

RENAL PATHOLOGY

Normal anatomy and physiology

Anatomic differences

Bovine

- Have lobulated kidneys with
 - multiple calices
 - separate ureter
 - separate blood supply

Dog and cats

- have a single renal ridge
- single papilla
- fat in tubular epithelium is present in cats

Arcuate vessel

Renal column

Pyramid

Medullary ray

Minor calyx

Medulla

Major calyx

Minor calyx

Cortex

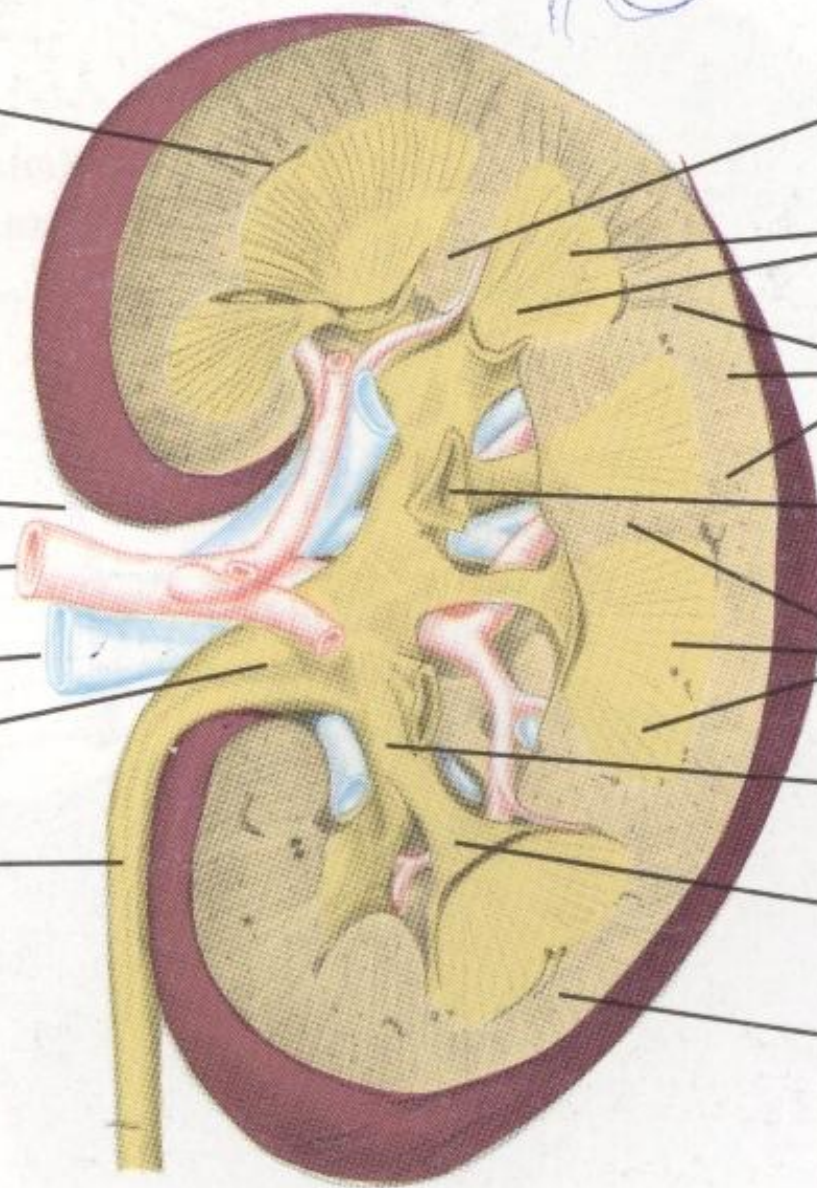
Hilus

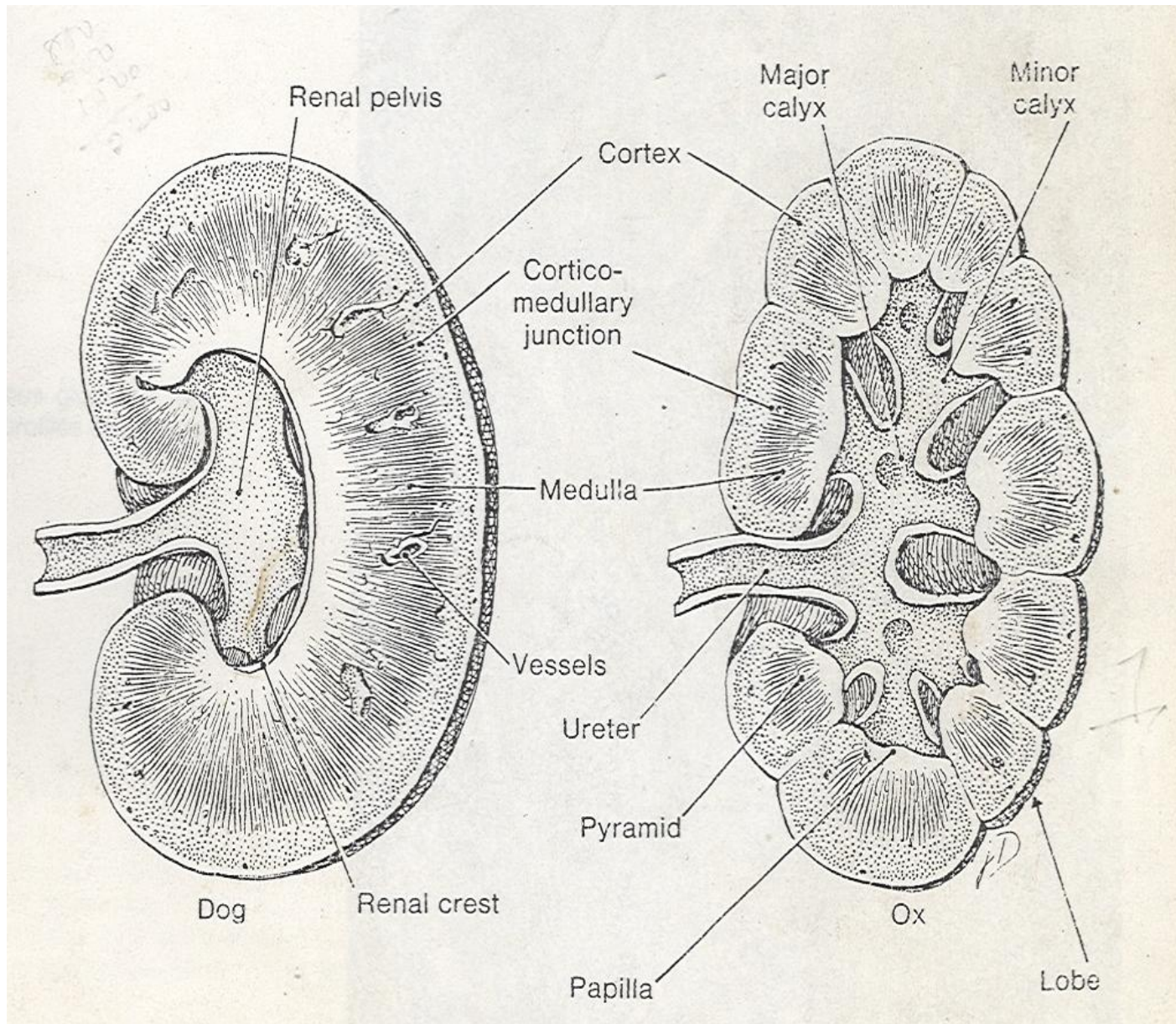
Renal artery

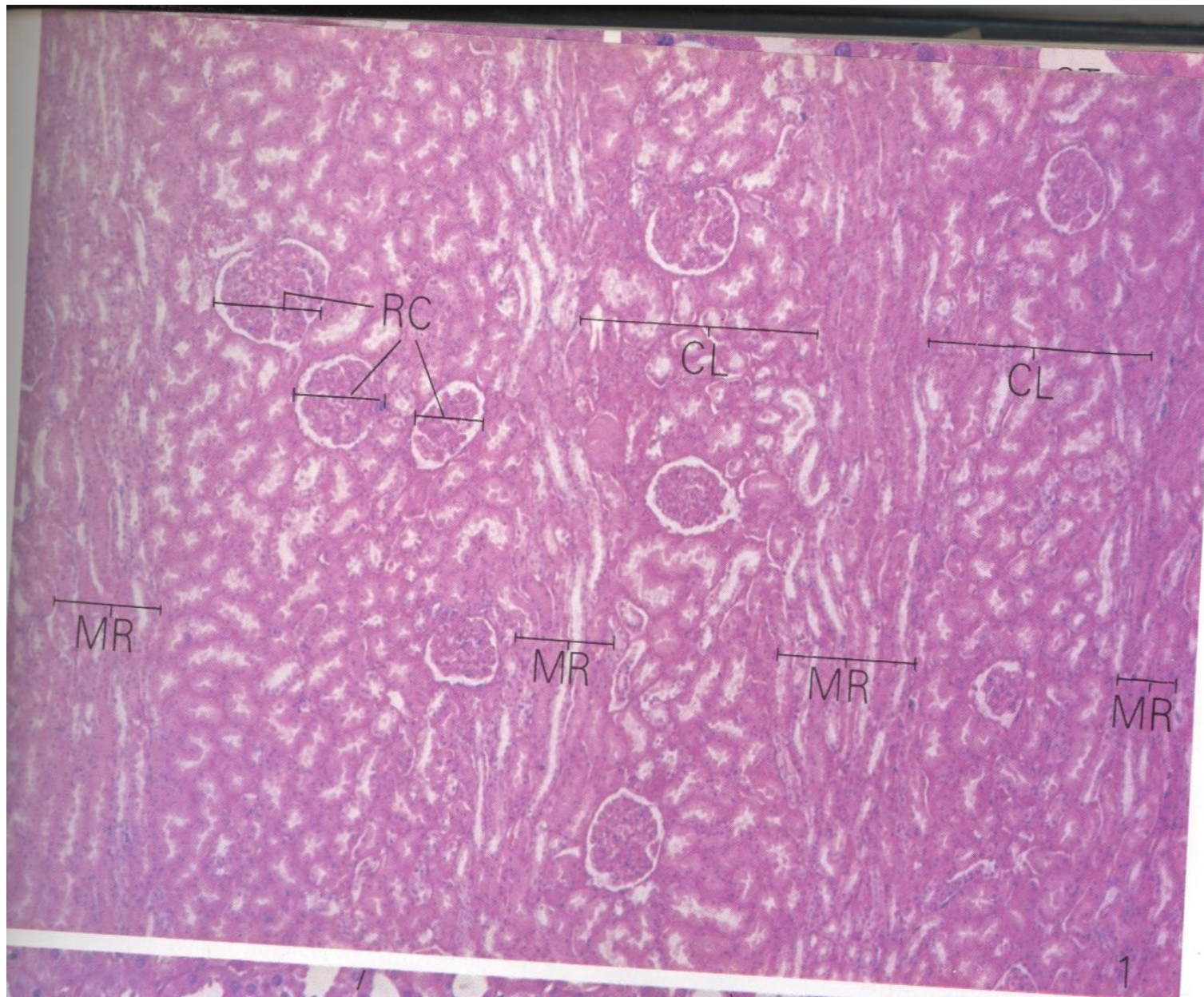
Renal vein

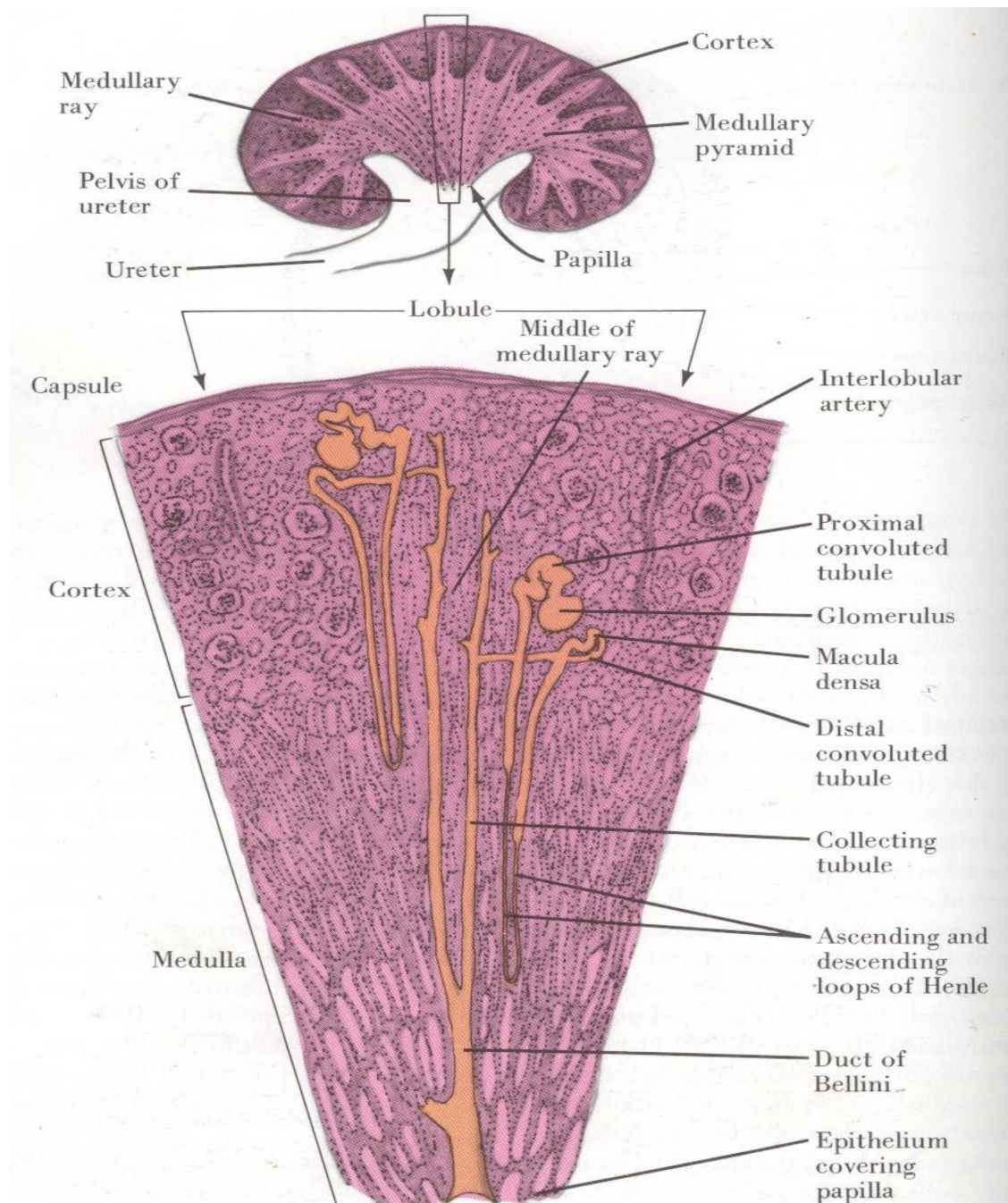
Renal pelvis

Ureter







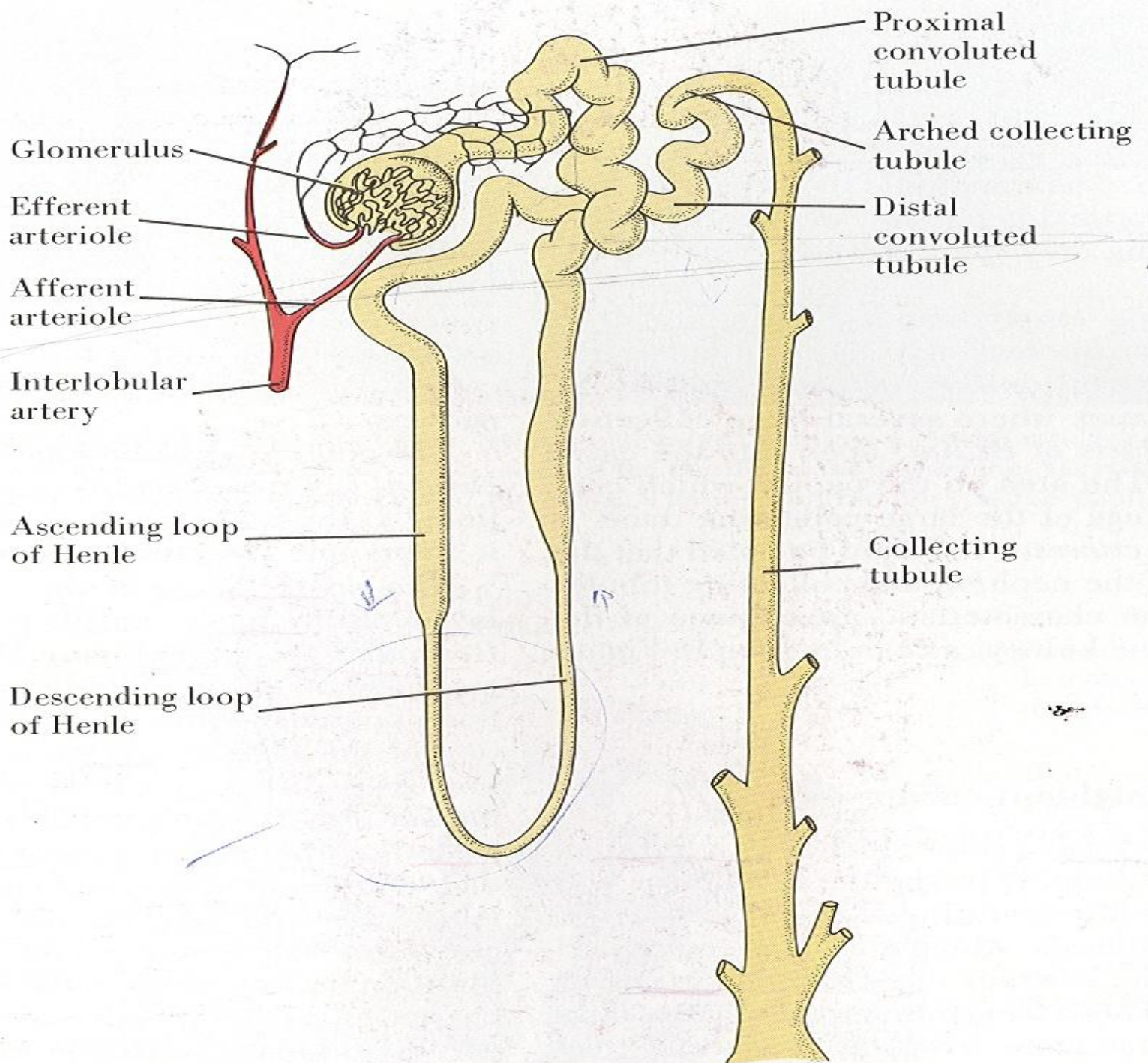


Normal anatomy and physiology

The nephron: essential anatomy and functional unit of kidney made up of glomerulus and renal tubule

Glomeruli-tufts of capillary

Renal corpuscle-glomerulo-Bowmans capsule



Renal vascular supply and Anatomy

- Kidneys receive 20-25% of total COP
- Cortex receives much more blood
- Interlobular arteries are end arteries with no anastomoses with each other, so infarction of renal cortex is common
- Interlobular artery → Afferent arterioles → Capillary tufts
→ Efferent arterioles leaving glomerulus → Efferent →
arterioles
Capillary network that surrounds the tubules

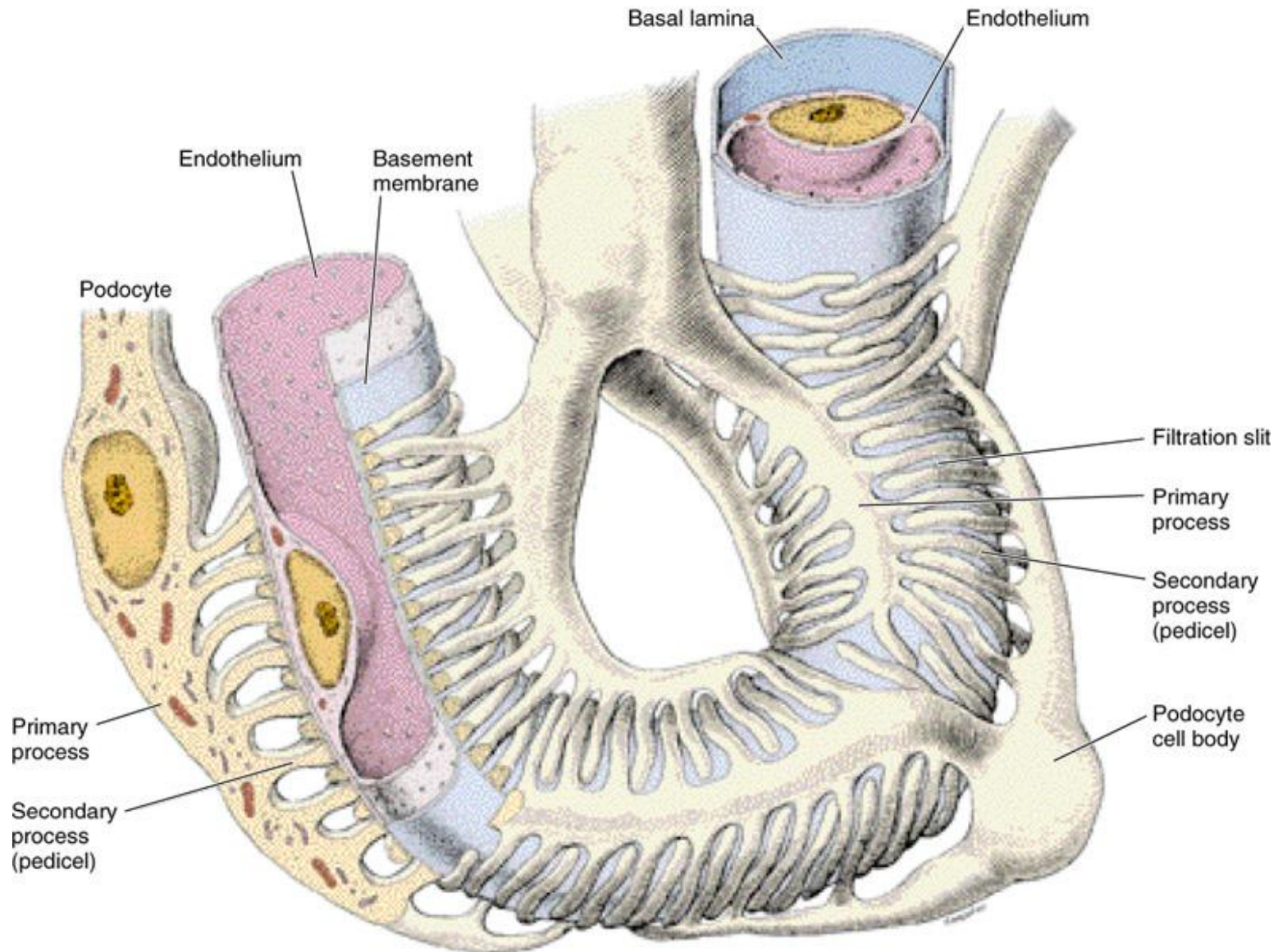
Renal vascular supply and Anatomy

- Cortex to medulla ratio in domestic animals is 1: 2 or 1:3
- Desert animals have wider medulla
- Cattle and pigs have lobulated kidneys

Note: The delicate epithelial cells of the tubules are dependent for their blood supply upon the free movement of blood via the tortuous passage ways of the glomerulus

Glomerular Filtration Barrier

- Fenestrated endothelial cells
- Basement Membrane
- Visceral epithelial cell and their podocytes
 - ⊗ GBM is freely permeable to water and small solutes
 - ⊗ GBM selectively filter macromolecules on the basis of size and charge
 - ⊗ Macromolecules such as plasma proteins are repelled by an electromagnetic shield due to negative charges



- ⌘ Uncharged molecules with an effective molecular radius of 1.8 nm pass freely via the filter
- ⌘ Larger molecules (> 4.00 nm) are restricted
- ⌘ Plasma albumin (3.6 nm in radius) would pass through readily, but repelled due to negative charges
- ⌘ Changes in porosity or charge of the barrier leads to leakage

Glomerulus do not regenerate, may undergo compensatory hypertrophy

1. Glomerular Basement Membrane (BM)

- ⌘ Basement membrane does not completely encircle the capillary lumen (absent at the mesangium)
- ⌘ Podocytes produce the BM

2. Endothelial Cells

- ⌘ Endothelium consists of a single layer of fenestrated endothelial cells
- ⌘ Coated with polyanionic sialoglycoprotein

3. Epithelial cells

- ⌘ Visceral epithelial cells with foot processes (podocytes) adhere to the outer aspect of BM
- ⌘ Podocyte surface is covered by polyanionic sialic acid (podocalyxin)
- ⌘ Podocyte pedicles are separated by **filtration slits**

4. Axial Mesangium

- ⌘ **Central region of glomerulus (where capillaries ramify)**
- ⌘ Composed of mesangial cells (intercapillary cells). Mesangial cells also act as macrophages
- ⌘ Functions include capillary support, modulation of filtration, phagocytosis, synthesis of active factors

5. Juxtaglomerular apparatus

- ⌘ Endocrine part

Anatomy of renal tubules and interstitium

Renal tubules

- Tubular epithelium can regenerate or hypertrophied rapidly, but new nephrons are not formed

Cats frequently have fat in renal tubular epithelium

Horses have many compound mucus glands in the renal pelvis

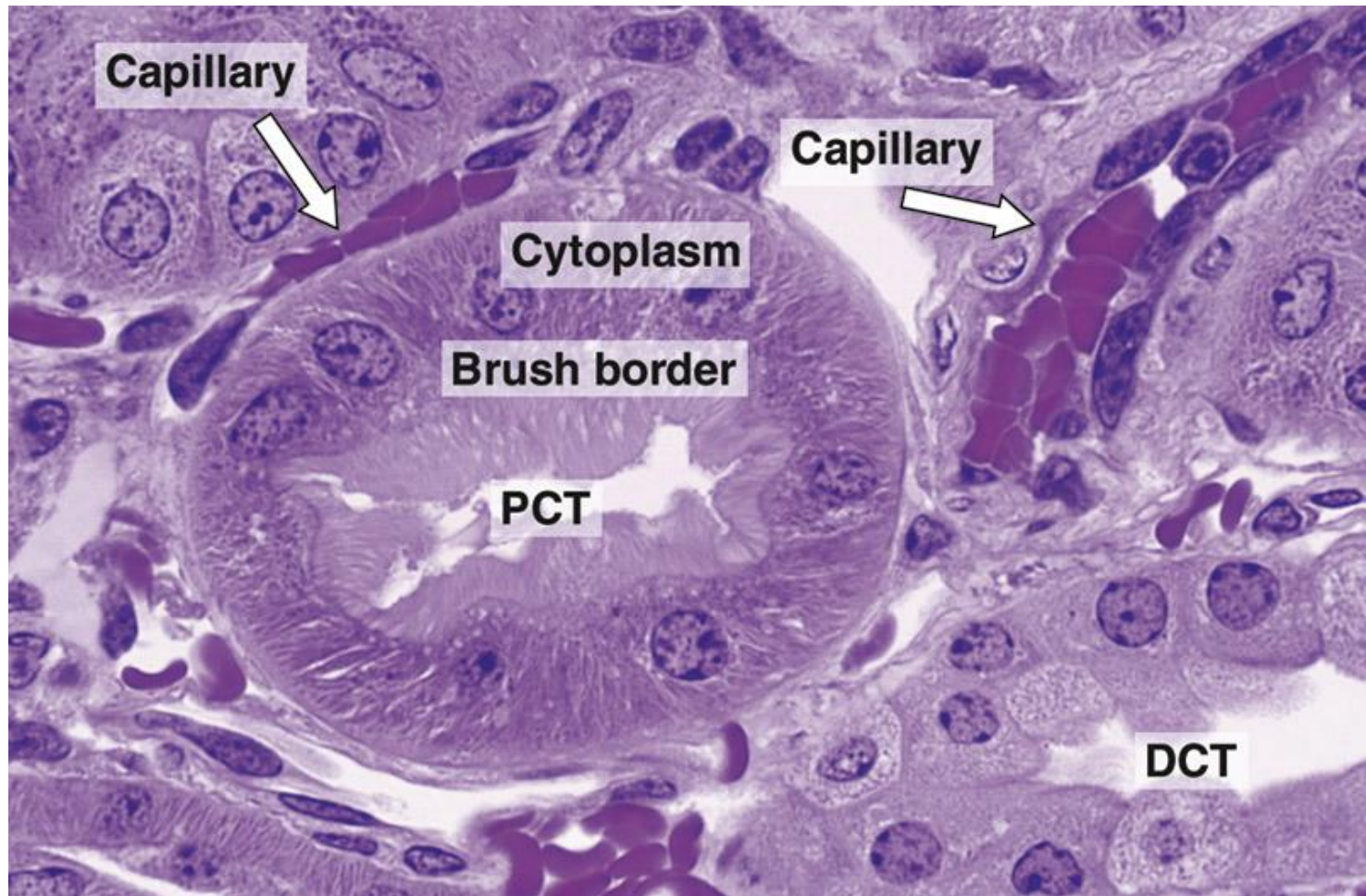
Renal tubules has part like:

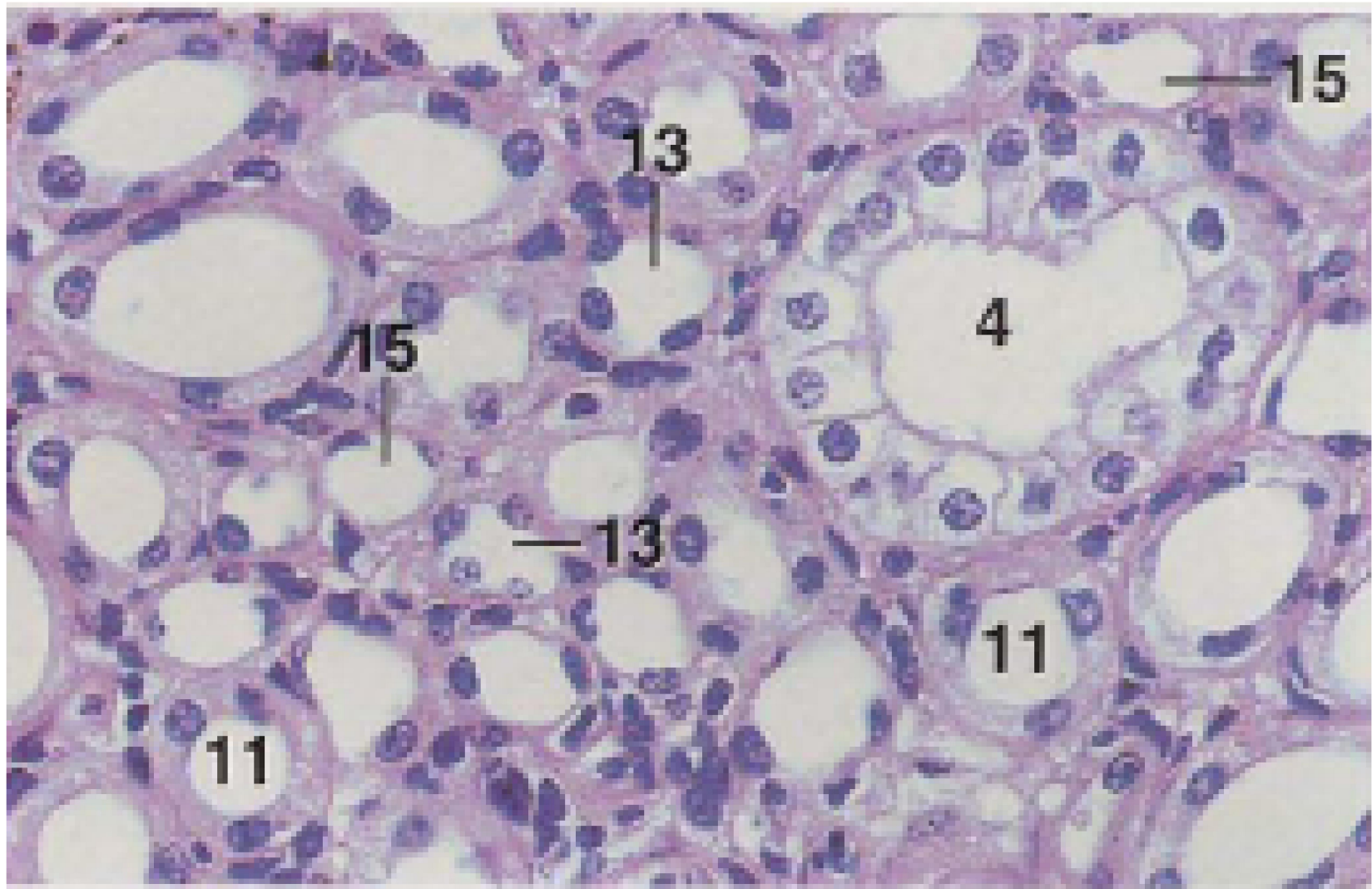
- **1. Proximal convoluted tubules**

Lined by columnar epithelium **with brush borders**

Metabolically active (contains many mitochondria) and are vulnerable

Function:-resorption of water, inorganic solutes (Na^+ , Cl^- , HCO_3^- , K^+ , Ca^{++})





Loop of Henle

- ⌘ Generally located in the kidney medulla
- ⌘ Descending-covered with flat epithelial with few mitochondria
- ⌘ Ascending-covered with cuboidal epithelial cells with some mitochondrial

Distal convoluted tubule

- ⌘ Starts from point of ascending limb return
- ⌘ Covered with columnar with no brush border

Juxtaglomerular apparatus

- Secrete renin

Renal interstitium

- ⌘ Contains peritubular capillaries and few fibroblasts¹⁹

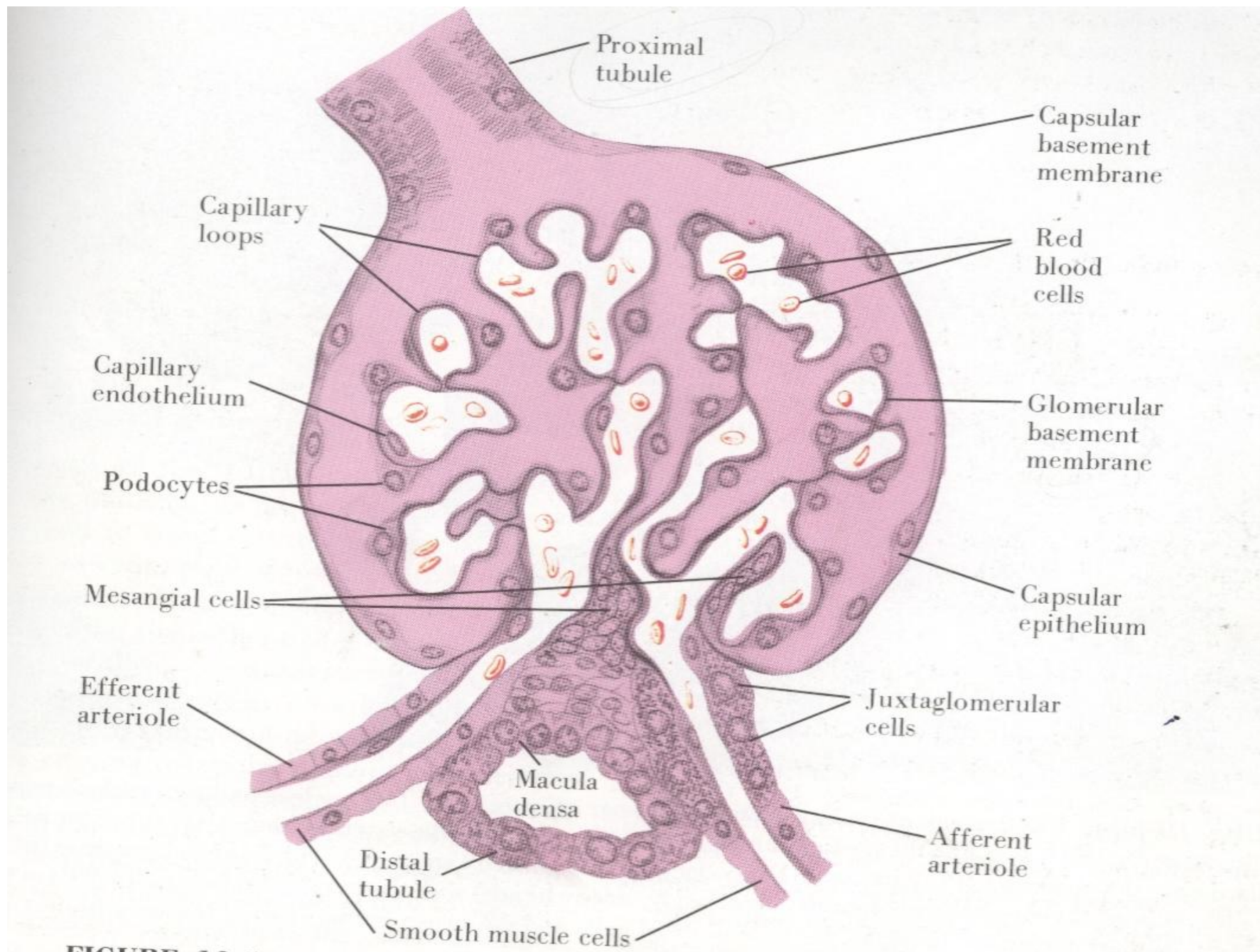
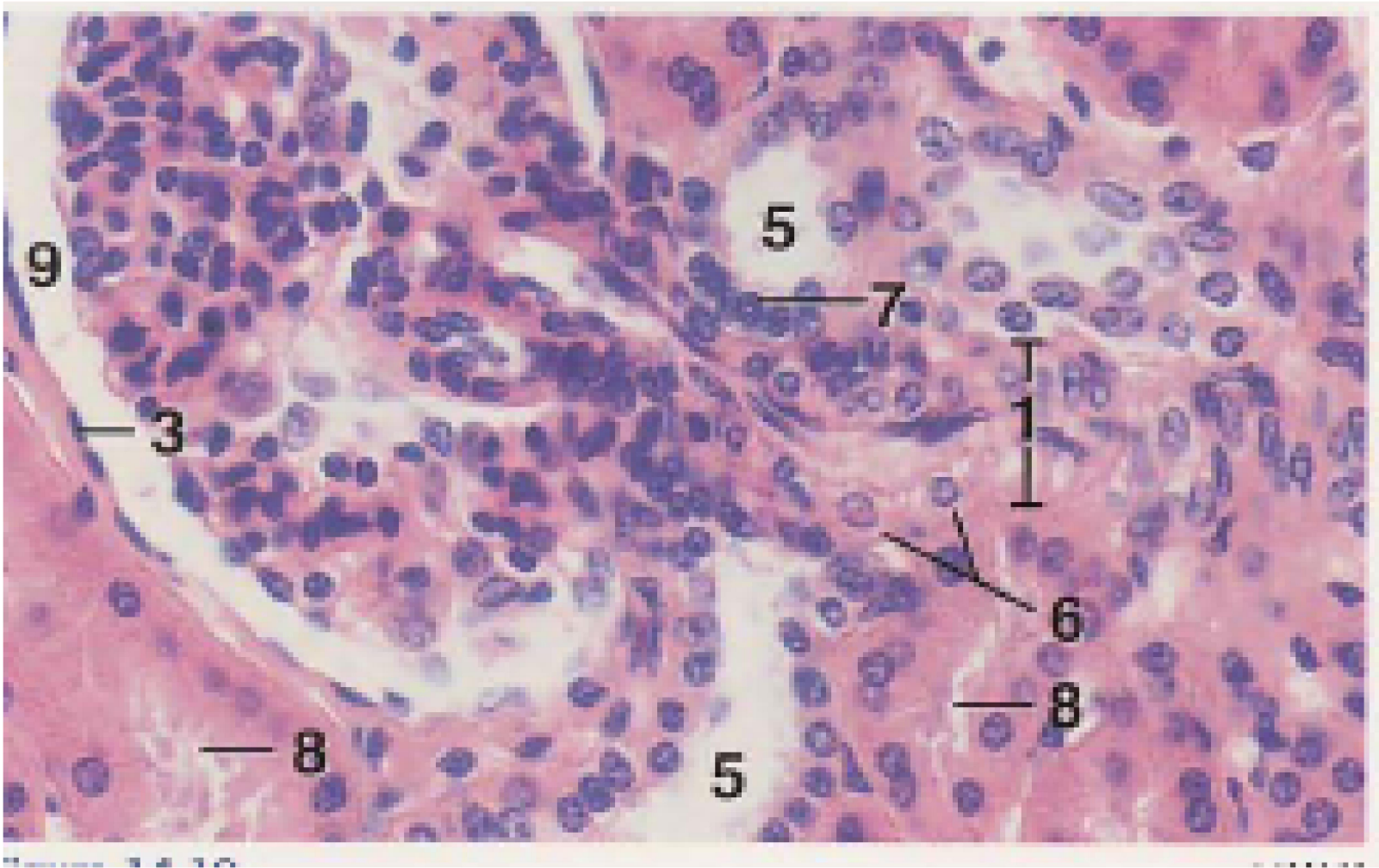


FIGURE 10-1

Note from this histomicrograph the afferent arteriole (#1), with juxtaglomerular cells (#6), is entering a glomerulus. The juxtaglomerular cells are epithelioid. Note that a macula densa (# 7) borders the afferent arteriole.



RENAL FAILURE

- ⌘ Renal disease leads to decreased renal function
 - Waste retention
 - Fluid & electrolyte imbalance
- ⌘ But wide safety margin to maintain normal function
 - Large number of nephrons
 - Existing nephrons can compensate
- ⌘ Continued loss (inflammation, necrosis) leads to **scar tissue**
- ⌘ If loss exceeds functional reserve renal failure occur

Causes of renal failure

- ⌘ Prerenal diseases-inadequate renal perfusion (ischemia)
- ⌘ Intra-renal diseases-glomerulonephritis & tubulointerstitial
- ⌘ Post-renal obstruction-urinary obstruction

Acute renal failure

- Sudden loss of 70-100% of nephrons in normal animal
- Abrupt, often reversible
- characterized by oliguria, even anuria & azotemia
- **Most common causes**-ischemia or toxic injury----acute tubular necrosis
- Normal nephron function often restored by removing injurious stimuli (unlike chronic)

Chronic renal failure

Characterized by :

slow sustained destruction of all nephrons-----chronic GN & severe
PN-----irreversible derangement of homeostasis

Excessive water loss (early case)----oliguria-----uremia

- ⌘ Irreversible and characterized by uremia and protein loss (nephrotic syndrome)
- ⌘ Dilute urine (fixed specific gravity) B/c of failing tubular concentration
- ⌘ May result from diseases of –blood vessels, glomeruli & tubules
 - ⌘ Bacterial infections,
 - ⌘ urinary obstruction,
 - ⌘ polycystic kidney (genetic)

Often end stage of many renal diseases

Consequences of renal failure

Azotemia-the intravascular elevation of nitrogenous wastes of protein catabolism

Urea and creatinine

Uremia:-

Toxicosis associated with multi-systemic clinical signs and lesions

Renal failure----decreased renal function----accumulation of waste product in blood produce clinical syndrome called uremia

Causes of failure of Urinary Mechanisms

1. Pre-renal

- Reduced renal blood flow (shock, hypovolemia, congestive heart failure)
- Distribution of blood to vital organs (brain and heart) further reduce renal flow
- Intrarenal mechanisms channel renal flow to juxtamedullary nephrons and this cause cortical ischemia and necrosis, which then cause renal failure

2. Renal

3. Post-renal

- Obstruction of urine outflow (inadequate discharge and reflux nephropathy)

Renal lesions of uremia

- 1. Mineralization** late in the course may diffusely involve glomerular and tubular BM
- 2. Interstitial fibrosis**
- 3. Glomerulosclerosis (end stage kidney)**
- 4. Hyperplasia and hypertrophy of the tubules**

Renal cyst

- Can be single/ multiple, small/large, located either in the cortical or medulla
- Cyst can be thin walled fluid filled spherical cavities
- Polycystic kidney diseases (multiple cysts) alter the kidney functions via compression of the parenchyma
- Glomerulocystic kidney in foals are present in Bowman's space

Mechanisms of renal cysts

1. Congenital renal cyst

- Occurs due to obstruction of nephrons that cause elevated luminal pressure and secondary dilation
- Defective tubular basement membrane allows saccular dilatation of tubules
- Focal tubular epithelial hyperplasia with production of new basement membrane causes dilated tubule

2. Acquired renal cyst

- Occurs due to renal interstitial fibrosis
- Also occurs due to intratubular obstruction

Circulatory disturbances

1. Hyperemia/congestion can be physiologic, hypostatic, active or passive

2. Hemorrhages

- **Cortical hemorrhages** occurs in septicemia and vasculitis
- **Petechiae in the cortex** occurs in pigs with Swine fever, Streptococci, Salmonellosis
- **Ecchymosis in the cortex** occur in puppies with herpes virus septicemia

3. Infarction (ischemic coagulative necrosis)

The causes include

- 1 Occlusion of vessels due to thrombosis or septic emboli
- 2 Endocardial thrombosis (of the left heart) results embolism of renal vessels
- 3 Multiple small infarcts occur in the kidney due to emboli arising from polyarteritis, mastitis, enteritis, grain overload, cardiovascular collapse or shock
- 4 Renal amyloidosis results in loss of plasma anticoagulants via urine and cause infarction

+

- ‖ Endotoxins of gram negative sepsis (endotoxic shock) cause arterial or capillary thrombosis that can induce infarction
- ‖ Septic emboli from endocarditis cause renal infarcts and abscesses
- ‖ Thrombi in the arcuate artery cause infarction of cortex and medulla
- ‖ Thrombi in the interlobular artery cause infarction of the cortex

Gross lesion

Sharply outlined lesion with its apex near zone of the arcuate arteries & base at the capsule

Microscopic lesions of renal infarcts

1. Central areas of necrosis (coagulation type)
2. Zone of hemorrhage (congestion)
3. An outer zone of inflammation (contains neutrophils, macrophages, and few lymphocytes)

Note: In the kidney the infarct has typical wedge appearance (the apex directs towards the medulla and the base towards the cortex)

Renal cortical necrosis

Causes include

- Widespread thrombosis in glomerular capillaries, interlobular arteries, and afferent arterioles that occurs in DIC
- Partial/complete renal cortical necrosis is a bilateral lesion due to gram negative septicemia or **endotoxemias**
- Hypotension

Pathogenesis of renal cortical necrosis

- Endotoxin induced endothelial damage, then activation of clotting mechanism induce widespread

- In hypotension, perfusion of outer cortex is reduced, while perfusion of inner cortical nephrons is maintained
- Intrarenal blood flow is re-distributed toward the inner cortex and medulla
- PGE_2 produced in the medulla in response to ischemia travels to the juxtaglomerular apparatus and cause local dilation on afferent arterioles

Papillary (medullary crest) necrosis

- Necrosis of the renal papillae/medullary crest may be due to ischemia of inner medulla
- Inner medulla including the papillae is less perfused with blood than outer zones of the kidneys

Causes include

- ↳ Lesions or processes that reduce medullary blood flow
- ↳ Secondary to scarring of the outer medulla
- ↳ Medullary amyloidosis/ Pyelitis
- ↳ Renal pelvis calculi

- Increased intrapelvic pressure due to obstruction of the lower urinary tract
- NSAIDS-Non-steroidal anti-inflammatory analgesics (analgesic nephropathy in man). The cause in this case is via inhibition of prostaglandin biosynthesis. PG maintains normal blood flow in the vasa recta.
- NSAIDS reduce blood flow and cause ischemic necrosis of the papillae.

In horses-due to phenylbutazone or banamine

In dogs & cats-due to ibuprofen, aspirin, acetaminophen

Acetaminophen by itself results in oxidative damage via covalent binding to medullary tubular epithelium

Tubulointerstitial diseases

- ▢ **Acute tubular necrosis**
- ▢ **Interstitial nephritis**
- ▢ **Granulomatous nephritis**
- ▢ **Pyelonephritis**
- ▢ **Hydronephrosis**

Acute tubular Necrosis (nephrosis)

- Starts with tubular degeneration (nephrosis)
- It causes acute renal failure, azotemia and uremia

Ischemic or toxic insult to the renal tubular epithelium

(PCT is most seriously affected by ischemia/toxic injury)

Acute tubular necrosis

Types of acute tubular necrosis

1. Ischemic tubular necrosis (tubulorrhectic tubular necrosis) is caused

A. Severe hypotension associated with shock results in pre-

glomerular vasoconstriction and reduced glomeruli filtration

resulting in renal ischemia and ischemic tubular necrosis

→ Prolonged ischemia result in epithelial necrosis through out the cortex and to a lesser extent in the medulla

Acute tubular necrosis

B. *Hypoperfused kidneys complicated by hemoglobinuria or myoglobinuria*

Hemoglobinuric nephrosis

- It is caused by severe intravascular hemolysis as in Cu toxicity, leptospirosis, babesiosis and autoimmune hemolytic anemia

Myoglobinuric nephrosis

- It is inflicted by acute rhabdomyolysis, azoturia, capture myopathy, severe trauma to the muscles
- Higher serum hemoglobin and myoglobin pass into GF, accumulate in renal tubules and causes obstruction of the lumen

Acute tubular necrosis

Gross lesions :swollen, smooth and pale capsule

Cut surface becomes pale, moist, striations muted or accentuated radially

The medulla becomes pale/congested

Microscopy: epithelial swelling

Microvilli are lost, vacuolated or granular (eosinophilic) cytoplasm

Pyknosis, karyorrhexis, karyolysis

Desquamation results in dilated, hypocellular tubules with debris, hyaline & granular cast

Gross lesions of hemoglobinuric and myoglobinuric nephrosis

- Renal cortex diffusely stained with red-brown material
- Medula stained dark red

Microscopic lesions hemoglobinuric and myoglobinuric nephrosis

- Eosinophilic hyaline and granular casts in the lumina of DCT and Collecting duct
- Epithelial cell degeneration

⌘ **Regeneration may be possible if the basement membrane is intact**

- within 3 days flattened & elongated, low cuboidal cells(basophilic mitotic figures)
 - 7-14 days-normal appearing cells
 - 21-56 days-normal tissue

Acute tubular necrosis

2. Nephrotoxic tubular necrosis

Nephrotoxins usually do not damage the tubular BM and is caused by

A. Heavy metals (arsenic, lead, mercury)

- └ Sources of heavy metals include herbicides, old paints, batteries
- └ Heavy metal toxicity damage the cell membrane or mitochondria of cells. i.e. they have direct effect on the cells of the renal tubules

Acute tubular necrosis

B. Therapeutic agents at higher doses

| Aminoglycosides (gentamycin, streptomycin)

- ⌘ Alter tubular cell membrane transport of ions via inhibition of Na-K-ATPase
- ⌘ So influx of hydrogen, sodium and water into the cell
- ⌘ This is characterized by cellular and mitochondrial swelling
- ⌘ Gentamycin also inhibits phospholipase, hence accumulation of phospholipids in the cells can cause lysosomal enzyme leakage and death

Note: The tubular cells are not affected by the swelling of the cell

Acute tubular necrosis

‣ **Amphotericin B (antifungal drug)**

- ⌘ Disrupt cell membrane by interfering cholesterol-lipid interactions
- ⌘ So, potassium ion is lost and hydrogen ion accumulate in the cell causing acute cell swelling and necrosis

‣ **Monensin**

‣ **Tetracycline**

‣ **Sulfonamides**

- ⌘ Cause tubular necrosis in dehydrated animals, crystallizes in the tubules
- ⌘ Local toxicity and mechanical effects produce lesions

Acute tubular necrosis

C. Mycotoxins (mycotoxin induced nephrosis)

- ⌘ Are xenobiotics, and exert effects by the active metabolite formed in the body by the action of oxidases
- ⌘ Aspergillosis causes tubular degeneration and necrosis

D. Nephrotoxic plants

- ⌘ Amaranthus species in pigs and cattle; Oak trees (contains tannins) in ruminants cause tubular necrosis

Acute tubular necrosis

E. Antifreeze in dogs and cats

- ⌘ Antifreeze cause damage due to direct interaction with the epithelium
- ⌘ Ethylene glycol (component of antifreeze) absorbed from GIT and by liver dehydrogenase converted into oxalate
- ⌘ Calcium oxalate precipitation in tubules cause intrarenal obstruction, degeneration and necrosis
- ⌘ Microscopy shows large numbers of birefringent crystals in polarized light

F. Prolonged and excessive vitamin D supplementation in dogs and

cats cause vitamin D intoxication or vitamin D

Acute tubular necrosis

G. Oxalate containing plants in sheep and cattle (Rumex species)

- ⌘ Following intestinal absorption, calcium oxalate precipitates in the vessels and tubules cause obstruction and necrosis
- ⌘ Are xenobiotics that affect the tubular epithelial cells by changing the nutritive or endogenous sub-strata
- ⌘ Neuromuscular dysfunction occurs due to hypocalcaemia as oxalate chelates calcium

H. Ingestion of plants containing vitamin D like substances (Solanum species)

- Excess vitamin D cause hypercalcemia

Tubular absorption of calcium causes mitochondrial

Inflammatory diseases of the kidney

The main types of inflammatory renal diseases

- ⌘ Glomerular disorders (eg. Glomerulo nephritis)
- ⌘ Tubulointerstitial disorders(eg. Pyelonephrits, interstitial nephritis)

Tubulointerstitial disorders

- ⌘ Problem in the cortex & medulla (tubules & supporting connective tissue)
- ⌘ Clinical presentation is based on faulty tubule processing
 - ⌘ Water & sodium loss
 - ⌘ Retention of acid
- ⌘ **Two principle forms:**
 - ♣ Interstitial nephritis
 - ♣ Pyelonephritis

Interstitial nephritis

Interstitial nephritis is inflammation of the renal interstitial tissue

⌘ Viral or bacterial septicemia-----kidney tubules----
inflammatory response in the interstitium

- Eg. L. interrogans, C. interohemorrhagic-----canine
- P.pomona-----pigs
- E. coli in calves/immune response to canine hepatitis virus
- Immune mediated tubulointerstitial diseases

⌘ Can be acute, subacute, or chronic

⌘ ***The cause or the organisms are found in the epithelium, but the inflammation is confined in the interstitium***

Interstitial nephritis

Pathogenesis of interstitial nephritis due to leptospira infection

- Leptospiremia following infection
- Localization in the renal interstitial capillaries
- Migration via vascular endothelium
- Persistence in the interstitial spaces and reach tubular lamina
- Leptospira then localized in the microvilli and phagosomes of the epithelium of the PCT and DCT
- Finally it induces degeneration and necrosis by its direct effect and the interstitial inflammatory

Interstitial nephritis

Pathogenesis of interstitial nephritis due to canine infectious hepatitis

Viremia

- Localize in glomeruli (induce viral glomerulitis)
- Also induces transient immune complex glomerulitis
- On recovery (immune development) virus disappear from glomeruli, but reappear in tubular epithelial cells causing tubular necrosis

Basophilic intranuclear inclusions are detected in infected epithelium

Interstitial nephritis

Gross lesions of interstitial nephritis

1. *Diffuse interstitial nephritis*

- Characterized by pale foci of inflammation in the cortex (**gray mottling**) in canine leptospirosis
- Gray mottling obscure radially striated cortical architecture
- Swollen and pale kidneys

2. *Multifocal interstitial nephritis*

- Composed of more discrete gray areas in the cortex
- Occurs in *E. coli* septicemia in calves (white spotted kidney), infectious canine hepatitis, MCF, porcine

Interstitial nephritis

Microscopic lesions of interstitial nephritis

- Few Neutrophils in tubular lumina (early stages)
- Monocytes, macrophages, epitheloid cells, lymphocytes, plasma cell infiltrates into the interstitium (chronic cases)
- Lymphoplasmacytic infiltration into the interstitium is characteristic
- Interstitial fibrosis and thickening of the Bowman's capsule (periglomerular fibrosis), and dilated tubules
- Epithelial cells degeneration and necrosis

Granulomatous nephritis

Causes include

- Viral diseases (Feline infectious peritonitis)
- Parasites (Ascarids and Toxocara canis on migration)
- Bacteria (Milliary TB)
- Fungi (Aspergillus, Histoplasma)

Pathology

- Small to large ***white granulomatous foci*** randomly scattered in the kidney
- Granulomatous inflammation (central necrosis, epithelioid and giant cells)

Pyelonephritis

Pyelonephritis is inflammation of the renal pelvis and renal parenchyma

- ⌘ It is **suppurative** tubulointerstitial disease
- ⌘ It is *ascending* infection from the lower tracts as in the case of reflux nephropathy
- ⌘ Ascending infections (from lower urinary tract) easily establish infection in medulla
- ⌘ Descending bacterial infection rare and is not the usual cause
- ⌘ More frequent in females as infection of the lower urinary tract is common

Pyelonephritis

Divided into acute & chronic

Acute:-most common renal disease

- Relatively mild (self limiting), but overwhelming infection----renal failure
- Sudden onset, pain, fever, pyuria, bacteriuria

Chronic:-slow but sustained loss of functional renal tissue-
replaced by scar

Scarring seen on kidney surface
tubulointerstitium & cortex

Asymptomatic until substantial renal damage has been incurred

Often progress to end-stage (urmic) kidney

Pyelonephritis

Pathogenesis of ascending pyelonephritis (as in reflux nephropathy)

θ Vesico-ureteral reflux

- ⌘ Increased pressure in the bladder as in urethral obstruction cause reflux of bacterial contaminated urine to renal pelvis and medulla
- ⌘ Bacterial infections of the lower tract enhance the reflux by many mechanisms
 - In cystitis, the vesicoureteral valve is compromised
 - Cystitis and uretheritis with stenotic urethra and obstruction by calculi increases intracystic pressure and reflux occurs
 - Endotoxins of gram negative bacteria affecting the

Pyelonephritis

θ **Medulla is highly susceptible to bacterial infections, because**

1. It has poor blood supply and its high interstitial osmolality inhibits neutrophil functions
2. It has high ammonia concentration that inhibit complement activation

Gross lesions of pyelonephritis

1. Pelvic and ureteral mucosa inflamed, or dilated and contains purulent exudate
2. Ulcerated and necrotic **medullary crest** (lesions are severe at the pole)
3. Irregular radially oriented red (hyperemic) or gray streaks (concurrent foci) *involving the medulla extending to renal*

Pyelonephritis

Microscopic lesions of pyelonephritis include

1. More severe lesion in the inner medulla
2. Intratubular and interstitial inflammation with ***neutrophils being the dominant cells***
3. Medullary tubules contain dense neutrophil aggregates and bacterial colonies
4. Similar tubular and interstitial lesions may ***extend radially*** to the cortical tubules and interstitium

Hydronephrosis

Hydronephrosis is the dilatation of the renal pelvis and calyces due to obstruction of urine outflow with associated parenchymal atrophy and cystic enlargement of the kidney

Back pressure results in gradual enlargement of renal pelvis at the expense of parenchyma

Causes include

1. Congenital malformation of ureter, urethra, vesicoureteral junctions
2. Enlargement of prostate glands and pressure on urethra
3. Ureteral or urethral blockage by calculi
4. Chronic cystitis, neoplasia of bladder and ureter

Hydronephrosis

- In unilateral cases, renal cystic enlargement become extensive
- In bilateral and complete cases, death occurs due to uremia before cystic enlargement
- Bilateral partial blockage result in bilateral hydronephrosis

Pathogenesis of hydronephrosis depends on

1. The presence of urinary obstruction
2. The development of ischemic lesions
 - In sudden complete obstruction, GF continues and filtrate diffuses to the renal interstitium and perirenal spaces and drained by lymphatic
 - Continued filtration creates increased pressure through out the nephrons, collecting ducts, calyces, and pelvis

Hydronephrosis

- Shearing forces develop between the compressible parenchyma and the resistant connective tissues
- **Pressure atrophy and apoptosis of tubular epithelium develops**
- Increased intrapelvic pressure, compresses interstitial vessels leading to papillary ischemia, necrosis, fibrosis and decreased renal blood flow and GFR

Gross lesions of hydronephrosis

- Dilated pelvis and calyces
- Rounded, thin walled kidneys, and in advanced cases fluid filled sac(can become hollow sac)

Hydronephrosis

Hydronephrotic kidneys if contaminated with bacteria, the thin walled sac becomes filled with pus (***pyonephrosis***)

Microscopic lesions of hydronephrosis

- Necrosis
- Cortical fibrosis (***thin fibrous mass remains in place renal pelvis***)
- dilated tubules, atrophied and sclerotic glomeruli

Note: Unilateral obstruction will produce the greatest degree of hydronephrosis, especially if the obstruction is incomplete or intermittent because GF will be little suppressed and such kidneys become massively enlarged.

Glomerular diseases

Glomerular diseases are important because

1. Interference with glomerular blood flow impairs peritubular perfusion and cause loss of the entire nephrons
2. Glomerular permeability may be altered

Glomerular diseases can cause

1. Leakage of proteins (proteinuria)- protein losing nephropathies
2. Hypoalbuminemia/hypoproteinemia causing edema
3. Hypercholesterolemia (hepatic response to hypoalbuminemia is generalized increased production of proteins including lipoproteins leading to hyperlipoproteinemia and hypercholesterolemia)
4. Hyaline droplets (microscopic eosinophilic intracytoplasmic

Glomerular diseases

Histologic terms(classification) describing glomerular diseases

1. **Generalized**- involves all glomeruli
2. **Focal**- involves some glomeruli
3. **Diffuse (global)**- involves the whole gloemrulus
4. **Segmental (local)**- involves only part of the glomerulus
5. **Mesangial**- affects primarily the mesangial area

Glomerular diseases

Etiologic Types of glomerular diseases

- Direct viral or bacterial
- glomerular diseases secondary to tubular diseases
- Immunologically mediated (Glomerulonephritis)
- Metabolic (Amyloidosis)

Glomerulitis

Viral glomerulitis

- Viral replication in capillary endothelium in acute systemic infections cause transient proteinuria
- Causes include
 - ↳ ICH, Equine arteritis, Hog cholera and NCD

Suppurative (embolic) glomerulitis

- Occurs due to bacteremia
- Multiple foci of inflammation (abscess) through out the cortex
- Causes include:
 - ⊗ Actinobacillosis in foals
 - ⊗ Erysipelothrix in pigs
 - ⊗ Streptococci and Corynebacterium species in pigs

Glomerulitis

Histopathology include

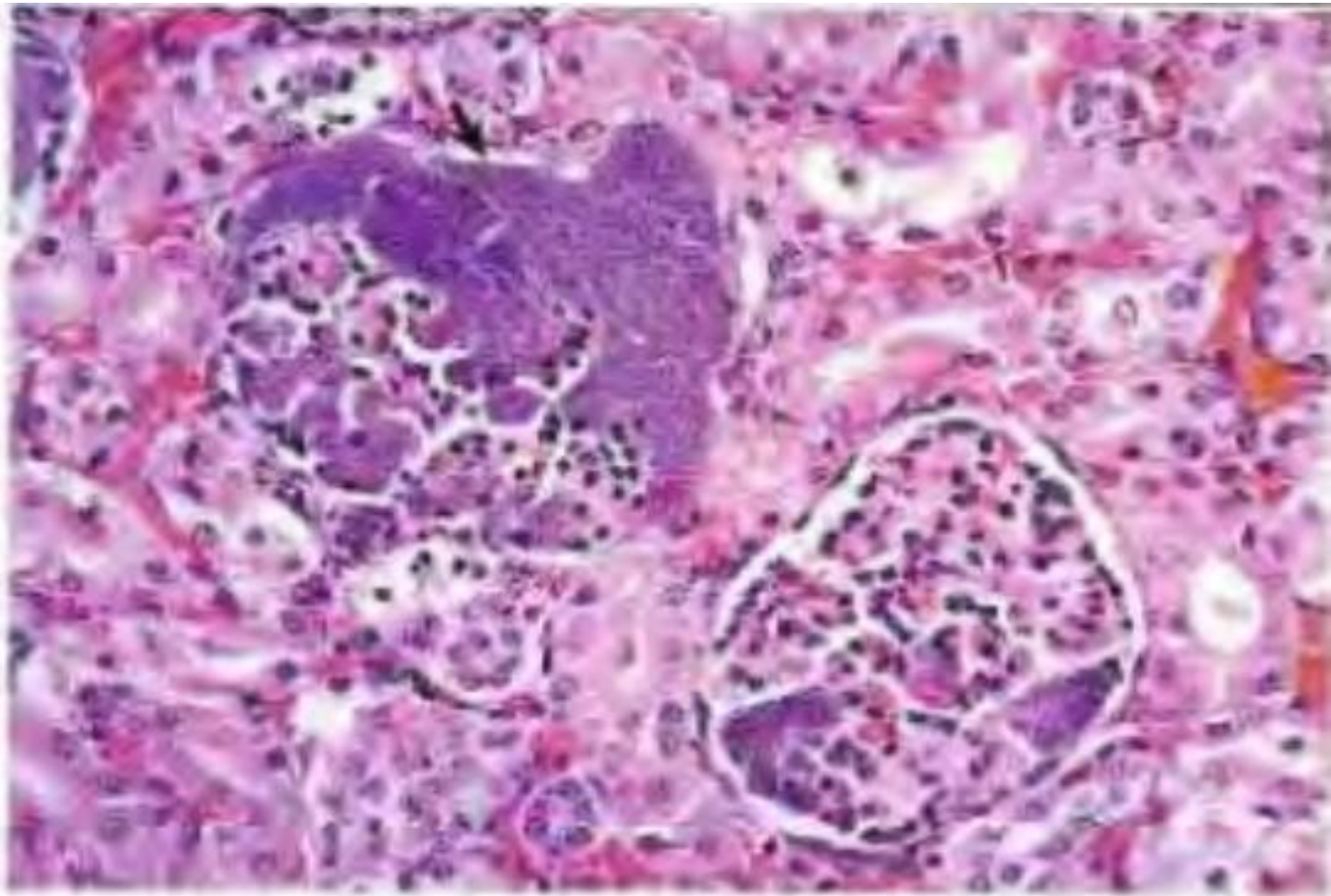
- ⌘ Necrosis, neutrophilic inflammation
- ⌘ Colonies of bacteria in the glomerular capillaries

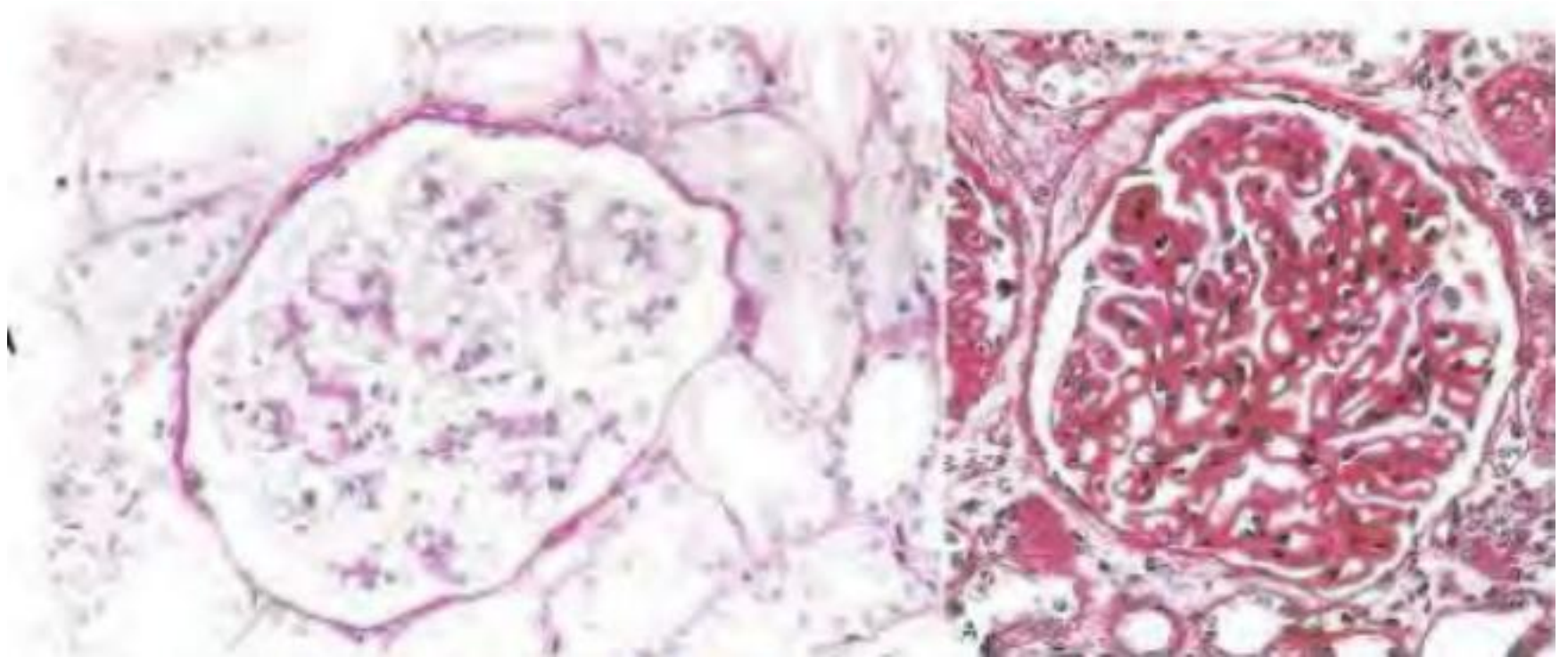
Glomerulonephritis

Immune mediated glomerulonephritis could be due to

⌚ ***In situ* immune complex formation**

- Antibodies may be formed against intrinsic GBM antigens (Anti-Membrane Diseases). This fixes complement and result in leukocyte infiltration and damage
- Well documented in human and lower primate
- Linear deposition of the ICXs are observed





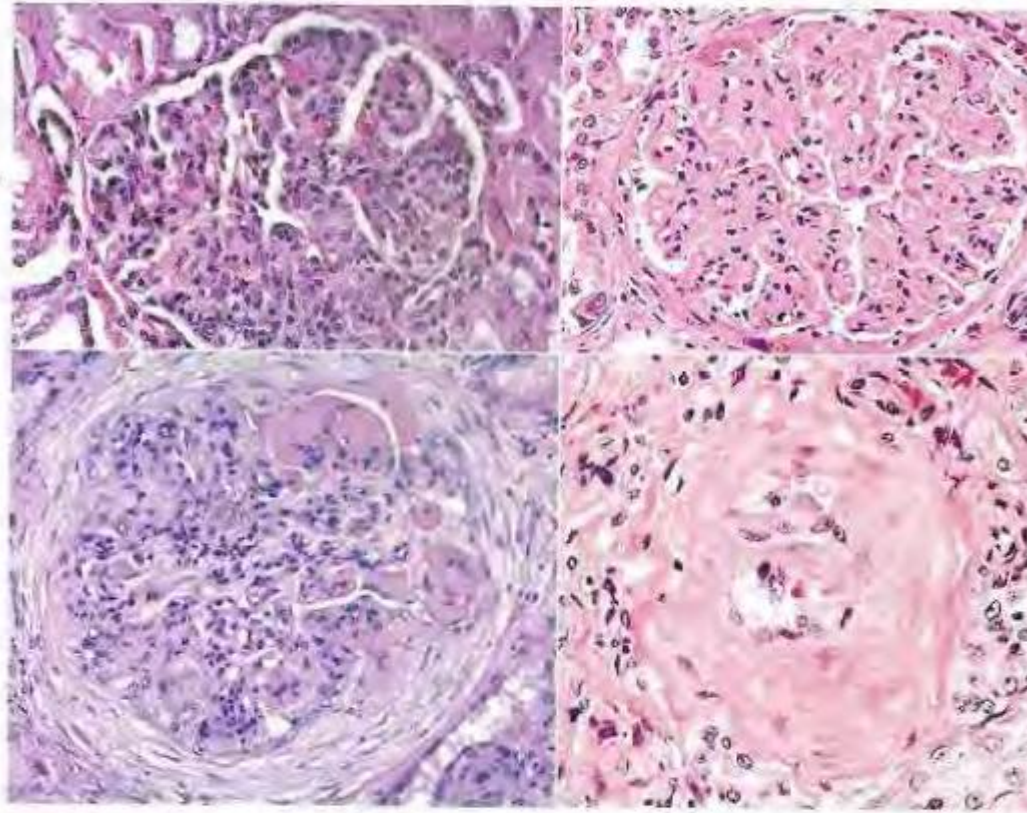


Fig. 11-21 Types of glomerulonephritis. **A**, Proliferative glomerulonephritis, pig. The lesion is characterized principally by hypercellularity of the glomerulus due to increased numbers of mesangial cells. H&E stain. **B**, Membranous glomerulonephritis, dog. The lesion is characterized by generalized hyaline thickening of glomerular capillary basement membranes. It can occur in dogs with dirofilariasis. H&E stain. **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. **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. (**A** and **C**, Courtesy Dr. W. Crowell, College of Veterinary Medicine, The University of Georgia; and Noch's Archive, College of Veterinary Medicine, The University of Georgia. **B** and **D**, Courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

Glomerulonephritis

⌘ **Deposition of soluble ICX in capillary walls (in case of Ag-Ab equivalence, or slight antigen excess)**

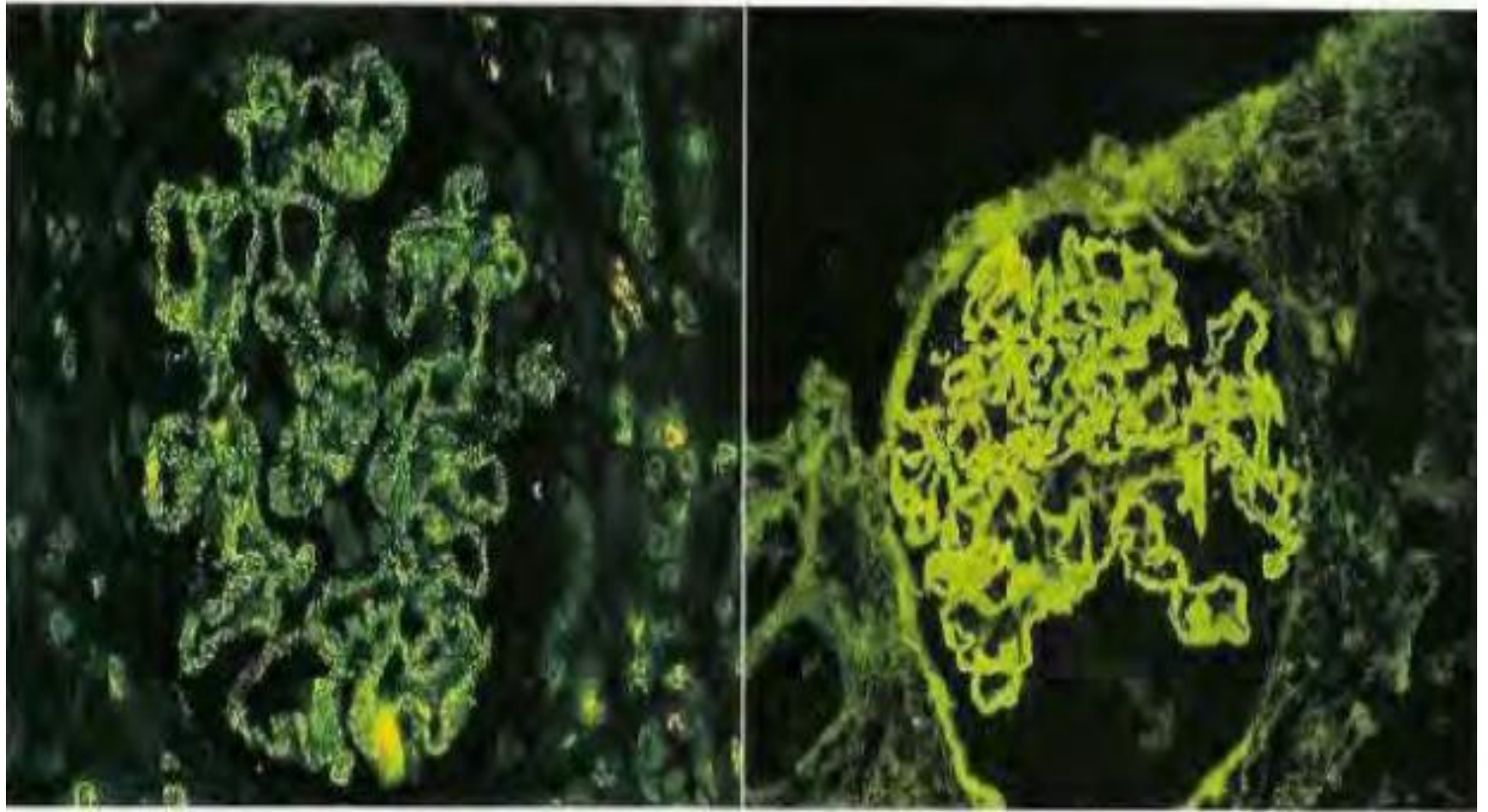
Factors involved for the deposition of soluble ICX include

- 1. Persistent ICXs in the circulation (persistent or prolonged antigenemia).** A good example is canine pyometra
- 2. Increased vascular permeability due to vasoactive substances (from platelets, basophils, mast cells)**
 - Complexes to leave the microcirculation and deposited in the glomerulus
 - Penetration of the BM by ICXs may be aided by products of inflammation (histamine and serotonin)⁷⁶

Glomerulonephritis

4. Strength of bond between antigen-antibody (avidity)

- Complexes that are poorly soluble, fairly large, high avidity localize in capillaries or enter the mesangium
- Within the capillary wall, soluble ICXs can become greatly enlarged due to interactions with free antibodies, free antigens and with complement components
- Complexes containing high avidity antibody localize in the mesangium; complexes with low avidity antibody may localize subepithelially



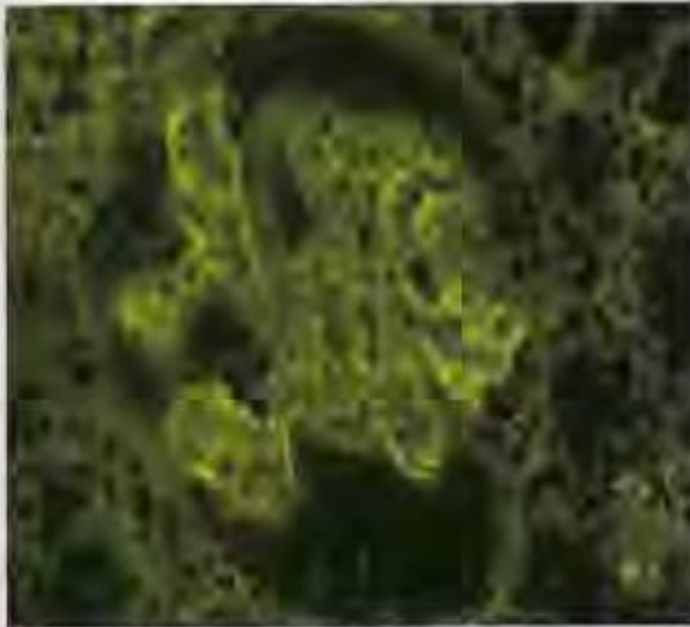


Fig. 11-17 Immune-complex glomerulonephritis, kidney, glomerulus, mink. Intraglomerular immunoglobulin deposits demonstrated by immunofluorescence. Note the granular ("lumpy-bumpy") pattern of fluorescence in this case of Aleutian mink disease. Immunofluorescence microscopy. (Courtesy Dr. S.J. Newman, College of Veterinary Medicine, University of Tennessee.)

has several histopathologic forms. Although various classifications of glomerulonephritis have been published,



Fig. 11-18 Proliferative glomerulonephritis, 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.)

Glomerulonephritis

Mechanisms of glomerular injury after deposition

1. Complement- leukocyte dependent mechanisms

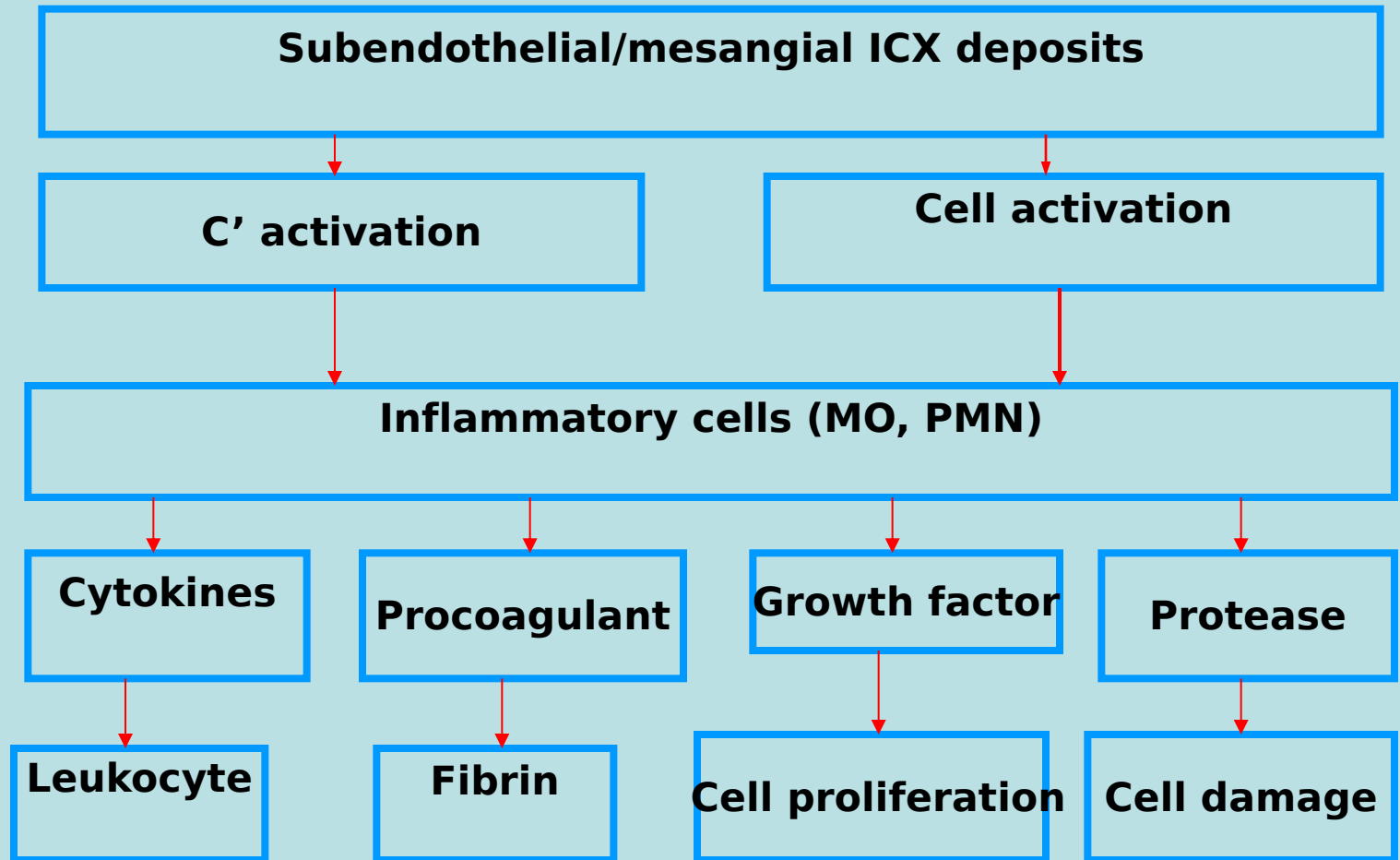
- Activation of complement components (C3a, C5a, C567) attracts neutrophils

2. Leukocyte independent mechanisms

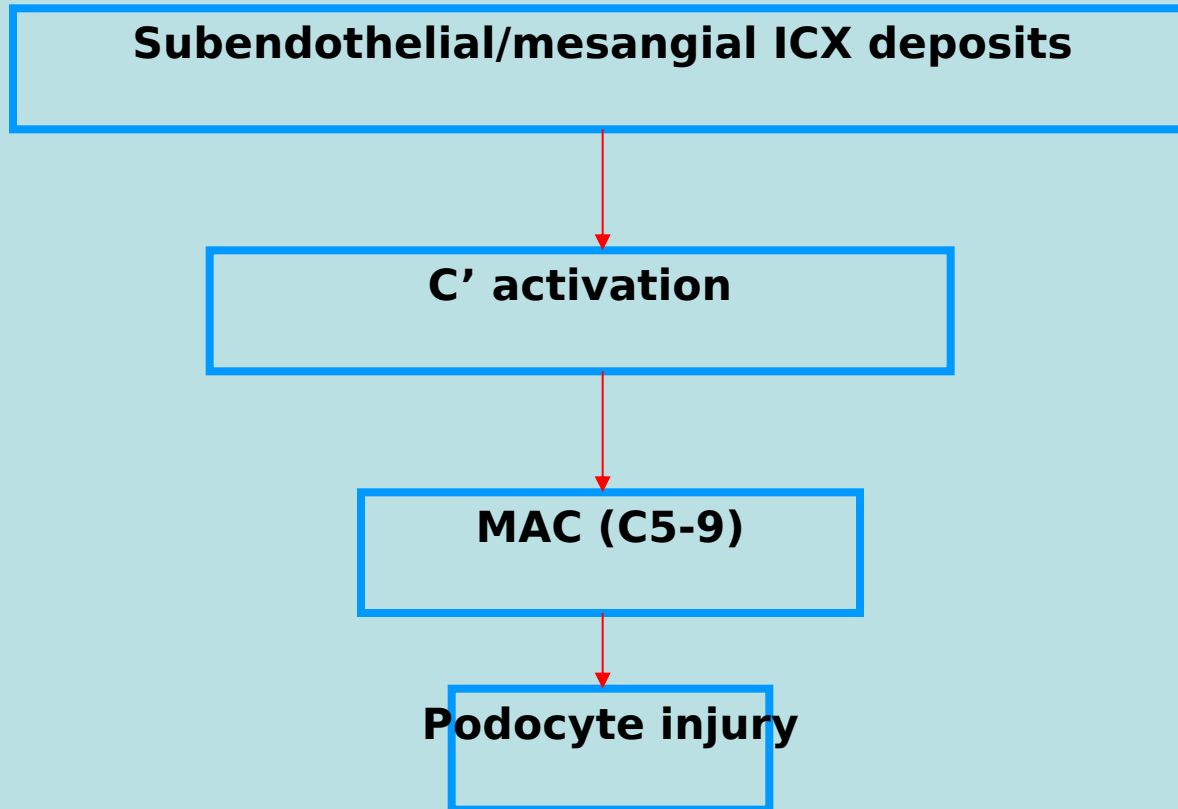
- Membrane attack complex (MAC)(C5b-9) are released

Note: **The damage allows further ICX depositions**

Antibody mediated glomerular diseases (I)



Antibody mediated glomerular diseases (II)



Glomerulonephritis

Histologic changes in ICX Glomerulonephritis

1. Cellularity of the glomerular tuft

- Increased by proliferation of endothelial, epithelial, or mesangial cells
- Proliferation of endothelial versus mesangial cells are difficult to distinguish and the term endocapillary GN is applied

2. Glomerular crescent formation

- Fibrin exudation into the urinary space cells, attracts monocytes and there is proliferation of the parietal epithelial cells

3. Neutrophils and monocyte infiltration

4. Swelling of the foot processes of the podocytes and their subsequent retraction

Glomerulonephritis

5. Hyalinization

- Eosinophilic PAS positive basement membrane like material in the mesangial area

6. Thickening of the Bowman's capsule

- This is due to hyperplasia of parietal epithelial cells

7. Glomerular tuft atrophy

8. Non-glomerular histologic changes

- Tubular proteinuria, hyaline deposits in PCT epithelium
- Tubular atrophy
- Interstitial fibrosis and scarring (end stage kidney) in advanced cases

Glomerulonephritis

Microscopically ICX GN has several Anatomic forms

⌘ Proliferative GN

- ⌋ Increased cellularity in the glomerular tuft (hypercellularity)
- ⌋ Characterized by proliferation of glomerular cells (podocytes, mesangial cells, endothelial cells)
- ⌋ ***Glomerulus fills the Bowman's space and contains numerous nuclei***
- ⌋ ***The most characteristics ultrastructural feature is the presence of deposits “humps” of ICX on the epithelial side of the BM***
- ⌋ PAS stain indicate disrupted BM by the deposits, the BM has “lumpy-bumpy” appearance
- ⌋ The ICX is less than a micron in diameter

Glomerulonephritis

⌘ Membranous GN

- Most frequent cause of nephrotic syndrome
- Morphologic changes include
 - ↳ Diffuse capillary BM thickening (hyalinization)
 - ↳ Splitting and reduplication of GBM
 - ↳ Loss of foot process of the podocytes
 - ↳ The space between cells increases
 - ↳ Dense deposits of ICX on the epithelial side of the BM forming “lumpy-bumpy” appearance
 - ↳ Small complexes penetrate the glomerular loop to produce either proliferative or membranous lesions

Glomerulonephritis

⌘ **Membranoproliferative (mesangiocapillary or Mesangioproliferative)**

- ‖ Podocytes and mesangial cells proliferation are combined with GBM thickening
- ‖ Large complexes are localized in in the mesangium and form mesangiopathic GN
- ‖ Characterized by splitting of the BM
- ‖ There is granular deposits of ICX on the subendothelial side of BM

Glomerulonephritis

⌘ Other forms or lesions

⌘ Glomerulosclerosis

- └ Occurs due to chronic GN
- └ Characterized by glomerular shrinkage
- └ Fibrosis
- └ Hypocellularity
- └ Hyalinization

⌘ Chronic renal fibrosis----hypertension-----renin----vicious cycle
(malignant hypertension, malignant nephrosclerosis)

Glomerulonephritis

Glomerular Crescent formation

- ‖ Chronic proliferative GN resulting in terminal uremia
- ‖ There is thickened and hyalinized Bowman's capsule
- ‖ Proliferation of parietal epithelial cells, influx of monocytes, deposition of fibrin form semicircular, hypercellular intraglomerular lesions
- ‖ There is fibrosis
- ‖ Bowman's capsule ruptured is followed by interstitial fibrosis

Amyloidosis

- ⌘ AA Amyloidosis is reactive type formed from SAA
- ⌘ Glomeruli are the common site of deposition
- ⌘ Deposition is mainly in the mesangial and subendothelial area
- ⌘ Glomerular amyloidosis is a protein losing nephropathy

Amyloidosis

Outcome of long standing amyloidosis

- Ischemia and pressure atrophy of nephrons induced by amyloid
- Proteinuria, hypoproteinemia
- Renal tubular atrophy
- Thyroidization (dilated tubules with pink hyaline casts)
- Diffuse fibrosis
- Amyloid may be present in renal tubular basement membrane resulting in hyalinization and thickening of the BM

Amyloidosis

Diagnosis of amyloidosis

- ‖ Application of iodine solution on the cut surfaces result in brown staining of glomeruli
- ‖ The usual Congo red staining is diagnostic
- ‖ Immunohistochemical diagnosis

Anatomy of the lower urinary tract

- Renal pelvis, ureters, and urinary bladder are lined by transitional epithelium
- Urethra is lined by transitional epithelium (cranially) and stratified squamous epithelium (caudally)
- Vesicoureteral valve is created by the oblique passage of the ureter (intravesical ureter) via the wall of the urinary bladder
- The valve prevents reflux of bladder urine into the ureter and renal pelvis
- Intravesical ureter is very short in puppies, so urine reflux is common

Urolithiasis

Urolithiasis is the presence of calculi (urolith) in the urinary passage

- Calculi contain urinary salts (inorganic salts), urinary proteins and proteinaceous debris
- In most calculi, the mineral part is dominant than the organic (protein) matrix
- Calculi can be present in the renal pelvis, ureter, bladder, and urethra
- Calculi in renal pelvis predispose to pyelitis/ pyelonephritis
- In bull calculi are commonly present at ischial arch, proximal end of sigmoid flexure
- In rams calculi commonly lodge at urethral process (vermiform appendage)
- In dog calculi lodge at the base of os penis

Urolithiasis

- Calculi cause urinary obstruction commonly in male due to
 1. Narrow urethral diameter
 2. Longer urethra
- In females it is not frequent, it may occur at renal pelvis and urinary bladder

Predisposing factors to calculi

1. Urine PH

- Some salt precipitate more readily in acidic PH (e.g. oxalates)
- Other at alkaline PH (e.g. carbonate)

2. Reduced water intake and dehydration

3. Presence of nidus : Exfoliated epithelium due to bacterial infection and infiltrated leukocytes can serve as nidus

Urolithiasis

4. Nutritional and dietary factors

- In sheep diets rich in phosphate (e.g. sorghum)
- Ingestion of oxalate containing plants
- Vitamin A deficiency induce metaplastic changes and act as nidus
- Ingestion of estrogen containing plants/injection of estrogens

Urolithiasis

Examples of calculi

1. **Silica calculi**- in the bladder of ruminants grazing grain stubble
2. **Struvite calculi**- in dogs, cats, and in ruminant bladder
3. Oxalate calculi- occur as calcium oxalate crystals in sheep grazing grain stubble
4. **Uric acid and urate calculi** - in dogs
5. **Cystine calculi**- in dogs and cats
6. **Clover stones** - in sheep grazing estrogenic pastures

Urolithiasis

Gross lesions of urolithiasis

- Visible calculi
- Distended, turgid or ruptured bladder
- Dilated ureters and renal pelvis
- Hemorrhagic bladder
- Ulceration and necrosis of mucosal surface

Microscopic lesions of urolithiasis

- Inflammation, hyperplasia of transitional epithelium
- Numerous goblet cells
- Neutrophils in the lamina propria

Lower urinary tract infection

Predisposing factors to urinary tract infection

1. Stagnation of urine due to obstruction

- Hydrolysis of urea by urease producing bacteria, such as *C. renale* release excessive ammonia that cause mucosal damage

2. Incomplete voiding at micturation, or urothelial trauma

3. Catheterization

4. Vaginoscopy

5. Urinary incontinence

Lower urinary tract infection

6. Vaginitis
7. Parturition causes erosion and hemorrhages
8. Calculi induce trauma to the urinary mucosa
9. Glucosuria as in D. mellitus enhance bacterial growth upon fermentation
10. Neurogenic causes related to spinal cord diseases lead urine retention and hence cystitis

Cystitis, Ureteritis, Urethrititis

Cause include

1. ***E. coli, Proteus vulgaris, Streptococci, Staphylococci*** in all species
2. ***C. renale*** in cows
3. ***Eubacterium suis*** in swine
4. ***Blastomycosis, Aspergillus, Candidia*** in dogs and acts
5. Decreased leukocyte efficiency
6. During estrus in cows, estrogen causes the urine PH to rise (alkaline), and enhance bacterial growth

Cystitis is common in females (short and wider urethra) than in males (long and

narrow urethra). Leukocytes in urine usually are not phagocytic.

Except for the distal urethra the lower urinary tract is normally

Cystitis

Acute cystitis

- It is caused mainly by bacteria
- It can be hemorrhagic, fibrinopurulent, necrotizing, ulcerative
- Characterized by thickened bladder wall (by edema and inflammatory cell)
- The urine appears cloudy and has foul smelling
- Hemorrhagic cystitis also occur in MCF (in cattle and deer)

Chronic cystitis

- Diffusely thickened, hyperplastic mucosa with goblet cell hyperplasia
- There is chronic lymphoplasmacytic infiltrate
- Fibrosis in the lamina propria

Cystitis

Three anatomic forms of chronic cystitis

1. Chronic polypoid cystitis

- Can be sessile/ pedunculated, single/ multiple nodules on the mucosa
- It may be covered by hyperplastic epithelium with goblet cell metaplasia
- It is composed of fibrous tissue, neutrophils and mononuclear leukocytes

2. Disseminated nodular, submucosal lymphoid proliferation

- Characterized by the presence of white gray lymphoid foci (lymphocytes)
- Also referred as follicular cystitis

Cystitis

3. Mycotic cystitis

- Occurs in aspergillus, or candida infection
- It may also occur secondary to chronic bacterial cystitis
- Characterized by ulceration, proliferation (fibrosis), and generalized thickening of the wall

Enzootic hematuria

- Syndrome in mature cattle characterized by persistent hematuria and anemia
- It can cause hemorrhagic cystitis and capillaries are highly engorged
- Occurs as a result of prolonged ingestion of bracken fern
- The fern contain several toxic substances including, thiaminase, carcinogens, and bleeding factors
- Several types epithelial and mesenchymal neoplasm may develop (papilloma, fibroma, hemangioma and carcinoma are frequent in 90% of the cases) in animals with enzootic hematuria