Figure 11-11A. Types of congenital developmental anomalies, kidney. A, Unilateral hypoplastic kidney, dorsal sections, young dog. Grossly, the affected right kidney is nearly identical structurally to the left kidney but smaller in size (hypoplasia)

Renal Hypoplasia
Inherited
White pigs in New Zealand
Foals
Dogs
Can be bilateral or unilateral
Rare
Figure 11-11B. Types of congenital developmental anomalies, kidney B, Unilateral hypoplastic kidney, young cat. The left kidney (ventral-dorsal view) is normal in shape and structure but reduced in overall size.
Figure 11-11C. Types of congenital developmental anomalies, kidney C, Juvenile progressive nephropathy, young dog. Bilateral abnormally shaped firm kidneys

Renal Dysplasia
Abnormal differentiation and presence of structures not normally found in the kidney
Sheep
Cystic renal dysplasia
Inherited AD
Microscopic features
ASynchronus differentiation of nephrons- aggregates of small hypercellular glomeruli in the cortex
Persistence of primitive mesenchyme- interstitial connective tissue has a myxomatous appearance
Persistence of metanephric ducts
Atypical (adenomatoid) tubular epithelium
Presence of cartilaginous and or osseus tissue, interstitial fibrosis, renal cysts, a few enlarged hypercellular gomeruli

Progressive Juvenile Nephropathy
Familial renal disease of Lhasa Apso, Shih Tzu, golden Retriever
AN example of renal dysplasia
Figure 11-11D. **Types of congenital developmental anomalies, kidney.**

D, Juvenile progressive nephropathy, dorsal sections, dog. Section of the kidneys from Fig 11-11,C
Figure 11-11E. Types of congenital developmental anomalies, kidney
E, Juvenile progressive nephropathy, chronic, dog. Note the interstitial fibrosis, tubular atrophy, dilated urinary space, and mineralization. H&E stain
Figure 11-11F. **Types of congenital developmental anomalies, kidney**

F, Polycystic disease, dorsal section, cat. Numerous variably sized tubular cysts are present in the cortex and medulla and affect approximately 60% of the kidney. The cysts contain clear colorless fluid. This condition is hereditary, and Persian cats are predisposed

Renal Cysts

Distentions of the cortical or medullary renal tubules filled with clear or watery fluid

Four plausible mechanisms

Obstruction of nephrons → secondary dilation

Weakened tubular basement membranes allowing saccular dilatations

Focal epithelial hyperplasia with production of BM, increased tubular secretion and increased intratubular pressure

De-differentiation of tubular epithelial cells → loss of polarity → loss of cell arrangements → reduced fluid tubular resorption

Congenital Polycystic Kidneys
Autosomal Dominant in Pigs and Lambs
Inherited with cystic biliary disease in Cairn and Westhighland White terriers
Persian cats have inherited Polycystic kidney Disease
Defects in Polycystin -1 and 2
Polycystin-1
Cell membrane associated protein with a large extracellular domain
Involved in normal cell proliferation and apoptosis
Also involved in cell adhesion- component of desmosomes
Polycystin-2
Localized plasma membrane calcium channel
Figure 11-12. **Emphysema, urinary bladder mucosa, cow.** The multiple “nodules” are mucosal gas bubbles that expand the mucosa and are secondary to bacterial infections of the lower urinary tract (principally by *Escherichia coli*, *Clostridium perfringens*, and rarely *Candida* yeasts), which result in splitting of glucose molecules to release CO2 into the bladder lumen, from where the gas can be absorbed into bladder lymphatics. 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.

Renal tubular function

Primary renal Glucosuria
Inherited in Norwegian elkhounds
Proximal tubular capacity to resorb glucose is reduced

Glucosuria
Most commonly from Diabetes Mellitus
Predisposes dogs to
Bacterial infections of the lower urinary tracts
Urinary bladder emphysema
E coli
Clostridium perfringens
Candida albicans
Release CO2

Fanconi Syndrome
Basenji dogs
Abnormal membrane structure of the proximal tubulae epithelial cell brush borders because of altered lipid content in the cell membrane.
Histological changes
Irregularly sized epithelial cells in the convoluted tubules and loops of henle
Progressive renal insufficiency and fibrosis
Aminoaciduria, glucosuria, proteinuria, phosphaturia, metabolic acidosis, multiple endocrine abnormalities

Sex-Linked Cystinuria
Predisposes to calculus formation
Obstruction of the lower urinary tract (Urolithiasis)

Glomerular Diseases
Leakage of various low molecular weight proteins
Protein reabsorptive properties are overwhelmed
Hyaline droplets
Intra-cytoplasmic protein accumulations in tubular epithelium reabsorbed from the lumen
Glomerular sclerosis
Persistent damage to glomerular capillaried results in fibrosis
Due to hyperfiltration by increased hydrostatic pressure
Immune complex deposition
Subepithelial
Subendothelial
Mesangial locations
Inflammatory progression
Recruitment of inflammatory cells
Release of inflammatory mediators and enzymes
Destruction of glomerular structures
Continued damage by hyperfiltration
Figure 11-13A. Embolic nephritis (suppurative glomerulitis), kidney, horse.

A, Multiple, small pale white necrotic foci and abscesses are present subcapsularly

Embolic Nephritis (suppurative Glomerulitis)
Bacteremia lodge in random glomeruli and interstitial capillaries formation of microabscesses in the renal cortex
Actinobacillus Equuli
Foals die soon after birth
Many microabscesses in various organs
Erysipelothrix rhusiopathiae
Pigs
Corynebacterium pseudotuberculosis
Goats and sheep
Grossly
Multifocal random raised, tan pinpoint foci- subcapsular and on cut surface in the renal cortex
Microscopically
Glomerular capillaries contain numerous bacterial colonies mixed with necrotic debris and neutrophils often obliterating the glomerulus
Figure 11-13B. **Embolic nephritis (suppurative glomerulitis), kidney, horse.**

_B, Dorsal section. Variably sized abscesses are scattered throughout the cortex (arrows).

**Viral Glomerulitis**

Direct Viral Insult- viral replication in capillary endothelium
Infectious canine hepatitis- CHV-1
Equine Viral Arteritis
Hog cholers (CSF)
Newcastle
Neonatal porcine cytomegalovirus
Gross Lesions
Swollen Kidneys
Renal capsular surface is smooth
Pale or normal color kidneys
Glomeruli look like visible as pinpoint red dots on cut surface of cortex
Microscopically
Intranuclear inclusions in glomerular capillary endothelium (CHV, Cytomegalovirus)
Large basophilic to magenta and either fill the nucleus or are separated from the nuclear membrane by a halo
FA antigen detection
Endothelium, epithelium, mesangial cells
EVA, CSF, AN
Endothelial hypertrophy
Thickened edematous mesangium
Hemorrhages
Necrosis of endothelium

Chemical Glomerulonephritis
Direct Injury to glomerular epithelial cells
Puromycin
Aminonucleoside
Adriamycin
Histamine receptor antagonists
Direct injury to capillary endothelium
Cyclosporine A
Altered renal blood flow
Cyclosporine A
Immunologic reactions
Drug reactions and immune complexes
Hyperimmune serum
Gold
D-penicillamine
Antigen-antibody complexes
Antinuclear antibodies
Procainaminde
hydralazine
Anti-basement membrane antibodies in the glomerular tuft
Hydrocarbon solvents
Functional loss of nephrons causes functional hypertrophy of other nephrons
Continuing physical loss of nephrons sets up a cycle for increase in glomerular hypertension and hyperfiltration leading to glomerular sclerosis, progressive nephron loss and interstitial fibrosis
Figure 11-13C. Embolic nephritis (suppurative glomerulitis), kidney, horse. 

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.
Figure 11-15. Immune-complex glomerulonephritis, kidney, glomerulus, dog. Transmission electron photomicrograph of a glomerulus with immune-complex deposits due to dirofilariasis. A heartworm microfilaria is present in the capillary lumen (arrowheads). The basement membrane is irregularly thickened and contains granular, electron-dense deposits (arrows). The podocytic foot processes are fused. TEM. Uranyl acetate and lead citrate stain.

Immune Mediated Glomerulonephritis
Anti-basement membrane glomerulonephritis
Deposits Ig and C3 in BM

Immune Complex Glomerulonephritis
Persistent infections
Prolonged antigenemia → formation of more soluble immune complexes
Specific Viral Infections'
FeLV
FIP
Chronic Bacterial Infections
Pahtogenesis
Form soluble immune complexes (ag-Ab): Antigen = Antibody; or Antigen slightly > Antibody
Selectively deposits in glomerular capillaries
Stimulates complement fixation → C5a, C3a, C567 (chemotactic for neutrophils)
Damage to BM through neutrophils, arachidonic acid metabolites, oxidants, hydrogen peroxide
Monocyte infiltrations continue to damage glomeruli
Circulating immune complexes can deposit but antigen binding to endogenous antigens is more common
Direct action of C5b-9 on glomerular components results in activation of both glomerular epithelial cells and mesangial cells to produce damaging chemicals and oxidative components.
An increase in local glomerular vascular permeability is necessary for immune complexes to leave the circulation
Mast cells release of vasoactive mediators
Or basophils or platelets
Can be stimulated by IgE binding, cationic proteins from neutrophils and C3a and C5a
PAF is released from mast cells, basophils or macrophages
Causes platelets to release vasoactive amines
Immune complexes deposited in capillary walls can grow larger
Aggregation of platelets causes activation of Hageman factor → results in fibrin thrombi → glomerular ischemia
Membrane attack complex C5a-9 can directly damage epithelial cells and ECM → epithelial cell detachment/ Basement membrane thickening → proteinuria
EM- immune complexes appear as dense bodies in the BM and sub-epithelial areas
IgG and IgM are the most common

Gross Lesions
Swollen, pale
Pinpoint red dots on cut surface of the cortex (normal in horses)
Distribution of microscopic lesions
Diffuse = most of the glomeruli are affected
Focally = a certain proportion of glomeruli are affected
Globally = An entire glomerular tuft
Segmental = only a portion of a glomerular tuft is affected
Figure 11-18. **Proliferative glomerulonephritis, kidney, dorsal section, dog.**
The small, white, round foci in the cortex are enlarged glomeruli.

**Proliferative glomerulonephritis**
A form of immune complex glomerular disease
Increased cellularity of the glomerular tuft
Proliferation of glomerular epithelium (visceral, podocytes)
Proliferation of glomerular endothelium (capillary)
Proliferation of mesangial cells (interstitial cells)
Influx of lymphocytes and neutrophils (Capillary and mesangium)

**Membranous Glomerulonephritis**
Diffuse glomerular capillary basement membrane thickening
The presence of sub-epithelial Ig deposits
Can replace the BM in foci, and when removed are replaced by sclerotic changes
(increased PAS positive material) and not fibrosis
(most common in cats)
Membranoproliferative Glomerulonephritis
Hypercellularity following proliferation of glomerular cells AND thickening of the capillary BM and mesangium
Most common in dogs
Type 1 = subendothelial deposits, granular pattern, and C3 deposition secondary to immune complex deposition
Type 2 = Dense deposit disease, unknown composition, small quantities of C3, form irregular deposits in the subendothelial space.

Accompanying Lesions
Synechiae
Adhesions between the parietal and visceral epithelium (Bowmans capsule and the epithelium of the tuft)
Parietal epithelium
Hypertrophy
Hyperplasia
Capillaries
Fibrinogen or fibrin thrombi in the capillaries
Secondary to glomerular damage
Tubules
Dilated
Filled with protein- homogenous fluid
MElasangial matrix
Increased amounts
Glomerular crescent
Chronic disease
Proliferation of parietal epithelium
Influx of monocytes
Deposition of fibrin
Forming a semicircular, hypercellular, intraglomerular lesion
Glomerular sclerosis 638
Chronic glomerulonephritis
Shrinking
“hyalinized”
Increase in both fibrous connective tissue and mesangial matrix
Loss of glomerular capillaries
Can be diffuse or multifocal, global or segmental
Reduces blood flow to the distal tubules causing epithelial cell death via apoptosis
Tubule atrophy and flattening of remaining tubular epithelium
Chronic proteinuria has been reported to cause tubular epithelial cell apoptosis
Factors Associated with glomerular Sclerosis
Unrestricted protein in diet
Increased glomerular capillary pressure
Cytokines
PDGF
These factors do the following
Cause glomerular hypertension and hyperfiltration
Cause mesangial cell proliferation
Increase mesangial matrix production
Cause synechia by advancing visceral epithelial cell loss
Lupoid nephrosis. The glomerulus appears normal, with a thin basement membrane. PAS reaction.

**Figure 11-19A.** Schematic diagram of lupoid nephrosis (A and C) and membranous glomerulonephritis (B and D). A, Lupoid nephrosis. The glomerulus appears normal, with a thin basement membrane. PAS reaction.
Figure 11-19B.  Schematic diagram of lupoid nephrosis (A and C) and membranous glomerulonephritis (B and D) B, Membranous glomerulonephritis. The glomerular basement membrane is diffusely thickened. PAS reaction
Figure 11-20A. Membranoproliferative glomerulonephritis, glomerulus, kidney. A, Note the increased mesangial matrix and thickened and focally split basement membranes (stained black). The glomeruli are also infiltrated by leukocytes (not visible here). Silver reticulum stain.
Figure 11-21A. **Types of glomerulonephritis. A,** Proliferative glomerulonephritis, pig. The lesion is characterized principally by hypercellularity of the glomerulus due to increased numbers of mesangial cells. H&E stain.
Figure 11-21B. Types of glomerulonephritis. B, Membranous glomerulonephritis, dog. The lesion is characterized by generalized hyaline thickening of glomerular capillary basement membranes. It can occur in dogs with dirofilariasis. H&E stain.
Membranoproliferative glomerulonephritis, horse.
Membranoproliferative glomerulonephritis has histologic features of both proliferative glomerulonephritis and membranous glomerulonephritis. Abundant periglomerular fibrosis surrounds this hypercellular glomerulus (mesangial cells). Mesangial matrix is prominent in the top-right area of the glomerulus. H&E stain.

**Figure 11-21C. Types of glomerulonephritis C**, Membranoproliferative glomerulonephritis, horse. Membranoproliferative glomerulonephritis has histologic features of both proliferative glomerulonephritis and membranous glomerulonephritis. Abundant periglomerular fibrosis surrounds this hypercellular glomerulus (mesangial cells). Mesangial matrix is prominent in the top-right area of the glomerulus. H&E stain.
Figure 11-21D. **Types of glomerulonephritis. 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 glomerulonephritis), glomeruli are essentially nonfunctional. H&E stain.
Figure 11-22. **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 glomerulonephritis. 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*).

**Glomerular Amyloidosis**

*Amyloid = insoluble fibrillar protein with Beta-pleated sheet conformation*

**Types**

- **AL- light chain**
  - From incomplete breakdown of pre-amyloid proteins from myelomas and B cell dyscrasias
- **AA- Reactive systemic amyloid**
  - Chronic inflammation causing increased SAA production form the liver

Causes proteinuria and uremia
Can result in nephrotic syndrome
Decreased renal blood flow
Tubular atrophy, degeneration and necrosis
Papillary necrosis
Gross
Enlarged pale
Smooth to finely granular cortical surface
Fine translucent dots in the surface
Quick dx- Lugols iodine + sulfuric acid = black spots
Microscopically
Amyloid in both mesangium and subendothelial locations
Can be segmental
Eosinophilic homogenous to slightly fibrillar material
When amyloidosis involves entire glomerulus
Glomerulus is enlarged
Capillary lumina become obliterated
Tuft appears as large hypocellular, eosinophilic, hyaline, sphere
Can be present in renal tubular BM
Hyalinized and thickened
Tubular epithelium can be atrophic
Can contain proteinaceous and cellular casts
Amyloid stains orange with congo red and when polarized has a green bi-refringence
Figure 11-23. **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.
Figure 11-24A.  **Amyloidosis, glomerulus, kidney, dog.**  A, All glomerular tufts are diffusely and notably expanded by amyloid (pale eosinophilic homogeneous deposits), with the result that they are relatively acellular. H&E stain.
Figure 11-24B. Amyloidosis, glomerulus, kidney, dog B, Amyloid, the pale eosinophilic homogeneous hyalinized deposits, expands the mesangium of the glomerulus (arrow). H&E stain.
The fine white dots in the cortex (both on the capsular and cut surfaces) are glomeruli with extensive glomerular capillary thrombosis.

**Figure 11-25A. Vasculopathy, renal (and cutaneous) vasculopathy syndrome, glomerulus, kidney, dog, greyhound.** A, The fine white dots in the cortex (both on the capsular and cut surfaces) are glomeruli with extensive glomerular capillary thrombosis.

**Miscellaneous Glomerular Conditions 640**

**Glomerular lipidosis**
- Small aggregates of lipid-laden macrophages in glomerular tufts
- Incidental finding in dogs
- Inherited hyperlipoproteinemia in cats
- Xanthogranulomas
- Atherosclerosis
- Hyperchylomicronemia

**Idiopathic renal glomerular vasculopathy and cutaneous vasculopathy**
- Inherited in greyhounds
- Similar conditions
- DIC
- Thrombotic thrombocytopenic purpura
Hemolytic-uremic syndrome
Gross
Kidneys swollen and congested
Cortical petechia
Multifocal erythematous and ulcerated skin lesions and distal limb edema
Microscopic
Fibrinous thrombi in glomeruli
Hemorrhage and necrosis
Canine Hyperadrenocorticism
Exogenous glucocorticoid therapy
Results in proteinuria
Lesions
Mesangial hypercellularity
Synechia
Thick BM’s
Effacement of epithelial foot processes
Necrotic glomerular endothelial cells and extensive glomerular capillary thrombosis (arrows) are typical of idiopathic glomerular (and cutaneous) vasculopathy syndrome in greyhound dogs.

Figure 11-25B. **Vasculopathy, renal (and cutaneous) vasculopathy syndrome, glomerulus, kidney, dog, greyhound.** 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.
Figure 11-27. Uremic gastritis, stomach (right), dog. Because of uremia, the stomach wall is hemorrhagic and the contents contain blood and mucus (not shown here). Note the edematous mucosal thickening (arrow).

Diseases of tubules and interstitium 641

Azotemia
Increased serum concentrations of urea, creatinine
Renal failure can result in the following
Increased concentrations of guanidines, phenolic acids, and large molecular weight alcohols
Metabolic acidosis
Alterations of blood plasma ion concentrations
Hypertension
Uremia
Syndrome associated with multisystemic lesions and clinical signs because of renal failure
Lesions
Endothelial degeneration and necrosis

- Vasculitis with secondary thrombosis and infarction

Caustic injury to epithelium of the oral cavity and stomach (ammonia)

Ulcerative stomatitis, catarrhal

Ulcerative and hemorrhagic gastritis with midzonal mineralization

Ulcerative and hemorrhagic colitis in horses and cattle

With neutrophilic inflammation and mineralization of arterioles

Fibrinous pericarditis – fine granular fibrin deposits on the epicardium (visceral pericardium)

Diffuse pulmonary edema

Secondary to vasculitis

Mucoarteritis

Leading to large mural thrombi in the heart
Uremic gastritis, stomach, dog. A, There is accentuation of the gastric rugae and calcification in the deep mucosa.

**Figure 11-28A.** Uremic gastritis, stomach, dog. A, There is accentuation of the gastric rugae and calcification in the deep mucosa.
Figure 11-28B. **Uremic gastritis, stomach, dog B**, The mucosa has laminar mineralization of gastric glands (arrow). von Kossa stain.
Figure 11-29. Nephrocalcinosis, kidney, dorsal section, dog. Note the white streaks 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.

Alterations in calcium and phosphate metabolism
High phosphorus
Low to normal calcium
Increased erythrocyte fragility (uremia)
GFR < 25% P is not adequately secreted
Because P increases, Calcium precipitates
Reduced serum calcium stimulates PTH
Osteomalacia and osteoporosis, and fibrous osteodystrophy
Decreased Vitamin D synthesis
Decreased intestinal absorption of calcium
Nephrocalcinosis: calcium precipitates intracellularly in the renal tubules (mitochondria and BM)
mineral (intercostal mineralization) are present in the subpleural intercostal connective tissue as a result of chronic uremia

Figure 11-30. 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

Subpleural calcification in dogs
Uremic mineralization
White-grey granular pleural thickenings with a horizontal ladderlike arrangement

Hyperkalemia
Decreased filtration
Decreased tubular secretion
Decreased tubular sodium transport
Cell lysis
Extracellular shift of fluid
Acute tubular necrosis

- nuclear karyolysis and intratubular nuclear and proteinaceous debris. Note that the nuclei, chiefly of endothelial cells of intertubular capillaries and fibroblasts are viable, which differentiates this lesion from an infarct in which all cells are dead.

Figure 11-38. Acute tubular necrosis, kidney, proximal tubules, cat. The lesion is characterized by coagulation necrosis of tubular epithelial cells (arrows), as demonstrated by nuclear karyolysis and intratubular nuclear and proteinaceous debris. Note that the nuclei, chiefly of endothelial cells of intertubular capillaries and fibroblasts are viable, which differentiates this lesion from an infarct in which all cells are dead. H&E stain. Inset: Normal proximal tubules, kidney. In this example, the proximal tubular epithelial cells lack both the nuclear and cytoplasmic changes characteristic of coagulation necrosis, as demonstrated in the main figure. H&E stain

Acute renal failure
Pre-renal (hypovolemia, shock)
Renal- impaired glomerular or tubular function
Post-renal- obstructive

Causes of tubular disease
Ascending pyelonephritis
Toxins in tubules
Ischemia

4 main pathologic alterations in acute renal failure
Decreased ultrafiltration
Intratubular obstruction
Fluid back leak
Intra-renal vasoconstriction

These can be caused by
Decreased renal perfusion
Decreased glomerular filtration
Ischemic tubular damage
Obstructive renal tubular damage
Tubulointerstitial inflammation, edema or fibrosis

Acute Tubular Necrosis 645
Ischemia
Early changes
Altered ion transport at the luminal surface
Reduced sodium resorption
Increased sodium concentration distally → stimulates RAAS → vasocostriction → ischemia
Basement membranes are not damaged
REGENERATION can occur
Causes of Ischemia
Hypotension → preglomerular vasoconstriction and decreased GFR
Can cause sublethal cell injury or cell death by necrosis or apoptosis

Direct toxic insult to nephron tubules
Intracellular conversion to reactive metabolites
Reabsorption or diffusion of toxic substances
Nephrotoxins
Vascular
Glycolic acid
Glycoaldehyde
Glyoxylic acid
Metabolites
Glycogen
Fat
Luminal
Aminoglycosides
Pigments (hemoglobin, myoglobin)
Metals (lead)
Ethylene glycol-induced oxalate crystals
Cell death
Decreased ATP synthesis
Causes secondary metabolic disturbances
Calcium ion influx
Purine depletion
Metabolic acidosis
Oxygen radicals activates phospholipase increases membrane permeability

Apoptotic Pathway
TNF receptor binding
Deficiency of cell growth factors
Imbalance between pro-apoptotic and anti-apoptotic factors
Increased reactive oxygen metabolites, caspases, ceramide

Proximal tubular epithelium
Microvillous apical border
Early ischemic changes include
apical blebs
loss of brush border
loss of cellular polarity
disruption of tight junctions
sloughing of cells resulting in intratubular casts

Damage to the cellular cytoskeleton
Modifies cellular polarity
Disruption of the terminal web
Breakdown of microvilli actin cores
Conversion of G actin to F actin
Redistributes from the apex to form diffuse aggregates
Breakdown of tight junctions
Manifests as altered cell permeability and cell polarity
Increased Na/K ATPase to apical membrane
Integrins move to apical membrane desquamation

Vascular derangements
Afferent arteriolar constriction
Efferent arteriolar constriction
Loss of autoregulation or renal blood flow - stasis of blood in tubule activates afferent vasoconstriction
Decreased production or response to vasodilative factors - prostaglandins and ANP

Tubular derangements
Decreased GFR is the result of afferent arteriole vasoconstriction and back leaking of tubule fluid and tubular obstruction
Increased tubule sodium concentration reaches the macular densa and turns on the RAAS vascoconstriction decreased GFR
Tubular cell swelling and casts contribute to tubule fluid stasis
Fluid in the interstitium can contribute to lumen constriction
Tubule Regeneration
If basement membrane is intact
Focal loss of BM causes bulges to occur where epithelial cells form syncytia and giant cells
Failure to fully differentiate can occur, and full function is not attained
Excessive tubular loss cannot regenerate enough replacement with fibrous tissue
Reperfusion following ischemia is necessary reperfusion injury, pro-inflammatory mediators and ROS, proteolytic enzymes, cytokines
Tubulorrhexis
Disruption of BM
Tubules that remain have flattened epithelium, atrophic and shrunken
Interstitial fibrosis

Microscopic appearance of ATN
Randomly distributed
Proximal convoluted tubules most affected
Swollen epithelium
Cytoplasmic vacuolation or granular cytoplasm
Pyknosis. Karyorrhexis, karyolysis
Sloughing
Dilated, hypocellular tubules containing necrotic cellular debris
Hyalinized or granular casts

Clinical Oliguria from ATN
Leakage of lumen fluid back into interstitium
Intratubular obstruction
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.

Hemoglobinuria - only causes nephrosis if the carrier protein haptoglobin is overwhelmed (additive to ischemic nephropathy - not directly toxic)
Chronic copper toxicity → hemolysis
Leptospirosis or Babesiosis in cattle
Red Maple toxicity in horses
Babesiosis or IMHA in dogs

Myoglobinuria - has no carrier protein (not directly toxic?)
Azoturia of horses (exertional rhabdomyolysis)
Capture Myopathy
Trauma
Hemoglobinuric and Myoglobinuric nephrosis

Gross
Diffuse red brown to black
Intratubular hemoglobin or myoglobin casts

Microscopically
Tubular epithelium degeneration and necrosis are severe
Abundant red-orange luminal casts
Hemoglobinuric nephrosis, kidney B, Sheep. Several distal tubules contain hyaline and coarsely granular hemoglobin casts that occurred following intravascular hemolysis (hemoglobinemia) from chronic copper toxicosis.

**Figure 11-39B.** Hemoglobinuric nephrosis, kidney 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
**Figure 11-40A.** Myoglobinuric nephrosis, kidney, horse. A, Diffuse myoglobin staining of the cortex and medulla (reddish-brown) is secondary to myoglobinemia from severe rhabdomyolysis.
Myoglobinuric nephrosis, kidney, horse B, Myoglobin casts are present in dilated distal tubules, which are lined by flattened epithelial cells.

Figure 11-40B. Myoglobinuric nephrosis, kidney, horse B, Myoglobin casts are present in dilated distal tubules, which are lined by flattened epithelial cells. H&E stain.
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.

Nephrotoxic tubular Necrosis
Arsenic
Mercury
Lead
Cadmium
Thallium
Direct damage to tubular epithelium
Mitochondrial damage
Cisplatin
Direct damage
Reduces renal blood flow via vasoconstriction (RAAS)
Aminoglycosides
Concentrate in lysosomes
Inhibit NA/K ATPase → increased intracellular sodium and water
Inhibit phospholipase → accumulation of phospholipids intracellularly
Alter mitochondrial function
Inhibit protein synthesis
Amphoteracin B
Direct disruption of cellular membranes
Monensin
Ionophore
NSAIDs
Papillary necrosis with dehydration
Decrease renal synthesis of PG’s
  → afferent arteriolar vasoconstrictor
Ochratoxin (esp pigs, monogastric animals)
Amaranthus
Oak swollen pale kidneys, perirenal edema
Acute tubular necrosis, oak toxicity, kidney, cow-The toxic principal is a metabolite of oak tannins and creates acute tubular necrosis, which heals by scarring.

**Figure 11-42. 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 principal is a metabolite of oak tannins and creates acute tubular necrosis, which heals by scarring.
Oxalate nephrosis, kidney. A, Pig. Oxalate nephrosis following ingestion of oxalate-containing plants. The kidney is diffusely pale beige and swollen.

**Figure 11-43A. Oxalate nephrosis, kidney. A, Pig.** Oxalate nephrosis following ingestion of oxalate-containing plants. The kidney is diffusely pale beige and swollen.

**Ethylene Glycol**

Ethylene Glycol → oxidation by hepatic alcohol dehydrogenase → glycoaldehyde, glycolic acid, and Glycoxylate, and Oxalate

→ direct Tubular toxin

Calcium oxalate crystals precipitate → tubular necrosis and obstruction (can form in lumens and cells)

Also occurs in animals after ingestion of toxic quantities of oxalate containing plants → cause renal tubule damage and hypocalcemia

**Vit D**

From rodenticide or plant analogs

Mitochondrial calcification, mineralization of BM and tubular epithelium
Figure 11-43B. **Oxalate nephrosis, kidney B**, Dorsal section, dog. The cortex is pale beige and finely mottled due to the deposition of multiple small foci of oxalate crystals in the renal tubules.
Figure 11-43C. Oxalate nephrosis, kidney 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.
Figure 11-43D. Oxalate nephrosis, kidney D, Cat. Birefringent radiating sheaves of calcium oxalate crystals (arrow) in renal tubules. Polarized light. H&E stain.
Figure 11-44A. **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, termed “pulpy kidneys.”

Clostridium Perfringens D  
Sheep  
Pulpy kidney  
Epsilon toxin  
Acute tubular degeneration and interstitial edema and hemorrhage
The soft pulpy nature of the kidney is the result of acute tubular epithelial cell degeneration and/or necrosis, interstitial edema, and hemorrhage.

**Figure 11-44B. Pulpy kidney disease, *Clostridium perfringens* type D toxin, kidney, lamb B**, The soft pulpy nature of the kidney is the result of acute tubular epithelial cell degeneration and/or necrosis, interstitial edema, and hemorrhage.
Figure 11-45. **Cloisonné kidney, dorsal section, goat.** The cortex is diffusely black; the medulla is unaffected.

Incidental Lesions of tubules
Pigment
Hemosiderin
Lipofuscin
Ferritin and hemosiderin **Cloisonné kidneys** cortex only, medulla is spared
Vacuolation of renal tubular epithelium by lysosomal storage diseases
Intranuclear eosinophilic crystalline pseudoinclusions
Old dog epithelium
Often distort the nuclei
Figure 11-46. *Klossiella equi* infection, kidney, horse. Tubular epithelium containing various developmental stages of *Klossiella equi* (arrows). H&E stain

*Klossiella equi*

Sporozoan parasite of horses

No gross lesions

PCT- shizogony

Renal function is normal
Interstial nephritis, acute leptospira infection, kidney, dog. Radiating pale streaks are caused by cortical tubular necrosis, and acute interstitial inflammatory infiltrates.

**Figure 11-47A. Acute leptospirosis.** A, Interstitial nephritis, acute leptospira infection, kidney, 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

**Acute Leptospirosis**

Leptospira interrogans

Serovars canicola and icterohemorrhagiae- most common in canines

Pomona is most common in pigs and less in cattle

Grippotyphosa and bratislava in other species

Following exposure leptospiremia occurs

Organisms localize in renal interstitial capillaries and migrate through the vascular endothelium

They persist in interstitial spaces

Reach tubule lumina via lateral intercellular junctions

They associate with epithelial microvilli

Persist in phagosomes in epithelium

Induce epithelial degeneration and necrosis by toxic effects or inflammation
Inflammatory Response

Interstitial macrophages, lymphocytes, and plasma cells
Figure 11-47B. **Acute leptospirosis.** B, Acute tubular necrosis, early regeneration, kidney, 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.
Numerous leptospira (arrow) are present in the lumens of tubules. Leptospira colonization of tubule epithelial cells is typical of this bacterium. Warthin Starry silver stain.

**Figure 11-47C. Acute leptospirosis.** C, Leptospira, kidney, cow. Numerous leptospira (arrow) are present in the lumens of tubules. Leptospira colonization of tubule epithelial cells is typical of this bacterium. Warthin Starry silver stain.
nodularity of the capsular surface (right) from cortical interstitial fibrosis and the reduced width of the cortex (atrophy).

Figure 11-48A. **Chronic tubulointerstitial nephritis.** 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*).
There is an intense lymphoplasmacytic interstitial infiltrate (arrows).

**Figure 11-48B.** Chronic tubulointerstitial nephritis **B**, Kidney, dorsal section, dog. There is an intense lymphoplasmacytic interstitial infiltrate *(arrows)*. H&E stain
Figure 11-48C. **Chronic tubulointerstitial nephritis C**, Exotic zoo animal. This disease is characterized by cortical and medullary fibrosis, variable degrees of tubular atrophy, and mononuclear cell interstitial infiltrate. Masson trichrome stain.
Figure 11-48D. **Chronic tubulointerstitial nephritis D**, Leptospirosis, dog.
The pale streaks and foci in the cortex are chiefly interstitial lymphoplasmacytic infiltrates.
Figure 11-49. Infectious canine hepatitis, kidney, cortex, dog. Renal glomerular endothelial cells contain intranuclear inclusion bodies (arrow). H&E stain.

Canine Adenovirus Infection
Virus goes to glomerulus
Via viremia
Transient immune complex glomerulonephritis
Recovery of acute phase
Systemic immune response
Virus disappears from glomerulus and appears in tubules epithelial cells (basophilic intranuclear inclusions)
Persistence of virus in tubules
Tubular epithelial cell necrosis by cytolytic effects
Chronic lymphocytic, plasmacytic, and sometimes histiocytic interstitial nephritis

Equine Arteritis Virus and PRRS
Multifocal Lymphohistiocytic chronic tubulointerstitial nephritis with interstitial edema
Especially bad in the medulla and corticomedullary junction
Severe vasculitis
Fibrinoid necrosis and lymphohistiocytic infiltrates (Adventitial and medial layers)
Virus found in endothelium and macrophages

Immune Complex deposition in tubular BM
Rare
Damaged tubules respond with epithelial cell proliferation and peritubular fibrosis
Multifocal interstitial nephritis (white-spotted kidney), 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).

Figure 11-50. Multifocal interstitial nephritis (white-spotted kidney), 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).

Gross Lesions of tubulointerstitial nephritis
Canine Leptospirosis- diffuse
KIDNEYS swollen and pale tan with random grey mottling. The cut surface bulges
Grey infiltrates obscure the normally radiating appearance
Multifocal- White spotted kidneys (E coli septicemia)
CAV-1
CHV
MCF
Bovine and Porcine Leptospirosis

Microscopic Lesions
Lymphocytes, plasma cells. Monocytes, and few neutrophils
Randomly scattered or intensely localized throughout the edematous interstitium
Tubular epithelium can be degenerate necrotic or both
Profound tubular loss is replaced by fibrosis
Figure 11-51A. *Canine herpesvirus nephritis (canine herpesvirus type I), kidney, neonatal puppy.* A, Abdominal viscera. Multifocal renal cortical hemorrhages are grossly characteristic of this disease.
Figure 11-51B. Canine herpesvirus nephritis (canine herpesvirus type I), kidney, neonatal puppy B, Dorsal sections. Multifocal cortical hemorrhages are due to viral-induced vasculitis with necrosis and secondary hemorrhage.
Figure 11-52. Interstitial nephritis, malignant catarrhal fever, kidney, dorsal section, gaur. Multiple, pale-white to gray, discrete interstitial inflammatory cells (lymphoplasmacytic) have effaced some of the cortical striations in affected areas.
Figure 11-53A. 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 lymphosarcoma, thus warranting histologic examination.

Granulomatous Nephritis
Tubulointerstitial disease
Often accompanies chronic systemic diseases
Causes
FIP (Coronavirus)
Multifocal pygranulomatous nephritis, secondary to severe primary vasculitis
Type IV hypersensitivity
Gross lesions resemble neoplasia
Figure 11-53B. Granulomatous nephritis, feline infectious peritonitis, kidney, cat 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
Figure 11-54A. Granulomatous nephritis, hairy vetch toxicosis, kidney, cow. 

A, Cortical striations are obliterated by coalescing granulomatous foci associated with hairy vetch toxicosis.

Hairy vetch toxicosis in bovines
Multifocal to coalescing cortical granulomas
Microscopically
Monocytes, lymphocytes, plasma cells, eosinophils, MNGC in the renal cortex
Xanthogranulomas
Inherited hyperlipoproteinemia in cats
Foamy lipid laden macrophages, lymphocytes, plasma cells and fibrosis with cholesterol clefts
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 poisoning because of its ability to induce granulomatous inflammation in addition to the necrosis.

**Figure 11-54B. Granulomatous nephritis, hairy vetch toxicosis, kidney, cow 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 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.
Figure 11-55A.  *Granulomatous nephritis, kidney, cortex, dog. A*, Multiple subcapsular, cortical, tan, raised granulomas caused by migrating ascarid larvae

Parasites (Toxocara)
Small grey to white granulomas randomly scattered throughout the subcapsular cortex of dogs
Cell mediated immune response to migrating larvae
Aggregates of macrophages, lymphocytes, and eosinophils surrounded by fibroblasts within concentrically arranged fibrous tissue
Lesions heal by fibrosis

Mycobacteria (Mycobacterium bovis)
Microscopically
Central foci of necrosis surrounded by epithelioid macrophages, variable minerals, and giant cells

Fungi (Aspergillus spp, phycomycetes, histoplasma)
Algae (prototheca)
Rickettsia (Ehrlichia)
Protozoa (Encephalitozoon caniculi)
Figure 11-55B. **Granulomatous nephritis, kidney, cortex, dog. 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.
Figure 11-58A. Pyelonephritis, kidney. A, Dorsal section, dog. Extensive pelvic inflammation has destroyed areas of the inner medulla and extends focally into the outer medulla

Pyelonephritis
Pyelitis (inflammation of the pelvis)
Plus inflammation of the renal parenchyma
Example of suppurative tubulointerstitial disease
Originates as an extension of lower urinary tract infection
Rarely results from descending infecciones (embolic nephritis)
Pathogenesis
Depends on vesicoureteral reflux
Abnormal reflux of bacteria from ureter to pelvis
Occurs more readily if there is urethral obstruction
Cystitis can compromise the vesicoureteral valve
Endotoxins can inhibit normal ureteral peristalsis

Figure 11-58B.  **Pyelonephritis, kidney. B,** Dorsal section, cow. Renal calyces in the cow contain suppurative exudate.

**Protective features of the urinary tracts**
- Mucoproteins on urothelium prevent adhesion of bacteria
- Desquamation of superficial epiuthelium minimizes colonization
- Goblet cell metaplasia
- Phagocytosis of bacteria by superficial mucosal cells

**The medulla is highly susceptible to infection**
- Poor blood supply
- High interstitial osmolality or osmolarity inhibits neutrophil function
- Ammonia concentration inhibits complement activation

**Agents**
- E coli
- Alpha hemolysin
- Adhesins
P fimbria
Proteus spp
Klebsiella
Staphylococcus spp
Streptococcus spp
Pseudomonas aeruginosa
Corynebacterium (cattle) and Eubacterium (pigs)
Lower urinary tract infections
Figure 11-58C. **Pyelonephritis, kidney C**, Dog. There is both intratubular and interstitial inflammation, characterized by infiltrates of principally neutrophils (arrow). *Inset*: Higher magnification of intratubular neutrophils

**Gross Lesions**
- Unilateral or bilateral
- Most severe at the renal poles
- Mucous membranes red and thickened
- Pelvis and ureters can be dilated with purulent exudate
- Medullary crest (papilla) can be ulcerated
- Renal involvement
- Irregular radially oriented red to grey streaks involving medulla

**Inflammation**
- Necrosis of the medulla
- Patchy fibrosis

**Microscopic Lesions**
- Inner medulla is most severe
Transitional epithelium is focally or diffusely necrotic and desquamated
Necrotic debris, fibrin and neutrophils and bacterial colonies can adhere to the
denuded surface
Medullary tubules are dilated containing neutrophils and bacterial colonies
Tubular epithelium is focally necrotic
Intersitial hemorrhages and edema
Coagulative necrosis because of obstruction of the vasa recta (Papillary
Necrosis)
Figure 11-59A. Hydronephrosis, kidney, dorsal section. A, Sheep. The pelvis of each kidney is markedly dilated.

Hydronephrosis
Causes
Ureteral blockage or urethral blockage due to urinary tract calculi
Chronic inflammation
Ureteral or urethral neoplasia
Neurogenic functional disorders
Increase in intrapelvic pressure
Tubular dilation - microscopic
Glomeruli remain functional and soon overwhelms the tubular resorptive capacity
Much of the glomerular filtrate diffuses into the interstitium
Removed by lymphatics and veins
Interstitial vessels collapse and renal blood flow is reduced
Results in hypoxia, tubular atrophy and interstitial fibrosis, and necrosis
Glomeruli remain morphologically normal for a long time, but eventually become atrophic and sclerotic
Occasionally a hydromephrotic kidney becomes contaminated with bacteria and the fluid filled sac becomes filled with Pus== pyonephrosis
Figure 11-59B. Hydronephrosis, kidney, dorsal section. 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. (
**Figure 11-60.** 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.
Figure 11-61A.  **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.

**Parasites**

*Dioctophyma renale* – the giant kidney worm
- Seen only in dogs 2 years or older
- Females = 20-100 cm long, 4-12 mm diameter
- Males = 14-45 cm long, 4-6 mm diameter
- Resides in the pelvis
- Causes severe hemorrhage or purulent pyelitis, ureteral obstruction, destruction of the renal parenchyma

*Stephanurus dentatus*
- Pig kidney worm
- Adult worms encyst in perirenal fat
- Fibrosis and granulation tissue can enclose the parasite
- Occasionally nemtode eggs are present in the urine sediment
Capillaria plica, Capillaria feliscati
Dogs and cats, infrequently
Attached to renal pelvis, ureter or bladder
Figure 11-61B. **Chronic interstitial nephritis, kidney, dog B**, Dorsal section. The cortex is pitted and granular because of multiple linear and focal scars, and it is also thinner than normal (atrophic).
Figure 11-62A.  *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.
Figure 11-62B. **Chronic pyelonephritis, kidney, dog 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 pyelonephritis.