral renal lesions termed *pulpy kidney* (Fig. 11-42, *A*). The pulpy texture of the kidney is due to acute tubular epithelial degeneration and/or necrosis and interstitial edema and hemorrhage (Fig. 11-42, *B*). Epsilon toxin binds to receptors on distal renal tubular epithelium causing this degeneration. Autolysis can produce similar changes, and this finding should be interpreted with caution, especially with a long post-mortem interval.

Food and Pet Food Contaminants. See the section on Kidney and Lower Urinary Tract, Disorders of Dogs, Toxic Tubulointerstitial Nephritis, Melamine and Cyanuric Acid for a discussion of toxic food and pet food contaminants.

Diseases of the Renal Pelvis

Hydronephrosis. Hydronephrosis refers to dilation of the renal pelvis and accompanying renal atrophy. The cause is partial or complete obstruction of urine outflow causing a progressive increase in pelvic pressure. Obstruction leading to hydronephrosis can be caused by congenital malformations of the ureter, vesicoureteral junction, or urethra or from congenitally malpositioned kidneys with secondary kinking of the ureter. The more common causes of hydronephrosis are as follows:

- Accidental ligation of the ureter
- Ureteral or urethral blockage due to urinary tract calculi (see the section on Lower Urinary Tract)
- Chronic inflammation
- Neoplasia of the ureter, bladder, and urethra
- Neurogenic functional disorders

Hydronephrosis occurs in all domestic animals. Depending on the location of the obstruction, hydronephrosis can be unilateral (ureteral) or bilateral (ureter, bladder trigone, or the urethra).

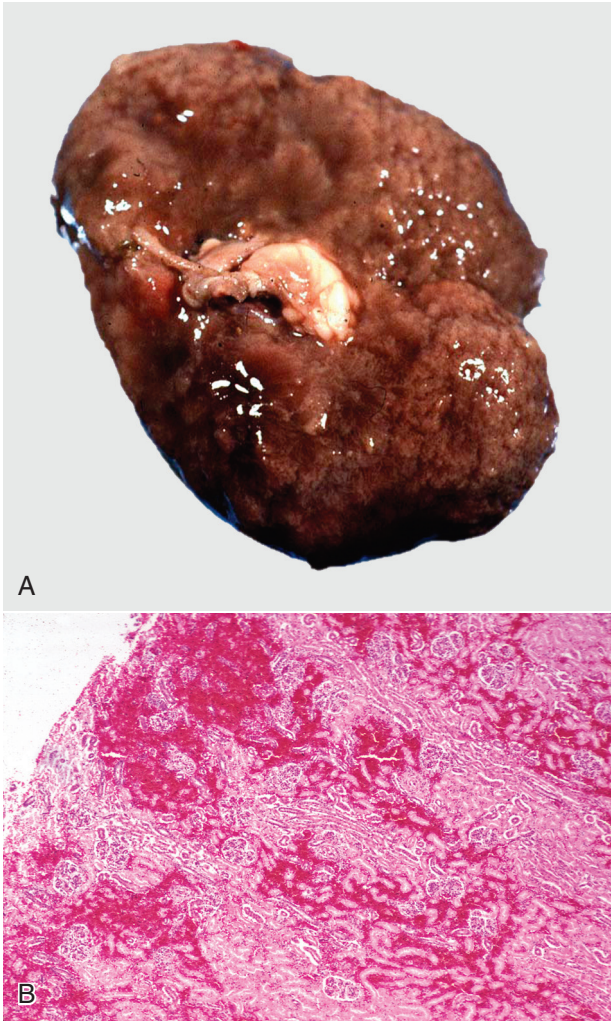


Figure 11-42 Pulpy Kidney Disease, *Clostridium perfringens* Type D Toxin, Kidney, Lamb. A, The epsilon exotoxin from an enteric overgrowth of *Clostridium perfringens* type D causes soft, swollen, and pale kidneys, often with hemorrhage, and are termed pulpy kidneys. **B,** The soft pulpy nature of the kidney is the result of acute tubular epithelial cell degeneration and/or necrosis, interstitial edema, and hemorrhage. H&E stain. (**A** courtesy Dr. J. King, College of Veterinary Medicine, Cornell University. **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

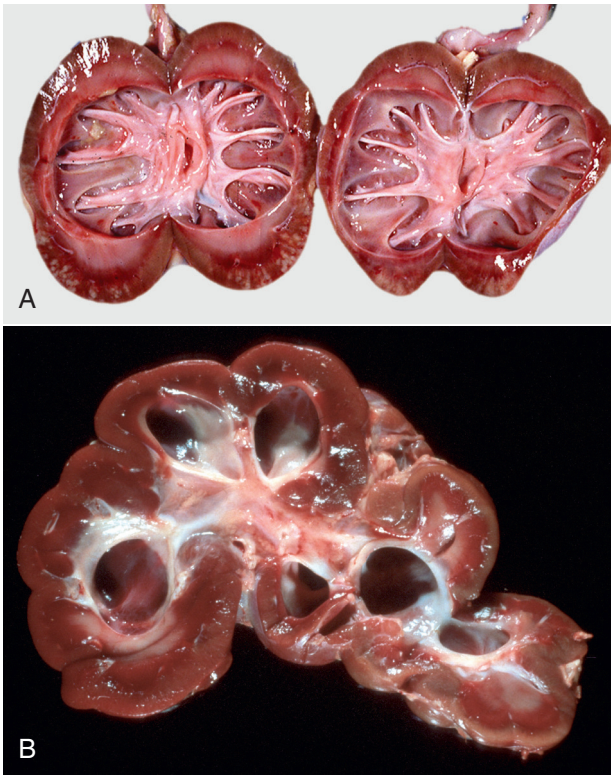


Figure 11-43 Hydronephrosis, Kidney, Dorsal Section. A, Sheep. The pelvis of each kidney is markedly dilated. **B,** Cow. Bovine kidneys are lobulated, and each lobule has its own renal papilla surrounded by a calyx, an extension of the pelvis. Thus in early hydronephrosis, each of these calyces is distended, and these distended calyces should not be confused with the cysts of a cystic or polycystic kidney. (**A** courtesy Dr. J. King, College of Veterinary Medicine, Cornell University. **B** courtesy College of Veterinary Medicine, University of Illinois.)

Unilateral hydronephrosis is caused by obstruction of a ureter anywhere throughout its length or at its entrance into the urinary bladder. Bilateral hydronephrosis can be caused by urethral obstruction, bilateral ureteral obstruction, or extensive urinary bladder lesions centered on the trigone. When hydronephrosis is unilateral, pelvic enlargement of the kidney can become extensive, even cystic, before the lesion is recognized clinically. If the obstructive process causes partial or intermittent blockage, bilateral hydronephrosis can become notable because of continual urine production and pooling of urine in the expanding pelvis. When obstruction is complete and bilateral, death as a result of uremia occurs before pelvic enlargement becomes extensive.

When the increase in intrapelvic pressure is substantial and sustained, the following occur:

- Intratubular pressure is increased resulting in microscopic renal tubular dilation.
- Glomeruli remain functional, and even with complete obstruction, glomerular filtration does not stop completely and soon overwhelms tubular reabsorption pathways.
- Much of the glomerular filtrate diffuses into the interstitium, where it is initially removed via lymphatic vessels and veins.
- As intrapelvic pressure increases, the interstitial vessels collapse and renal blood flow is reduced, resulting in hypoxia, tubular atrophy, and, if the pressure increase is continued, interstitial fibrosis.
- The glomeruli have a relatively normal morphologic appearance for a prolonged period, but they eventually become atrophic and sclerotic.

Early changes of hydronephrosis include dilation of the pelvis and calyces and blunting of the renal crest and papillae (Fig. 11-43). When pelvic dilation is progressive, the kidney silhouette is enlarged and rounder than normal, and the cortex and medulla are progressively thinned (Fig. 11-44). Interstitial vascular obstruction from compression produces an expanding front of medullary and later cortical ischemia and necrosis. Continued pelvic dilation causes loss of tubules by degeneration and atrophy, followed by condensation of interstitial connective tissue and fibrosis of the renal parenchyma. In its most advanced form, the hydronephrotic kidney is a thin-walled (2- to 3-mm), fluid-filled sac. This sac is lined by flattened transitional epithelium, which is spared during lesion development. Occasionally, a severely hydronephrotic kidney becomes contaminated by bacteria and the thin-walled sac becomes filled with pus

Figure 11-44 Chronic Hydronephrosis, Kidney, Dorsal Section, Cat. Advanced hydronephrosis is characterized by loss of medullary tissue and atrophy or even loss of the entire cortex in response to elevated pelvic fluid pressure. Note that this case was so severe that only the renal capsule, which contains clear yellow fluid, remains. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

instead of urine. This lesion, referred to as *pyonephrosis*, is likely the result of blood-borne bacteria lodging in a hydronephrotic kidney.

Pyelonephritis. Bacterial infection of the pelvis with extension into the renal tubules causing concomitant tubulointerstitial inflammation is referred to as *pyelonephritis*. Because of differences in pathogenesis, lesion distribution, and microscopic appearance, pyelonephritis is considered a form of tubulointerstitial nephritis.

Although pyelitis refers to inflammation of the renal pelvis, pyelonephritis is inflammation of both the renal pelvis and the renal parenchyma and is an excellent example of suppurative tubulointerstitial disease. The condition usually originates as an extension of a bacterial infection arising in the lower urinary tract that ascends the ureters to the kidneys and establishes an infection in the pelvis and inner medulla (Fig. 11-45). Therefore anything that predisposes an animal to lower urinary tract infection, such as recent or frequent catheterization, uroliths, or urine stagnation, can potentially result in pyelonephritis. Rarely, pyelonephritis can result from descending bacterial infections, wherein bacterial infection of the kidneys occurs via the hematogenous route (i.e., embolic nephritis). In human pathology, the term *pyelonephritis* is used to include both ascending and descending infections. Ascending infection, however, is by far the most common cause of pyelonephritis in animals.

The pathogenesis of ascending pyelonephritis depends on the abnormal reflux of bacteria-contaminated urine from the lower tract to the renal pelvis and collecting ducts (vesicoureteral reflux). Normally, little vesicoureteral reflux occurs during micturition. Vesicoureteral reflux occurs more readily when pressure is increased within the urinary bladder, as with urethral obstruction. This mechanism has been postulated for end-stage pyelonephritis with mild dysplasia seen in young boxer dogs in Norway. Bacterial infection of the lower urinary tract can enhance vesicoureteral reflux by several other mechanisms as follows:

- When the bladder wall is inflamed (cystitis), the normal competency of the vesicoureteral valve can be compromised because of mucosal thickening due to inflammatory cells and edema. This outcome increases the opportunity for urine to reflux.
- Endotoxin, liberated from Gram-negative bacteria infecting the ureter and bladder, can inhibit normal ureteral peristalsis, increasing reflux.

The urinary tract has a number of protective features in place to help prevent bacterial colonization, including the following:

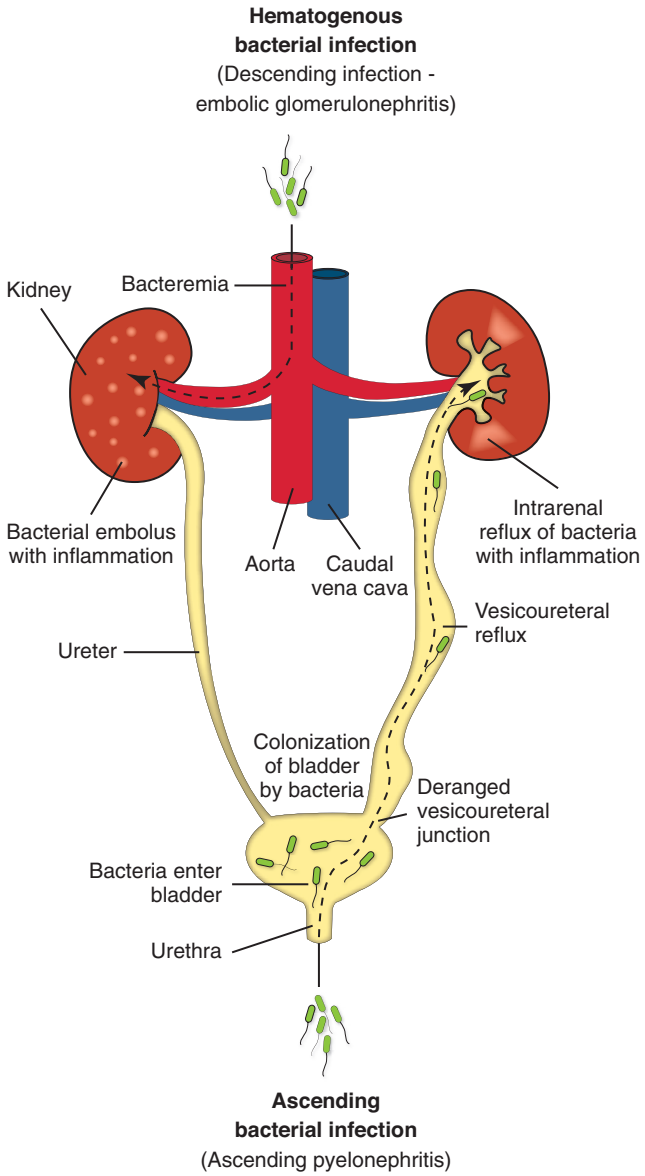


Figure 11-45 Descending (Hematogenous) and Ascending Bacterial Infections of the Kidney. Hematogenous (descending) infections of the kidney can result from bacteremia. Common microbes that cause such infections include *Escherichia coli* and *Staphylococcus* spp. The outcome is bacterial emboli in the renal cortex (see Fig. 11-35). Ascending infections result from a combination of urinary bladder infection and vesicoureteral reflux leading to pyelitis and concurrent intrarenal reflux leading to pyelonephritis (see Figs. 11-46 and 11-47). (Courtesy Drs. M.A. Breshears and A.W. Confer, Center for Veterinary Health Sciences, Oklahoma State University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

- Mucoproteins on the surface urothelial mucosal lining that prohibit bacterial adherence
- Progressive desquamation of superficial urothelial cells to minimize surface colonization
- Goblet cell metaplasia with enhanced mucus production
- Phagocytosis by superficial mucosal urothelial cells
- Bacteria-specific mucosal IgA production can block adhesion and colonization by bacteria

Bacteria that colonize the renal pelvis can readily infect the inner medulla. The medulla is highly susceptible to bacterial infection because of the following:

- A poor blood supply
- High interstitial osmolality and/or osmolarity that inhibits neutrophil function
- Large ammonia concentration that inhibits complement activation

Thus bacteria can infect and ascend collecting ducts, cause tubular epithelial necrosis and hemorrhage, and incite a neutrophilic inflammatory response. Bacterial infection can progressively ascend within tubules and the interstitium until the inflammatory lesions extend from pelvis to capsule. Recurrent or progressive infections can lead to chronic inflammation and scarring.

Because most occurrences of pyelonephritis are ascending infections and because females are more susceptible to lower urinary tract infections, pyelonephritis occurs more frequently in females. *Escherichia coli*, especially uropathogenic strains that produce virulence factors such as α-hemolysin, adhesions, and P fimbria, is one of the most common causes of lower urinary tract disease and pyelonephritis in all domestic animal species. *Proteus* sp., *Klebsiella* sp., *Staphylococcus* sp., *Streptococcus* sp., and *Pseudomonas aeruginosa* are also common causes of lower urinary tract infection and pyelonephritis in all species. *Corynebacterium renale*, *Trueperella pyogenes*, and *Actinobaculum* (*Eubacterium*) *suis* are specifically pathogenic for the lower urinary tract of cattle and pigs, respectively, and are common causes of pyelonephritis. Granulomatous and necrotizing pyelonephritis associated with *Aspergillus* sp. or *Paecilomyces* sp. can occur in rare instances.

A gross diagnosis of pyelonephritis is accomplished by recognizing the existence of pelvic inflammation with extension into the renal parenchyma (Fig. 11-46, A). Pyelonephritis can be unilateral, but it is often bilateral and most severe at the renal poles. The pelvic and ureteral mucous membranes can be acutely inflamed, thickened, reddened, roughened, or granular and coated with a thin exudate. The pelvis and ureters can be markedly dilated and have purulent exudate in the lumina (Fig. 11-46, B). The medullary crest (papilla) is often ulcerated and necrotic. Renal involvement is notable by irregular, radially oriented, red or gray streaks involving the medulla extending toward and often reaching the renal surface. Occasionally, inflammation extends through the surface of the kidneys to produce patchy areas of subcapsular inflammation.

Microscopically, the most severe acute lesions of pyelonephritis are in the inner medulla. The transitional epithelium is usually focally or diffusely necrotic and sloughed. Necrotic debris, fibrin, neutrophils, and bacterial colonies can be adherent to the denuded surface. Medullary tubules are notably dilated, and their lumina contain neutrophils and bacterial colonies. Focally the tubular epithelium is necrotic. An intense neutrophilic infiltrate is present in the renal interstitium, and it can extend into tubules. Lesions can be accompanied by interstitial hemorrhages and edema (Fig. 11-46, C). If obstruction of vasa recta has occurred, coagulative necrosis of the inner medulla (papillary necrosis) can be severe. Similar tubular and interstitial lesions, although less severe, extend radially into the cortical tubules and interstitium. When the lesions become

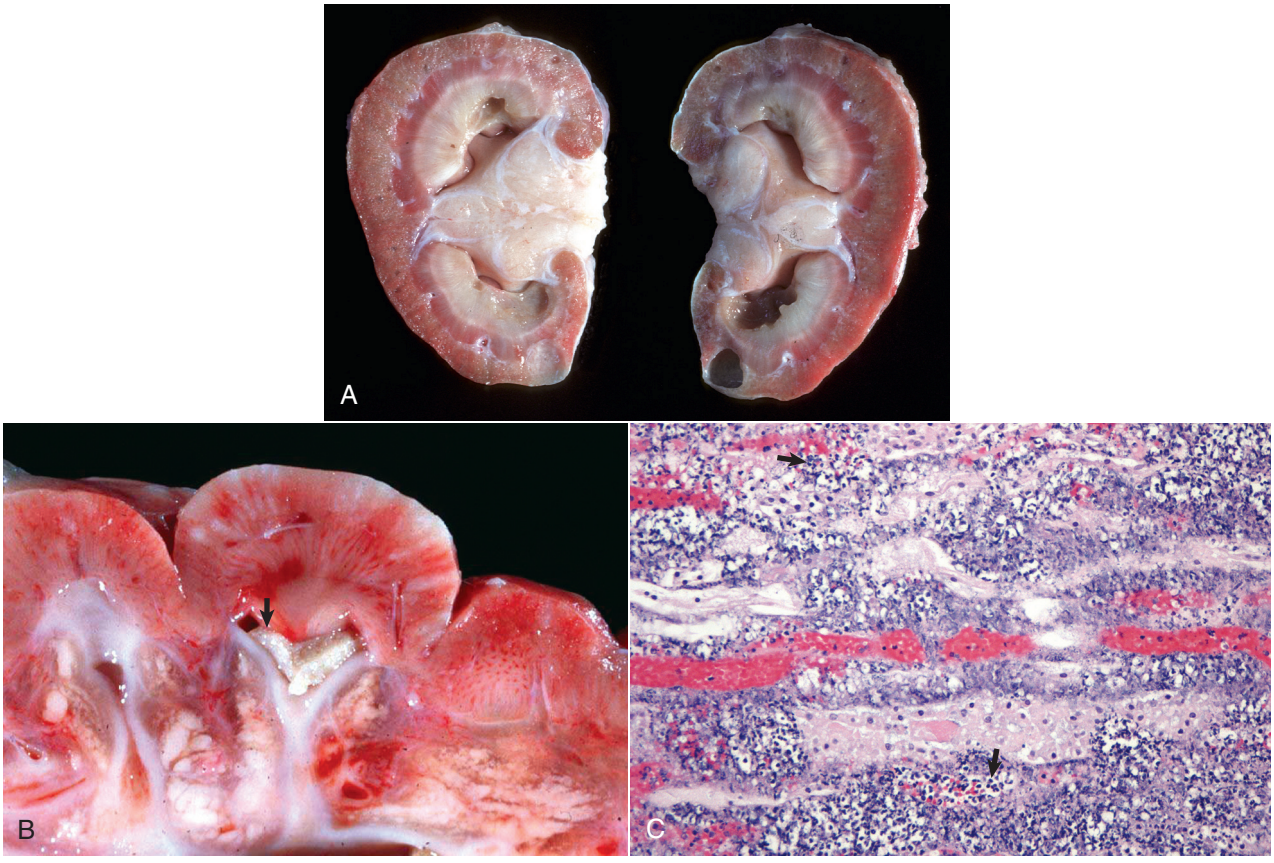


Figure 11-46 Pyelonephritis, Kidney. A, Dorsal section, dog. Extensive pelvic inflammation has destroyed areas *(gray-white)* of the inner medulla and extends focally into the outer medulla. **B,** Dorsal section, cow. Renal calyces in the cow contain suppurative exudate *(arrow)*. **C,** Dog. There is both intratubular and interstitial inflammation with tubular necrosis, characterized by infiltrates of principally neutrophils *(arrows)*. H&E stain. (**A** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **B** courtesy Dr. K. Read, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **C** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

subacute, the severity of the neutrophilic infiltrates diminishes, and lymphocytes, plasma cells, and monocytes infiltrate the interstitium. Chronic lesions have severe fibrosis. If active bacterial infection persists or is untreated, an intense infiltrate of all inflammatory cell types interspersed with tubular necrosis and fibrosis can be seen. All stages of disease progression can occur in a single kidney.

The renal lesions of chronic pyelonephritis, in which an active bacterial infection exists, include most of the elements of acute inflammation described previously and extensive necrosis of the medulla, patchy fibrosis in the outer medulla and cortex, and variable amounts of pelvic inflammatory exudates. Chronic pyelonephritis often produces a grossly visible deformity of the renal parenchyma because of extensive interstitial inflammation and scarring (Fig. 11-47). Fibrosis secondary to the tubulointerstitial inflammation of pyelonephritis follows the pattern of the acute disease (targeting the renal poles) and results in irregularly distributed, patchy scarring that is seen as deeply depressed regions on the renal capsular surface and linear areas extending through both the cortex and the medulla to the pelvis. Such lesions often resemble chronic polar infarcts.

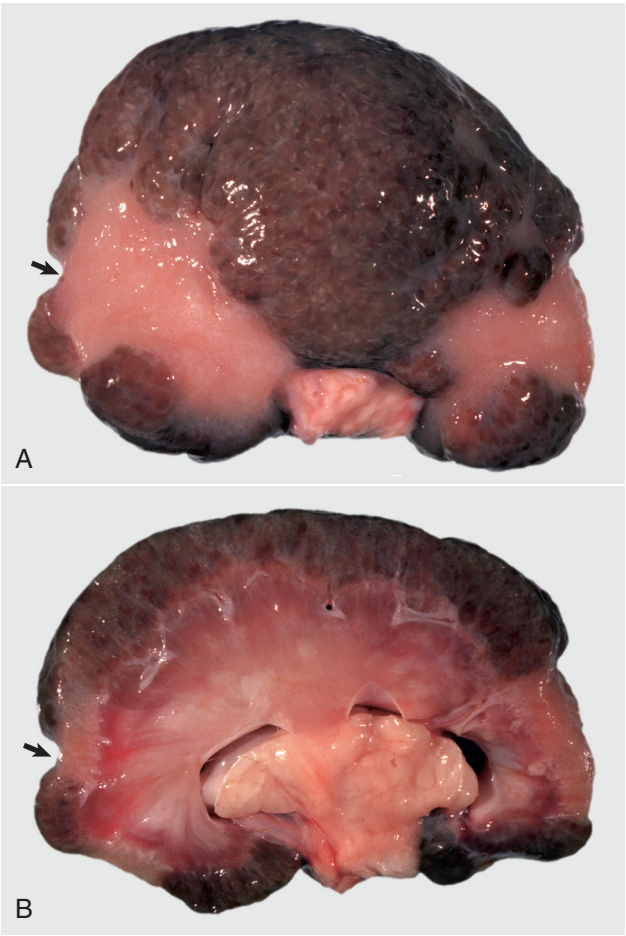


Figure 11-47 Chronic Pyelonephritis, Kidney, Dog. A, Note the two large polar scars visible as large indentations on the capsular surface *(arrow)*. The fine gray spots are regions of chronic inflammatory infiltrates and fibrosis. **B,** Dorsal section. The cortical scars are localized to the renal poles *(arrow)*, but there is a finely stippled pattern of nodularity and fibrosis in the remaining kidney. This polar pattern of scarring suggests previous bouts of pyelonephritis. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

Papillary (Medullary Crest) Necrosis. Necrosis of the renal papillae, or their counterpart, the medullary crest, is a response of the inner medulla to ischemia. Papillary necrosis can be a primary or secondary lesion. When papillary necrosis occurs as a primary lesion, it can, in some cases, be severe enough to cause clinical disease. This scenario usually occurs in animals treated with NSAIDs, which can result in a clinical disease analogous to analgesic nephropathy in human beings. Primary papillary necrosis occurs quite frequently in horses treated for prolonged periods with phenylbutazone or flunixin meglumine. Additionally in horses, simultaneous treatment with two NSAIDs increases the risk of clinical disease. It is important in dogs and cats because of accidental ingestion of or treatment with ibuprofen, aspirin, or acetaminophen at excessive dosages. Drugs associated with papillary necrosis have been referred to as *papillotoxins*. Medullary interstitial cells are the primary targets of papillotoxins. These cells synthesize prostaglandins, antihypertensive factors, and the glycosaminoglycan matrix of the medullary interstitium. Interstitial cell damage decreases prostaglandin synthesis, which reduces normal blood flow and causes ischemia, increases tubular transport, and modifies the interstitial matrix; the net effect is degenerative changes in tubular epithelial cells in the inner medulla. In addition to its inhibition of prostaglandin biosynthesis, acetaminophen also causes direct oxidative damage to medullary tubular epithelium after covalent binding to the cells, further enhancing necrosis of the renal papillae.

Secondary papillary necrosis results from the following:

- Reduced blood flow in vasa recta
- Glomerular lesions restricting blood flow—amyloid, hyalinization
- Compression of vasa recta—within the medulla
- Interstitial fibrosis—chiefly in the outer medulla, secondary to ischemia (see later discussion)
- Interstitial renal medullary amyloidosis (cats)
- Pyelitis—ascending tubular and interstitial inflammation, edema, and fibrosis
- Compression of renal papilla due to increased intrapelvic pressure secondary to
  - Pelvic calculi
  - Lower urinary tract obstruction
  - Vesicoureteral reflux

Decreased perfusion and compression cause papillary necrosis because the inner medulla is the least well perfused of any zone of the kidneys. Most of the medullary blood supply comes from the cortex after passing through the glomeruli and entering the vasa recta. Because of limited blood flow and high metabolic medullary cellular demand, any lesion or disease process that further reduces medullary blood flow can cause ischemic necrosis (infarction) of the papillae. In addition, the high metabolic demand for cell transport and the maintenance of an ion gradient to enhance urinary concentration makes this area particularly vulnerable. This is most evident after ischemic tubular damage where swollen endothelial and tubular epithelial cells, in conjunction with neutrophil adhesion in small vessels, upset the balance of oxygenation and energy demand by the medullary tubular cells. Medullary blood flow is ultimately balanced through concentrations of vasodilators, such as prostaglandin, nitric oxide, and adenosine, and vasoconstrictors, such as endothelin and angiotensin II.

Typically, acute lesions are irregular, discolored areas of necrotic inner medulla sharply delineated from the surviving medullary tissue (Fig. 11-48). The affected tissue, which initially undergoes coagulation necrosis, is yellow-gray, green, or pink. With time, the necrotic tissue sloughs, resulting in a detached, friable, and discolored tissue fragment in the pelvis. The remaining inner medulla is usually

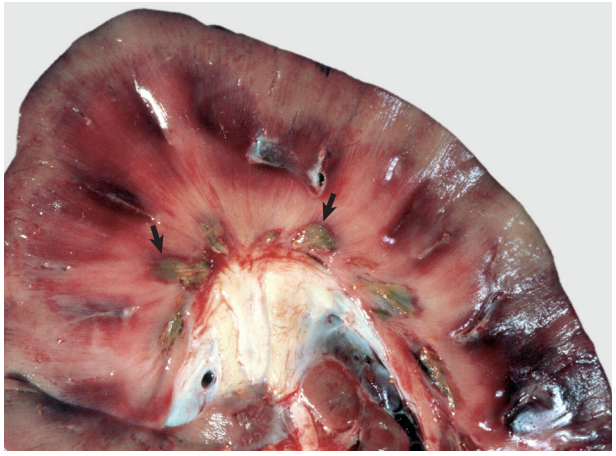


Figure 11-48 Papillary (Medullary Crest) Necrosis, Chronic Nonsteroidal Antiinflammatory Drug Treatment, Kidney, Dorsal Section, Horse. Acute coagulation necrosis of the medullary crest and inner medulla *(green areas [arrows])*. There is also hemorrhage of the outer medulla. The term *papillary necrosis* is retained for all animals, although only the pig and cow have distinct renal papillae. In other animals, these have fused to form the medullary crest. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

attenuated and on cross section is narrowed. Overlying cortex can be somewhat shrunken because of atrophy of some of the nephrons caused by blockage of their tubules in the affected medulla. Small pieces of sloughed necrotic medullary tissue pass inconsequentially into the ureter. However, large pieces can obstruct the ureter, causing hydronephrosis, or form a nidus for precipitation of minerals, resulting in the formation of pelvic or ureteral calculi.

Diseases of the Interstitium

Granulomatous Nephritis. Granulomatous nephritis is an interstitial disease that often accompanies chronic systemic diseases that are characterized by multiple granulomas in various organs. In domestic animals, granulomatous nephritis can be caused by a variety of granuloma-inducing infectious microbes. These can include fungi such as *Aspergillus* sp., *Phycomycetes*, or *Histoplasma capsulatum* (E-Figs. 11-5 and 11-6); algae such as *Prototheca* sp.; parasites (*Toxocara* sp. and *Angiostrongylus vasorum* larvae/eggs); protozoa such as *Encephalitozoon cuniculi*; bacteria such as *Mycobacterium bovis*; and viruses such as feline coronavirus (see Disorders of Cats) and porcine circovirus. Common to each are small, gray-white to tan, granulomatous foci (2 to 5 mm in diameter) or larger nodules (up to 10 cm in diameter) scattered randomly throughout the kidneys, especially the cortex. Foci are often granular and can have calcified, caseous centers. Microscopically, lesions are characterized by central foci of necrosis with variable numbers of neutrophils and are surrounded by epithelioid macrophages, variable degrees of mineral deposits, and possibly giant cells.

In cattle, granulomatous nephritis is part of the multisystemic granulomatous disease caused by hairy vetch (*Vicia villosa*) toxicosis (see the section on Kidney and Lower Urinary Tract, Disorders of Ruminants). Lesions are characterized by multifocal to coalescing cortical granulomas (Fig. 11-49, *A*). Microscopically, infiltrates of monocytes, lymphocytes, plasma cells, eosinophils, and multinucleated giant cells are seen primarily within the interstitium of the renal cortex (Fig. 11-49, *B*).

Migratory *Toxocara canis* larvae can induce small, gray-to-white granulomas (2 to 3 mm) randomly scattered throughout the subcapsular renal cortex of dogs (Fig. 11-50, *A*). Such lesions probably are

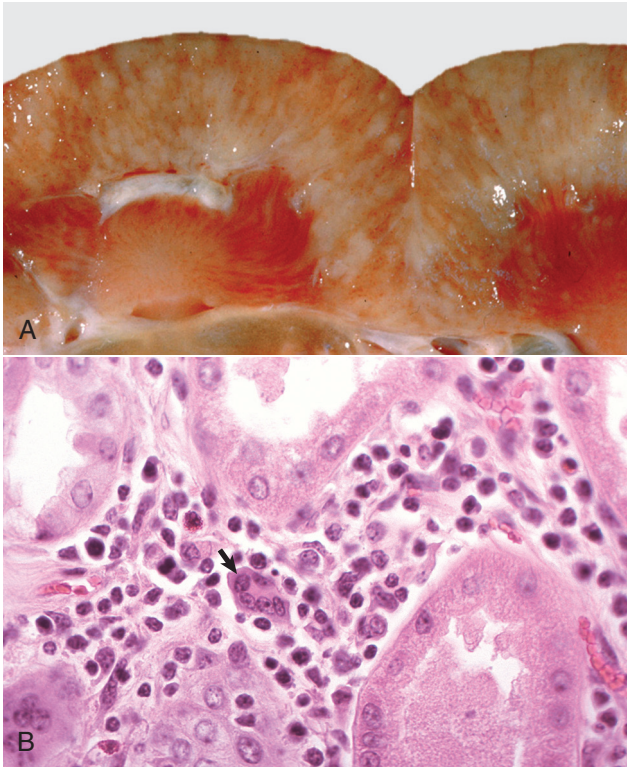
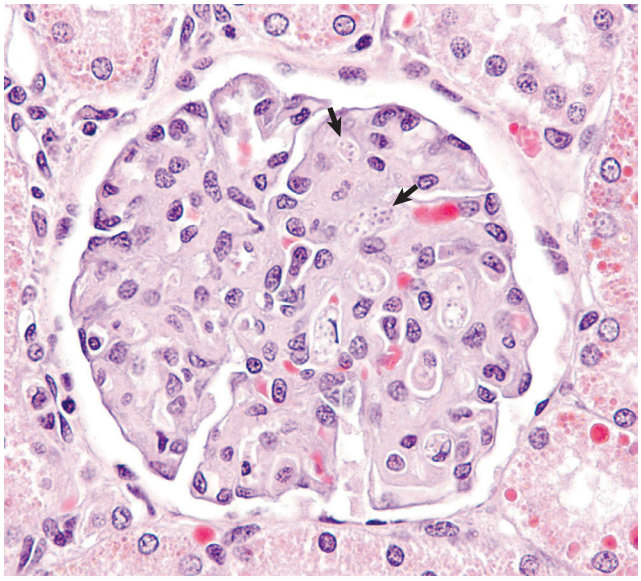


Figure 11-49 Granulomatous Nephritis, Hairy Vetch Toxicosis, Kidney, Cow. A, Cortical striations are obliterated by coalescing granulomatous foci associated with hairy vetch toxicosis. **B,** Cortex. Lesions associated with hairy vetch toxicosis are characterized by a mixed cell interstitial inflammatory infiltrate (macrophages, lymphocytes, and occasional multinucleated giant cell *[arrow]*) with renal tubular atrophy. It is specifically known as an unusual type of poisoning because of its ability to induce granulomatous inflammation in addition to the necrosis. The kidney is not the primary organ affected. H&E stain. (**A** courtesy Dr. J. King, College of Veterinary Medicine, Cornell University; and Dr. J. Edwards, College of Veterinary Medicine, Texas A&M University. **B** courtesy Dr. R. Panciera, Center for Veterinary Health Sciences, Oklahoma State University.)

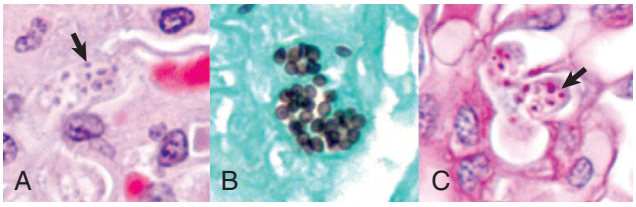
due to cell-mediated foreign body immune response to the migrating larvae and are composed of aggregates of macrophages, lymphocytes, and eosinophils surrounded by fibroblasts within concentrically arranged fibrous connective tissue (Fig. 11-50, *B*). In recently acquired lesions, nematode larvae can often be seen in the center of these lesions (see Fig. 11-50, *B*). Following death, the larvae become fragmented, and the debris is either phagocytosed and eliminated or, less commonly, retained with a resultant granulomatous response. Lesions heal by fibrosis, leaving a few finely pitted (contracted) foci on the capsular surface.

Xanthogranulomas. Cats with inherited hyperlipoproteinemia have xanthogranulomas in various organs, including the kidneys. Similar renal xanthogranulomas can occur in dogs with hypothyroidism and severe atherosclerosis. These lesions are characterized by foamy, lipid-laden macrophages, lymphocytes, plasma cells, and fibrosis interspersed with cleftlike spaces typical of cholesterol deposits (cholesterol clefts).

Renal Interstitial Amyloidosis. Although glomeruli are the most common renal sites for deposition of amyloid in most domestic animal species, deposition can occur in the medullary interstitium (see the section on Amyloidosis). Renal amyloidosis commonly occurs in association with other diseases, particularly chronic inflammatory or neoplastic diseases. However, idiopathic renal



E-Figure 11-5 Glomerulus, Histoplasmosis, Dog. The mesangial matrix within the glomerulus functions as part of the monocyte-macrophage system. Therefore it is often a target for microbes that use this system to enter and colonize cells, tissues, and organs to complete their life cycles. The small (2 to 5 μm in diameter) intracellular blue dots are the organism, *Histoplasma capsulatum (arrows)*. H&E stain. (Courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)



E-Figure 11-6 Glomerulus, Histoplasmosis, Dog. A, Higher magnification of E-Fig. 11-5. *Histoplasma capsulatum (arrow)*. H&E stain. **B,** *Histoplasma capsulatum* stains black with a sliver stain, and this stain often better demonstrates the morphology and size of the organism. Grocott-Gomori's methenamine silver stain (GMS). **C,** The organism *(arrow)* can also be demonstrated with other histochemical stains such as the periodic acid–Schiff (PAS) stain. (Courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

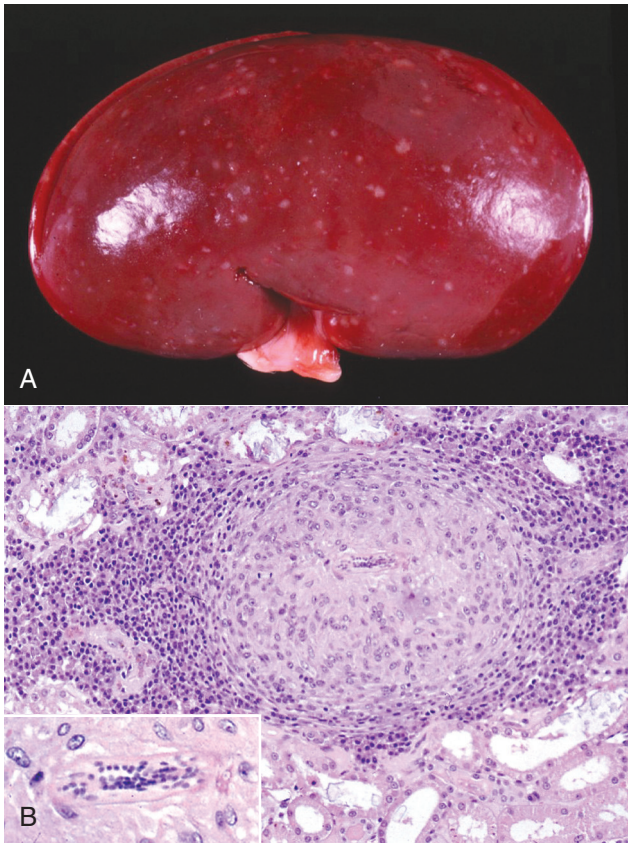


Figure 11-50 Granulomatous Nephritis, Kidney, Cortex, Dog. A, Multiple subcapsular, cortical, tan, raised granulomas caused by migrating ascarid larvae. **B,** A mature granuloma composed of a central ascarid larva surrounded by epithelioid macrophages and concentrically arranged fibrous connective tissue and inflammatory cells. H&E stain. *Inset,* Ascarid larva. (Courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

amyloidosis (i.e., amyloidosis in which an associated disease process is not recognized) is also described in dogs and cats. The underlying pathogenic mechanisms of idiopathic renal amyloidosis are not known. Medullary amyloidosis is usually asymptomatic unless it obstructs blood flow and causes papillary necrosis. A hereditary predisposition for the development of reactive amyloidosis (AA) has been found in Abyssinian cats, and a familial tendency is suspected in Siamese cats. Shar-Pei dogs are one of the most commonly affected canine breeds to have systemic AA amyloidosis, and amyloid often accumulates in the renal medullary interstitium. Shar-Pei amyloidosis is thought to be autosomal recessive in its familial inheritance. Medullary amyloidosis may predispose the dog to various aspects of end-stage renal disease, including interstitial fibrosis, lymphoplasmacytic infiltration, tubular atrophy, tubular dilation, mineralization, deposition of oxalate crystals, glomerular atrophy, and glomerulosclerosis.

Neoplasia. The prevalence of primary renal neoplasms in domestic animals is less than 1% of the total neoplasms reported. They are usually unilateral and can be epithelial, mesenchymal, or embryonal in origin. A study of canine cases revealed carcinomas (49/82), sarcomas (28/82), and nephroblastomas (5/82) with a 4% bilateral involvement. Median survival for carcinomas was 16 months, for sarcomas was 9 months, and for nephroblastoma 6 months. Primary renal tumors are highly malignant and metastatic disease is common (77%). Inappropriate polycythemia is a paraneoplastic condition seen in association with excess erythropoietin production by renal carcinomas and sarcomas.

Epithelial Tumors

Renal Adenomas. Renal adenomas are rare, benign, epithelial neoplasms composed of proliferations of renal cortical epithelial cells, most often reported in dogs, cats, and horses. They are incidental findings at autopsy (syn: necropsy) and are usually small (1 to 3 cm), white-to-yellow, solitary, well-circumscribed, nonencapsulated masses in the cortex. Microscopically, adenomas are composed of solid sheets, tubules, or papillary proliferations of cuboidal epithelial cells of uniform size and have granular eosinophilic cytoplasm and small, round to oval nuclei. Mitotic figures, necrosis, and fibrosis are rare. These incidental tumors are clinically asymptomatic.

Oncocytomas. Oncocytomas are rare benign epithelial tumors that can occur in a variety of tissues. Grossly, renal oncocytomas are tan, homogeneous, well-encapsulated masses. Histologically, oncocytomas are composed of large eosinophilic, granular, round cells with condensed round nuclei. Ultrastructurally, they are characterized by numerous prominent cytoplasmic mitochondria. Their origin in the kidney is speculated to be from the intercalated cells of the collecting ducts. These tumors are clinically asymptomatic.

Renal Carcinomas. Renal carcinomas are the most common primary renal neoplasms and occur most frequently in older dogs. The specific causes of renal adenocarcinomas in human beings are well determined compared with those in animal species, but several mechanisms have been proven in natural animal disease or experimental models, including the following:

- Viruses: Ranid herpesvirus 1 adenocarcinoma (Lucke's tumor) in the kidney of frogs and avian erythroblastosis virus (strain ES4), an oncovirus, induce renal adenocarcinomas in chickens.
- Chemical carcinogens: Several known carcinogens, particularly the nitrosamines, can be causative agents and typically exert their neoplastic influence by direct DNA damage or inhibition of DNA synthesis or repair.
- Autosomal dominant gene mutations in Eker rats: These mutations predispose these rats to bilateral renal cell carcinoma and a variety of other secondary cancers, resembling the human von Hippel-Lindau disease.

Primary renal carcinomas are usually large (up to 20 cm in diameter), spherical to oval, and firm. They often are pale yellow and contain dark areas of hemorrhage and necrosis and foci of cystic degeneration. The masses usually occupy and obliterate one pole of the kidney and grow by expansion, compressing the adjacent normal renal tissue (Fig. 11-51, *A* and *B*). Histologic types include papillary, tubular, multilocular cystic, and solid (Fig. 11-51, *C*). Solid variants can be poorly differentiated and sometimes can be subclassified as clear cell or chromophobe variants if the cytoplasm is clear or vacuolated or granular and eosinophilic, respectively. Metastasis to the lungs, lymph nodes, liver, and adrenal gland occurs frequently, with metastasis reported in 50% to 60% of canine cases.

A variant of the typical renal carcinoma has been seen in German shepherd dogs in conjunction with nodular dermatofibrosis. The lesions are hereditary (autosomal dominant) and consist of multifocal, bilateral, renal cystadenomas or cystadenocarcinomas. Grossly, these tumors resemble the carcinomas described previously, but cysts are more prominent. Neoplastic cells form solid sheets, tubules, or papillary growth patterns within a moderate fibrovascular stroma. Cells are polymorphic ranging from cuboidal and columnar to polyhedral. Clear or granular eosinophilic cytoplasm is usually more atypical and anaplastic than other renal carcinoma variants.

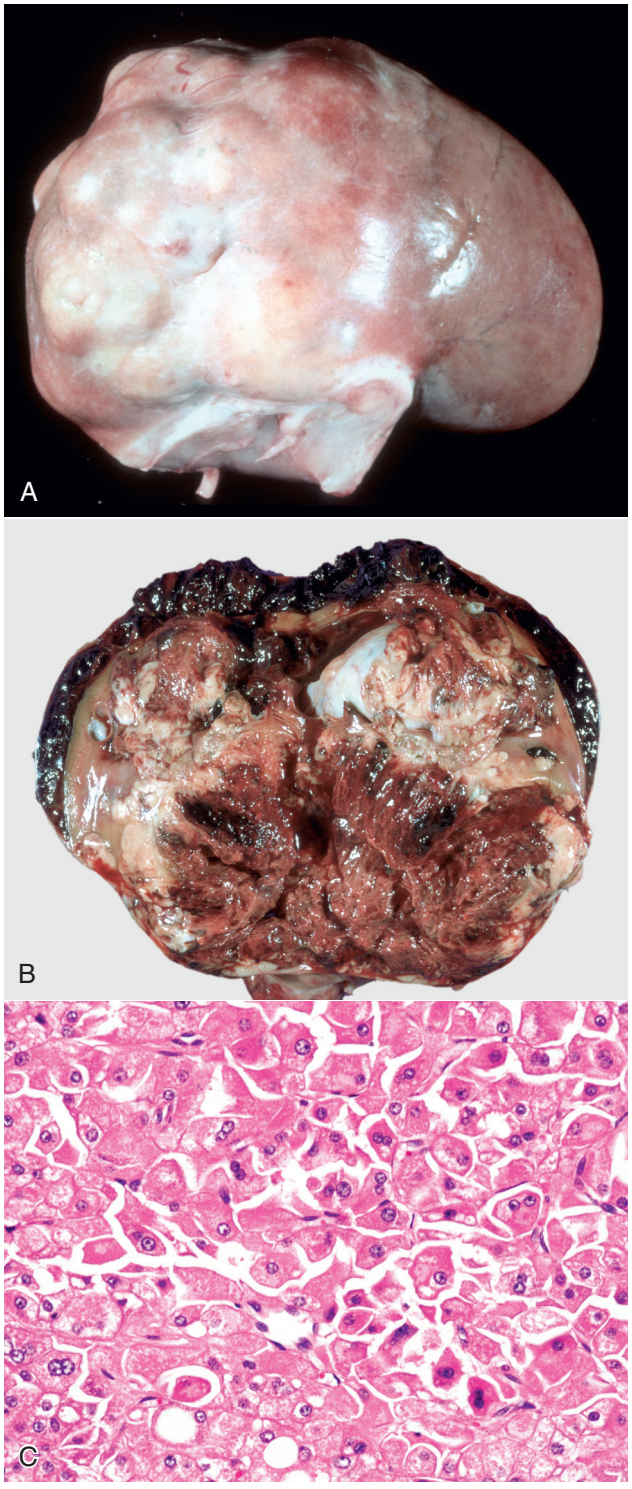


Figure 11-51 Renal Carcinoma, Kidney, Dog. A, The neoplasm is pale white with reddish areas, lobulated, and has infiltrated and replaced one pole of the kidney. **B,** Dorsal section. The normal architecture of the cranial half of the kidney has been obliterated by the tumor, which has hemorrhaged caudally into the adjacent kidney and subcapsularly. **C,** The tumor consists of anaplastic renal epithelial cells, typical of the solid, more poorly differentiated variant of renal carcinoma. H&E stain. (**A** and **B** courtesy College of Veterinary Medicine, University of Illinois. **C** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

Nuclei range from small, round, granular, and uniform to large, oval, vesicular, and pleomorphic. Mitotic figures are numerous.

Transitional Cell Papillomas and Carcinomas. Transitional cell papillomas and transitional cell carcinomas arise in the renal pelvis and lower urinary tract and, when large, can obstruct urinary outflow. Renal pelvic transitional cell carcinomas can invade into the kidney and typically carry a poor prognosis. The morphologic features of transitional cell neoplasms are discussed later with the urinary bladder neoplasms (see the section on the Lower Urinary System).

Mesenchymal Tumors. Fibromas, fibrosarcomas, hemangiomas, hemangiosarcomas, renal interstitial cell tumors, and undifferentiated sarcomas can occur in the kidneys. Primary renal sarcomas occur less frequently than primary epithelial tumors and constitute approximately 20% of the primary renal tumors of dogs and cats. Microscopically, fibromas, fibrosarcomas, hemangiomas, and hemangiosarcomas are similar to those in other organs. Undifferentiated sarcomas are often the most common mesenchymal tumor and may require immunohistochemistry to determine with surety that it is a mesenchymal tumor. Renal interstitial cell tumors usually arise at the corticomedullary junction and are similar to fibromas but contain cytoplasmic lipid droplets.

Metastatic Tumors. Carcinomas and sarcomas (metastatic tumors) arising in other organs can metastasize to the kidneys and are characteristically composed of randomly scattered multiple nodules, usually involving both kidneys (Fig. 11-52). Renal lymphoma (lymphosarcoma) occurs with some frequency in cattle and especially cats, particularly as part of generalized or multicentric lymphoma, which is secondary to retrovirus infection. These neoplastic foci appear as single or multiple homogeneous gray-white nodules (Fig. 11-52, *B* and *E*) or as diffuse lymphomatous infiltrates that cause uniform enlargement and pale discoloration of the kidney (Fig. 11-52, *C*). In cats, renal lymphoma must be differentiated histologically from the necrotizing, fibrinous, and granulomatous renal vasculitis of feline infectious peritonitis and less commonly systemic mycoses (Fig. 11-52, *E*). Microscopically, neoplastic lymphocytes form obliterative sheets of cells within the renal parenchyma, unrelated to the vasculature (Fig. 11-52, *F*). Neoplastic lymphocytes have distinct cellular borders, moderate amounts of basophilic cytoplasm, and large round vesicular nuclei with variable prominence to the nucleoli.

Tumors of Embryonal Origin. Nephroblastomas (embryonal nephroma or Wilms tumor) are the most common renal neoplasms of pigs and chickens, in which they are usually recognized as incidental findings at slaughter. They occur in cattle and dogs as well, but less frequently. These neoplasms arise from metanephric blastema and thus occur in young animals, less than 2 years old. It is speculated that neoplasms result from malignant transformation during normal nephrogenesis or from neoplastic transformation of nests of embryonic tissue that persists in the postnatal kidneys. At autopsy (syn: necropsy), nephroblastomas can be solitary or multiple masses that often reach a great size and in which recognizable renal tissue can be difficult to detect. They usually are soft to rubbery and gray with foci of hemorrhage. On a cut surface, they are often lobulated. Because nephroblastomas arise from primitive pluripotential tissue, histologic features vary but are morphologically similar to the developmental stages of embryonic kidneys. Characteristically, three components—including primitive, loose myxomatous mesenchymal tissue interspersed with primitive tubules lined by elongated, deeply staining cells and structures that resemble primitive glomeruli—are present. Nests of cells resembling the metanephric blastema can be present. Nephroblastomas also have mesenchymal components such as cartilage, bone, skeletal muscle, and adipose tissue. Clinically, these tumors can be incidental findings; however,

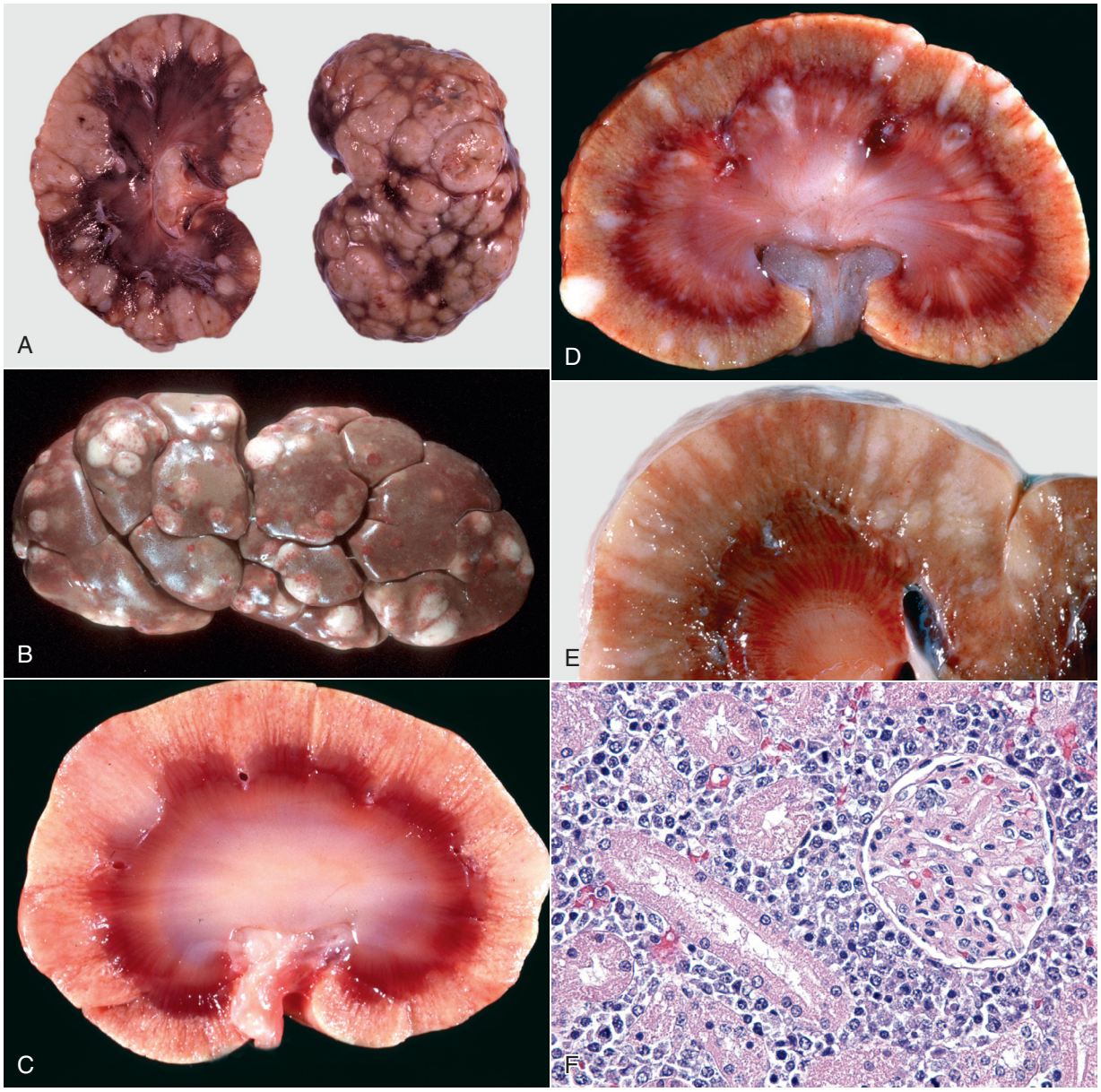


Figure 11-52 Primary and Metastatic Renal Tumors, Kidney. A, Metastatic mast cell tumor, dorsal section, dog. Multiple pale tan, raised nodules are randomly scattered throughout the renal cortex. **B,** Lymphoma (lymphosarcoma), cow. Multifocal raised pale white nodules are typical of nodular renal lymphoma. **C,** Lymphoma (lymphosarcoma), dorsal section, cat. Note the pale white areas in the cortex, which bulge from the surface. This lesion can be confused with the granulomatous vasculitis of renal feline infectious peritonitis, thus warranting histologic evaluation. **D,** Systemic cryptococcosis (*Cryptococcus neoformans*), cat. This is not a neoplasm, but the multiple pale, occasionally raised nodules can be confused with the nodular form of lymphoma **(C)**, thus requiring histologic examination. **E,** Lymphoma (lymphosarcoma), dorsal section, bovine. Multiple coalescing pale white nodules are present throughout the cortex. **F,** Lymphoma (lymphosarcoma), cow. Neoplastic lymphocytes infiltrate and distend the renal interstitium. H&E stain. (**A** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy College of Veterinary Medicine, University of Illinois. **C** courtesy Dr. K. Read, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia. **D** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee. **E** courtesy Dr. J. King, College of Veterinary Medicine, Cornell University; and Dr. J. Edwards, College of Veterinary Medicine, Texas A&M University. **F** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

in dogs and cats, greater than 50% may metastasize to lymph nodes and visceral organs. In young dogs, a unique spinal cord nephroblastoma has been described. These tumors likely arise from remnants of renal blastema trapped subdurally that grow by expansion and compress the spinal cord.

Disorders of the Lower Urinary Tract

Developmental Anomalies

Aplasia and Hypoplasia. Ureteral aplasia (agenesis) is the lack of formation of a recognizable ureter, and hypoplasia is the presence of a notably small-diameter ureter. Agenesis of the ureters is the result of failure of the ureteral bud to form and may be unilateral or bilateral. Both conditions are rare. If these defects occur alone, disruption of urinary flow from the kidney to the urinary bladder results in obstructive diseases such as hydronephrosis. If these defects occur with concurrent renal aplasia, they are clinically silent if aplasia is unilateral, and incompatible with life if aplasia is bilateral.

Ectopic Ureters. Ectopic ureters are ureters that empty into the urethra, vagina, neck of the bladder, ductus deferens, prostate, or

other secondary sex glands rather than terminating normally at the trigone of the bladder. The two possible causes are as follows:

- The ureteral bud arises too far craniad to be incorporated into the urogenital sinus.
- The differential growth of the sinus is abnormal, and the ureter fails to migrate to its usual location.

Ectopic ureters are more subject to obstruction or infection, and thus they predispose animals to pyelitis and pyelonephritis. Ectopic ureters occur most frequently in dogs, and certain breeds, especially the Siberian husky, are at greater risk. Affected animals present clinically with urinary incontinence and consequent urine dribbling.

Patent Urachus. The most common malformation of the urinary bladder is patent urachus (pervious urachus), and it is seen most frequently in foals. This lesion develops when the fetal urachus fails to close, therefore forming a direct channel between the bladder's apex and the umbilicus. As a result, affected animals dribble urine from the umbilicus. The patent urachus is susceptible to infection and abscess formation. Conversely, umbilical inflammation and abscess formation may lead to failure of the urachal remnant and the umbilical arteries and vein to involute, potentially causing a patent urachus. Rupture of the urachus causes uroperitoneum, which must be differentiated from perinatal rupture of the bladder. Occasionally, during urachal closure, the mucosa closes but closure of the bladder musculature is incomplete. When this occurs, a bladder diverticulum (outpouching) at the apex of the bladder can develop. Diverticula of the bladder may also be acquired secondary to partial obstruction of urine outflow and result from pressure changes exerted during normal contractions of the bladder. Urine stasis can occur in the diverticulum, predisposing the animal to cystitis or urinary calculi.

Hydroureter. Hydroureter refers to dilation of the ureter(s) and is most often caused by obstruction of urine outflow due to blockage of the ureter(s) by calculi, chronic inflammation, luminal or intramural neoplasia, or accidental ligation during surgery. Hydroureter can be unilateral or bilateral and is often accompanied by concurrent hydronephrosis (see the previous section on Hydronephrosis). The clinical signs of this condition are related to obstruction.

Urolithiasis (Obstructive Disease). Urolithiasis is the presence of stones or calculi (uroliths) in the urinary collecting system. Uroliths form when familial, congenital, and pathophysiologic factors occur together and cause the precipitation of excretory metabolites in urine into grossly visible stones. These concretions may form anywhere in the urinary collecting system, and although some clearly originate in the lower urinary tract or as microscopic calculi in the renal collecting tubules, the point of development of most is not known. Uroliths may be found in any portion of the lower urinary tract, from the renal pelvis to the urethra, but occur least commonly in the renal pelvis (accounting for 1% to 4% of canine uroliths). The diseases caused by uroliths are among the most important urinary tract problems of domesticated animals, especially cattle, sheep, dogs, and cats, and are of lesser importance in horses and pigs.

Mechanistically, factors that are important either in predisposing to calculus formation or in precipitating disease include the following:

- Urine concentrations of calculus precursor material sufficient to be precipitated
- Unusual metabolism of certain substances, such as uric acid in Dalmatian dogs
- Hereditary defects leading to abnormal processing of substances by the kidney, such as cystine or xanthine
- Abnormally high concentrations of substances in the diet, such as the following:
  - Silicic acid in native pastures (silica calculi)
  - Phosphorus in grain-based rations (struvite calculi)
  - Estrogen in subterranean clover (clover stones containing benzocoumarins; calcium carbonate related to isoflavones)
  - Magnesium in commercial dry cat food
  - Oxalate in oxalate-accumulating plants

Regardless of the type of calculus, factors of variable importance in calculus formation include the following:

- Urinary pH, in terms of its effect on solute excretion and precipitation (oxalates increase at acid pH; struvites and carbonates precipitate at alkaline pH)
- Reduced water intake, in relation to the degree of urine concentration and mineral supersaturation
- Bacterial infection of the lower urinary tract (struvite calculi in dogs)
- Obstruction or structural abnormalities of the lower urinary system
- Foreign bodies (suture, grass awn, catheter, or needle) or a conglomerate of bacterial colonies, exfoliated epithelium, or leukocytes, which can serve as a nidus for precipitation of mineral constituents
- Drug metabolites excreted in the urine (e.g., sulfonamides and tetracyclines)

Supersaturation of urine with the components of stone-forming salts is the essential precursor to initiation of urolith formation (nucleation). Supersaturation may be in the unstable range, in which precipitation occurs spontaneously (homogeneous nucleation), or the metastable range, in which precipitation occurs by epitaxy (one type of crystal grows on the surface of another type; heterogeneous nucleation). In some instances, uroliths may have distinct layers composed of different mineral types. These compound uroliths form when factors promoting precipitation of one mineral type are superseded by factors promoting precipitation of a different type of mineral.

Microscopically apparent crystals are much more common in urine than are grossly visible aggregates of mineral (calculi). Although equine urine is normally supersaturated with calcium carbonate, and crystalluria is normal, horses experience a low prevalence of calculi. In all species, the factors that promote or prevent crystal growth and crystal aggregation are poorly understood. Although it was formerly thought that urinary proteins such as uromodulin (Tamm-Horsfall protein), which make up 5% to 20% or more of some calculi, were initiators of crystal formation, it is now believed that uromodulin and other urinary macromolecules have a role in preventing formation of kidney stones by reducing the aggregation of calcium crystals.

Macroscopically, calculi are grossly visible aggregations of precipitated urinary solutes, principally mineral admixed with urinary proteins and proteinaceous debris. Calculi typically are hard spheres or ovoids, with a central nidus, surrounded by concentric laminae, an outer shell, and surface crystals. Many calculi contain significant quantities of "contaminants" such as calcium oxalates in "silica" calculi; few are relatively pure. Large renal pelvic calculi (nephroliths) classically have a "staghorn" appearance because they take the shape of the renal calyces in animal species that have true calyces (Fig. 11-53). These calculi predispose affected animals to pyelitis and pyelonephritis. Urinary bladder calculi can be single or multiple, variable in size (2 to 10 cm), and sometimes are composed of a fine, sandlike material, which causes cloudy urine (Fig. 11-54).

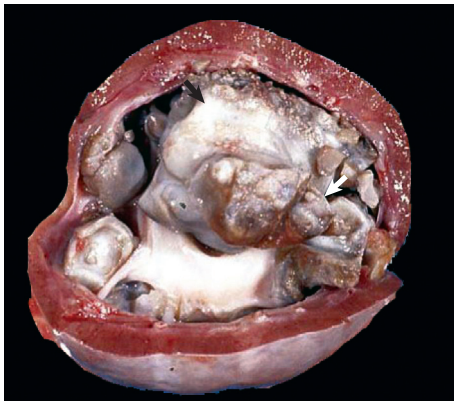


Figure 11-53 Urolithiasis, Kidney, Dorsal Section, Goat. A calculus fills and distends the renal pelvis *(arrows)* and has caused pressure atrophy of the medulla. (Courtesy Dr. M.A. Breshears, Center for Veterinary Health Sciences, Oklahoma State University.)

Figure 11-54 Urolithiasis, Urinary Bladder, Dog. Multiple smooth calculi are present in the urinary bladder. The bladder wall is diffusely thickened. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

Calculi can have smooth or rough surfaces and may be solid, soft, or friable. Depending on the composition of calculi, their color varies and may be inconsistent, even among calculi of similar composition. The calculi can be white to gray (e.g., struvite and oxalate), yellow (e.g., urate, cystine, benzocoumarin, and xanthine), or brown (e.g., silica, urate, and xanthine), although gross diagnosis of specific mineral type is precluded by variation in appearance and mixed composition.

Small calculi may be voided in the urine, but typically calculi cause urinary obstruction. This is more common in males because of their long and narrow-diameter urethra. The most common sites of lodgment of urethral calculi vary with the animal species. In male cattle, calculi lodge in the urethra at the ischial arch and at the proximal end of the sigmoid flexure; in rams and wethers, the urethral process (vermiform appendage) is the most common site (Fig. 11-55, *A*); and in dogs, calculi lodge proximal to the base of the os penis (Fig. 11-55, *B*). At the site in which calculi lodge, there is local pressure necrosis, ulceration of the mucosa, and acute

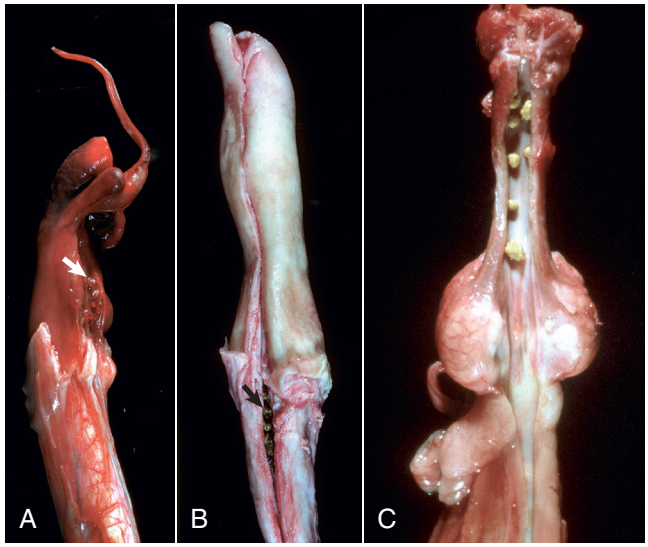


Figure 11-55 Urolithiasis, Penile Urethra. A, Sheep. Multiple calculi are present in the penile urethra *(arrow)* and the urethral process (vermiform appendage). **B,** Ventral aspect, dog. Calculi have lodged in the urethra proximal to the caudal end of the os penis *(arrow)*. **C,** Cat. Calculi are present throughout the penile urethra, several just caudal to the external urethral orifice at tip of the penis. (**A** and **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy College of Veterinary Medicine, University of Illinois.)

hemorrhagic urethritis. Because urethral sites are prone to rupture, hydronephrosis after complete urethral obstruction is less common than with unilateral long-standing ureteral impaction.

In male cats, urethral plugs composed of fine struvite crystals (sand) within abundant rubber-like protein matrix can fill the entire urethra, and they are distinct from calculi, which are composed predominantly of mineral. Either urethral plugs or urethral calculi may be the cause of *feline lower urinary tract disease* (FLUTD) (Fig. 11-55, *C*). When obstruction or dysuria occurs in females, calculi are usually large and located in the renal pelvis or urinary bladder.

At autopsy (syn: necropsy), animals that have died of urinary obstruction have greatly distended (Fig. 11-56, *A*), turgid, or ruptured urinary bladders and may have bilaterally dilated ureters and renal pelves. The bladder wall is thin and often has mucosal to transmural ecchymoses or diffuse hemorrhage (Fig. 11-56, *B*). When urine is released from the bladder, because of either rupture or incision at surgery or autopsy (syn: necropsy), the wall of the bladder is flaccid, the mucosa is often dark red and ulcerated, and the urine contains blood clots. Mucosal ulceration, localized lamina propria hemorrhage, and mucosal necrosis are usually present in the ureter, bladder, or urethra adjacent to an obstructive calculus or urethral plug. If the bladder ruptures antemortem, blood clots and fibrin are adhered at the site of rupture, and in some cases there is an acute, localized chemical (urine-induced) peritonitis.

Microscopically, inflammation and hemorrhage are present in the lower urinary tract. Lesions are most severe in cases in which obstruction has been complete. The mucosa is usually ulcerated, and areas of hyperplastic transitional epithelium are interspersed with goblet cells. The lamina propria is usually infiltrated with inflammatory cells. Neutrophils are present at foci of ulceration, and lymphocytes and plasma cells infiltrate perivascularly or uniformly throughout the lamina propria. Hemorrhage is often transmural but is most evident in the mucosa and can cause separation of the smooth muscle bundles. Degeneration and necrosis of smooth muscle occurs in severe cases.

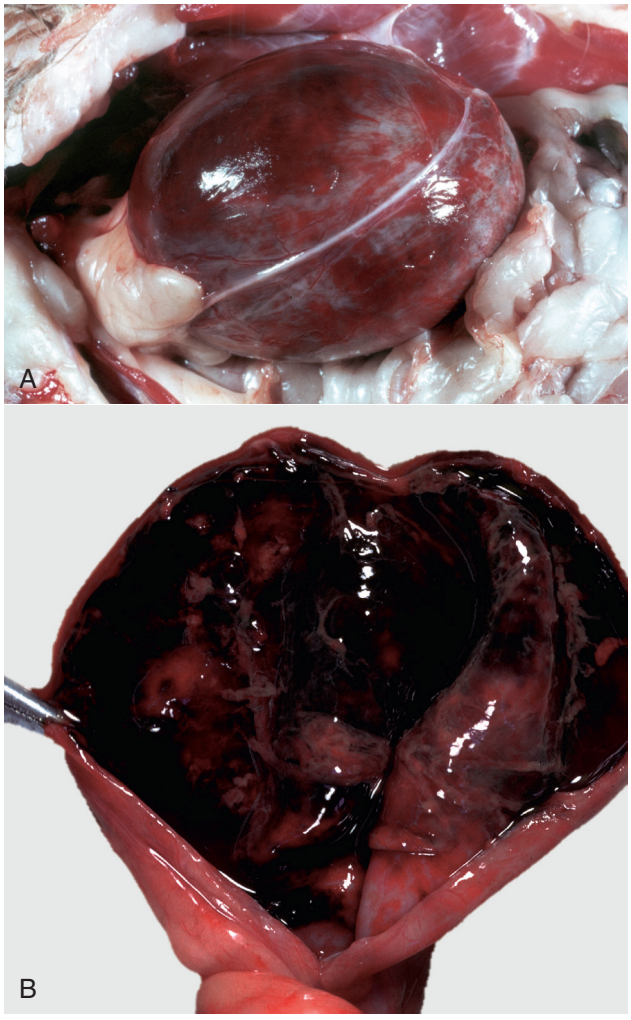


Figure 11-56 Hemorrhagic Urocystitis (Feline Lower Urinary Tract Disease) Urinary Bladder, Cat. A, Obstructive urolithiasis. The bladder is overdistended and turgid as the result of urethral obstruction. Note the serosal and intramuscular ecchymotic and suffusive hemorrhages at the neck and apex of the bladder. **B,** Urolithiasis, acute hemorrhagic cystitis. The severe diffuse transmural hemorrhage throughout the urinary bladder wall is secondary to blockage of the urethra by calculi and distention of the urinary bladder. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Clinically, urolithiasis can cause urinary obstruction or traumatic injury to the urinary bladder mucosa. Lesions of the urinary bladder are manifested clinically as difficult or painful urination (stranguria; dysuria), with or without grossly apparent hematuria. Small calculi may be voided in the urine, but typically calculi cause urinary obstruction. Dysuria can result from large calculi in the urinary bladder, but urinary tract obstruction with azotemia most commonly occurs because of nearly complete or complete urethral obstruction by small calculi.

Inflammatory Diseases

Acute Cystitis. Inflammation of the urinary bladder (cystitis) is common in domestic animals and may be acute or chronic. Because inflammation of the ureter (ureteritis) or urethra (urethritis) in the absence of cystitis is rare, this discussion focuses on cystitis. The causes of acute cystitis are varied; however, for all animal species, bacterial infection is the most common cause. In health, the bladder is resistant to infection, and contaminating bacteria are quickly eliminated by the flushing action of normal urine flow. Predisposition to urinary tract infection (UTI) occurs when there is stagnation of urine because of urinary tract obstruction, incomplete voiding during urination, or urothelial trauma. Other risk factors for UTI include urinary catheterization, vaginoscopy, vaginitis, urinary incontinence, or recent administration of medications such as antibiotics or corticosteroids. Bacterial cystitis is more common in females because their relatively short urethra provides less of a barrier to ascending infections than the longer, narrower male urethra. In all domestic animal species, the bacterial agent that most commonly causes cystitis is uropathogenic *Escherichia coli* (α-hemolysin–producing strains). Other bacterial pathogens that are important causes of cystis include *Corynebacterium renale* in cattle, *Actinobaculum suis* (*Eubacterium suis*) in pigs, *Enterococcus faecalis* in cats, and *Klebsiella* sp. in horses. In addition, *Proteus* sp., *Streptococcus* sp., and *Staphylococcus* sp. have been isolated from cases of cystitis in several animal species.

Except for the distal urethra, the lower urinary tract is normally free of bacteria. Sterility of the urinary bladder is maintained by normal intermittent voiding of urine and because of the antibacterial properties of urine. These antibacterial properties are attributed to the following:

- The acidic urine of carnivores
- Secretory IgA
- Secreted mucin that inhibits bacterial adhesion
- The high concentration of urea and organic acids
- High urine osmolality

Cystitis occurs when bacteria are able to overcome normal defense mechanisms and adhere to or invade (colonize) the urinary bladder mucosa. Several factors can enhance colonization and predispose animals to cystitis. Bacterial virulence factors, such as the expression of surface molecules that enhance adhesion (e.g., the P and type 1 fimbriae of certain strains of *Escherichia coli* and *Actinobaculum suis* and the pH-dependent adherence by pili of *Corynebacterium renale*) increase the likelihood of bacterial colonization. Other bacterial virulence factors, such as the *Escherichia coli* hemolysin, enhance pathogenicity and help bacteria overcome antibacterial factors of the urinary bladder and urine.

Host factors, such as decreased frequency of urination, incomplete voiding, and urine retention as a result of obstruction or neurogenic causes (e.g., spinal cord disease), often lead to cystitis. Disruption of the urothelium within the urethra or bladder is another factor that increases the risk for bacterial cystitis. Bacterial growth can be enhanced when glucosuria is present, such as in diabetes mellitus. Compromise of the host immune system can also increase susceptibility to bacterial cystitis. Trauma to the mucosa from urinary calculi, faulty catheterization, or other causes can result in mucosal erosion and hemorrhage, which predisposes to bacterial invasion of the lamina propria. Bladder mucosa may also be damaged by excessive ammonia production by urease-producing bacteria, such as *Corynebacterium renale* in cattle and *Actinobaculum suis* in pigs.

Once bacteria gain access to the lamina propria, they cause vascular damage and inflammation. Acute cystitis is often grossly described as hemorrhagic, catarrhal, fibrinopurulent, necrotizing, or ulcerative, and these changes often occur sequentially over time. Vascular damage predisposes to hemorrhage, leakage of fibrin, and, if severe, ischemic necrosis of the bladder. This is often accompanied by mucosal ulceration. Neutrophils are present as a component of vascular damage and in any lesion with accompanying bacterial colonization. In most cases, components of several of these processes are present. The urinary bladder wall often is thickened by edema, an inflammatory cell infiltrate, and is focally or diffusely

hemorrhagic. Hemorrhage is most common when obstruction is concurrently present with cystitis or after direct trauma from catheterization. Urine in such cases is described as cloudy, flocculent, foul smelling, and red-tinged. The mucosa can have foci of erosion or ulceration, patches or sheets of adherent exudate and necrotic debris, or adherent blood clots (Fig. 11-57, *A*). *Corynebacterium urealyticum* in dogs and cats and *Corynebacterium matruchotii* in a horse were implicated in a condition known as *encrusted cystitis*, in which plaques and accumulation of sediment predominate. Rarely, surgical debridement in addition to appropriate antimicrobial therapy is required.

Microscopically, acute cystitis is characterized by epithelial denudation with bacterial colonies present on the surface. The lamina propria is markedly edematous and has a diffuse neutrophilic infiltrate. Superficial hyperemia and hemorrhage are usually present (Fig. 11-57, *B*). A mild perivascular leukocytic infiltrate can occur beneath the mucosa and submucosa and also within the tunica muscularis.

Clinically, acute bacterial cystitis results in dysuria, stranguria, and hematuria. An inflammatory sediment is detected on urinalysis, and bacteria can be grown in pure culture from urine samples.

Viral causes of acute cystitis are relatively rare in veterinary medicine. In cats, a cell-associated herpesvirus has been found in some cases of mild cystitis. Hemorrhagic cystitis sometimes occurs in malignant catarrhal fever in cattle and deer and occasionally is the dominant gross feature of the disease.

Acute noninfectious cystitis can result from a variety of chemical causes. Activated metabolites of cyclophosphamide, a drug used to treat neoplastic and immune-mediated diseases of dogs and cats, can cause a sterile hemorrhagic cystitis characterized by mucosal ulceration and hemorrhage. Cantharidin toxicosis in horses results from ingestion of blister beetles (*Epicauta* spp.) in alfalfa hay, and hemorrhagic and erosive or ulcerative cystitis develops from cantharidin excreted through the urinary tract. Chronic ingestion of bracken fern (*Pteridium aquilinum*) by cattle can result in the syndrome of enzootic hematuria, which can manifest as acute urinary bladder hemorrhage, chronic cystitis, or urinary bladder neoplasia.

Chronic Cystitis. Chronic cystitis presents in several different forms based on the pattern and type of inflammatory response. These forms include diffuse, follicular, and polypoid variants. In the diffuse variant of chronic cystitis, the bladder mucosa is irregularly reddened and usually thickened. There is some epithelial desquamation, and the submucosa is heavily infiltrated with mononuclear inflammatory cells accompanied by few neutrophils. In addition, connective tissue of the submucosa is often thickened and the muscularis layer is hypertrophied.

The follicular variant of chronic cystitis is common in dogs and is characterized by multifocal and disseminated, nodular, submucosal lymphoid proliferations that are 1 to 3 mm in diameter, giving the mucosa a cobblestone appearance (follicular cystitis) (Fig. 11-58). This response is particularly common when cystitis occurs concurrently with chronic urolithiasis. A red zone of hyperemia often surrounds these white-gray raised nodules. Microscopically, these raised nodules are aggregates of lymphocytic cells in the superficial lamina propria. Epithelium overlying these foci may be normal or ulcerated and may be accompanied by fibrosis in the lamina propria. Hypertrophy of the tunica muscularis may also be present.

Polypoid masses that characterize chronic polypoid cystitis are seen predominantly in dogs but may occur in any species. They likely develop from inflammatory and hyperplastic responses secondary to chronic irritation, which most often results from persistent bacterial urinary tract infection and/or uroliths. The polyps arising in the bladder mucosa are composed of a core of proliferative connective tissue covered by surface epithelium. Mononuclear inflammatory cells are often present within the connective tissue core. In some cases, eosinophilic inflammation predominates within the core

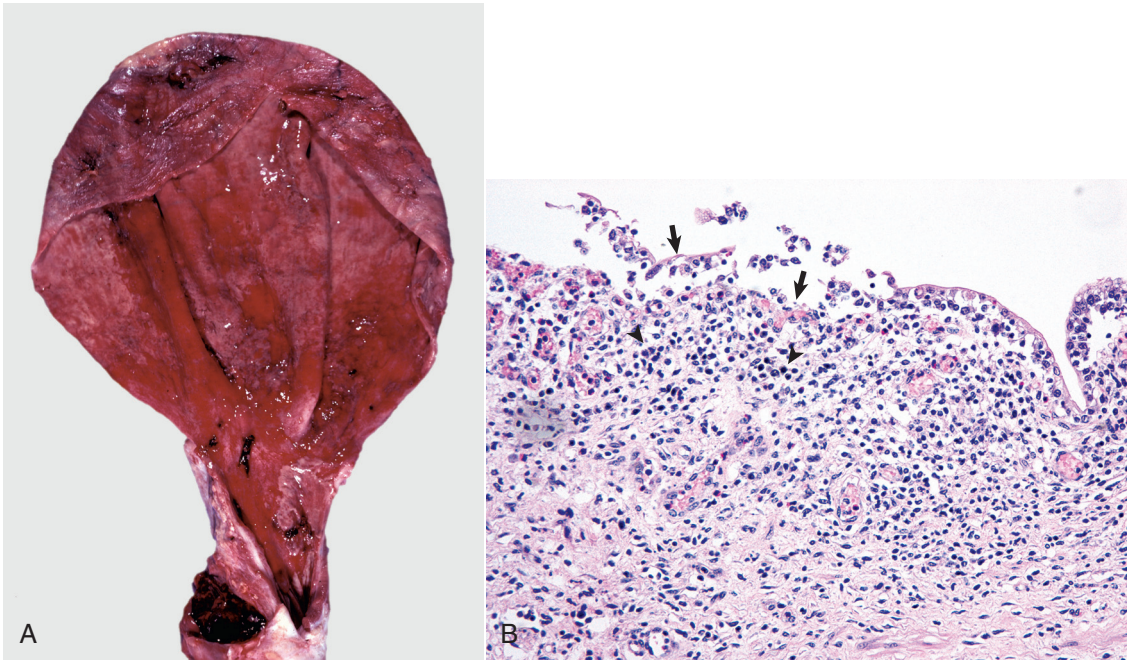


Figure 11-57 Acute Cystitis, Urinary Bladder. A, Mucosal and serosal surfaces, calf. Patchy areas of ulcerated mucosa are interspersed with areas of hemorrhagic mucosa. Note the subserosal hemorrhages *(top)*. **B,** Mucosal surface, dog. The mucosa has been partially denuded of transitional epithelium *(arrows)*. There are mucosal and submucosal infiltrates of neutrophils *(arrowheads)*, which extend into the adjacent tunica muscularis. Note the congested vessels with active hyperemia in the lamina propria. H&E stain. (**A** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

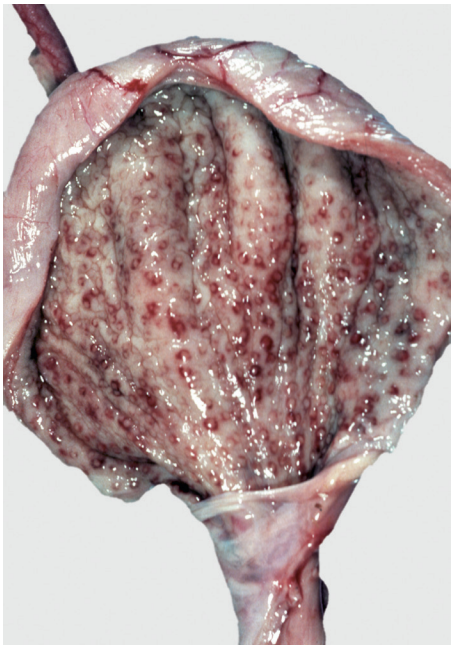


Figure 11-58 Chronic Follicular Cystitis, Urinary Bladder, Mucosal Surface, Dog. Multiple small raised red nodules are present on the mucosal surface. These nodules are foci of hyperplastic lymphoid cells surrounded by hyperemia and hemorrhage. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

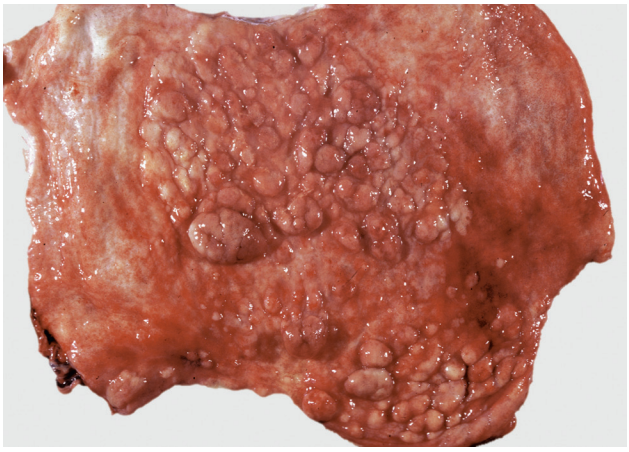


Figure 11-59 Chronic Polypoid Cystitis, Urinary Bladder, Mucosal Surface, Dog. This type of cystitis is characterized by multiple masses composed of proliferative nodules of connective tissue (polyps) mixed with chronic inflammatory cells. (Courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University.)

of plump spindloid cells composed of fibroblasts and myofibroblasts. Surface epithelium may form nests of hyperplastic transitional epithelial cells in the lamina propria (Brunn's nests) or undergo metaplasia to a mucus-secreting, glandular epithelial type (cystitis glandularis). The resulting polypoid masses, which are composed of inflammation, fibroplasia, and epithelial proliferation, occur most frequently in the cranioventral bladder wall (Fig. 11-59). The masses may be broad-based or pedunculated, ulcerated, or covered by hyperplastic epithelium with goblet cell metaplasia. Chronic polypoid cystitis is often accompanied by clinically evident hematuria.

Toxic Cystitis

Bracken Fern–Induced Hemorrhagic Urocystitis
(Enzootic hematuria)

Information on this topic is available at www.expertconsult.com.

Mycotic Cystitis. Mycotic cystitis is occasionally seen in domestic animals when opportunistic fungi, such as *Candida albicans* or *Aspergillus* sp., colonize the urinary bladder mucosa. Such fungal infections usually occur secondary to chronic bacterial cystitis, especially when animals are immunosuppressed or subjected to prolonged antibiotic therapy, which alters the density and diversity of normal bacterial flora. Occasionally, *Blastomyces dermatitidis* can produce lower urinary tract lesions in dogs. The urinary bladder mucosa is usually ulcerated with proliferation of underlying lamina propria; a generalized thickening of the urinary bladder wall is the result of extensive inflammation consisting of neutrophils, lymphocytes, plasma cells, macrophages and edema, and fibrosis.

Neoplasia. Neoplasms of the lower urinary tract occur predominantly in the urinary bladder, and are less common in the urethra and are rare in the ureter. They occur most frequently in dogs, occasionally in cats, and rarely in other species, with the exception of bracken fern–induced bladder neoplasms in cattle. Urinary bladder neoplasms comprise less than 2% of total canine neoplasms. Most occur in older dogs, with a higher frequency in females seen in many studies and with certain breeds, including Scottish terrier, Shetland sheepdog, beagle, and collie, at an increased risk. Multiple factors likely play a role in the development of bladder cancer, but specific risks that have been identified in dogs include the following:

- Topical insecticides
- Exposure to marshes sprayed with chemicals for mosquitoes
- Environments with high industrial activity
- Female gender
- Obesity
- Breed (e.g., Scottish terrier)

Retention of urine in the bladder and longer exposure of mucosal epithelium to carcinogens result in a higher incidence of tumors in the urinary bladder compared to other regions of the urinary tract. Many chemicals, including intermediate components of aniline dyes, aromatic hydrocarbons, and tryptophan metabolites, have been found experimentally or epidemiologically to induce urinary bladder neoplasms. Chemically induced and spontaneous epithelial tumors progress through a series of histologic stages from hyperplasia, squamous metaplasia, papilloma, adenoma, dysplasia, and carcinoma in situ to overt carcinoma.

Epithelial Tumors. Approximately 80% of the neoplasms of the lower urinary tract are epithelial in origin and are classified as transitional cell papillomas, transitional cell carcinomas, squamous cell carcinomas, adenocarcinomas, and undifferentiated carcinomas, as follows:

- Papillomas tend to be multiple and may have a pedunculated or sessile appearance. Microscopically, they are composed of well-differentiated transitional epithelium separated from underlying supporting stroma by an intact basement membrane.
- Transitional (urothelial) cell carcinomas are focal, raised nodules or diffuse thickenings of the urinary bladder wall that are most common in the trigone region of the bladder (Fig. 11-60, A). They are composed of pleomorphic to anaplastic transitional epithelium. Neoplastic transitional cells cover the mucosal surface as irregular layers, readily invade the lamina propria in the form of solid nests and acini, and are found within lymphatic

Enzootic hematuria is a syndrome in mature cattle characterized by persistent hematuria and anemia due to hemorrhages or neoplasia in the lower urinary tract, and it is caused by chronic ingestion of bracken fern (*Pteridium aquilinum*). All parts of the plant contain several toxic substances, including a thiaminase, a variety of carcinogens (quercetin, shikimic acid, prunasin, ptaquiloside [braxin C], ptaquiloside Z, aquilide A, and others), a "bleeding factor" of unknown structure, and substances that act as immunosuppressants. Experimental ptaquiloside administration in guinea pigs leads to hemorrhagic cystitis, suggesting that this is one of the toxic principles in bracken fern hematuria.

The extent and persistence with which toxic ferns are grazed probably influence the incidence of bladder lesions. Cattle fed low amounts of bracken fern develop microscopic, followed by grossly apparent, hematuria. Microhematuria usually is associated with grossly visible petechial, ecchymotic, or suffusive hemorrhages in the urothelium of the renal calyces, pelvis, ureter, and bladder. Microscopically, ectasia and engorgement of capillaries are present. Altered vessels are prone to hemorrhage into the bladder wall or lumen, and nodular hemangiomatous lesions develop in affected areas. In a few animals, macroscopic hematuria is due solely to these nonneoplastic changes, but usually it is caused by development of tumors, which ulcerate and bleed into the lumen. Neoplastic changes are usually accompanied by chronic cystitis.

Bracken fern–induced neoplasia is discussed later in more detail in the section on Kidney and Lower Urinary Tract, Disorders of Ruminants (Cattle, Sheep, and Goats).

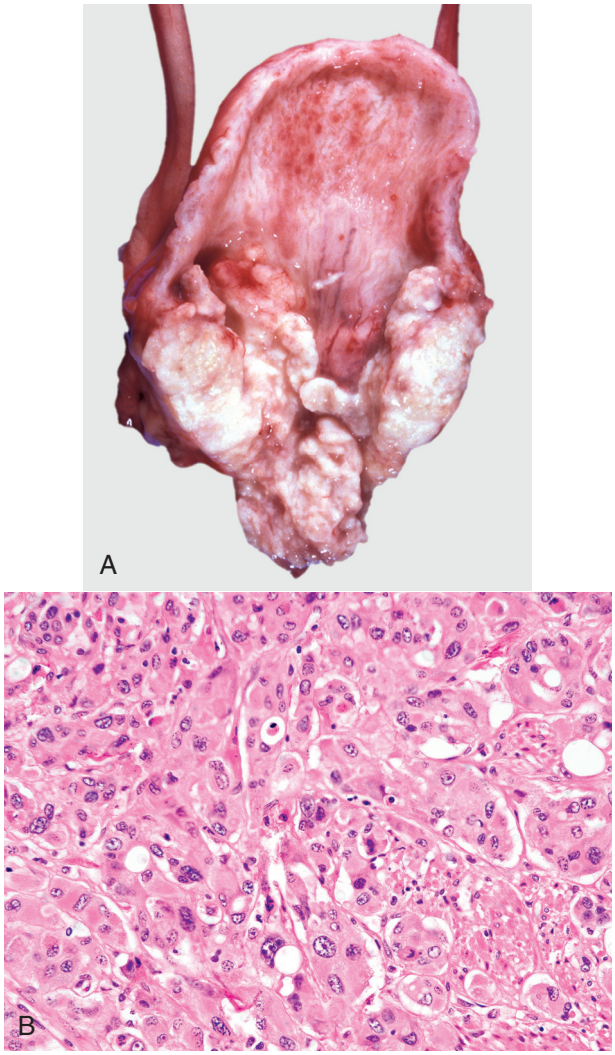


Figure 11-60 Transitional Cell Carcinoma, Urinary Bladder, Dog. A, Transitional cell carcinomas are typically adjacent to the trigone (as here), where they can become large enough to obstruct the opening of one or both ureters and result in secondary hydroureter and/or hydronephrosis. **B,** Lamina propria. The tumor is formed by anaplastic cells grouped in small islands and clusters. Nuclei are vesicular with prominent nucleoli, and some nuclei show remarkable anisokaryosis. H&E stain. (**A** courtesy Dr. A. Confer, Center for Veterinary Health Sciences, Oklahoma State University. **B** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

vessels of the submucosal and muscle layers (Fig. 11-60, *B*). Approximately 40% of these neoplasms have metastasized by the time of clinical diagnosis and are present in 50% to 90% of clinically affected dogs at autopsy (syn: necropsy). Lymph nodes and lungs are the most common sites of metastasis; however, more widespread metastasis to other tissues, including bone, is possible. Terriers may be at a slightly elevated risk for transitional carcinoma development, and there has been an association made between occurrence of these tumors and exposure to lawn pesticides. In cats, transitional cell carcinomas are rare but aggressive, and, unlike in dogs, they are more prevalent in males and tend to arise at sites in the bladder distant from the trigone.

- Squamous cell carcinomas and adenocarcinomas comprise a small portion of bladder neoplasms and most likely arise in areas of squamous or glandular metaplasia, respectively. In the bitch, squamous cell carcinomas occur most often in the urethra, which is lined by squamous epithelium in the distal two-thirds. These neoplasms are less likely to metastasize than transitional cell carcinomas. Undifferentiated carcinomas are rare and do not fit into one of the previously mentioned histologic types.

Metastasis of urinary bladder carcinomas is most often first seen in regional lymph nodes adjacent to the aortic bifurcation, including the deep inguinal, medial iliac, and sacral lymph nodes. Other potential sites of metastasis include lungs and kidneys, with metastasis to other parenchymatous organs occurring later.

Mesenchymal Tumors. Mesenchymal tumors, including fibromas, fibrosarcomas, leiomyomas, leiomyosarcomas, rhabdomyosarcomas, lymphomas, hemangiomas, and hemangiosarcomas, comprise fewer than 20% of the neoplasms in the lower urinary tract. Primary fibrosarcomas, leiomyosarcomas, hemangiomas, and hemangiosarcomas are rare. Mesenchymal tumors are classified as follows:

- Leiomyomas arise from smooth muscle of the tunica muscularis and are the most common mesenchymal neoplasms of the lower urinary tract. They may be solitary or multiple and are circumscribed, firm, and pale white to tan masses in the urinary bladder wall. Leiomyomas have the macroscopic consistency and microscopic appearance of normal smooth muscle. Malignant counterparts (leiomyosarcoma) are much rarer, and although they are locally infiltrative, they rarely metastasize.
- Fibromas arise from lamina propria connective tissue and project into the bladder lumen as solitary nodules.
- Lymphoma occasionally infiltrates the wall, not only of the bladder but also of the ureters and renal pelves in cattle, pigs, dogs, and/or cats. Common complications include hydronephrosis and hydroureter.
- Rhabdomyosarcomas are rare but occur in the bladder and urethra of young large breed dogs (younger than age 18 months), suggesting an embryonal origin. The cell of origin is speculated to be embryonic myoblasts from the urogenital ridge. These masses are described as botryoid (grapelike) masses (4 to 18 cm in diameter) that protrude into the bladder lumen. Local invasion and occasional metastasis to lymph nodes characterize the typical behavior. Microscopically, the neoplastic cells form disorganized sheets or lobules in poorly differentiated regions and interlacing streams of fusiform cells in more well-differentiated areas. Microscopic demonstration of cross-striations typical of skeletal muscle or immunohistochemical demonstration of the intermediate filament, desmin, are useful to confirm the diagnosis of rhabdomyosarcoma. Clinical presentation includes hematuria, urinary obstruction, hydroureter, hydronephrosis, and hypertrophic osteopathy.

Disorders of Horses

Embolic Nephritis (Actinobacillus equuli)

Two subspecies of *Actinobacillus equuli* (*A. equuli* subsp. *equuli* and *A. equuli* subsp. *haemolyticus*) are normal inhabitants of the mucous membranes of the alimentary tract. Fecal contamination or extension from oral mucous membranes is the method of inoculation. Umbilical contamination in foals is the most common route of infection resulting in septicemia. Microabscesses occur in a variety of organs, including the liver, adrenal gland, joints, and the kidney, as multifocal random, raised, tan pinpoint foci on the cut surface throughout the renal cortex (see Fig. 11-35, *A* and *B*). Microscopically, glomerular capillaries and to a lesser extent interlobular arterioles contain numerous large bacterial colonies intermixed with necrotic debris and extensive infiltrates of neutrophils that often obliterate the glomerulus (see Fig. 11-35, *C*). If the affected foal survives, the neutrophilic infiltrates will either persist as focal

residual abscesses or be progressively replaced by increasing numbers of lymphocytes, plasma cells, macrophages, reactive fibroblasts, and ultimately coalescing scars.

Myoglobinuric Nephrosis (Rhabdomyolysis)

A set of events leading to ischemic tubular necrosis frequently occurs in hypoperfused kidneys complicated by myoglobinuria. In rhabdomyolysis, serum concentrations of myoglobin are increased, as these products pass into the glomerular filtrate, producing greatly increased intraluminal concentrations that cause myoglobinuric nephrosis. Myoglobin does not use a carrier protein for transportation, and because it is a small molecule, it freely passes through the glomerulus and is excreted in the urine. Myoglobin is not nephrotoxic in itself, and intravenous infusions into healthy animals produce no recognizable lesions. However, large concentrations of myoglobin in the glomerular filtrate can increase the tubular necrosis caused by renal ischemia. The mechanism of pigment-induced renal injury is not fully understood, but increased hydroxyl radical formation associated with reduction of ferrous iron compounds and tubular obstruction by myoglobin casts are likely contributing factors.

For example, in equine rhabdomyolysis, renal ischemia is most likely secondary to hypovolemic shock or severe accompanying anemia. Myoglobinuria can have an additive deleterious effect on tubular epithelium already undergoing ischemic necrosis. At autopsy (syn: necropsy), the renal cortices in myoglobinuria are diffusely stained red-brown to blue-black and have intratubular orange-red, refractile myoglobin casts (see Fig. 11-40).

The pathophysiology of this condition is not known; however, exertional rhabdomyolysis is usually the inciting cause. Predisposing and triggering factors are required in this multifactorial disorder, and it typically involves a combination of events, of which exertion is often the main trigger. Possible predisposing factors include carbohydrate overload, local hypoxia, thiamine deficiency, vitamin E and selenium deficiency, metabolic pathway abnormalities, alterations in reproductive hormones, thyroid hormones and cortisol, viruses, electrolyte imbalances, and polysaccharide storage myopathy. Clinical signs tend to occur intermittently during or after exercise and can range from mild to severe. Dark urine occurs when myoglobin level exceeds 40 mg/100 mL. Renal damage may be inconsequential to severe.

Papillary Necrosis

Hypovolemia and dehydration during prolonged or excessive NSAID administration can predispose to papillary necrosis. It is often seen on post-mortem examination in horses with a clinical history of NSAID administration, but rarely does it produce clinical signs.

Necrosis of renal papillae, or in the horse the medullary crest, is a response of the inner medulla to ischemia. Papillary necrosis can be a primary or secondary lesion; however, papillary necrosis occurs as a primary disease in horses treated with NSAIDs. The primary disease occurs quite frequently in horses treated for prolonged periods with phenylbutazone or flunixin meglumine. The medullary interstitial cells are the primary targets for NSAIDs, and interstitial cell damage results in inhibition of cyclooxygenase and decreased prostaglandin synthesis. The resulting reduction in inner medullary blood flow causes ischemia/hypoxia, and it also causes degenerative changes in tubular epithelial cells and ischemic necrosis (infarction) of the medullary crest.

Affected horses also often have ulcers within various areas of the alimentary tract. Usually, clinical cases of NSAID toxicosis present with signs of alimentary tract disease ranging from excessive salivation and inappetence to diarrhea and colic. At autopsy (syn: necropsy), medullary crest necrosis may be present. Acute renal lesions are irregular, discolored areas of necrotic inner medulla sharply delineated from the surviving medullary tissue (see Fig. 11-48). The affected inner medulla is yellow-gray, green, or pink. The cortices may be slightly swollen. With time, the necrotic tissue sloughs, resulting in a detached, friable, and discolored tissue fragment in the pelvis. The remaining inner medulla is usually attenuated and on cross section is narrowed. Overlying cortex can be somewhat shrunken because of atrophy of some of the nephrons caused by blockage of their tubules in the affected medulla.

Patent Urachus

See Kidney and Lower Urinary Tract, Disorders of Domestic Animals, Disorders of the Lower Urinary Tract, Developmental Anomalies, Patent Urachus.

Klossiella equi Infection

Klossiella equi is a sporozoan parasite of the horse, which has various stages of development in the kidney after oral infection. No gross lesions are noted. Various stages of schizogony can be found microscopically in proximal convoluted tubular epithelium and to a lesser extent in glomerular endothelium (Fig. 11-61). Stages of sporogony are present in the epithelial cells of the loop of Henle, but different coccidial stages occur multifocally in affected tubules. Occasionally, however, *Klossiella equi* has been associated with multifocal lesions of mild tubular necrosis and, in the case of tubular rupture, with interstitial infiltrates of lymphocytes and plasma cells. Renal function is typically normal.

Disorders of Ruminants (Cattle, Sheep, and Goats)

Oak Toxicity: Acute Tubular Necrosis (Quercus Spp.)

Ruminants develop tubular necrosis after ingestion of leaves, buds, or acorns from oak trees and shrubs (*Quercus* spp.). The toxic substances are metabolites of tannins and include tannic acid, gallic acid, and pyrogallol; however, the mechanism of tubular damage is unknown. Acutely affected cattle often have swollen, pale kidneys that occasionally have cortical petechial hemorrhages (Fig. 11-62). Perirenal edema, which may be hemorrhagic, is a common lesion, and the body cavities contain excessive amounts of a clear fluid. Endothelial cells are a target for the binding of the toxic metabolites, subsequently resulting in vascular leakage. The kidneys are swollen and pale, and they may have fine, often pinpoint hemorrhages on capsular and cortical surfaces. Microscopically, acute proximal tubular necrosis with casts and intratubular hemorrhage are

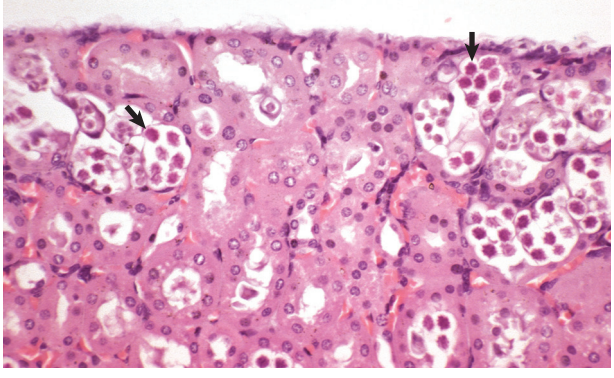


Figure 11-61 *Klossiella equi* Infection, Kidney, Horse. Tubular epithelium containing various developmental stages of *Klossiella equi (arrows)*. H&E stain. (Courtesy Dr. J. Simon, College of Veterinary Medicine, University of Illinois.)

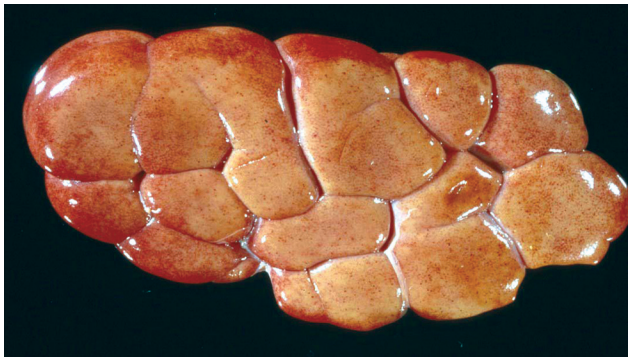


Figure 11-62 Acute Tubular Necrosis, Oak Toxicity, Kidney, Cow. Ingestion of leaves, buds, or acorns from oak trees produces cortical petechiation, acute tubular necrosis, and perirenal edema. The toxic principle is a metabolite of oak tannins and causes acute tubular necrosis, which heals by scarring. (Courtesy Dr. K. Read, College of Veterinary Medicine, Texas A&M University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

characteristic, whereas chronic cases develop chronic interstitial nephritis with the usual changes of fibrosis, atrophy, thinned cortex, and a finely pitted surface.

Pulpy Kidney Disease

Pulpy kidney disease is a unique manifestation of *Clostridium perfringens* type D enterotoxemia in small ruminants, especially sheep. *Clostridium perfringens* epsilon toxin binds to renal tubular epithelial cells and causes selective degeneration of distal tubules. The disease is precipitated by access to excessive starch in the small intestine, which allows for anaerobic bacterial proliferation therein. Hyperglycemia and glucosuria can occasionally be detected. Postmortem interval is critical for assessment of "pulpiness" because these changes resemble autolysis. Classic autopsy (syn: necropsy) lesions are medullary congestion and hemorrhage and also soft to almost liquified (pulpy) cortex (see Fig. 11-42, A). Histologic lesions include mild degeneration and necrosis of epithelium of the proximal convoluted tubules with edema, congestion, and interstitial hemorrhage in the renal cortex and congestion of the medulla (see Fig. 11-42, B).

Multifocal Lymphoplasmacytic Interstitial Nephritis (Embolic Nephritis; White-Spotted Kidney)

Multifocal interstitial nephritis, or white-spotted kidney, is a well-known example of multifocal lymphoplasmacytic interstitial nephritis in ruminants. It occurs as a result of low-grade, vascular-derived, renal bacterial infection, which likely initially manifested as multiple suppurative foci. In cattle, white-spotted kidneys are seen in calves and are often incidental findings at slaughter or necropsy arising from other systemic causes. *Escherichia coli*, *Salmonella* spp., *Leptospira* spp., and *Brucella* spp. have all been implicated. Usually, by the time the lesion is found, bacteria cannot be cultured from the kidneys. Molecular studies of potential causative microbes of white-spotted kidneys in calves have demonstrated differing findings indicating that the lesion can result from one of several microbes. Lesions can be small to larger, patchy, coalescing areas of pale cortex readily visible from the capsular surface (Fig. 11-63). Histologically, acute lesions, which are rarely seen in cattle, are consistent with neutrophilic embolic nephritis or tubulointerstitial inflammation. Most cases are subacute to chronic and consist of interstitial lymphocytes, plasma cells, and macrophages interspersed with varying numbers of fibroblasts, variable fibrous connective tissue, and atrophic nephron components. Capsular adhesions may be present.

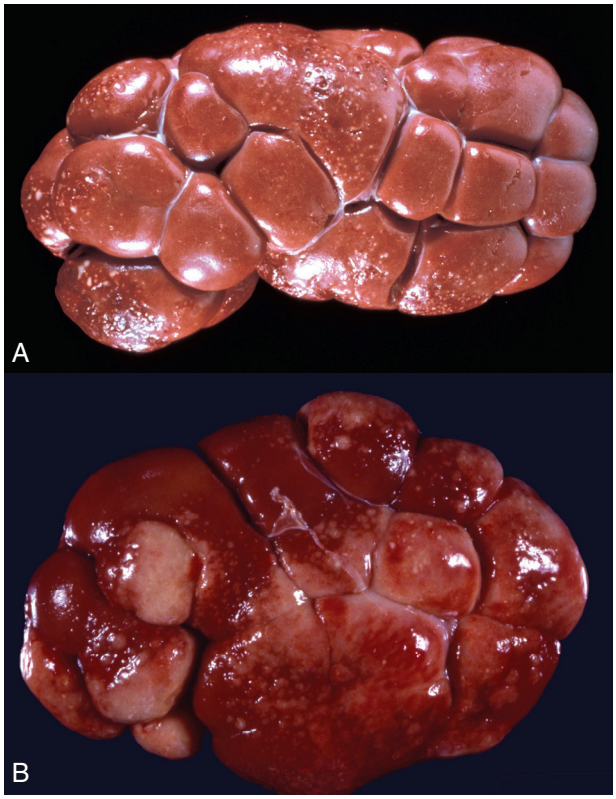


Figure 11-63 Multifocal Interstitial Nephritis (White-Spotted Kidney). **A,** Kidney, calf. Multiple pale-yellow to white 2- to 5-mm foci of inflammatory cells (usually neutrophils) are scattered randomly throughout and over the surface of the kidney (as shown here). **B,** Kidney, calf. More severe form of multifocal interstitial nephritis compared to **A**. (**A** courtesy College of Veterinary Medicine, University of Illinois. **B** courtesy Dr. B. Njaa, Center for Veterinary Health Sciences, Oklahoma State University.)

Interstitial Nephritis (Renal Leptospirosis)

In cattle, serovars belonging *to Leptospira interrogans*, *Leptospira kirschneri*, and *Leptospira borgpetersenii* have been associated with carrier status and/or diseases including reproductive failure and abortion, hemolytic anemia and hemoglobinuric nephrosis, and occasionally interstitial nephritis. The pathogenesis of renal leptospirosis was discussed previously as an example of acute bacterial tubulointerstitial nephritis. Although neutrophils can be present in tubular lumina, the predominant chronic lesion is in the interstitium, which becomes infiltrated with monocytes, macrophages, lymphocytes, and plasma cells. Serovars *hardjo*, *pomona*, and *grippotyphosa* are the most commonly implicated in renal infection in cattle. Small ruminants are relatively resistant to infection. Infection with bovine-adapted serovar *hardjo* rarely causes overt dysfunction. Nonadapted serovars create renal lesions from direct damage to the vascular endothelium, hypoxia caused by anemia, tubular epithelial damage from intratubular hemoglobin accumulation, and interstitial nephritis. Lesions range from few to mild interstitial nephritis to diffuse severe lymphocytic interstitial nephritis with fibrosis (see Fig. 11-66).

Chronic interstitial nephritis has mononuclear cell infiltrates, interstitial fibrosis, and generalized tubular atrophy. In the case of exposure to gamma herpesvirus of malignant catarrhal fever, lesions of a chronic interstitial nephritis are characterized by chronic ongoing inflammatory infiltrates composed of lymphocytes and fewer plasma cells within the interstitium accompanied by variable amounts of fibrosis. Occasionally, with this condition, vasculitis can be detected in vessels around which much of the interstitial inflammation occurs and can help differentiate the two microbes.

Hairy Vetch Toxicosis (Vicia Spp.)

Hairy vetch is a legume used throughout regions with extensive farming and can be fed as pasture, hay, or silage. Hairy vetch toxicosis is uncommon and is a unique manifestation of toxic plant ingestion that can result in lesions of eosinophilic and granulomatous inflammation within the kidney, skin, and other viscera. The toxic mechanism is not clearly determined for the visceral disease. It has been postulated that the visceral inflammation is similar to a type IV hypersensitivity reaction and may be caused by plant lectins that serve as haptens (see Chapter 5) or as a complete antigen that sensitizes lymphocytes. Although gross lesions at autopsy (syn: necropsy) can involve multiple organs, the kidney contains multifocal to radiating cortical infiltrates (see Fig. 11-49, *A*). These are often oriented around the vasculature. Histologically, infiltrates are mixed and include monocytes, lymphocytes, plasma cells, multinucleated giant cells, and eosinophils (see Fig. 11-49, *B*). Clinical disease develops several weeks after ingestion of the plant, and dermal manifestation of pruritus is consistently seen concurrently. Mortality can result 10 to 20 days after illness begins, and older Holstein or Angus cattle breeds are the most susceptible. Diagnosis is often made by exclusion.

Pyelonephritis

In cattle, numerous bacteria cause cystitis and pyelonephritis, including *Escherichia coli* and *Trueperella pyogenes*. In addition, *Corynebacterium renale* is an obligate urinary mucosal organism and a potential pathogen in bovine cases because this organism has pili to accommodate mucosal adhesion and to resist shedding from the lower urinary tract. Furthermore, the bacterium produces a urease that hydrolyzes urea, releasing ammonia that causes localized epithelial damage and increased urine pH.

Acute pyelonephritis is uncommon in cattle and often seen as an incidental finding at autopsy (syn: necropsy) (see Fig. 11-46). Subacute to chronic bovine pyelonephritis is a slowly progressive suppurative tubulointerstitial nephritis. The pelvis and calyces are dilated with fluid ranging from turbid urine containing fibrinopurulent clumps to a completely purulent exudate. Bacteria localize in the medulla, and inflammation and medullary necrosis can be so severe that only a thin rim of cortex remains. More commonly, radially distributed interstitial infiltrates with or without fibrosis are present (see Fig. 11-47). As fibrosis progresses, there is contraction of scars that extend from the cortical surface throughout the medulla to the level of the pelvis.

Renal Lymphoma (Lymphosarcoma)

Renal lymphoma can occur in cattle and is one of the most common bovine tumors; however, involvement of the kidney is not as common as it is in feline lymphoma. The cause is bovine leukosis virus (BLV), a retrovirus known to be spread by blood contact between animals. Gross lesions may be seen as diffuse renomegaly or more commonly as multiple poorly defined tan, soft, raised cortical nodules (see Fig. 11-52, *E* and *F*). Peripelvic and periureteral infiltrates are common in cattle and can produce concurrent hydronephrosis. Focal or diffuse infiltrates of neoplastic lymphocytes efface interstitium and/or tubules.

Urolithiasis

In cattle, uroliths result in obstruction most frequently in bulls and castrated males (steers). The urethra narrows in the region of the sigmoid flexure, which is the most commonly affected site. The obstruction can be caused by a large discrete mineral aggregate (urolith) or by accumulation of fine sandlike material within the urethral lumen. Hemorrhage and necrosis of the urethral mucosa typically occurs at the site of urolith lodgment. In more severe cases, leading to subsequent urethral rupture, there can be subcutaneous accumulation of urine in the inguinal area, prepuce, and ventral abdomen (commonly referred to as "water belly").

Silica calculi (75% silica dioxide) are a problem for sheep and cattle grazing native rangeland grasses of western North America. Certain grasses contain as much as 4% to 5% silica; most of the silica is insoluble, except that which is in the cell sap (unpolymerized silicic acid). After absorption, silica is returned to the gut in digestive secretions, such that less than 1% of dietary silica is excreted in urine and up to 60% is resorbed from the filtrate. However, when the volume of urine production is very low, the concentration of silicic acid excretion in urine may reach five times the saturation concentration and precipitation from solution occurs in the presence of proteins or other substances in the urine. Silica calculi are hard, white to dark-brown, radiopaque, often laminated, up to 1-cm-diameter stones and are a major cause of urinary tract obstruction. Silica calculus formation may be reduced to subclinical levels by adding salt to the ration to ensure high water consumption, acidifying the diet, or reducing the dietary calcium to phosphorus ratio.

Struvite calculi are white to gray, chalky, usually smooth, and easily broken. This type of calculus usually forms a gritty sludge within a proteinaceous matrix and develops in feedlot ruminants on cereal-grain rations, particularly those that are pelleted and high in phosphorus. Reduction of the dietary calcium to phosphorus ratio as well as a balance of magnesium, sodium, and potassium in the ration are important in preventing urolith formation.

See the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals for illustrations.

Enzootic Hematuria

Information on this topic is available at www.expertconsult.com.

Bracken Fern–Induced Neoplasia

Information on this topic is available at www.expertconsult.com.

Amyloidosis

Amyloidosis is a sporadic protein-losing nephropathy of cattle. Chronic diarrhea, poor productivity, and weight loss are common. Amyloid is classified as AA type, which is associated with chronic inflammation, and such conditions are often seen concurrently. AA fibrils are created through abnormal catabolism of serum amyloid A (SAA). On gross examination, kidneys are yellow tan and appear waxy on cut section. Histologic deposition of amyloid occurs in the glomerulus, interstitium, and tubular lumens.

Disorders of Pigs

Glomerulonephritis of Pigs

Although an uncommon entity in pigs, glomerulonephritis (GN) is seen as a sequel to chronic infections with hog cholera, African swine fever, systemic cytomegalovirus, and group A streptococcal abscesses. In addition, inherited forms of membranoproliferative GN in Yorkshire pigs are due to an autosomal recessive deficiency of the complement inhibitory protein factor H. GN and systemic vasculitis can be observed in porcine circovirus 2 infection manifested as porcine dermatitis and nephropathy syndrome. In acute GN, grossly, there is enlargement, pallor, edema, and cortical petechiation of the kidney. Eventually, this process progresses to granular cortical infiltrates and the kidney may appear shrunken and contracted due to cortical fibrosis. Kidney lesions in the acute form of

Enzootic hematuria is a disease of cattle caused by chronic ingestion of bracken fern (*Pteridium aquilinum*). Bracken fern is one of the most common plants on the planet, and it is one of the few to cause both cystitis and naturally occurring tumors in animals. There are two subspecies of bracken fern: *Pteridium aquilinum* ssp. *aquilinum*, containing eight varieties, and *Pteridium aquilinum* ssp. *caudatum*, containing four varieties. It is not known whether all varieties are toxic. *Pteridium revolutum*, a species of bracken fern common in south Asia, and *Pteridium esculentum*, a bracken fern of Australia, also produce enzootic hematuria. In areas where bracken does not grow, other ferns, such as the Australian *Cheilanthes sieberi* (mulga or rock fern), are capable of producing enzootic hematuria.

All parts of the plant are toxic. Bracken fern contains several toxic substances, including a thiaminase, a variety of carcinogens (quercetin, shikimic acid, prunasin, ptaquiloside [braxin C], ptaquiloside Z, aquilide A, and others), a "bleeding factor" of unknown structure, and substances that act as immunosuppressants. Experimental ptaquiloside administration in guinea pigs leads to hemorrhagic cystitis, suggesting that this is one of the toxic principles in bracken fern hematuria.

The extent and persistence with which toxic ferns are grazed probably influences the incidence of bladder lesions. Cattle fed low concentrations of bracken fern develop microscopic, followed by macroscopic, hematuria. Microscopic hematuria is usually associated with grossly apparent petechial, ecchymotic, or suffusive hemorrhages in the urothelium of the renal calyces, pelvis, ureter, and bladder. Microscopically, ectasia and engorgement of capillaries are present. Altered vessels are prone to hemorrhage into the bladder wall or lumen, and nodular hemangiomatous lesions develop in affected areas. In a few animals, macroscopic hematuria is due solely to these nonneoplastic changes, but usually it is caused by development of tumors, which ulcerate and bleed more profusely into the lumen.

A large proportion of bracken fern–induced neoplasms are located in mucosa of the ventral and lateral walls of the bladder, which is in constant contact with urine and, presumably, the excreted toxins. Less commonly, tumors can develop in the renal pelvis and ureter. In general, lower urinary tract neoplasms occupy space and often cause mucosal ulceration, resulting in clinical signs of dysuria, hematuria, or obstruction. It is possible for neoplasms to invade or block the ureters, causing obstruction of ureteral urine flow, increased ureteral pressure, and hydronephrosis.

Epithelial neoplasms appear to develop from the hyperplastic and metaplastic (squamous and mucous) changes in the urothelium, which often accompany the vascular lesions described previously. In addition, Brunn's nests (solid or branched clusters of epithelial cells in the lamina propria or submucosa) may act as the site of origin for these neoplasms. Chronic cystitis usually accompanies the neoplastic changes. Several types of epithelial and mesenchymal neoplasms, either benign or malignant, may develop, including transitional cell carcinoma, squamous cell carcinoma, papilloma, adenoma, hemangioma, hemangiosarcoma, leiomyosarcoma, fibroma, and fibrosarcoma. In one large study of 433 cattle bladders, epithelial tumors were identified in 51.2%, mesenchymal tumors in 17.3%, and mixed forms in the remaining 31.4% of cases. Multiple tumors of more than one type may be present, and in more than 50% of affected cattle, mixed epithelial-mesenchymal neoplasms develop. Grossly, the more benign proliferations tend to variably fill the bladder lumen because they are exophytic, whereas the more malignant variants tend to invade through the muscular wall. For the latter, metastatic spread to local pelvic and sublumbar lymph nodes or lungs occurs in approximately 10% of cases.

In general, microscopic lesions include the presence of space-occupying masses that expand, invade, and/or obliterate normal lower urinary tract mucosa with variable degrees of invasion into the wall. The cells in the case of benign proliferations closely resemble their normal counterparts and, in the case of malignancies, tend to show cellular pleomorphism and high mitotic rates.

Uroplakins are products of urothelial cell differentiation, which form a major portion of the asymmetric unit membrane and are more consistently expressed in the superficial transitional epithelium. Although not necessarily of use in prognosticating tumors, staining for this molecule may confirm urothelial origin and assist identification of metastatic urothelial cell clusters. In addition, evidence of bovine papillomavirus-2 (BPV-2) positivity within the urinary bladder lesions of affected animals suggests a role for this virus infection in the development of cystitis and more specifically proliferative bladder lesions. Other studies showed BPV-2 was present in all vascular tumors examined, and two of its oncoproteins, E5 and E7, were expressed in neoplastic but not normal endothelium. Synergistic action of BPV-2 and bracken fern is implicated in development of chromosomal aberrations, which were consistently seen in animals with chronic enzootic hematuria and not in controls.

this syndrome are fibrinonecrotizing GN with lymphoplasmacytic tubulointerstitial nephritis and/or granulomatous interstitial nephritis. With prolonged disease, chronic glomerulonephritis may develop. It is thought that this response is an immune-mediated (type III) hypersensitivity response to circovirus and possibly concurrent PRRS viral infection.

Toxic Nephritis

Ingestion of several species of pigweed may cause acute renal failure in pigs. Gross lesions include marked perirenal edema and blood-tinged serous effusions elsewhere in the body. Histologically, swelling and necrosis of the lining epithelial cells, the presence of casts, dilated tubules, and mild interstitial edema are characteristic.

Leptospirosis

Host-adapted *Leptospira* serovars *pomona*, *tarassovi*, and *australis* cause significant disease in pigs. Preferential localization of the organism occurs in the renal proximal tubules and passage to the interstitium results in multifocal interstitial nephritis, similar to that seen in cattle and dogs. Grossly, poorly circumscribed white foci of various shapes and sizes that correspond to infiltrates of lymphocytes, plasma cells, and macrophages in the interstitial tissues are present. In addition, in chronic cases, concurrent interstitial fibrosis occurs.

Urolithiasis

Pigs most commonly have calcium carbonate uroliths formed by calcium phosphate or calcium oxalate. Struvite uroliths occur less frequently. As with other species, obstructive disease and/or rupture can occur at sites of lodgment, which is most commonly seen in castrated males. Neonatal piglets with low nutrient intake after birth may develop uric acid or urate crystals in the kidneys, ureters, and/or urinary bladder as a result of increased purine catabolism.

See the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals for illustrations.

Kidney Worm

In North America, the kidney worm (*Stephanurus dentatus*) is found most often in adult pigs in southern regions of the United States. The parasite is also a problem in other countries with warm climates. *Stephanurus dentatus* is a strongyloid worm that migrates to the kidney after cycling through the liver. Adult worms normally encyst in perirenal fat; however, some parasites may reside in the kidney. Peripelvic cysts often communicate with the renal pelvis and ureter, and fibrosis and chronic granulation tissue can enclose the parasite. Occasionally, shed nematode eggs are present in the urine sediment.

Erysipelothrix

Erysipelothrix rhusiopathiae is the most common bacterial cause of embolic nephritis in pigs, which can be a renal manifestation of classical diamond skin disease. The organism may spread to the kidney after cutaneous involvement or much more commonly because of bacteremia related to the development of septic valvular endocarditis. Grossly, the disease presents as either glomerular hemorrhages seen as multifocal regions of pinpoint hemorrhage throughout the renal cortex or as multiple foci of tan to white inflammatory infiltrates within the renal interstitium (Fig. 11-64). Histologically, the change described in the former situation is characteristic of septic embolic GN with fibrin and neutrophil aggregates noted within glomerular capillary tufts or as small abscesses within the interstitium.

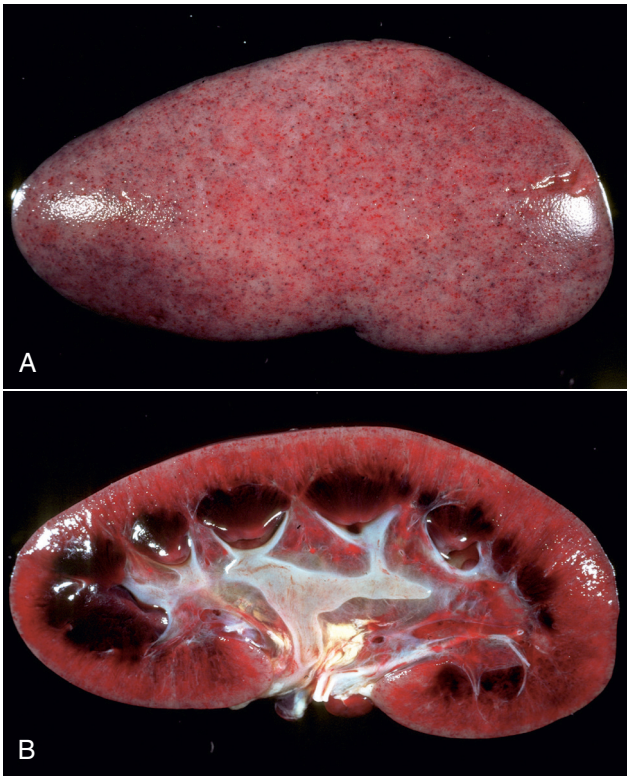


Figure 11-64 Bacterial-Induced Septicemic Renal Cortical Hemorrhages, Erysipelas, Kidney, Pig. A, Petechial hemorrhages caused by septic emboli of *Erysipelothrix rhusiopathiae* are randomly scattered over the capsular surface of the kidney. **B,** Dorsal section. Similar petechiae are present on the cut surface of the renal cortex. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Disorders of Dogs

Greyhound Vasculopathy

An idiopathic renal glomerular and cutaneous vasculopathy, formerly known as *Alabama rot*, occurs in greyhounds in the United States and the United Kingdom and is a potentially fatal disease of unknown etiology. As the name suggests, it typically affects the skin and kidneys of racing- and training-age greyhounds. Typically, there are multifocal erythematous and/or ulcerated skin lesions, commonly accompanied by distal limb edema as the result of a similar cutaneous vasculitis, with concurrent thrombocytopenia and acute renal insufficiency. The cause of the disease is unknown, but renal lesions are similar to those seen in acute DIC, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome in human beings. Grossly, kidneys from affected dogs are swollen and congested and show cortical petechiae (see Fig. 11-37, *A*). Microscopically, numerous glomeruli have segmental or global fibrinous thrombi, hemorrhage, and necrosis (see Fig. 11-37, *B*). At the glomerular vascular pole, the walls of afferent arterioles have fibrin deposits and foci of necrosis. In addition, electron microscopy findings indicate that glomerular endothelial damage is an important early event in the pathogenesis of this condition.

Ethylene Glycol Intoxication

Ethylene glycol (antifreeze) ingestion is one of the most common causes of intoxication and acute tubular necrosis in dogs, cats, and occasionally pigs. Ethylene glycol, the major constituent of antifreeze, is readily absorbed from the gastrointestinal tract, and a small percentage is oxidized by hepatic alcohol dehydrogenase to the toxic

metabolites glycolaldehyde, glycolic acid, glyoxylate, and oxalate. Ethylene glycol and its toxic metabolic products are filtered by the glomeruli, and acute tubular necrosis is caused by the direct interaction of these toxic metabolites, especially glycolic acid, on tubular epithelium (Fig. 11-65, *A* and *B*). Of particular significance is that large numbers of pale yellow foci of calcium oxalate crystals precipitate in renal tubular lumens, tubular epithelial cells, and the interstitium (Fig. 11-65, *C*). These crystals cause intrarenal obstruction with degeneration and necrosis of tubular epithelium that is postulated to be the direct effect of mechanical damage. With polarized light, the microscopic image is one of large numbers of birefringent, round to pyramidal crystals arranged in rosettes or sheaves within renal tubules, and they are virtually pathognomonic for ethylene glycol ingestion in dogs and cats (Fig. 11-65, *D*).

Acute Tubular Necrosis (Aminoglycosides)

Aminoglycoside antimicrobials, such as gentamicin, neomycin, kanamycin, tobramycin, amikacin, and streptomycin, are nephrotoxic. Relative renal toxicity varies among the different aminoglycoside drugs and correlates with the concentration of the compound in the renal cortex. Neomycin, which is highly nephrotoxic, concentrates to the greatest extent in the renal cortex, whereas streptomycin, the least nephrotoxic, does not concentrate appreciably in the renal cortex. Although gentamicin is intermediate in its nephrotoxicity between neomycin and streptomycin, tubular damage from gentamicin occurs with some frequency because it is a commonly used drug in veterinary medicine.

The susceptibility of animal species to the nephrotoxic effects of these drugs is variable and is related to differences in susceptibility of renal tubules and differences in the rate of excretion or inactivation of the drug among animal species. Aminoglycosides become concentrated in lysosomes, and their toxic effects occur after release of large concentrations of the drugs from these organelles. Toxic concentrations of aminoglycosides produce the following changes:

- Become concentrated in lysosomes
- Subsequently escape from lysosomes to accumulate in the cytoplasm
- Alter tubular cell membrane transport by the inhibition of Na^+/K^+-ATPase, causing an intracellular influx of hydrogen, sodium ions, and water
- Inhibit phospholipase activity so that phospholipids accumulate intracellularly
- Alter mitochondrial function
- Inhibit protein synthesis

These biochemical changes are responsible for the lesions of acute swelling of proximal tubular epithelial cells, mitochondrial swelling, rupture of lysosomes, dilation of endoplasmic reticulum, shedding of the tubular brush border, and cellular death.

Leptospirosis

Dogs are susceptible to several serovars of *Leptospira* spp. Leptospires enter the body through breaches in the mucous membranes, multiply and spread to the kidney, where they persist in the renal tubular cells. Affected dogs may exhibit fever, anorexia, vomiting,

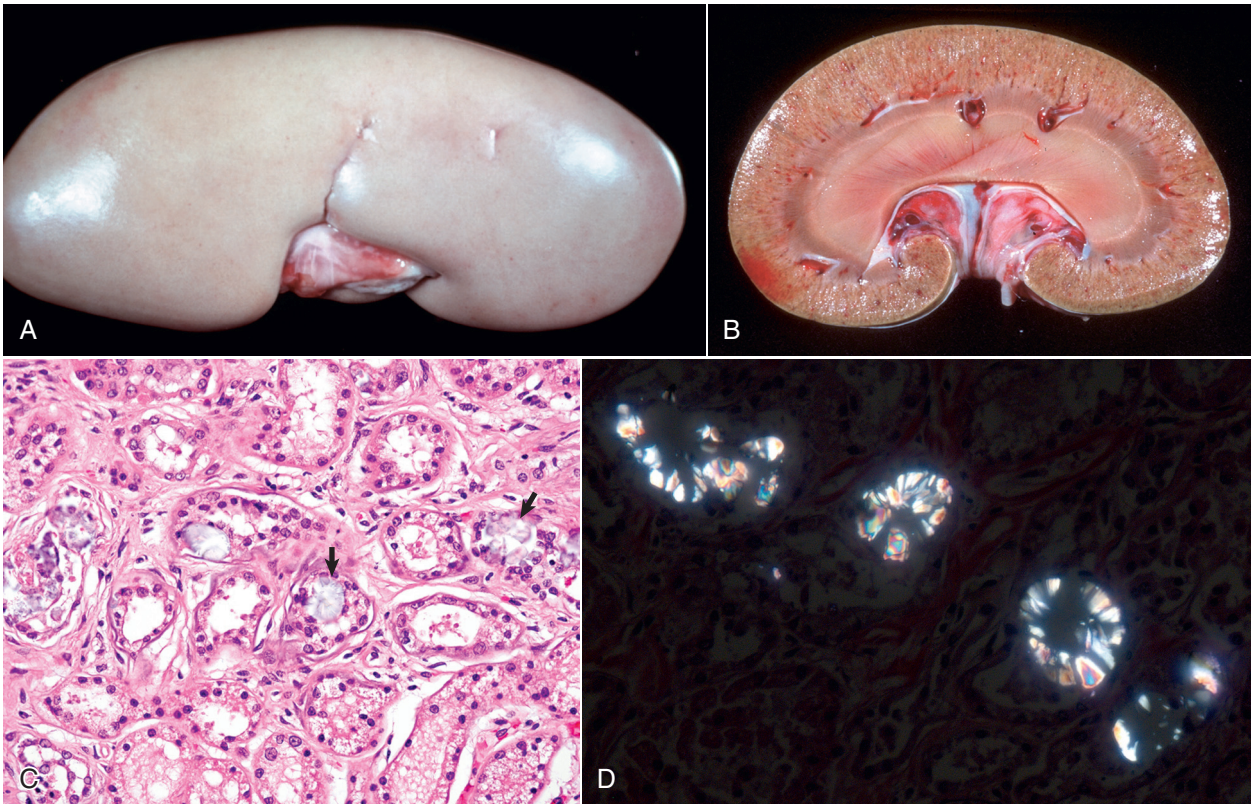


Figure 11-65 Oxalate Nephrosis, Kidney. A, Pig. Oxalate nephrosis following ingestion of oxalate-containing plants. The kidney is diffusely pale beige and swollen. **B,** Dorsal section, dog. The cortex is beige and finely mottled due to the deposition of multiple small foci of oxalate crystals in the renal tubules. **C,** Dog. Tubular dilation, necrosis, and early regeneration (increased numbers of epithelial cells lining several tubules). Numerous tubules contain oxalate crystals *(arrows)*, which have dilated the tubules and compressed their epithelium. H&E stain. **D,** Cat. Birefringent radiating sheaves of calcium oxalate crystals in renal tubules. Polarized light. H&E stain. (**A** and **B** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **C** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee. **D** courtesy Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

dehydration, icterus, muscle pain, and evidence of coagulopathy. In the more chronic infections, fever, anterior uveitis, anorexia, and weight loss are noted. Grossly, multifocal, coalescing inflammatory infiltrates that extend from the cortical medullary junction to the capsular surface are present (Fig. 11-66, *A*). In the more acute stages, in which tubular damage is prominent, there will be neutrophilic infiltrates, but this rapidly changes to lymphocytes and plasma cells (Fig. 11-66, *B*). In more chronic cases, variable amounts of fibrosis and subcapsular scarring occur (Fig. 11-14, *D*). Leptospires may often be identified within the cytoplasm and the lumen of affected tubules when special silver stains or immunohistochemistry are used (Fig. 11-66, *C*).

Infectious Canine Hepatitis

Transient glomerulitis, caused by a direct viral insult to the glomerulus, occurs in acute systemic viral diseases such as acute infectious canine hepatitis. The lesions are mild, usually transient, and result from viral replication in capillary endothelium. Acute viral GN produces the following gross lesions:

- Kidneys are often slightly swollen.
- Renal capsular surface is smooth.
- Kidneys are normal color or pale.
- Glomeruli are visible as pinpoint red dots on the cut surface of the cortex.

Viral-induced intranuclear inclusions are present in glomerular capillary endothelium in cases of infectious canine hepatitis. The inclusions are usually large, basophilic to magenta, and either fill the nucleus or are separated from the nuclear membrane by a clear halo. In cases of viral glomerulitis, lesions include endothelial hypertrophy, hemorrhages, necrosis of endothelium, and a thickened and edematous mesangium. Clinically, animals are systemically ill from the viral infection, but the glomerular signs are specifically those of a transient proteinuria. In addition, in dogs recovering from acute infectious canine hepatitis, lesions of lymphoplasmacytic interstitial nephritis can occur.

Canine Herpesvirus

In puppies younger than 3 to 5 weeks of age, intrauterine or neonatal infections can occur with pathognomonic kidney lesions consisting of petechial and ecchymotic hemorrhages. Typically, there is acute tubular necrosis with hemorrhage and the presence of intraepithelial intranuclear eosinophilic to amphophilic inclusions (Fig. 11-67). Once the puppies are older, typically more than 6 weeks of age, herpesvirus infections fail to induce renal lesions.

Pyelonephritis

Dogs with acute pyelonephritis can exhibit fever, depression, arched back from lumbar or renal pain, polydipsia, and polyuria. The most common causes of bacterial pyelonephritis in order of frequency include infection with *Escherichia coli*, *Staphylococcus aureus*, *Proteus mirabilis*, *Streptococcus* sp., *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter* sp. For the most part, these organisms take advantage of altered lower urinary tract defense mechanisms and ascend from the lower urinary tract to colonize the renal pelvis. Grossly, there can be accumulation of suppurative exudate in the pelvis with variable extension of tan cellular infiltrates from the medulla to variable portions of the overlying cortex (see Fig. 11-46, *A* and *B*). Histologically, there is tubular necrosis and loss with extension of bacterial colonies and variable amounts of neutrophils within tubules and the interstitium (see Fig. 11-46, *C*). In the more chronic forms, neutrophil numbers are reduced and lymphocytes and plasma cells predominate.

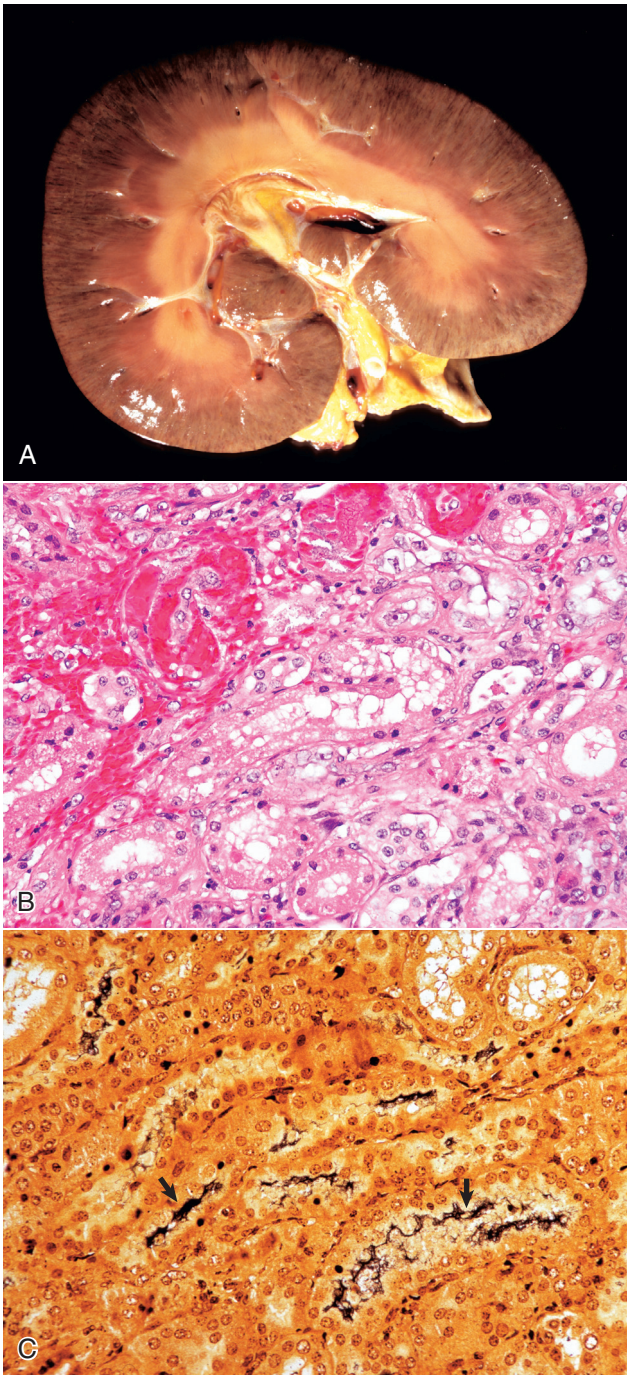


Figure 11-66 Acute Leptospirosis, Kidney. A, Interstitial nephritis, acute leptospira infection, dorsal section, dog. Radiating pale streaks are caused by cortical tubular necrosis and acute interstitial inflammatory infiltrates. The hilar fat and medulla are yellow from jaundice. **B,** Acute tubular necrosis, early regeneration, dog. Note the segments of tubular epithelium devoid of nuclei (coagulation necrosis) *(top left)* and the hemorrhage. At this early stage, there is an almost complete lack of inflammatory cells in the interstitium, but later in the subacute stage of leptospirosis there are interstitial infiltrates of lymphocytes and plasma cells, which tend to be near the corticomedullary junction. H&E stain. **C,** Leptospira, cow. Numerous leptospira *(arrows)* are present in the lumens of tubules. Leptospira colonization of tubule epithelial cells is typical of this bacterium. Warthin Starry silver stain. (**A** and **C** courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee. **B** courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

Figure 11-67 Canine Herpesvirus Nephritis (Canine Herpesvirus Type I), Kidney, Neonatal Puppy. A, Abdominal viscera. Multifocal renal cortical hemorrhages are grossly characteristic of this disease. **B,** Dorsal sections. Multifocal cortical hemorrhages are due to viral-induced vasculitis with necrosis and secondary hemorrhage. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Progressive Juvenile Nephropathy

The development of severe bilateral renal fibrosis has been described in young dogs of several breeds and referred to as *progressive juvenile nephropathy* or *familial (hereditary) renal disease*. In many dog breeds, a familial tendency is demonstrated (Box 11-11), but the mode of inheritance has been determined with certainty in only a few dog breeds. In Samoyeds, the lesion is x-linked; in bull terriers, it is autosomal dominant; and in the shih tzu, French mastiff, and English cocker spaniel, the disease appears to have a simple autosomal recessive inheritance.

Progressive juvenile nephropathy is a syndrome in which the morphologic manifestations can be the result of any of several chronic pathologic processes. The main manifestations include the following:

- Type IV collagen defect in the glomerular basement membrane
- Membranoproliferative GN
- Tubular disease of unknown cause with tubular atrophy and interstitial fibrosis
- Renal dysplasia

Gross renal lesions of progressive juvenile nephropathy are variable among affected breeds and among affected dogs within a breed. Generally, kidneys are notably shrunken, pale tan to white, and firm (see Fig. 11-26, C and *D*). The renal surface can be diffusely pitted and have a fine granular pattern, particularly in those dogs in which glomerular disease is the primary event. In addition, numerous small cortical cysts may be seen due to dilation of Bowman's capsule and glomerular atrophy. In cases of juvenile nephropathy that are tubular or dysplastic, the renal surface can have patchy, deeply depressed areas of cortical scarring. On the cut surface, the cortex is thin and has linear radial scars. The medulla is usually diffusely fibrotic. Small (1 to 2 mm), variably sized cysts are seen often in the cortex and the medulla.

Box 11-11 Breeds of Dogs with Progressive Juvenile Nephropathy

- American cocker spaniels
- English cocker spaniels
- Norwegian elkhounds
- Samoyeds
- Doberman pinschers
- Lhasa apsos
- Shih tzus
- Soft-coated Wheaten terriers
- Bull terriers
- Standard poodles
- Alaskan malamutes
- Miniature schnauzers
- German shepherds
- Keeshounds
- Chow Chows
- Weimaraners
- Golden retrievers

In the Doberman pinscher, the primary lesion is a glomerulopathy that appears microscopically as a membranoproliferative GN. Later in the clinical course of the disease, the lesions include extensive periglomerular fibrosis, tubular atrophy, and cystic dilation of Bowman's (urinary) space and tubules. In affected Samoyeds and English cocker spaniels, multilamellar splitting of the GBM is caused by inherited abnormalities in basement membrane type IV collagen. These lesions progress to severe glomerulosclerosis.

In Norwegian elkhounds, a tubular disorder of unknown cause has been described and is characterized by progressive tubular atrophy, periglomerular and interstitial fibrosis, and glomerulosclerosis without any indication of a primary glomerular disease.

Progressive juvenile nephropathy has been described in Lhasa apsos, shih tzus, soft-coated Wheaten terriers, Standard poodles, and golden retrievers as a condition resembling renal dysplasia, defined as an abnormality of renal development as a result of anomalous differentiation. Small, shrunken, fetal-like glomeruli composed of small cells with dense nuclei, minimal mesangial tissue, and nonpatent capillaries can be seen interspersed with normal, sclerotic, or hypertrophied glomeruli. Other lesions include marked interstitial fibrosis and tubular dilation. Most of the kidneys have minimal lymphoplasmacellular interstitial cell infiltrates.

Juvenile nephropathy in boxer dogs is characterized by pericapsular and interstitial fibrosis, inflammatory cell infiltration, dilated tubules, sclerotic glomeruli, and dystrophic calcification.

Although variations exist in gross and microscopic lesions (see Fig. 11-26, *E*), as well as in the pathogenesis of progressive nephropathy among the different breeds, a typical case is a dog 4 months to 2 years of age that has polyuria, polydipsia, and uremia. The clinical presentation, gross lesions, and microscopic changes are identical to those of chronic renal disease and renal fibrosis in mature or aging dogs.

Renal Carcinoma

Renal carcinomas are the most common primary renal neoplasms and occur most frequently in older dogs at an incidence of 1.5 in 100,000. The specific causes of renal carcinomas in human beings

are well determined compared with those in animal species, and little is specifically known about the pathogenesis of this entity in dogs. These renal neoplasms are usually large (up to 20 cm in diameter), spherical to oval, and firm. They often are pale yellow and contain dark areas of hemorrhage and necrosis and foci of cystic degeneration. The masses usually occupy and obliterate one pole of the kidney and grow by expansion, compressing the adjacent normal renal tissue (see Fig. 11-51). Histologic types include papillary, tubular, and solid (see Fig. 11-51, C), with tubular variants being the most common and solid variants being the most poorly differentiated. Metastasis to the lungs, lymph nodes, liver, and adrenal glands occurs frequently. Renal carcinoma has been associated with paraneoplastic conditions, principally polycythemia. This is because of concurrent overexpression of erythropoietin, which increases bone marrow production of red blood cells.

A variant of the typical renal carcinoma has been seen in German shepherd dogs in conjunction with nodular dermatofibrosis that is inherited as an autosomal dominant trait. The lesions are hereditary and consist of multifocal, bilateral, renal cystadenomas or cystadenocarcinomas. Grossly, these resemble the carcinomas described previously, but cysts are much more prominent. The neoplastic cells form solid sheets, tubules, or papillary growth patterns, and the cells in the carcinomas are more atypical and anaplastic. Cells vary in shape from cuboidal and columnar to polyhedral, vary in size, and have clear or granular eosinophilic cytoplasm. Nuclei range from small, round, granular, and uniform to large, oval, vesicular, and pleomorphic. Mitotic figures are numerous. These neoplasms have a moderate fibrovascular stroma.

Urolithiasis

See the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals for illustrations and a general discussion of urolithiasis.

Struvite Calculi

Information on this topic is available at www.expertconsult.com.

Calcium Oxalate Calculi

Information on this topic is available at www.expertconsult.com.

Uric Acid and Urate Calculi

Information on this topic is available at www.expertconsult.com.

Xanthine Calculi

Information on this topic is available at www.expertconsult.com.

Cystine Calculi

Information on this topic is available at www.expertconsult.com.

Chronic Cystitis

Several manifestations of chronic cystitis exist in dogs and include those with prominent follicular lymphoid proliferation in the submucosa (follicular cystitis) and those with prominent polypoid epithelial change (polypoid cystitis). Follicular cystitis (see Fig. 11-58) has a grossly recognized cobblestone appearance as a result of the presence of multifocal, disseminated, nodular, submucosal lymphoid proliferations (1 to 3 mm in diameter). This form of cystitis is particularly common in response to chronic urolithiasis. A red zone of hyperemia often surrounds these white-gray lymphoid foci. Microscopically, these raised foci are aggregates of lymphocytic cells in the superficial lamina propria. Epithelium overlying these foci may be normal or ulcerated and may be accompanied by fibrosis in the lamina propria. Hypertrophy of the tunica muscularis may also be present.

Polypoid masses (chronic polypoid cystitis), seen predominantly in dogs, typically develop from inflammatory and hyperplastic responses secondary to chronic irritation, which most often arise from persistent bacterial urinary tract infection or uroliths. The polyps arising in the bladder mucosa are composed of a core of proliferative connective tissue covered by surface epithelium. Mononuclear inflammatory cells are often present within the connective tissue core. Surface epithelium may form nests of hyperplastic transitional epithelial cells in the lamina propria (Brunn's nests) or undergo metaplasia to a mucus-secreting, glandular epithelial type (cystitis glandularis). The resulting polypoid masses, which are composed of inflammation, fibroplasia, and epithelial proliferation, occur most frequently in the cranioventral bladder wall (see Fig. 11-59). The masses may be broad-based or pedunculated, ulcerated, or covered by hyperplastic epithelium with goblet cell metaplasia. Chronic polypoid cystitis is often accompanied by clinically evident hematuria.

Transitional Cell Carcinoma

Transitional cell carcinomas are focal, raised nodules or diffuse thickenings of the urinary bladder wall, most common in the trigone region of the bladder (see Fig. 11-60, A). They are composed of pleomorphic to anaplastic transitional epithelium. Neoplastic transitional cells cover the mucosal surface as irregular layers, readily invade the lamina propria in the form of solid nests and acini, and are found within lymphatic vessels of the submucosa and muscle layers (see Fig. 11-60, B). Approximately 40% of these neoplasms have metastasized by the time of clinical diagnosis and are present in 50% to 90% of affected dogs at autopsy (syn: necropsy). Lymph nodes and lungs are the most common sites of metastasis; however, more widespread metastasis to other tissues, including bone, is possible. Terriers may be at a slightly elevated risk for transitional cell carcinoma development, and an association has been made between occurrence of these tumors and exposure to lawn pesticides.

Toxic Tubulointerstitial Nephritis

Melamine and Cyanuric Acid. Relatively recently, pet food contaminated with melamine and cyanuric acid to artificially elevate the dietary protein content produced large-scale outbreaks of renal failure–related mortality in dogs and cats in the United States and Korea. Sick animals had inappetence, vomiting, polyuria, polydipsia, and lethargy. Azotemia was recorded in many affected animals. The unique aspects of this food toxicity outbreak included necrosis that was localized to the distal rather than the proximal tubules. Unique intratubular rough and irregular brown birefringent crystals were noted in the more distal tubular portions of the nephron, and these may have been mistaken for oxalates in some early cases. In contrast, these crystals failed to stain with von Kossa calcium stains or alizarin Red S. A combination of both melamine and cyanuric acid was required to produce the ultimate renal failure in these cases.

Grape Ingestion

Ingestion of grapes or raisins as part of the diet or inadvertently by dogs can lead to a syndrome of acute renal failure and uremia accompanied by vomiting, lethargy, anorexia, and diarrhea. The mechanism for induction of acute proximal renal tubular necrosis is unclear, but tannins, similar to those in oak poisoning, are implicated as a toxic principle in these cases. The gross changes are those of an enlarged pale tan bulging kidney, and the histologic changes are not characteristic but are represented by acute proximal tubular necrosis.

Struvite is magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$), formerly referred to by the misnomer "triple phosphate." Struvite calculi are important in dogs, cats, and ruminants. In past decades, struvite was the most common type of urolith in dogs; however, in more recent years (since 2004), calcium oxalate has surpassed struvite as the most common type of canine urinary calculus. Some evidence supports changes in dietary formulations as a potential cause of this shift, and it is discussed further in the section on Calcium Oxalate Calculi. Females more commonly develop struvite calculi than do males because of the common association of these stones (infection calculi) with lower urinary tract infections. Bacterial ureases can induce supersaturation of urine with struvite by increasing urine pH, which decreases struvite solubility and increases ionization of trivalent phosphate, both of which favor calculus formation. Struvite stones are white or gray, radiopaque, chalky, usually smooth, and easily broken. They may be single and large, or numerous and sandlike.

The incidence of calcium oxalate urolithiasis, resulting from the aggregation of calcium salts in urine oversaturated with calcium and oxalate, has been increasing in dogs during the past two decades. Some evidence supports the hypothesis that nutritional factors, especially urine-acidifying diets designed to aid in dissolution of struvite calculi, may inadvertently increase the risk for calcium oxalate calculi. Oxalate calculi are white or yellow, heavy, hard, and often covered with jagged spines, although they may occasionally be smooth.

Uric acid is a metabolite of purine metabolism. These calculi contain ammonium urate with some uric acid and phosphate, or they contain sodium urate. Urate stones are most common in dogs, especially male Dalmatians, because they excrete high concentrations of uric acid in their urine. This is due to defective hepatocellular uptake of uric acid from the blood, which results in incomplete conversion of uric acid to allantoin, a more soluble product of purine metabolism. This defect is an inherited autosomal recessive trait. In addition, the transport system in renal tubules is also defective, which prevents reabsorption of uric acid from glomerular filtrate and contributes to urine supersaturation (hyperuricosuria). In addition to Dalmatians, other dog breeds that are predisposed to the development of urate urolithiasis include English bulldogs, miniature schnauzers, shih tzus, and Yorkshire terriers.

Dogs with portosystemic shunts have ammonium biurate crystals in their urine, and they may have urate-containing calculi in the kidneys and bladder. Urate calculi are usually multiple, hard, concentrically laminated, brown-green, and moderately radiodense. In the bladder, they are frequently spherical and less than 5 mm in diameter.

Xanthine is another metabolite of purines. It seldom appears in urine because normally it is degraded by xanthine oxidase to uric acid. As in human beings, two pathogenic forms of xanthine urolithiasis exist in dogs. The primary form, due to an inborn enzyme defect of either xanthine oxidase or xanthine dehydrogenase, is inherited as an autosomal recessive trait. These hepatic enzymes catalyze two sequential steps in degradation of purines:

- Conversion of hypoxanthine to xanthine
- Conversion of xanthine to uric acid

This form has been noted most often in dachshunds and recently in a family of Cavalier King Charles spaniels. The secondary form (iatrogenic) is the more common in dogs, especially Dalmatians, and is usually the result of previous treatment with allopurinol, which binds to and inhibits the action of xanthine oxidase, producing a similar metabolic end result to that seen in the hereditary forms. Xanthine stones are yellow to brown-red, friable, often concentrically lamellated, irregularly shaped, and radiolucent.

Many cystine calculi consist of pure cystine; others may also contain calcium oxalate, struvite, brushite (calcium hydrogen phosphate dihydrate), and complex urates. Cystine stones occur in dogs and rarely in cats. Cystinuria occurs in both males and females, but cystine calculi and urinary obstruction occur almost exclusively in males. Predisposed breeds include Newfoundlands, dachshunds, bulldogs, mastiffs, basset hounds, and Tibetan spaniels. The mode of inheritance of cystinuria is unknown in most breeds of dogs, but it is transmitted as a simple autosomal recessive trait in Newfoundlands. An inborn error of metabolism causes high concentrations of urinary cystine in affected dogs, although blood cystine concentrations remain normal. High urine concentrations of cystine are due to defective proximal tubular reabsorption from glomerular filtrate, and many affected dogs also have high concentrations of other amino acids in their urine. The other amino acids in the urine are more soluble than cystine, which precipitates in acidic urine, although the formation of cystine stones is also influenced by factors other than urine pH. Cystine calculi are small and irregular, soft and friable, waxy, and light yellow to red-brown turning to green on exposure to daylight.

Parasites

The giant kidney worm (*Dioctophyma renale*) is seen infrequently in dogs from temperate and cold countries worldwide. It is endemic in Canada and in northern regions of the United States. Because of a prolonged and complex life cycle, this nematode is seen only in dogs 2 years old or older. The adult nematode is red and cylindric; the females measure 20 to 100 cm long and 4 to 12 mm in diameter, and the males measure 14 to 45 cm long and 4 to 6 mm in diameter. This nematode resides in the renal pelvis where it causes severe hemorrhagic or purulent pyelitis, subsequent ureteral obstruction, and destruction of the renal parenchyma, resulting in a hydronephrotic kidney that appears as a cyst containing the nematode and purulent exudate.

Capillaria plica and *Capillaria feliscati* have been identified infrequently in dogs and cats worldwide. Typically, these nematodes are attached to the renal pelvis, ureter, or bladder of animals of various ages. Microscopically, inflammatory cells infiltrate and focal hemorrhages are associated with sites of attachment in the underlying submucosa. Clinical effects usually are not present, but hematuria and dysuria are produced occasionally.

Disorders of Cats

Granulomatous Nephritis

Cats with feline infectious peritonitis (FIP), particularly the noneffusive (dry) form, often have multifocal pyogranulomatous nephritis, secondary to severe primary vasculitis. The FIP virus is a mutated strain of feline enteric coronavirus that has lost its predilection for enterocytes and replicates in macrophages. The pathogenesis of the granulomatous form of FIP may be a cell-mediated immune response to the FIP virus that is partially effective in containing the virus to a relatively small number of macrophages at focal sites. The immune response causes a granulomatous necrotizing vasculitis and development of renal interstitial pyogranulomas characterized grossly by multiple, large, irregular, and pale gray subcapsular cortical foci (Fig. 11-68, A) that are firm and granular on cut surface (Fig. 11-68, B). These lesions are somewhat circumscribed and bulge from the capsular surface. They may be misinterpreted as neoplastic infiltrates, such as those associated with renal lymphoma or metastatic neoplasms, which tend not to have such a vascular orientation to the infiltrates. Microscopically, extensive accumulations of macrophages interspersed with lymphocytes, plasma cells, and neutrophils (pyogranulomas) surround foci of necrotizing fibrinoid vasculitis.

Renal Lymphoma (Lymphosarcoma)

Lymphoma is one of the most common neoplasms in cats and can affect the kidney as part of a systemic (multicentric) syndrome or may involve the kidney alone. Most affected cats are FeLV positive. The gross appearance of the kidney is that of diffuse renomegaly or multinodular enlargement (see Fig. 11-52). Multiple, white to tan, homogeneous masses of variable sizes are present on capsular surface of the kidney. Occasionally, feline lymphoma can appear as diffuse cortical infiltrates, wherein the kidneys are enlarged, paler than normal, and the subcapsular veins are obscured. Unlike with FIP-induced renal granulomas, the orientation of these neoplastic infiltrates does not typically center on vessels. Histologically, diffuse or nodular infiltrates and/or sheets of neoplastic lymphocytes, especially immunoblastic type, often obliterate normal renal architecture. Immunophenotyping for T or B lymphocyte origin can be performed; however, some feline lymphomas are of a non-B/non-T phenotype and genotype.

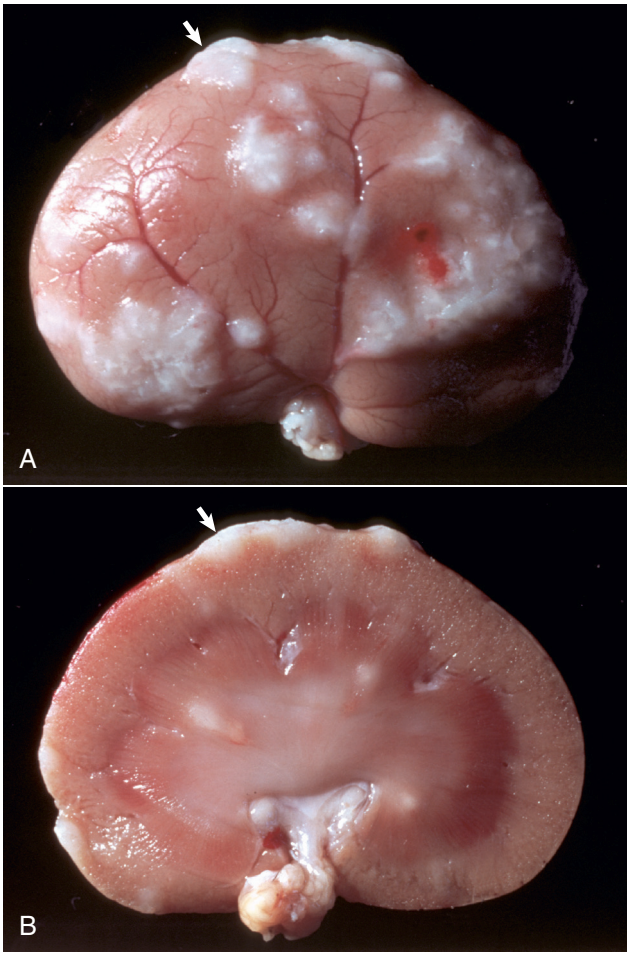


Figure 11-68 Granulomatous Nephritis, Feline Infectious Peritonitis, Kidney, Cat. A, Lesions are typical of the noneffusive (dry) form of feline infectious peritonitis. There are multifocal, coalescing white to gray granulomas *(arrow)*, which can be confused with the nodular form of lymphoma (lymphosarcoma), thus warranting histologic examination. **B,** Dorsal section. Multifocal, coalescing white to gray granulomas extend into the cortical parenchyma *(arrow)*. The pathogenesis of this lesion is determined by the effectiveness and/or ineffectiveness of both humoral and cellular immune responses. Depending on the immune response, the pathogenesis can involve a primary immune complex vasculitis (type III hypersensitivity [effusive form]) and/or delayed hypersensitivity response (type IV hypersensitivity [noneffusive form]); thus the lesions are oriented around blood vessels (primarily capillaries and venules) and are granulomatous. (Courtesy Dr. M.D. McGavin, College of Veterinary Medicine, University of Tennessee.)

Urolithiasis

See the section on Kidney and Lower Urinary Tract, Disorders of Domestic Animals for illustrations and a general discussion of urolithiasis.

Struvite Calculi

Information on this topic is available at www.expertconsult.com.

Calcium Oxalate Calculi

Information on this topic is available at www.expertconsult.com.

Feline Idiopathic Cystitis (Hemorrhagic Urocystitis)

Feline idiopathic cystitis (FIC) is a condition diagnosed in cats that is the most common cause of feline lower urinary tract disease (FLUTD). Feline idiopathic cystitis has also been referred to as

Struvite is magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$), formerly referred to by the misnomer "triple phosphate." Struvite calculi are important in dogs, cats, and ruminants. Struvite is one of the most common uroliths in cats, although during the past few decades, trends in the occurrence of struvite uroliths and calcium oxalate uroliths have shifted substantially, often in a reciprocal manner. In cats, struvite calculi are most often sterile (not associated with bacterial infection), although infection-induced struvite uroliths may be seen, especially in young or old cats (<1 year or >10 years of age). Nutritional factors, including high dietary magnesium, phosphorus, and dietary protein concentrations that cause aciduria, decrease the risk of sterile struvite calculi. Struvite stones are white or gray, radiopaque, chalky, usually smooth, and easily broken. They may be single and large, or numerous and sandlike, and they are one cause of feline lower urinary tract disease (FLUTD).

Of considerably more importance than discrete struvite calculi are the amorphous accumulations of protein, cellular debris, and struvite crystals that form sabulous (gritty or sandy) urethral plugs that are also a manifestation of FLUTD. These plugs are thought to result from concomitant occurrence of urinary tract inflammation and the presence of various types of urine crystals. The obstructive material is composed of a mixture of struvite "sand" and a rubber-like protein matrix, the latter of which is composed of inflammatory cells, proteins including Tamm-Horsfall mucoprotein (secreted by the cells lining the ascending limb of the loop of Henle and the distal tubules), and cellular debris. The incidence of urethral plugs has decreased as more cats have been fed magnesium-restricted and/or acidifying diets.

The formation of calcium oxalate uroliths results from the aggregation of calcium salts in urine oversaturated with calcium and oxalate. During the past two decades, trends in the incidence of calcium oxalate urolithiasis have varied dramatically and often in inverse proportions to struvite urolithiasis in cats. Beginning in the mid-1980s, the incidence of feline calcium oxalate calculi increased to become the most common urolith type by 2002. Then, beginning in 2003, the occurrence of calcium oxalate uroliths began to decrease progressively, most likely due to reformulations of feline diets that reduce urine acidity and provide adequate concentrations of magnesium. The inverse relationship between the incidence of calcium oxalate uroliths and struvite uroliths is presumed to be a result of reciprocal risk factors for the two calculi types (i.e., reduced urine acidity decreases the risk of calcium oxalate urolithiasis but increases the risk of struvite urolithiasis).

With the previously mentioned increased occurrence of calcium oxalate uroliths in cats, there has been a parallel increase in these uroliths in the kidneys (nephroliths) and ureters. The frequency of uroliths diagnosed in the upper urinary tract (kidneys and ureters) of cats has increased 10-fold during the past 20 years, the majority of which are composed of calcium oxalate. This recent increase in prevalence of upper urinary tract uroliths in cats has shifted the diagnostic considerations in these patients. Oxalate calculi are white or yellow, heavy, hard, and often covered with jagged spines, although they may occasionally be smooth.

"feline interstitial cystitis" because of some commonalities to the condition of a similar name in human beings. In cats, FIC is believed to be the result of complex interactions between the urinary bladder, nervous system, adrenal glands, and environmental factors. Typical clinical signs include dysuria, stranguria, and hematuria. It is a diagnosis of exclusion, made by ruling out the presence of urolithiasis, urethral plugs, trauma or strictures, bacterial cystitis, or urinary tract neoplasia. FIC, as a component of FLUTD, is more common in middle-aged, overweight male cats with indoor housing. Histologic lesions of FIC are nonspecific, but they include submucosal edema, dilation of blood vessels with neutrophil margination, and submucosal hemorrhage. Erosion, ulceration, or thinning of urothelial epithelium is common in chronic cases of FIC. Several other alterations that may reflect the pathogenesis are usually noted in the urinary bladders of affected cats. These changes include an increase in the number of submucosal mast cells, a decrease in the concentration of urothelial glycosaminoglycans, an increase in urothelial permeability, and neurogenic inflammation. It is possible that mast-cell degranulation contributes to inflammation. Decreased glycosaminoglycans may allow urine to penetrate the urothelial barrier and induce submucosal inflammation. Disruption of the tight junctions between urothelial cells results in increased permeability. Neurogenic inflammation may occur after local release of neurotransmitters that results in vasodilation and leakage. Thus potential abnormalities in local, sensory, central, and efferent nervous systems may play a role in this syndrome that arises, at least in part, from complex interactions between the urinary bladder and the nervous system.

Toxic Renal Disease

Melamine and Cyanuric Acid. Cats are similarly affected by melamine/cyanuric acid contamination of pet foods as are dogs (see previous section on Kidney and Lower Urinary Tract, Disorders of Dogs).

Lily Toxicity. Cats are prone to a species-specific toxicity associated with ingestion of leaves or flowers of lily plants. This is often seasonal when Easter lily (*Lilium longiflorum*) plants are purchased and brought into the cat's environment. Day lily (*Hemerocallis* spp.), tiger lily (*Lilium* sp.), Japanese show lily (*Lilium hybridum*), and rubrum lily (*Lilium rubrum*) can all cause renal toxicosis in cats. Vomiting and lethargy within 1 to 5 days of ingestion are common. The toxic ingredient is not known, but renal damage in the form of acute tubular necrosis from exposure seems particularly severe in these cases.

Suggested Readings

Suggested Readings are available at www.expertconsult.com.

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