URINARY SYSTEM

PRESENTED BY

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LECTURE OF PATHOLOGY

FACULTY OF VETERINARY MEDICINE

SOUTH VALLEY UNIVERSITY

Lecture 1

INTRODUCTION

KIDNEY

Mammalian kidneys are paired organs present in the retroperitoneum, their function in excretion, metabolism, secretion, the four major anatomic structures of the kidney:

the glomeruli, tubules, interstitium, and vasculature.

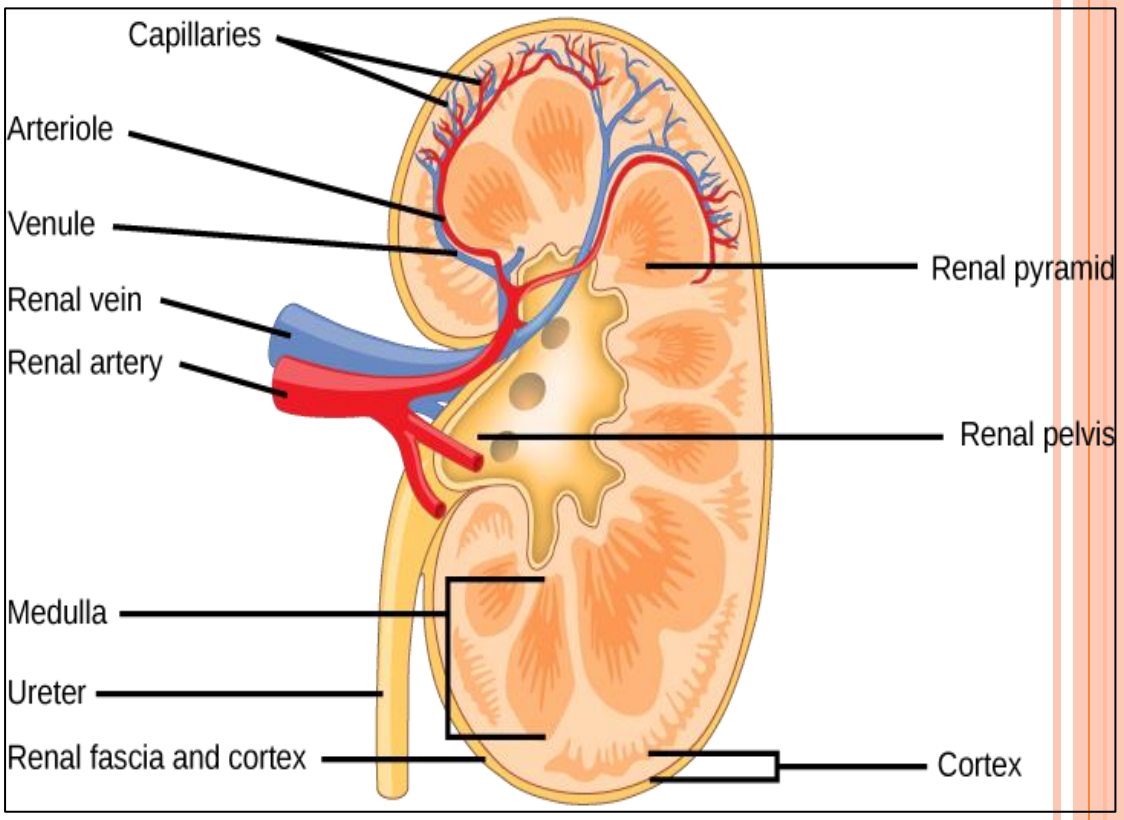
Because of the limited ways that renal tissue can respond to injury, the patterns of injury and outcomes that initially may be distinctive in severe and prolonged diseases will result in a similar end point- chronic renal disease and failure.

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.

STRUCTURE AND FUNCTION

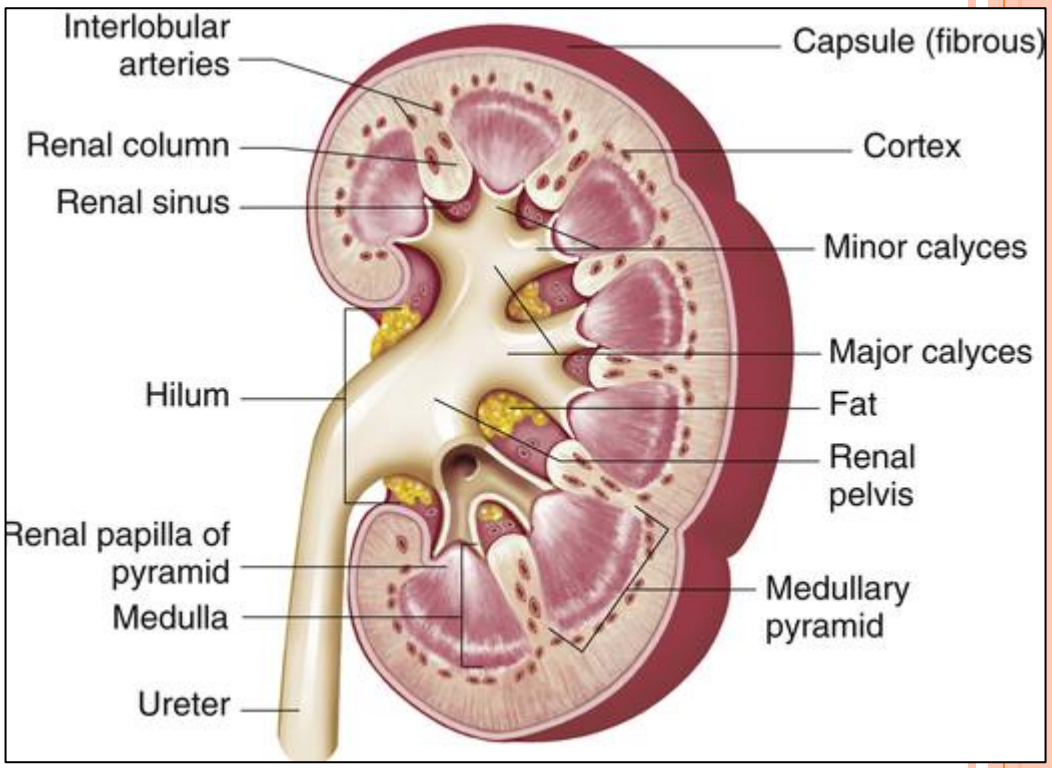
MACROSCOPIC STRUCTURE

Kidneys are divided into lobules. Each lobule represents collections of nephrons separated by the medullary rays. Each lobe is represented by a renal pyramid.



Among domestic animals, carnivores and horses have uni lobar (or uni pyramidal) kidneys. Porcine and bovine kidneys are multi lobar (or multi pyramidal), but only bovine kidneys have external lobation.

Kidneys are covered by a diffuse fibrous capsule that in normal kidneys can be easily removed from the renal surface.

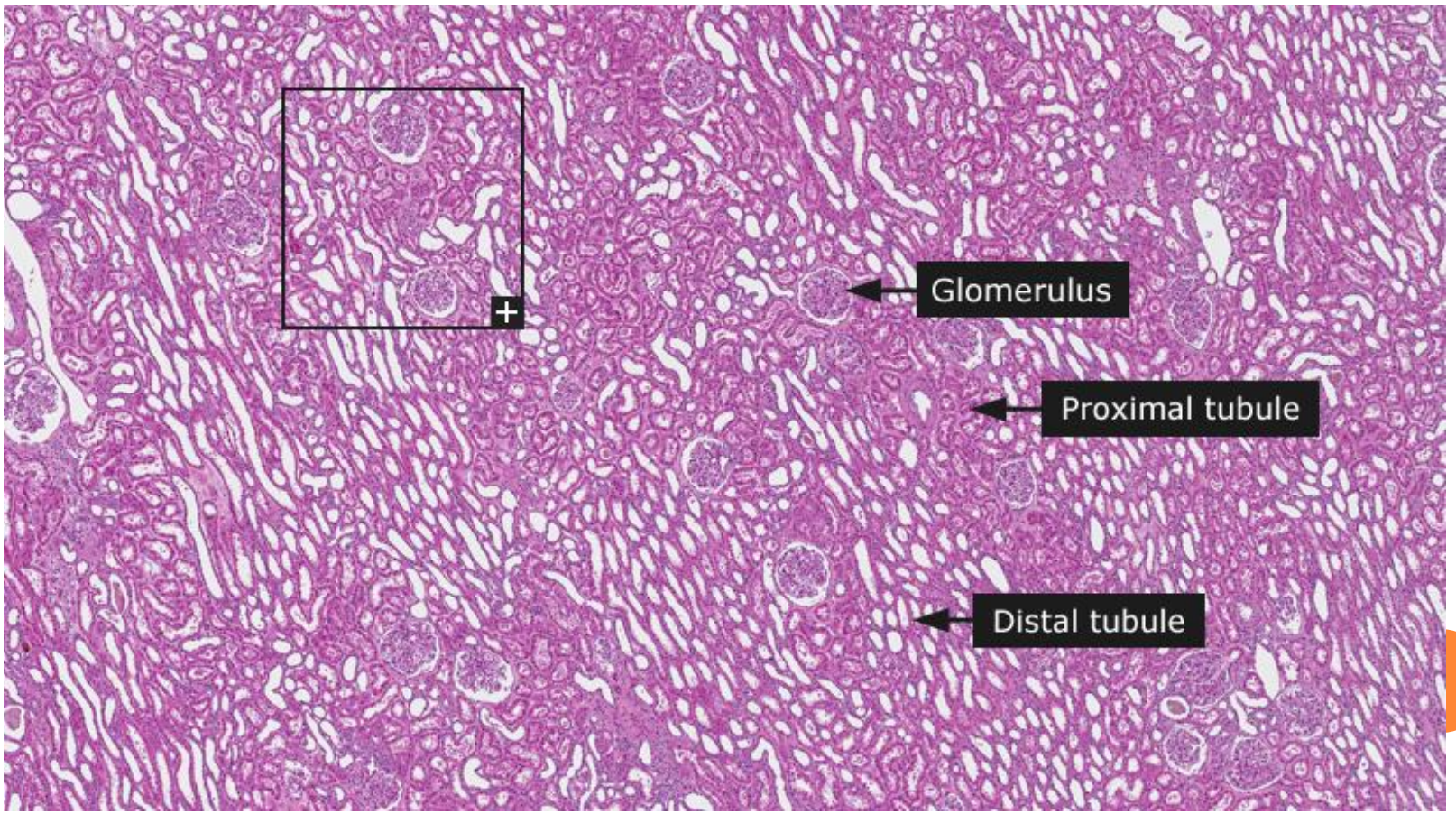


The renal parenchyma is divided into a cortex and medulla.

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.

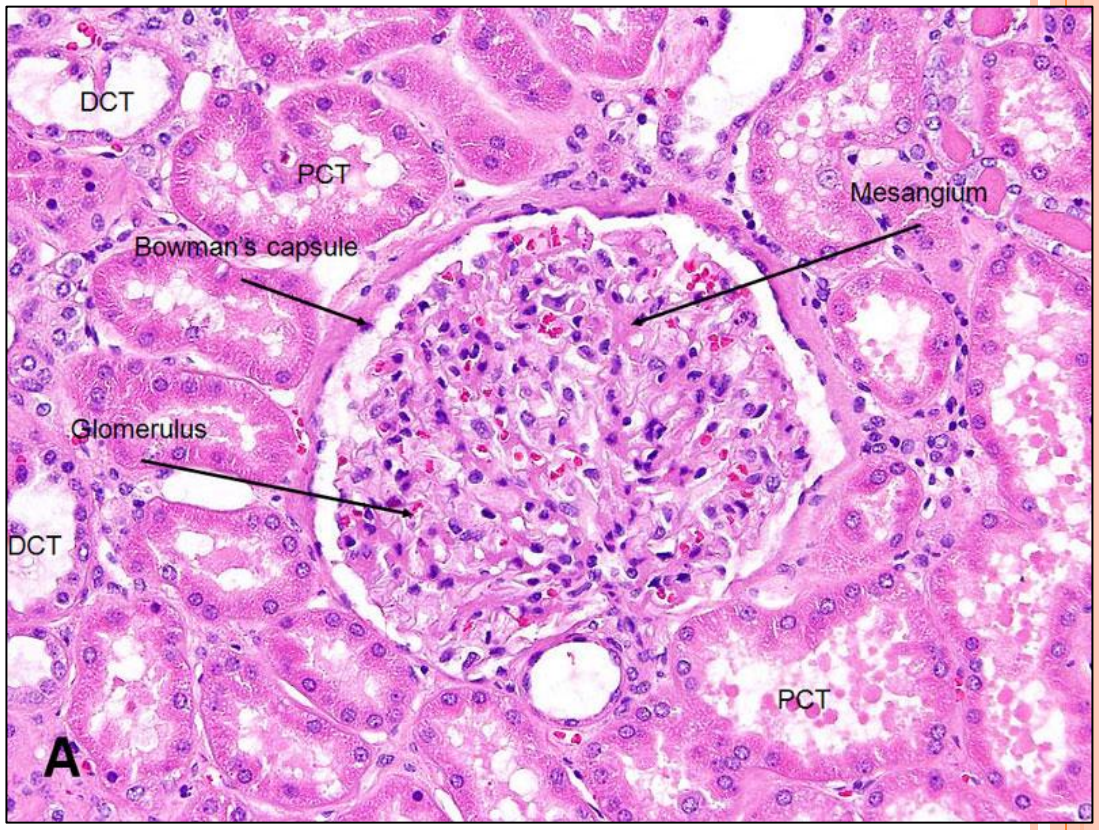
MICROSCOPIC STRUCTURE

The functional unit of the kidney is the nephron, which includes the renal corpuscle (glomerulus within Bowman's capsule), and a tubular system that includes the proximal convoluted tubules, the loop of Henle, and the distal convoluted tubule, which empties into the collecting tubule.



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.

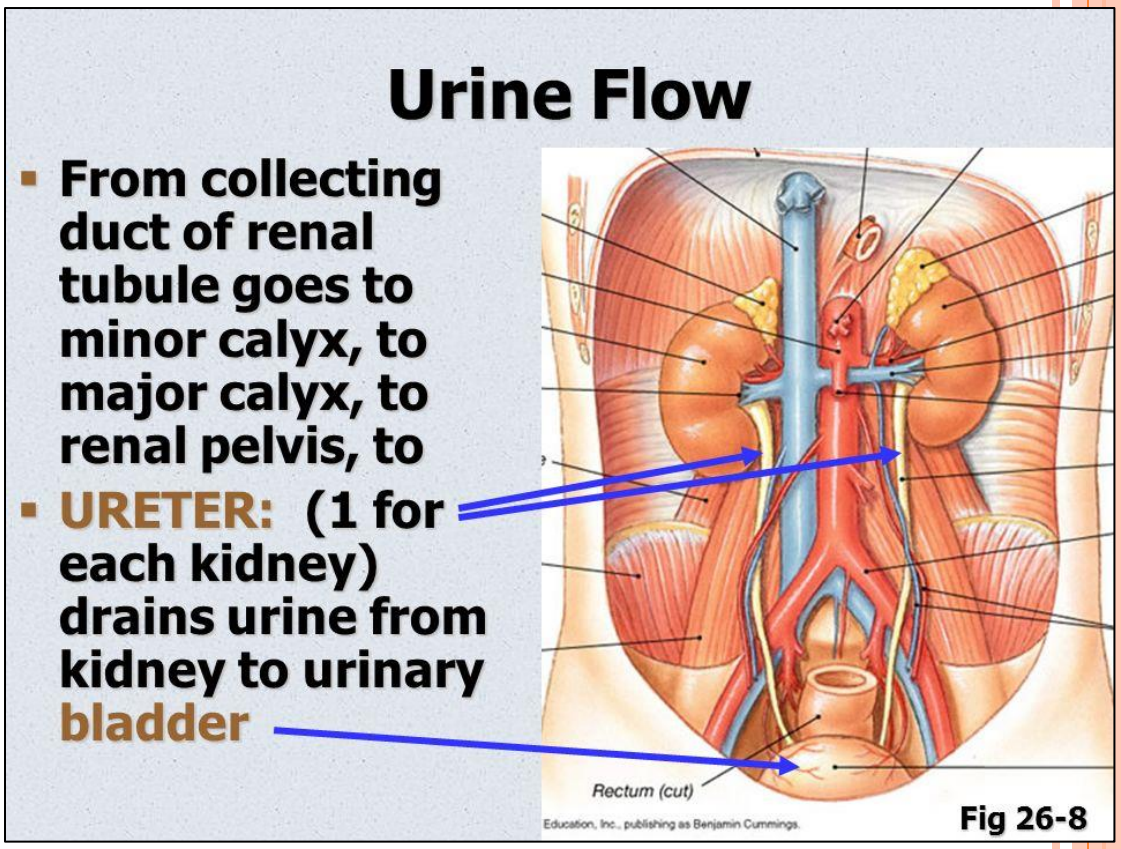
The capillary tuft is covered by the visceral epithelial cells(podocytes) and is contained within a membranous "cap," called Bowman's capsule, which is lined by parietal squamous epithelium).



Urine flow:

The fluid that filters through the glomerulus into the capsular space is called glomerular filtrate and it arises after passage through the glomerular filtration membrane.

This ultra filtrate of plasma (primary urine), which contains water, salts, ions, glucose, and albumin, passes into the capsular space (Bowman's space) and then empties into the proximal Convoluted tubule at the urinary pole.

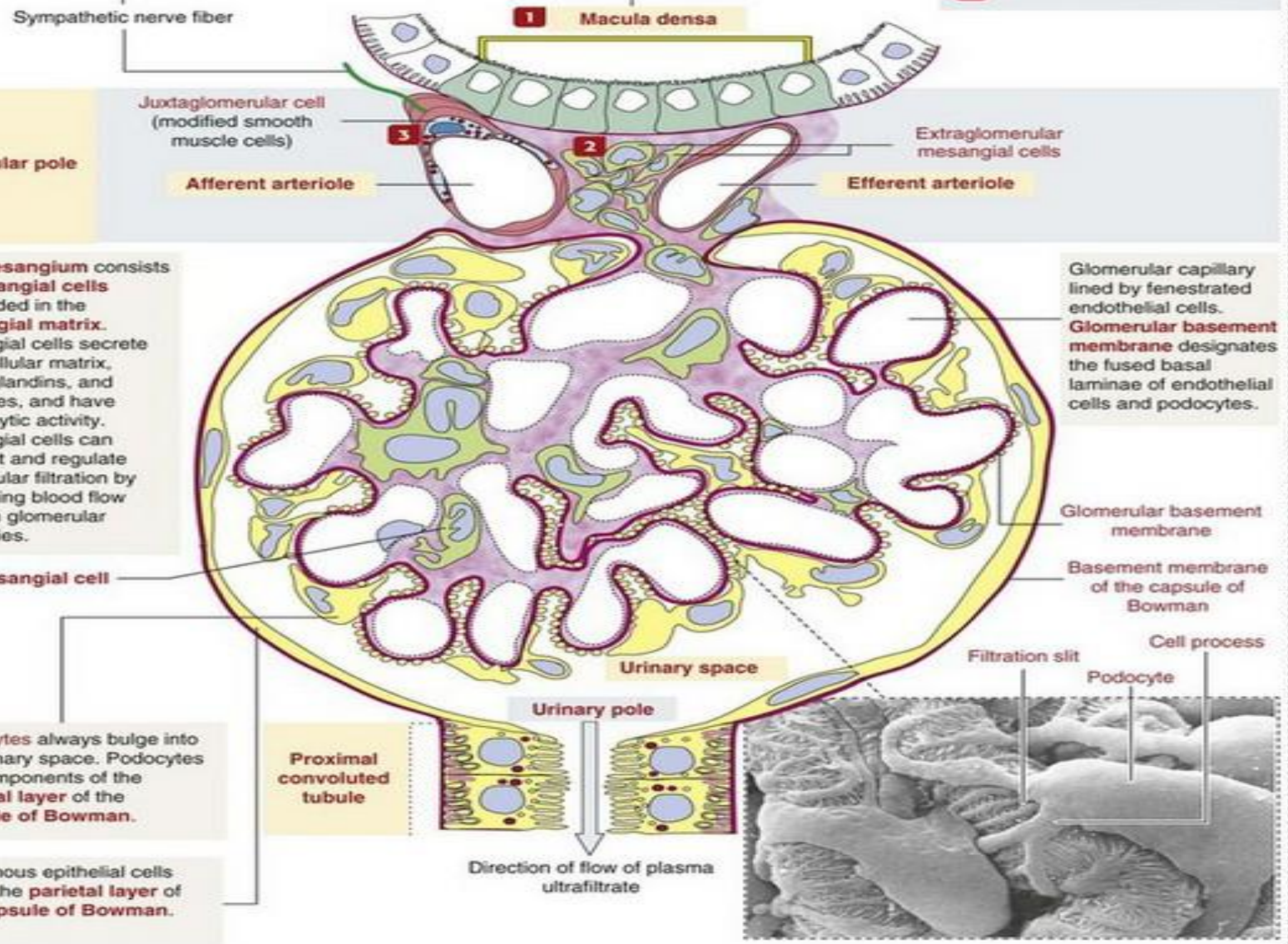


Sympathetic nerve fibers reach the afferent arteriole and innervate juxtaglomerular cells.
An increase in sympathetic activity stimulates renin secretion.

The **macula densa** is a distinct epithelial region found at the thick ascending limb–distal convoluted tubule junction. The macula densa faces the triangular area formed by the afferent and efferent arterioles of the **same** nephron. The cells of the macula densa are in contact with **extraglomerular mesangial cells**.

Components of the juxtaglomerular apparatus

1. The macula densa
2. The extraglomerular mesangial cells
3. The juxtaglomerular cells



The **mesangium** consists of **mesangial cells** embedded in the **mesangial matrix**. Mesangial cells secrete extracellular matrix, prostaglandins, and cytokines, and have phagocytic activity. Mesangial cells can contract and regulate glomerular filtration by controlling blood flow through glomerular capillaries.

Glomerular capillary lined by fenestrated endothelial cells. **Glomerular basement membrane** designates the fused basal laminae of endothelial cells and podocytes.

Glomerular basement membrane

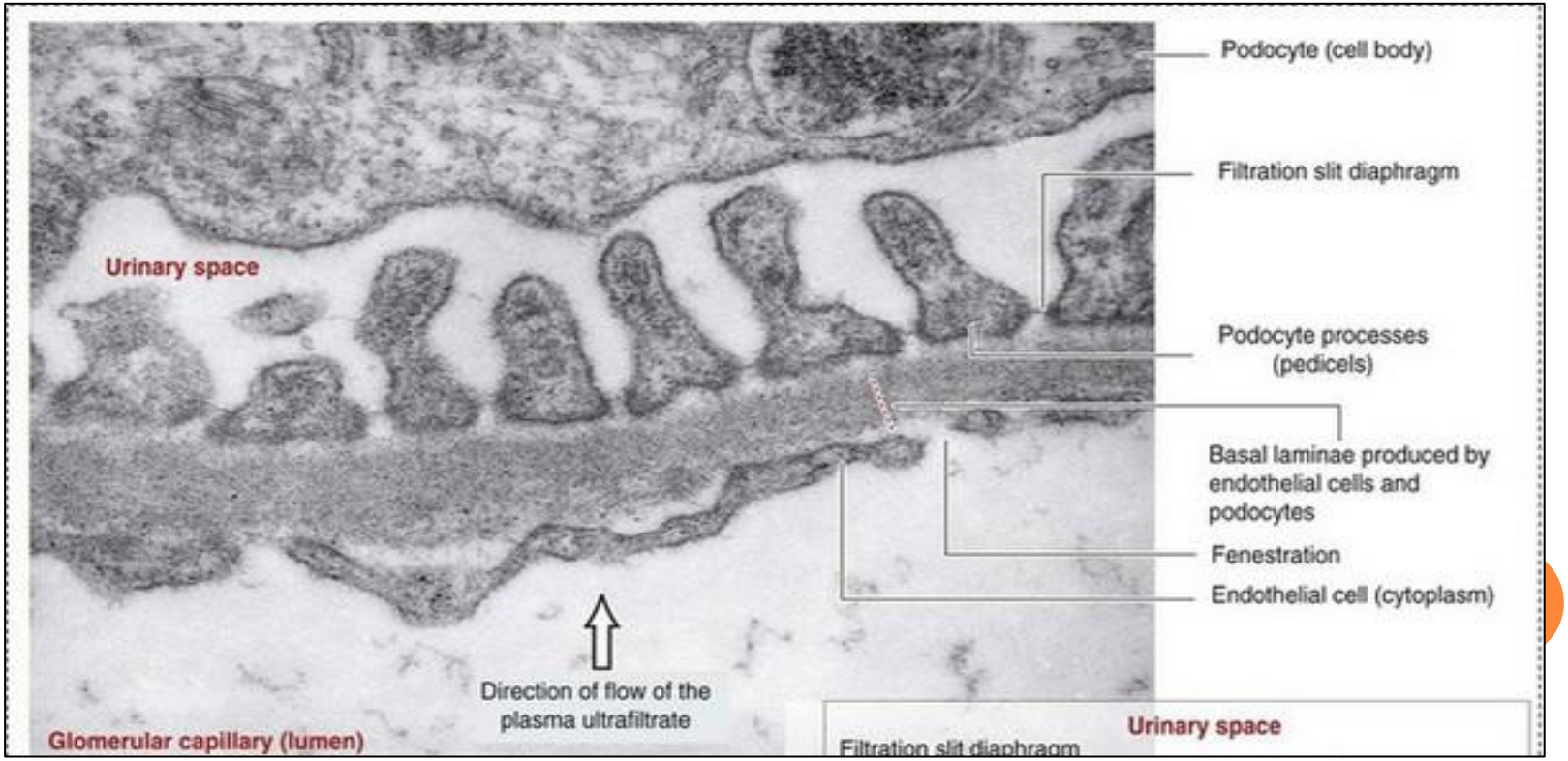
Basement membrane of the capsule of Bowman

Podocytes always bulge into the urinary space. Podocytes are components of the **visceral layer** of the **capsule of Bowman.**

Squamous epithelial cells cover the **parietal layer** of the **capsule of Bowman.**

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.

The juxtaglomerular apparatus functions in tubuloglomerular feedback by autoregulating renal blood flow and glomerular filltration rate.



Glomerular capillary (lumen)

plasma ultrafiltrate

Components of the filtration barrier

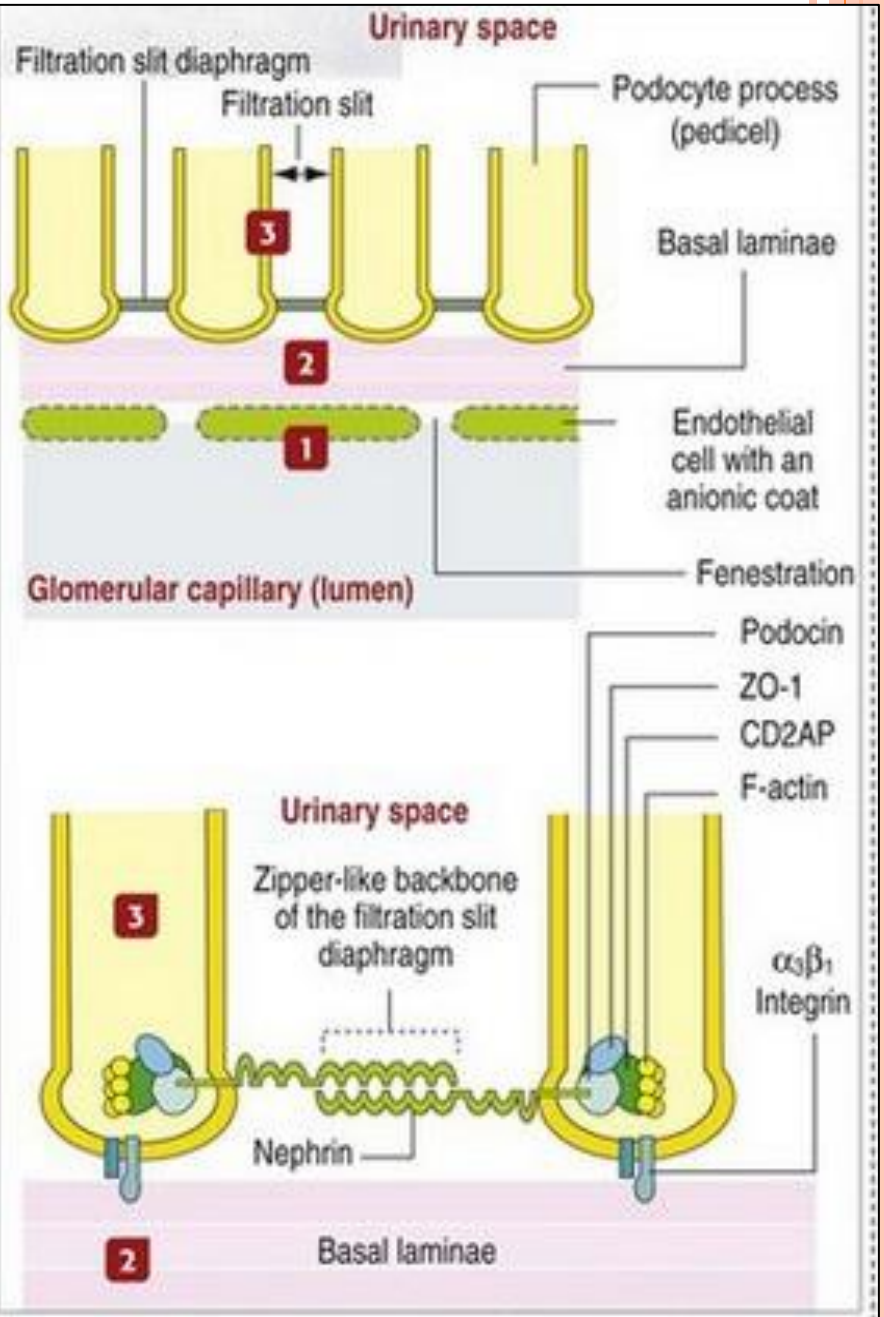
1 The **endothelium** of the glomerular capillaries is **fenestrated** and permeable to water, sodium, urea, glucose, and small proteins. Endothelial cells are coated by **negatively charged glycoproteins** (heparan sulfate), which slow down the filtration of large anionic proteins.

2 The **basal lamina**, a product of endothelial cells and podocytes, contains type IV collagen, laminin, fibronectin, and proteoglycans rich in the glycosaminoglycan heparan sulfate—which also slows down the filtration of anionic proteins.

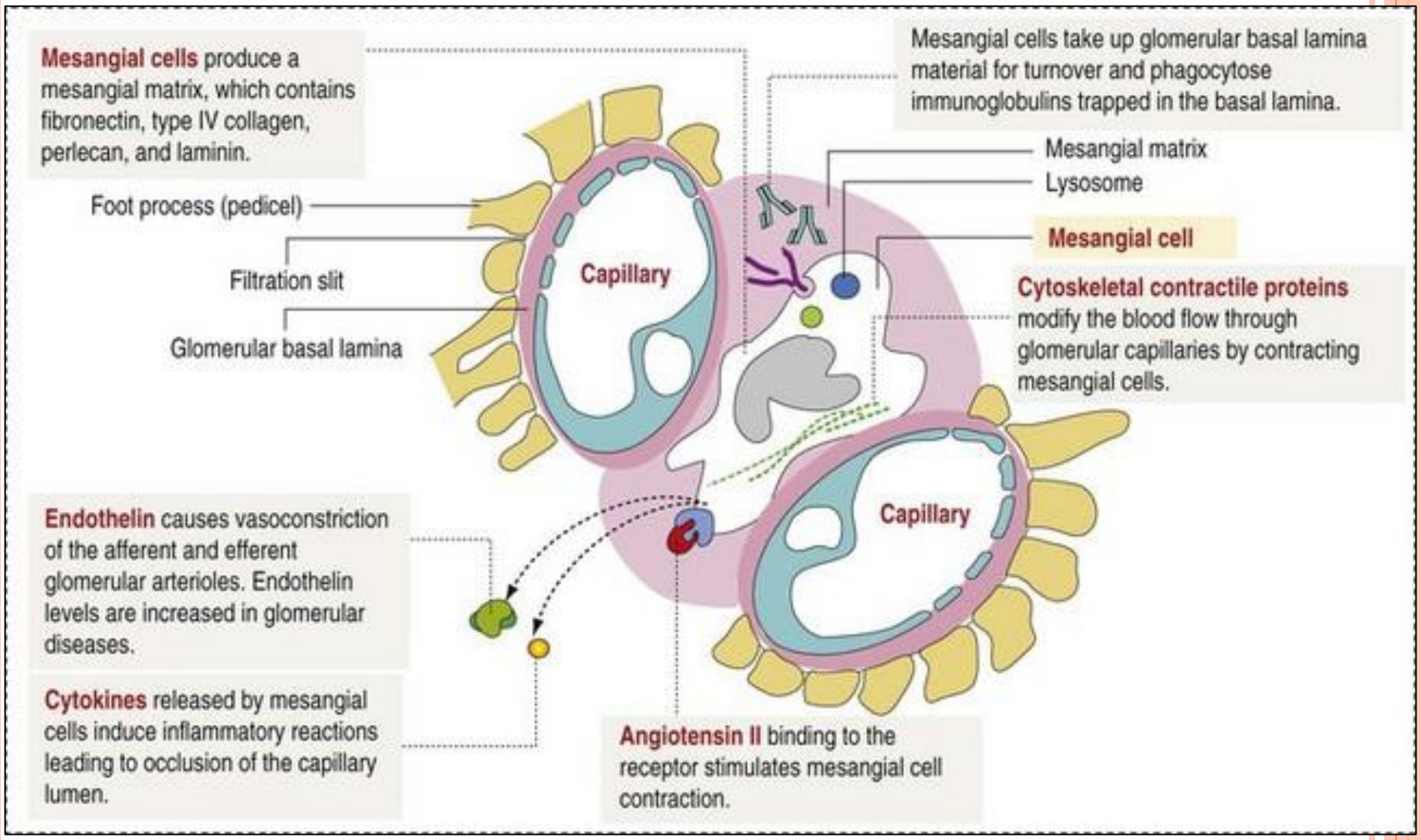
3 The pedicels are interdigitating cell processes of podocytes covering the basal lamina and coated by a negatively charged glycoprotein coat. The space between adjacent pedicels is called the **filtration slit**. A **filtration slit diaphragm** links adjacent pedicels.

The diaphragm consists of **nephrin**, a cell adhesion molecule of the immunoglobulin superfamily, anchored to actin filaments within the pedicel by the proteins CD2AP, zonula occludens (ZO)-1, and podocin.

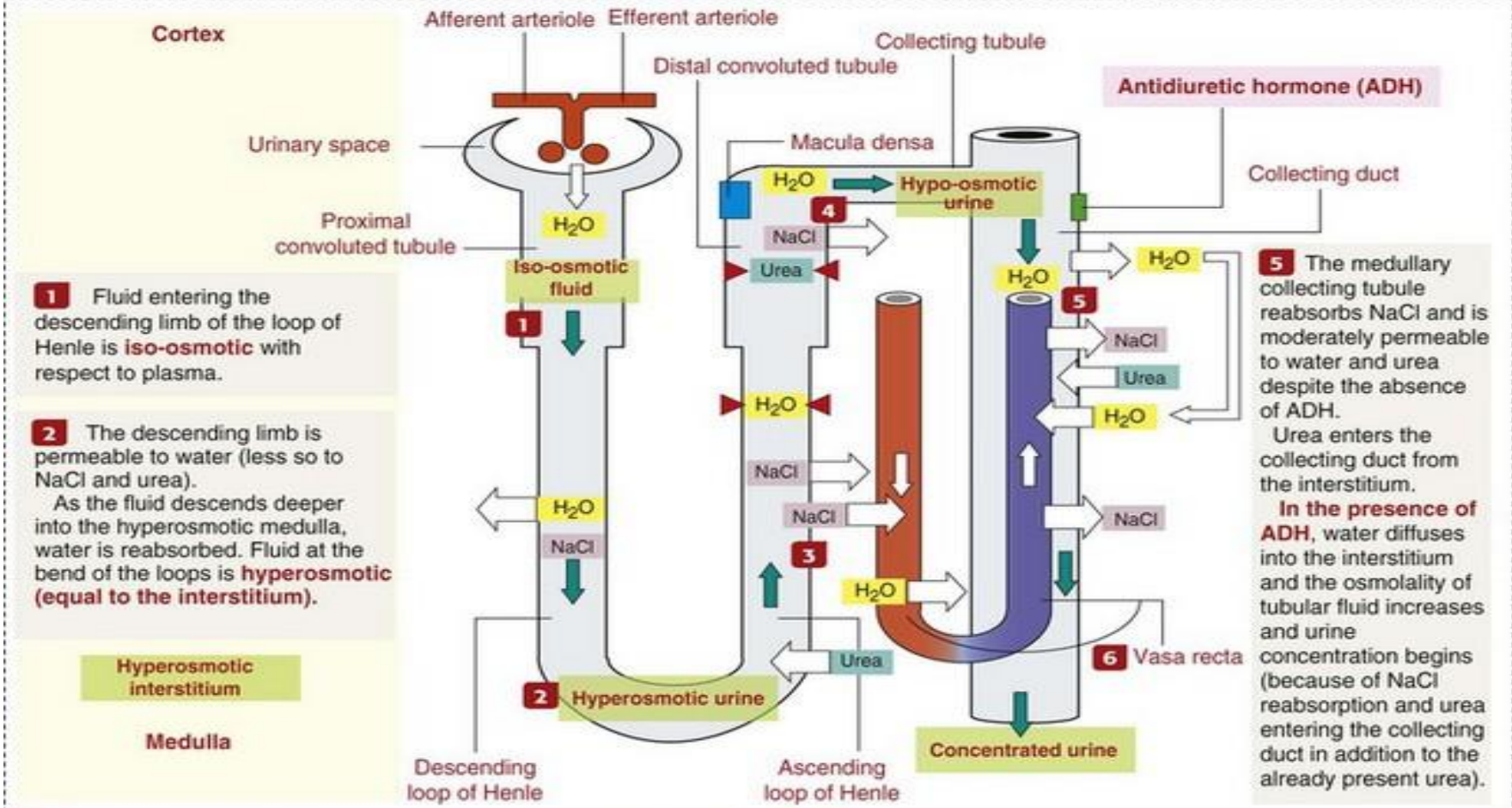
A mutation of the gene encoding nephrin causes **congenital nephrotic syndrome**, characterized by massive proteinuria (leakage of albumin in urine) and edema.



Schematic diagram of the functions and organization of the mesangium.



Schematic diagram of the counter-current multiplier and exchanger



RENAL FUNCTION

1. Formation of urine for the purpose of elimination of metabolic wastes.

2. Acid-base regulation, predominantly through reclamation of bicarbonate from the glomerular filtrate.

3. The conservation of water through reabsorption by the proximal convoluted tubules, the countercurrent mechanism of the loop of Henle, antidiuretic hormone 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.

4. The 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.

5. Endocrine function through three hormonal axes: renin-angiotensin , 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 [calcitriol, which facilitates calcium absorption by the intestine.

Portals of Entry to the Kidney

ASCENSION

- 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)

HEMATOGENOUS

- Localization within corticomedullary vessels
- Septic-embolic nephritis
- Non septic necrosis with infarction
- Localization within large renal vasculature
- Massive infarction
- Localization within glomerular tufts
- Localization within interstitial vessels

METABOLIC PROCESSING IN RENAL TUBULES

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

Renal Responses to Injury

GLOMERULI

- Necrosis
- Glomerular cell proliferation
- Glomerular basement membrane proliferation
- Mesangial cell proliferation
- Infiltration of leukocytes
- Reduced vascular perfusion
- Increased vascular permeability
- Atrophy of the glomerular tuft
- Fibrosis of the glomerular tuft

TUBULES

- Cell degeneration , necrosis, apoptosis , atrophy and Cell regeneration
- Basement membrane rupture and Basement membrane thickening
- Compensatory hypertrophy

INTERSTITIUM

- Edema
- Hemorrhage
- Inflammation Fibrosis

VASCULATURE

- Thrombosis
- Sclerosis
- Basement membrane thickening
- Endothelial cell hypertrophy

Diseases of the kidney

DEVELOPMENTAL ABNORMALITIES :

***RENAL APLASIA,**
***HYPOPLASIA,**
***DYSPLASIA**

Renal aplasia (agenesis)

is the **failure of development** of one or both kidneys.

In these cases, the ureter may be present or absent.

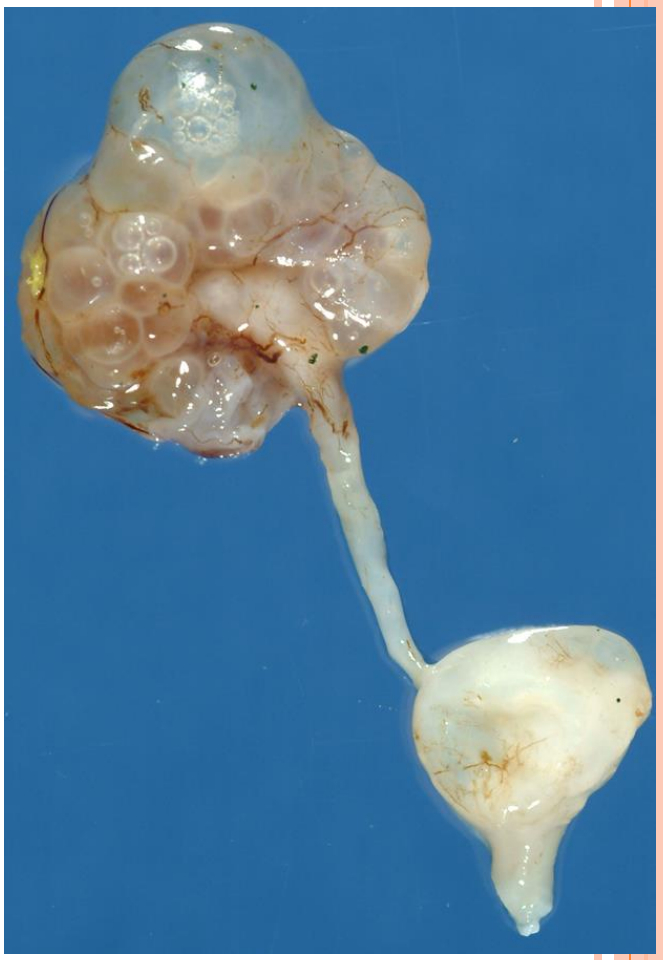
If present, the cranial extremity of the ureter begins as **a blind pouch**.

A familial tendency for renal aplasia has been observed in **dogs.**

unilateral aplasia is compatible with life provided that the **other kidney is normal**.

It can be recognized at necropsy.

Bilateral aplasia occurs sporadically.



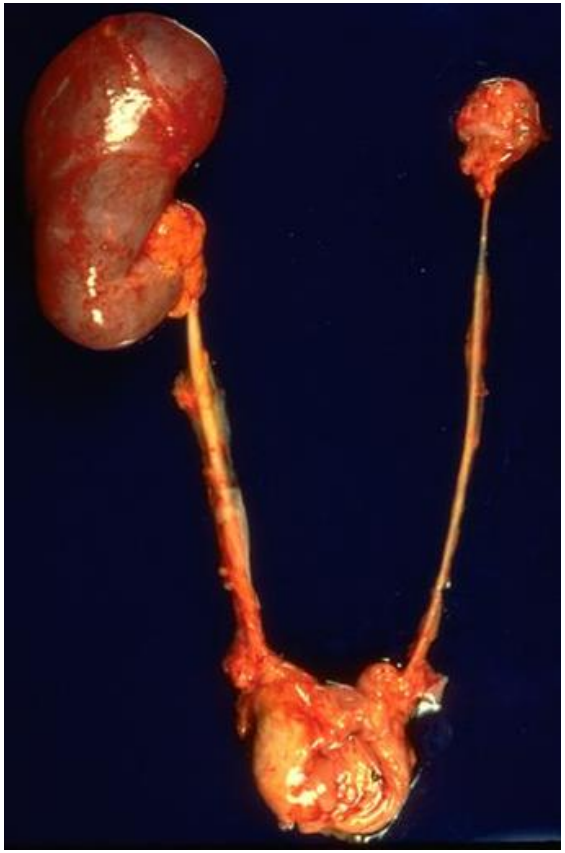
Renal hypoplasia

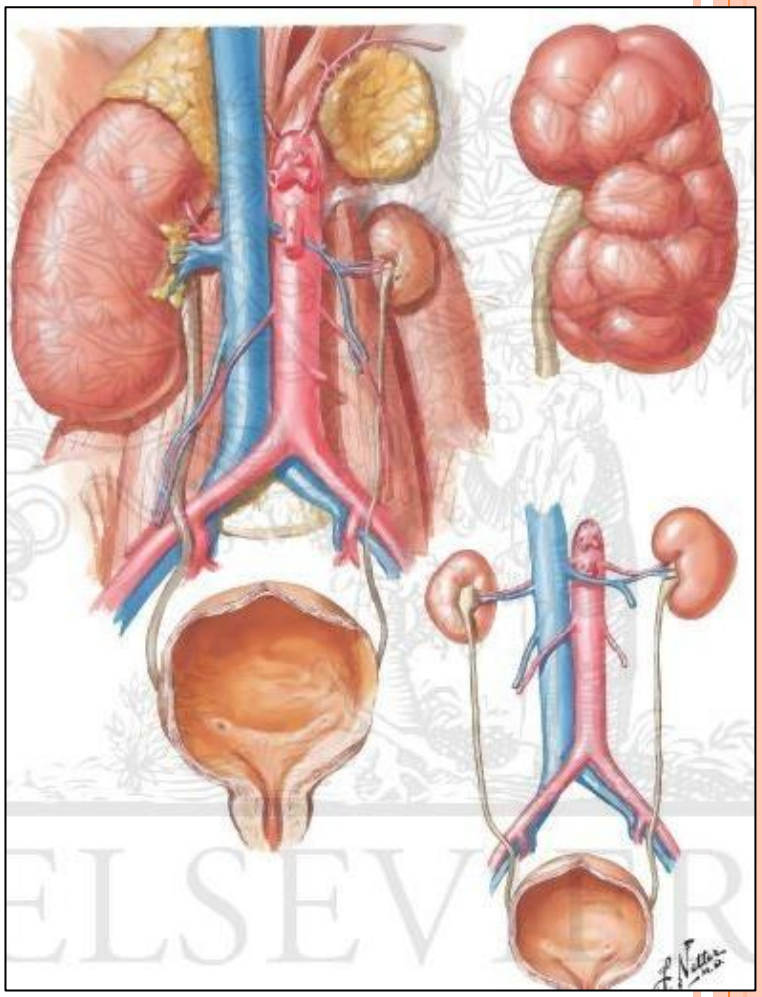
Incomplete development of the kidneys, such that **fewer than normal** nephrons are present **at birth.**

Renal hypoplasia has been documented as an inherited disease **pigs** as well as in **dogs** and **cats.**

Hypoplasia can be **unilateral or bilateral.**

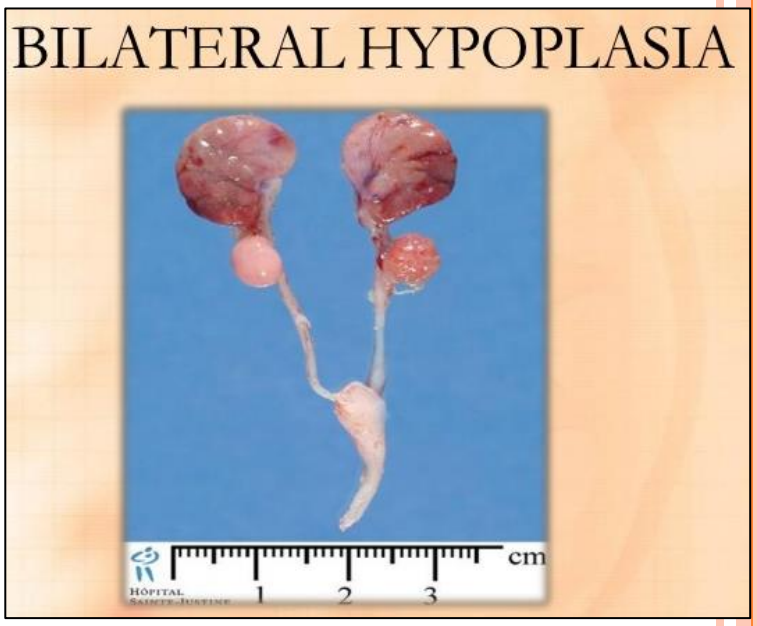
It is rare, and it is difficult to diagnose at necropsy or microscopically.





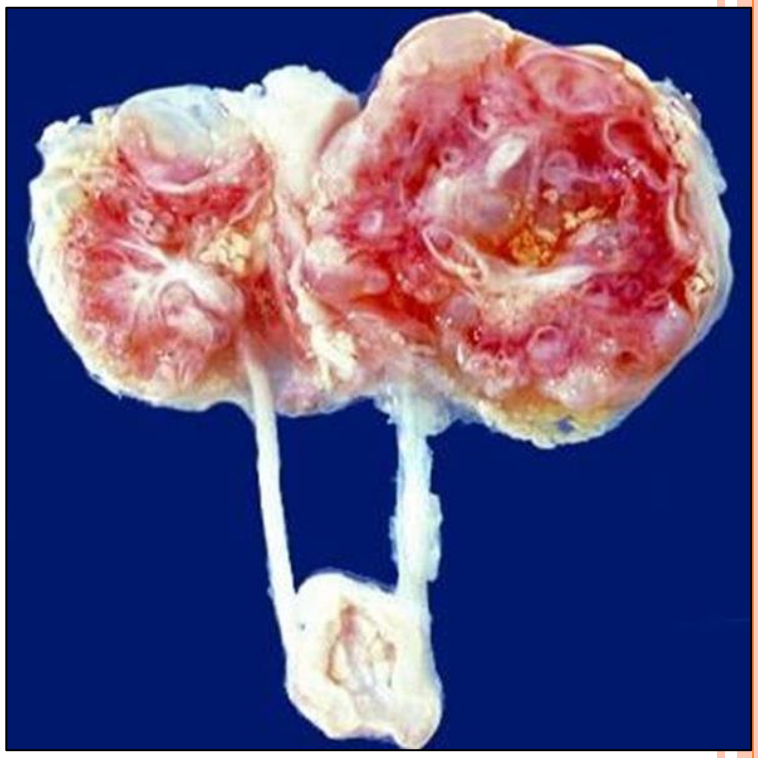
Small kidneys are due to the following:

1. **Renal fibrosis** resulting from renal disease.
2. **Dysplasia**
3. Progressive **nephropathy .**

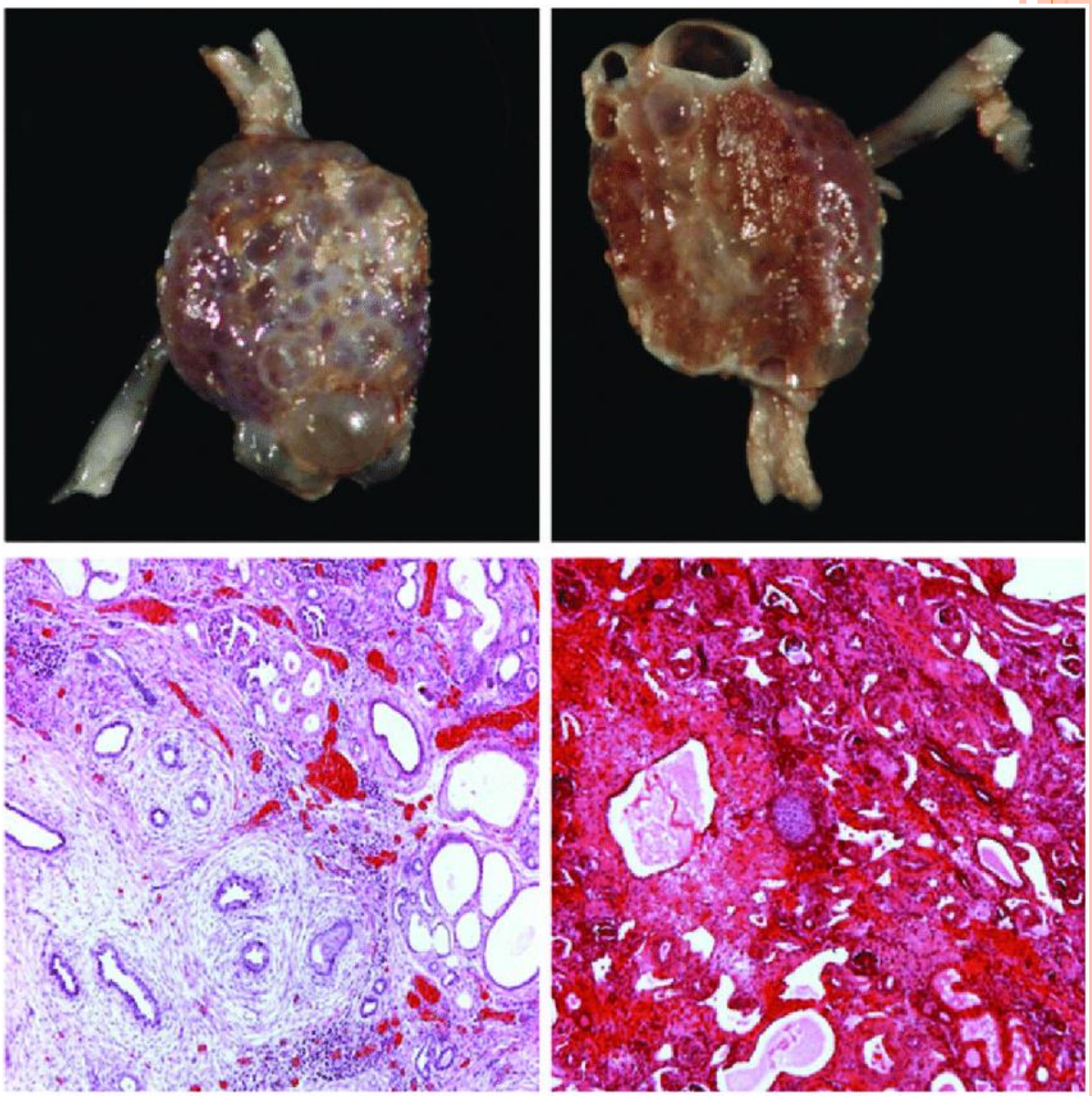


Renal dysplasia

is an **abnormality of altered structural organization** resulting from abnormal differentiation and the presence of structures not normally present in nephrogenesis.



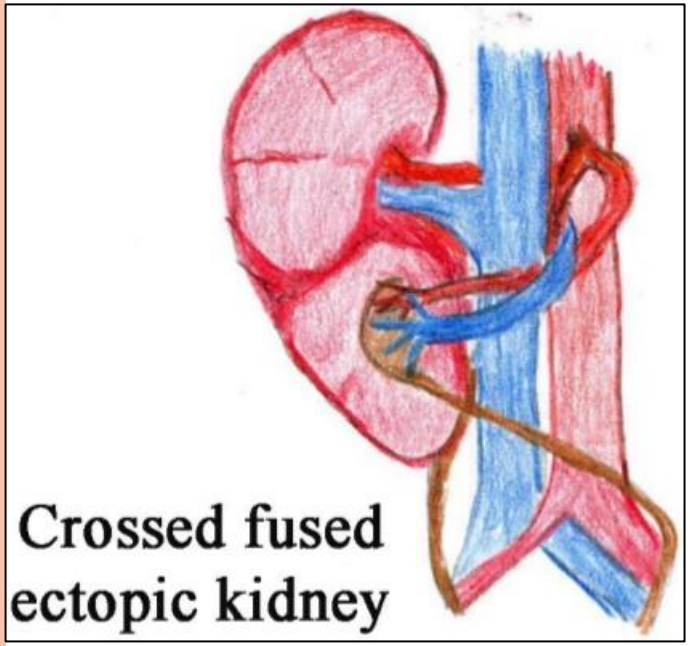
Renal dysplasia. (A) Gross morphology of cystic dysplastic kidneys. The image on the left shows the irregular shape of the kidney and on the right is the cut surface showing multiple cysts and no organization. (B) Histology of renal dysplasia. Both images show no normal renal structures or organization into cortex, medulla and papillae. Numerous cysts are scattered in the kidney. The image on the left highlights collecting ducts in the center surrounded by concentric immature mesenchymal cells (arrows). The image on the right additionally has cartilage (white arrow) in the center that can be seen in about a third of dysplastic kidneys. Dysplasia can arise from abnormal UB budding or branching morphogenesis and nephrogenesis.

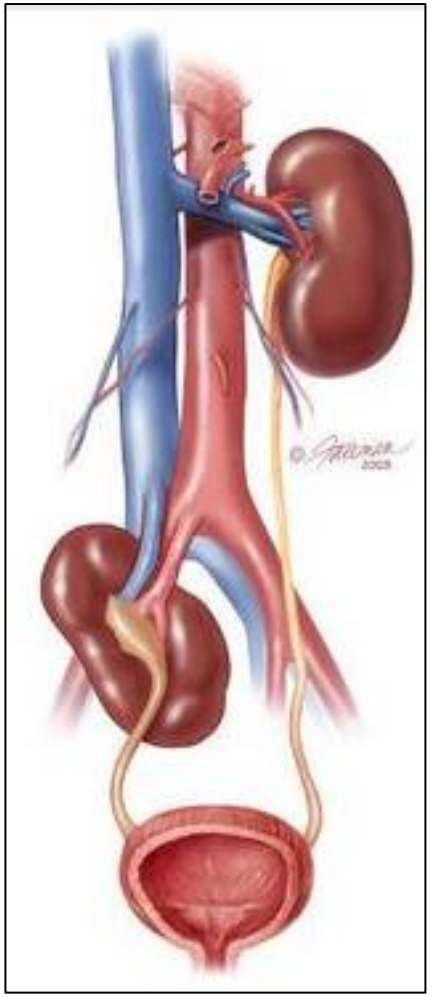


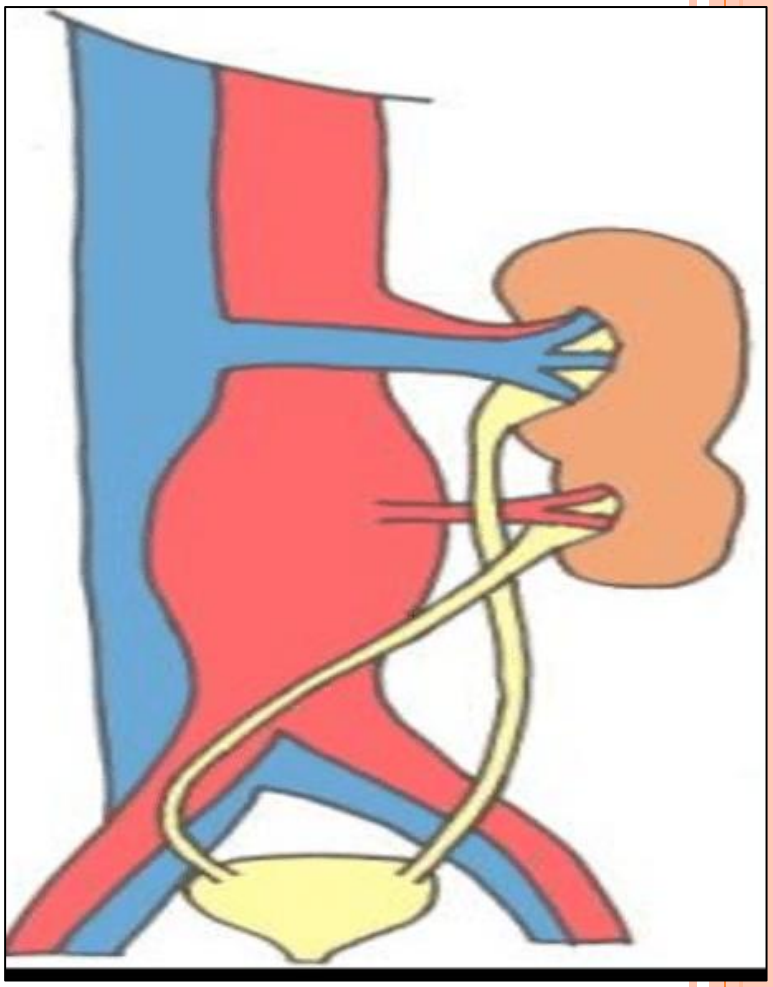
Ectopic and fused kidneys

Ectopic kidney (or “renal ectopia”) describes a kidney that **isn’t located in its usual position**. They may be found while treating other conditions.

Ectopic kidneys don’t move up to the usual position. They can be located anywhere along the path they usually take to get to their normal place in the upper abdomen.







Kidney Cysts

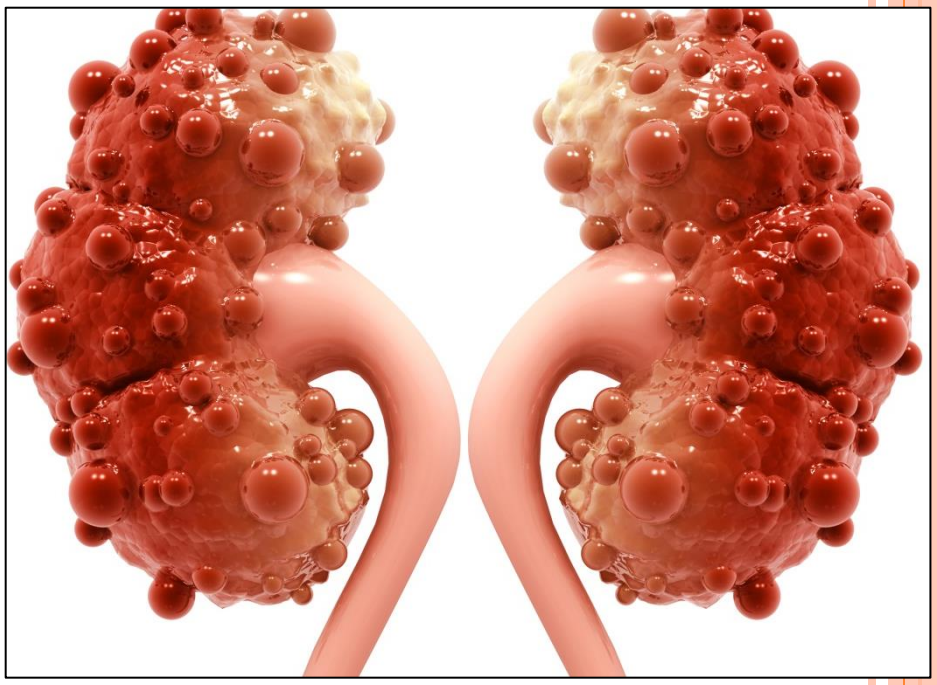
Kidney cysts are **fluid filled sacs** that can form on the outside or inside of a kidney.

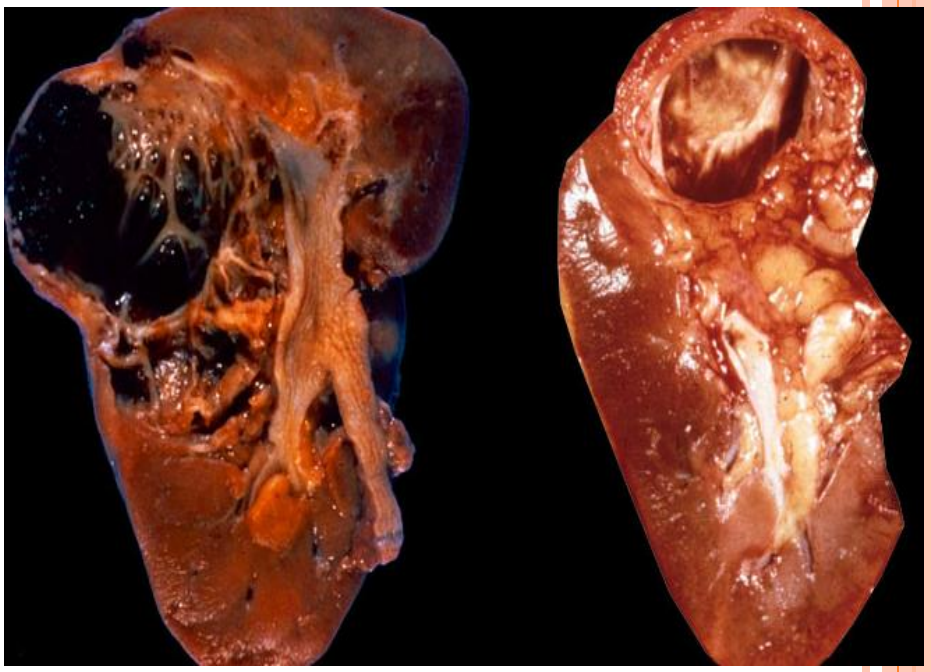
simple cysts cause little to no trouble. More **complicated cysts** (complex kidney cysts or complex renal cysts) can interfere with kidney function, or create other complications.

Kidney cysts are relatively **common**, and the incidence of forming cysts increases with advanced **aging**.

Kidney cysts may also be part of a **genetic** disease that results in a slow, progressive decrease in kidney function.

A kidney cyst diagnosis may involve the presence of one or more cysts. **Polycystic kidney disease** involves numerous cysts that cover one or both kidneys.



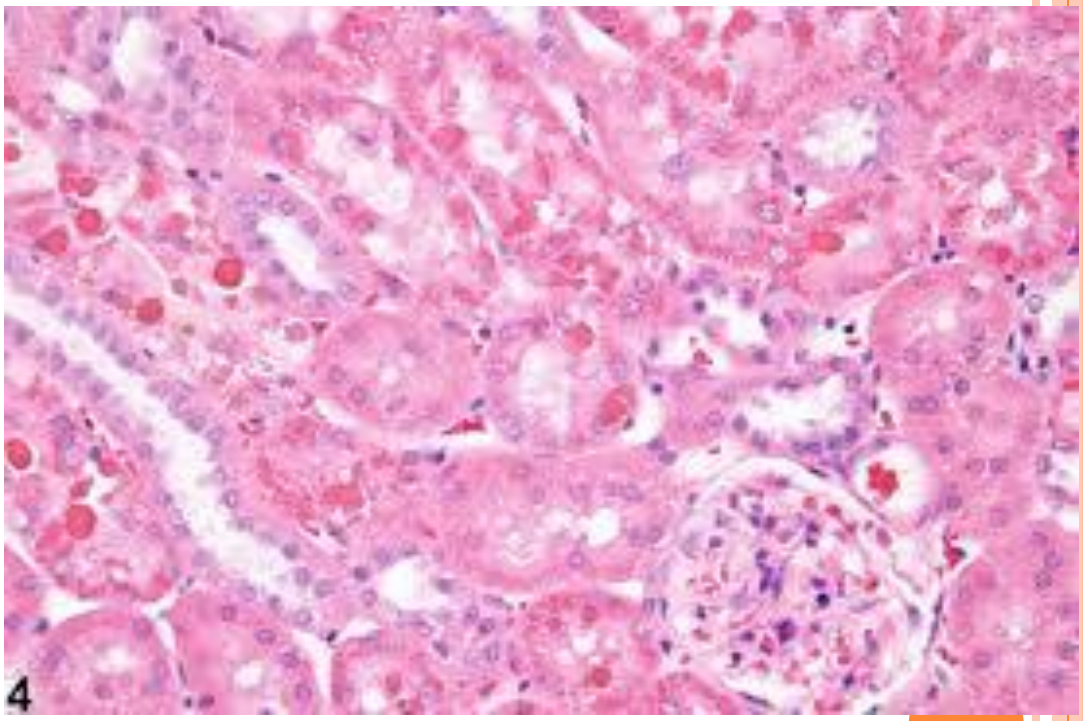


GLOMERULAR DISEASES

All functions of the glomerulus include the following:

1. Plasma ultrafiltration
2. Blood pressure regulation
3. Peritubular blood flow regulation
4. Tubular metabolism regulation
5. Circulating macromolecule removal

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.

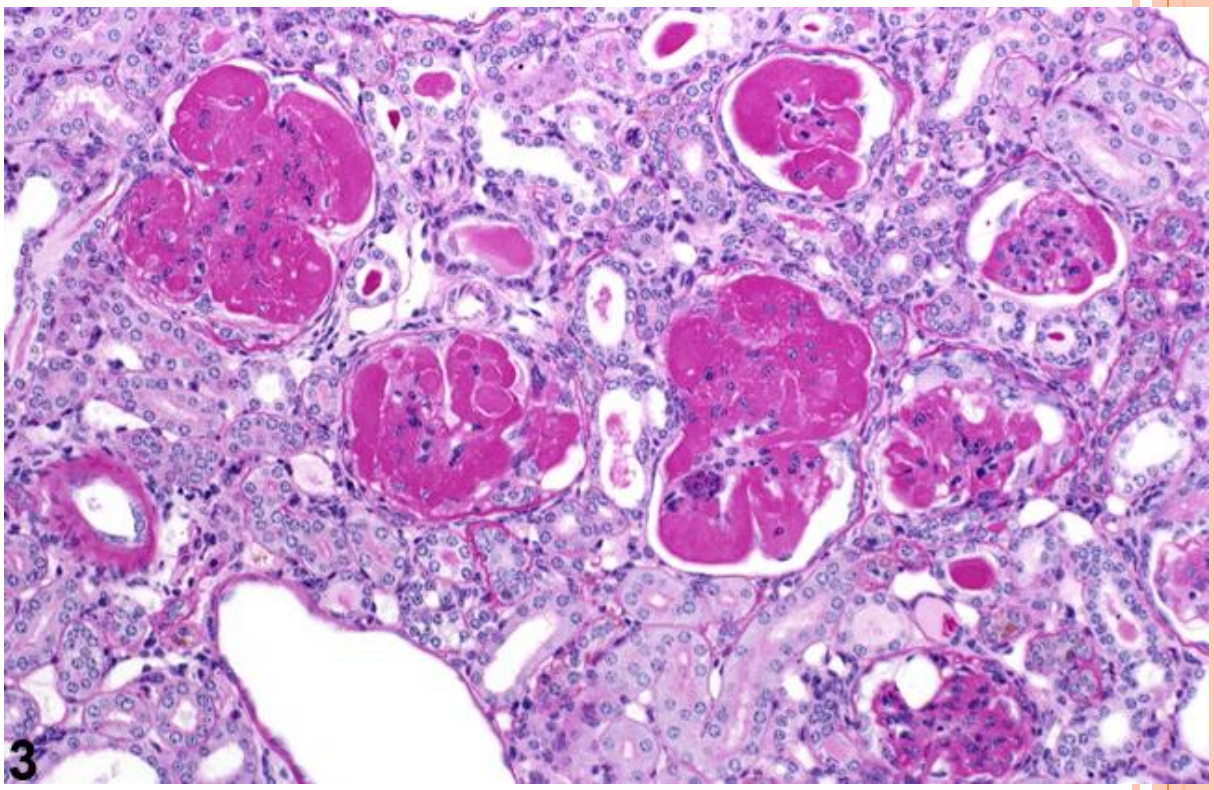


As a result, large quantities of albumin overload the protein reabsorption capabilities of the proximal convoluted tubular epithelium to such an extent that protein-rich glomerular filtrate accumulates in the variable dilated tubular lumina and protein subsequently appears in the urine.

In such diseases, the proximal tubular cells often have **microscopic eosinophilic intracytoplasmic bodies** referred to as **hyaline droplets**, which represent accumulations of intracytoplasmic protein absorbed from the filtrate.

Renal diseases that result in **proteinuria** are called **protein-losing nephropathies**. Protein-losing nephropathy is one of several causes of severe **hypoproteinemia** in animals. The nephrotic syndrome is further characterized by **generalized edema, ascites, pleural effusion, and hypercholesterolemia**

(when the protein level in the blood decreased, liver start to work to compensate low levels of protein but also it produce lipid Leading to hypercholestrolemia).



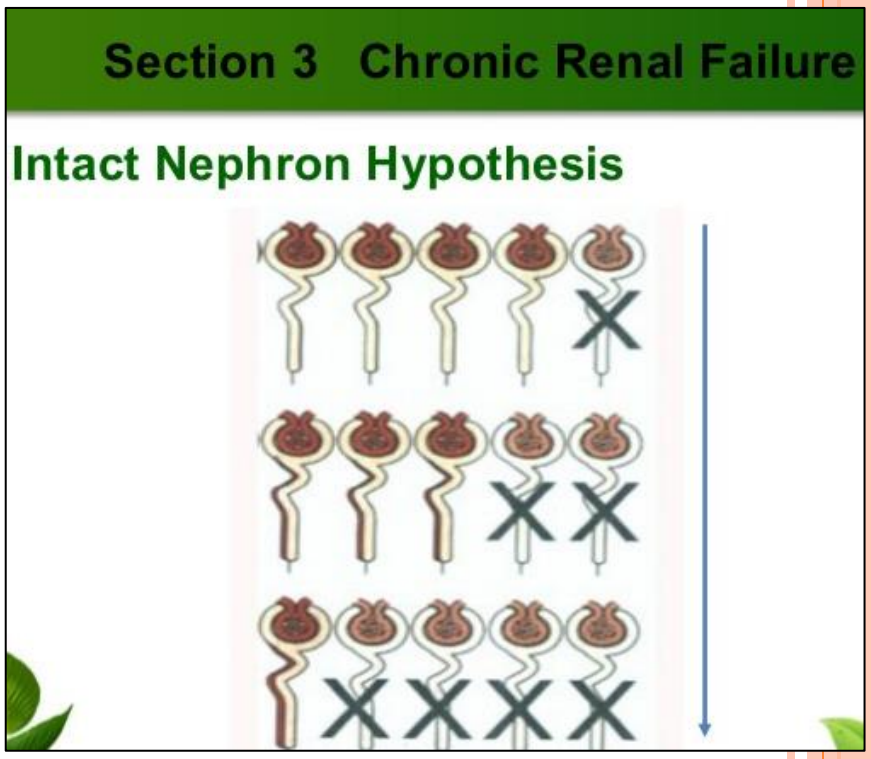
The pathophysiologic mechanisms of glomerular injury from infectious or chemical insults have been summarized by three theories:

1. **Intact nephron hypothesis**
2. **Hyperfiltration hypothesis**
3. **The theory of complex deposition**

***The intact nephron hypothesis proposes that damage to any portion of the nephron affects the entire nephron function.**

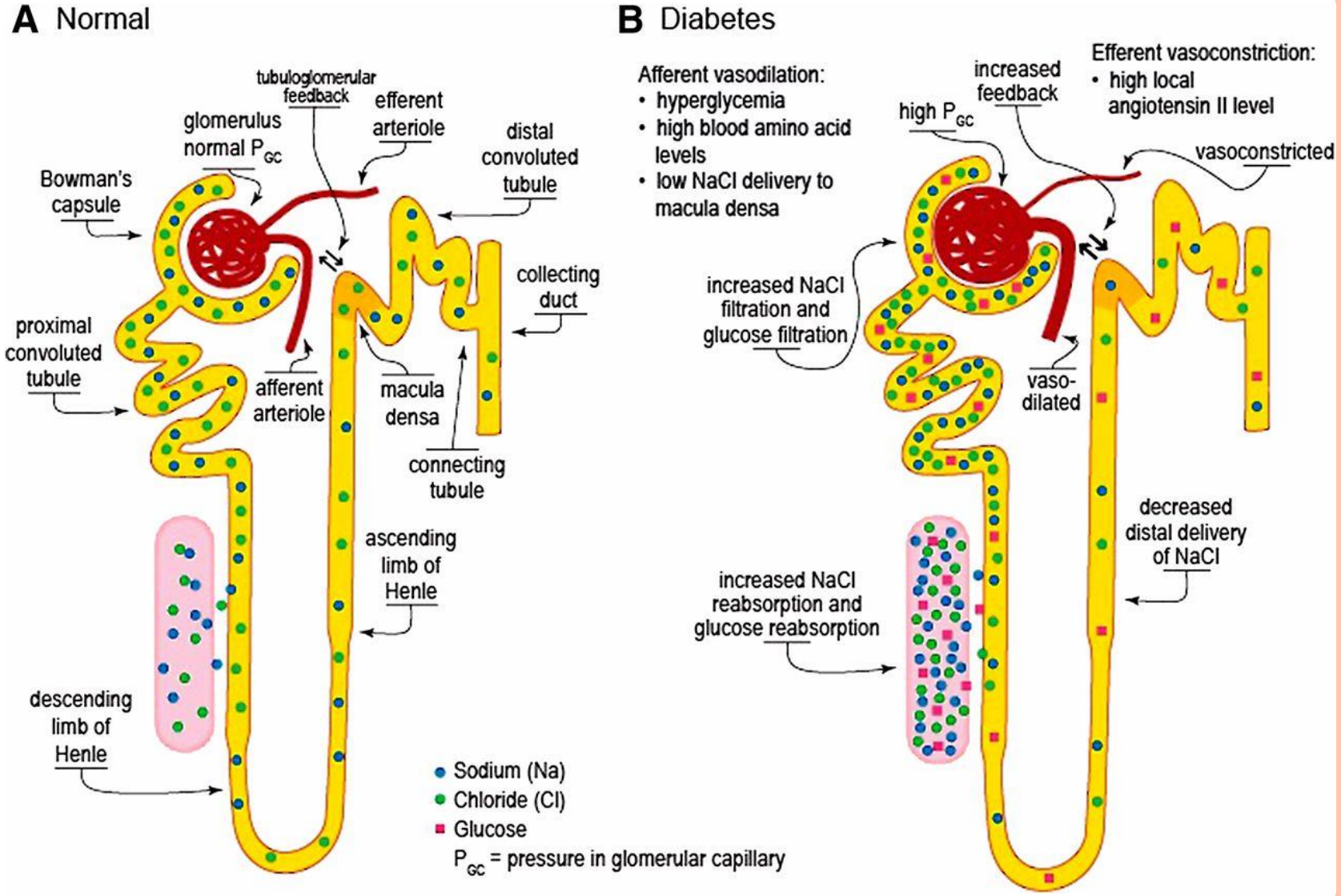
This is seen when glomerular damage interferes with peritubular blood flow and results in decreased tubular resorption or secretion.

Not all nephron damage is irreversible, but nephrons are not capable of regeneration and thus outcomes vary from hypertrophy to repair.



***Glomerular hyperfiltration**

is a result of increased hydrostatic pressure that damages glomerular capillaries and in cases of prolonged hypertension produces a sustained repeating 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, as dogs that undergo experimental hyperfiltration .

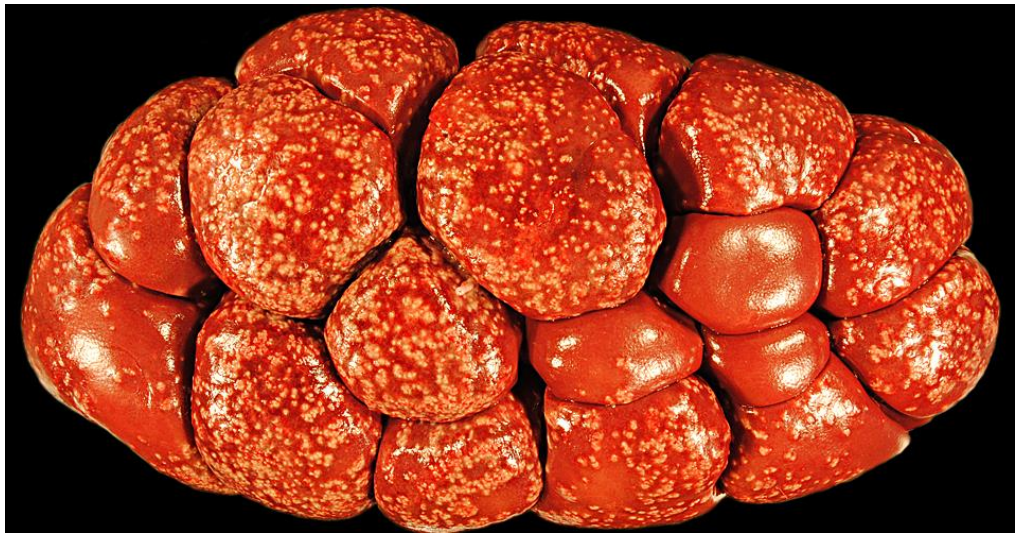
The theory of complex deposition:
is derived from the fact that glomeruli are the primary site for removal of macromolecules (principally immune complex) from the circulation.
Complexes may be deposited in subepithelial, subendothelial, or mesangial locations.

These immune complexes are capable of triggering a sequence of inflammatory events including the following:
1. Recruitment and localization of inflammatory cells at the site
2. Release of inflammatory mediators and enzymes
3. Destruction of glomerular structures
4. Further compromise of nephron function
5.· Continuing damage by altered transglomerular hyperfilltration and perfusion shifts between nephron populations.

Different forms of glomerulonephritis including bacterial, viral, chemical, and immune-mediated .

SUPPURATIVE GLOMERULITIS (EMBOLIC NEPHRITIS)

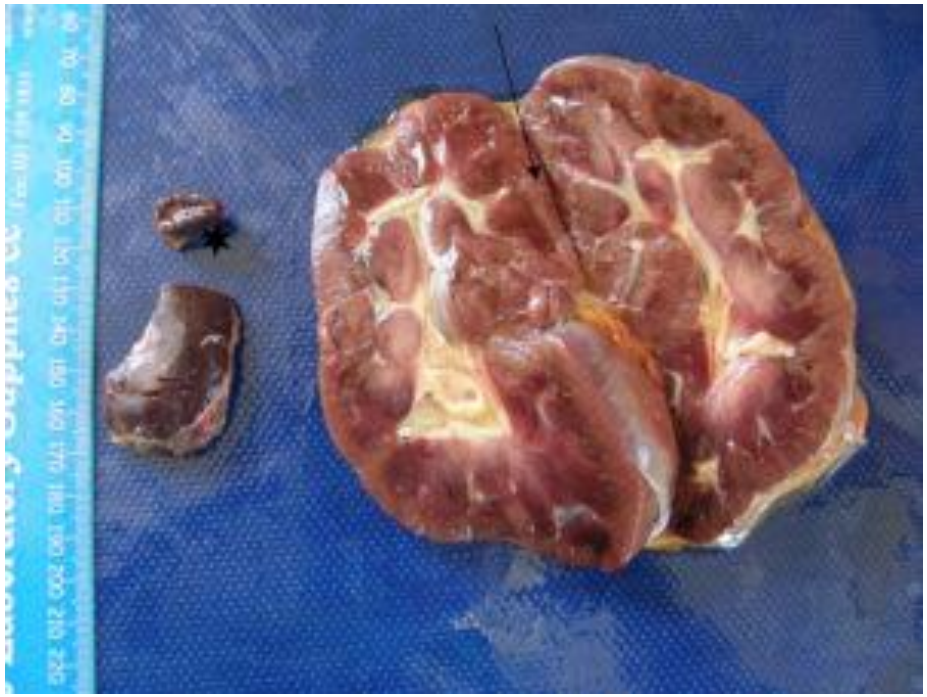
Suppurative glomerulitis, which can also be referred to as acute embolic nephritis, is the result of a bacteremia, in which bacteria lodge in random glomeruli and to a lesser extent in interstitial capillaries, and cause the formation of multiple foci of inflammation (microabscesses) throughout the renal cortex.



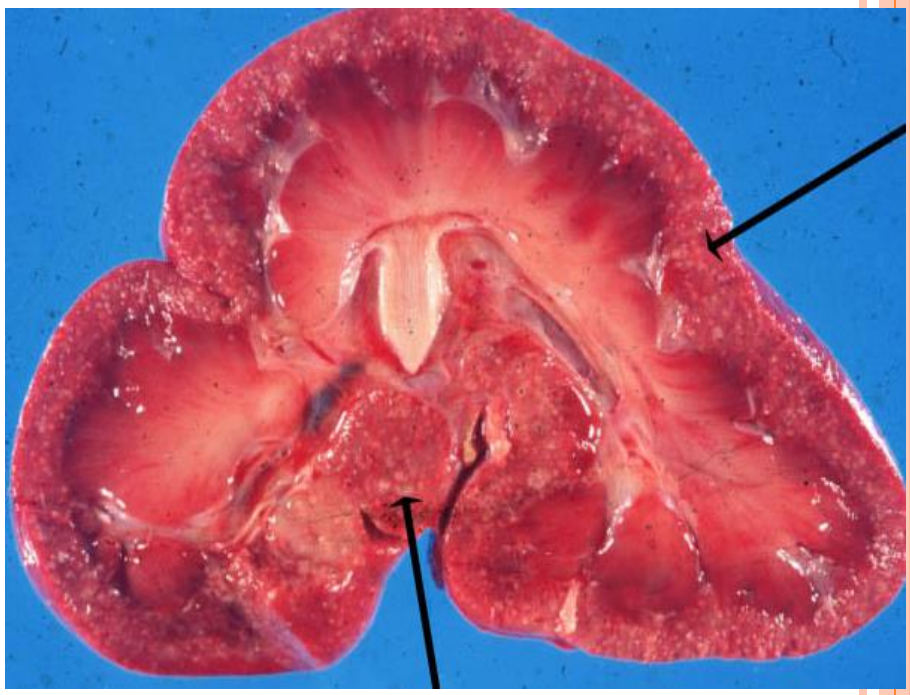
A specific example of embolic nephritis is actinobacillosis of foals caused by Actinobacillus equuli.

These foals usually die within a few days of birth and have small abscesses in many visceral organs, especially the renal cortex.

Embolic nephritis also occurs commonly in the bacteremias of pigs infected with Erysipelothrix rhusiopathiae or sheep and goats infected with Corynebacterium pseudotuberculosis.



Foal kidney and adrenal gland – note the early and subtle embolic nephritis (arrow) with enlarged and hemorrhagic adrenal gland due to extensive bacterial emboli station of the adrenal with associated vasculitis and hemorrhage



foal Kidney – multifocal embolic bacterial nephritis with microabscesses (arrows).

Grossly,

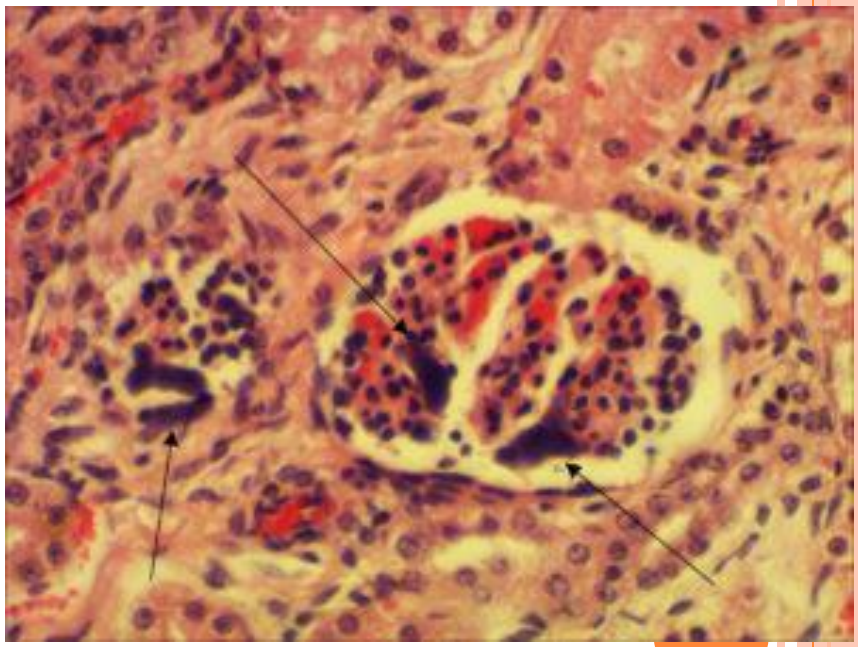
multifocal random, raised, tan pinpoint foci are seen subcapsularly and on the cut surface throughout the renal cortex.

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 will either persist as focal residual abscesses

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



Foal kidney histopathology – note the plugging of glomerular and periglomerular bloodvessels by large bacterial emboli (arrows)

VIRAL GLOMERULITIS

Glomerulitis:

caused by a direct viral insult to the glomerulus, occurs in acute systemic viral diseases, such as:-

- **acute infectious canine hepatitis,**
- **equine arteritis virus infection,**
- **hog cholera,**
- **avian Newcastle disease,**
- **neonatal porcine cytomegalovirus infection.**

The lesions are mild, usually transient, and result from viral replication in capillary endothelium.

Acute viral glomerulonephritis produces the following gross lesions:

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

Direct viral damage to glomerular endothelial cells secondary to viral replication in endothelium

Microscopically:

Intranuclear basophilic inclusions are present in glomerular capillary endothelium.

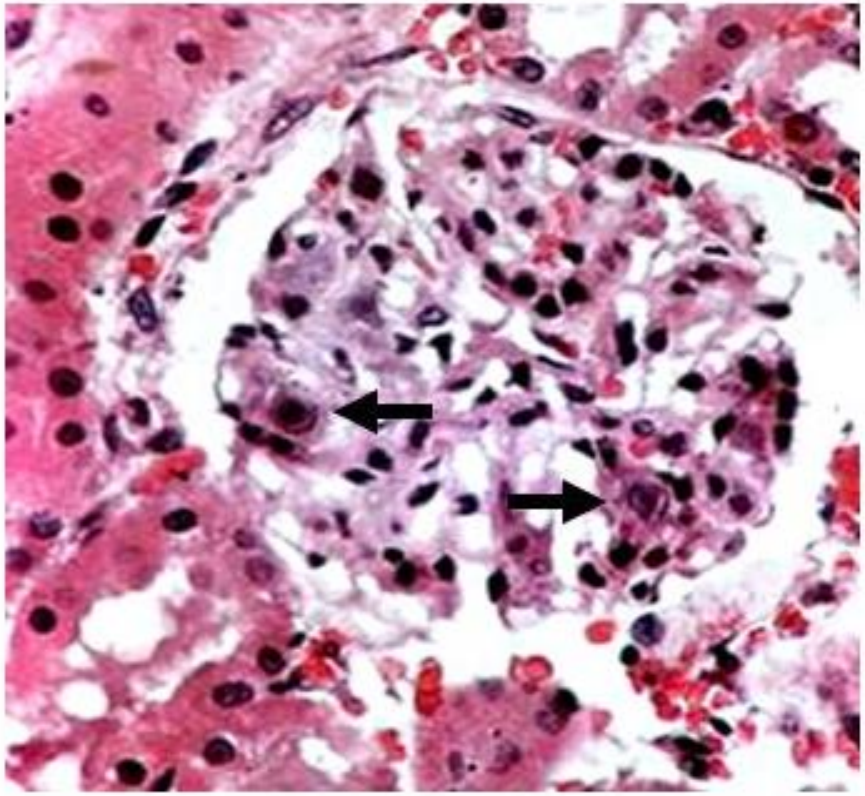
The inclusions either fill the nucleus or are separated from the nuclear membrane by a clear halo.

In cases of viral glomerulitis, lesions include:

***endothelial hypertrophy,**

***thickened and edematous mesangium,**

***hemorrhages, and necrosis of endothelium.**



ICH - Intranuclear Viral Inclusions

CHEMICAL GLOMERULONEPHRITIS

Chemicals typically induce glomerular injury by any of the following:

1. Direct injury to glomerular epithelial cells.

2. Direct injury to endothelial cells of the glomerulus.

3. Altered renal blood flow.

4. Induction of immunologic reactions and inflammatory responses, which may occur following:

a. Incorporation of drugs into immune complexes.

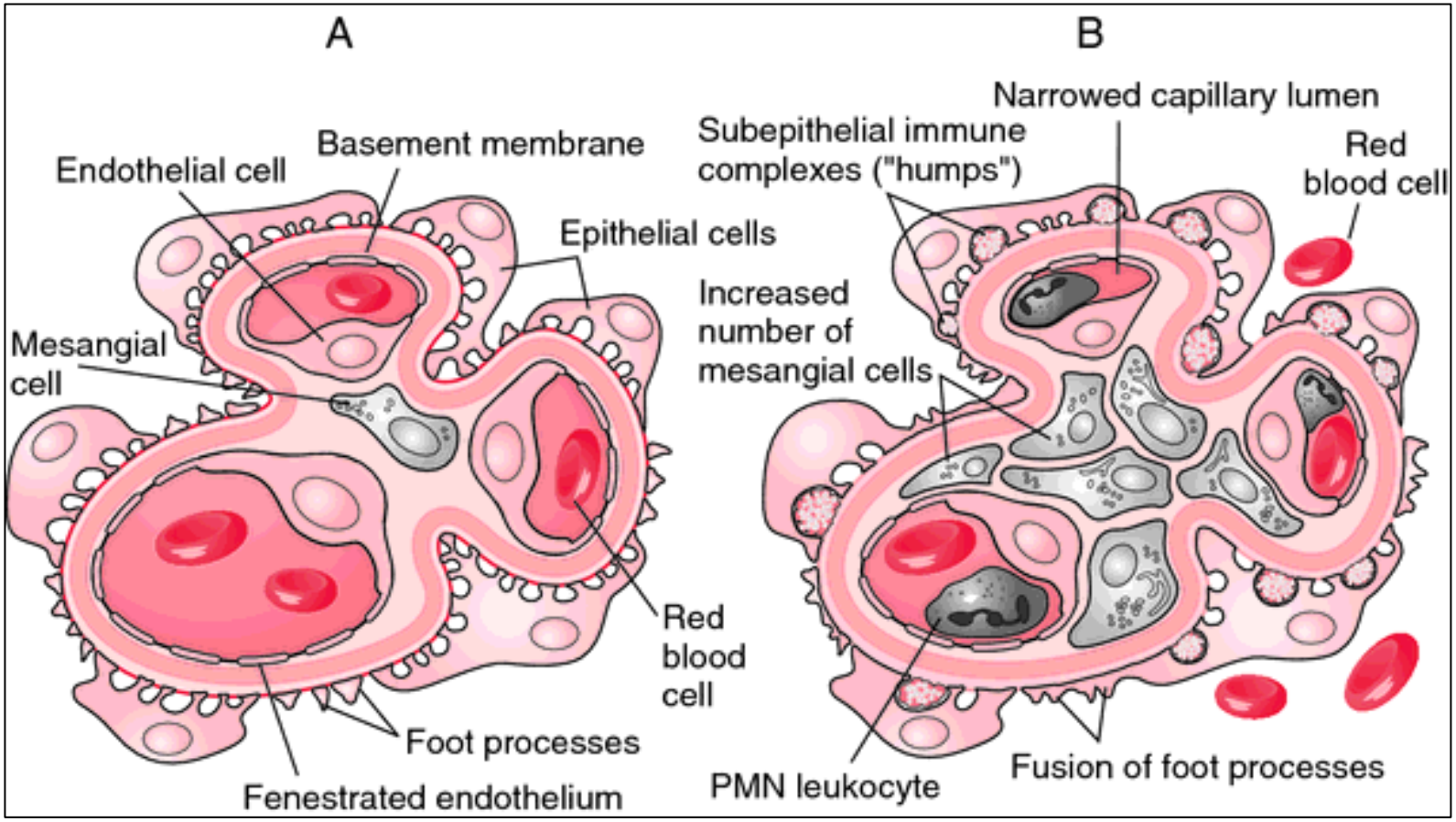
b. The formation and targeted deposition of antigenantibody complexes.

c. The formation of antinuclear antibodies .

d. The formation of antibasement membrane antibodies within the glomerular tuft.

Immune mediated glomerulonephritis

a variety of NEPHRITIS characterized by inflammation of the capillary loops in the glomeruli of the kidney. It occurs in acute, subacute, and chronic forms and may be secondary to an infection, especially with the hemolytic streptococcus.

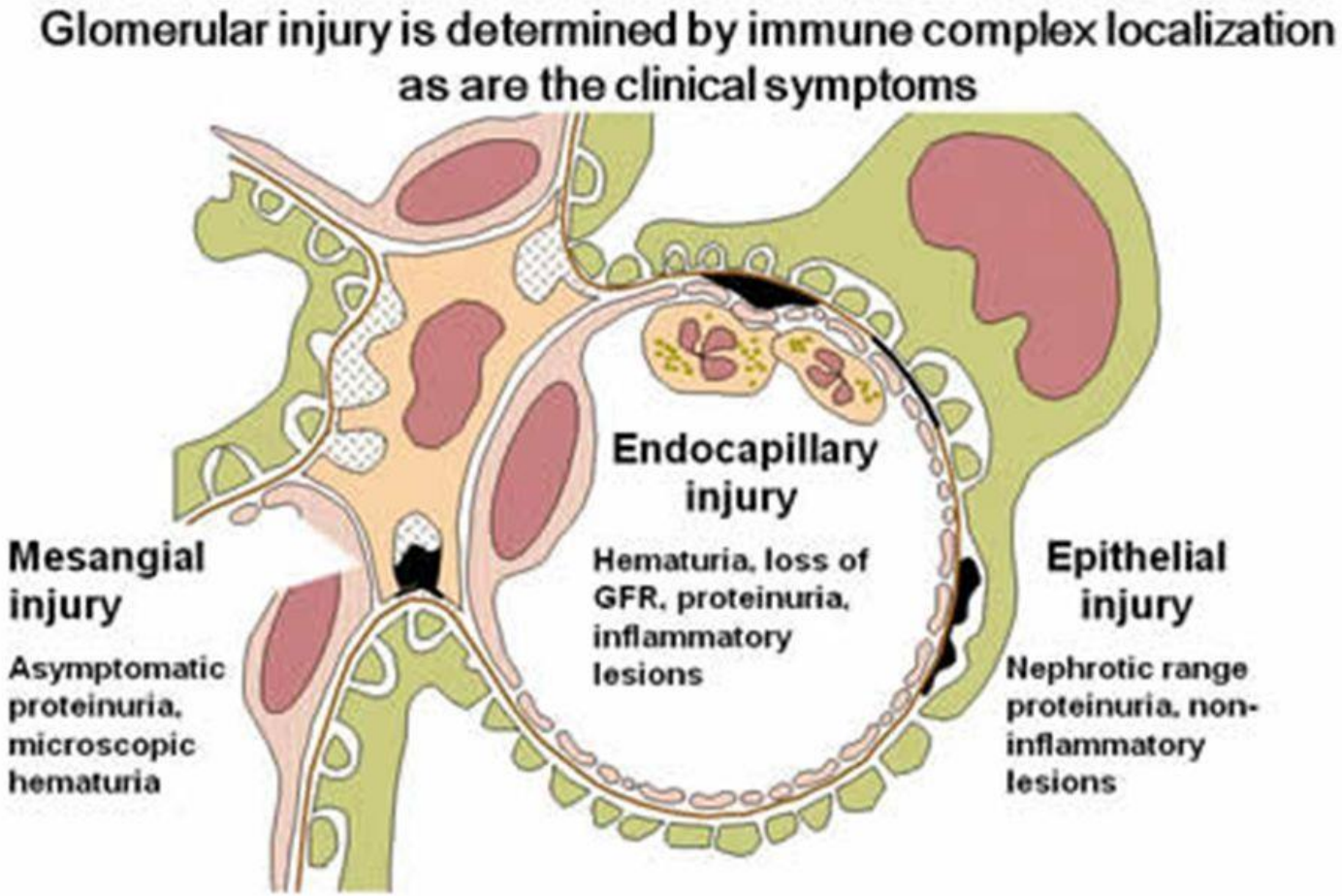


Histologic appearance of acute glomerulonephritis. *A*, Normal glomerulus. *B*, Glomerulonephritis. The glomerulus appears hypercellular and the capillaries are narrowed or occluded.

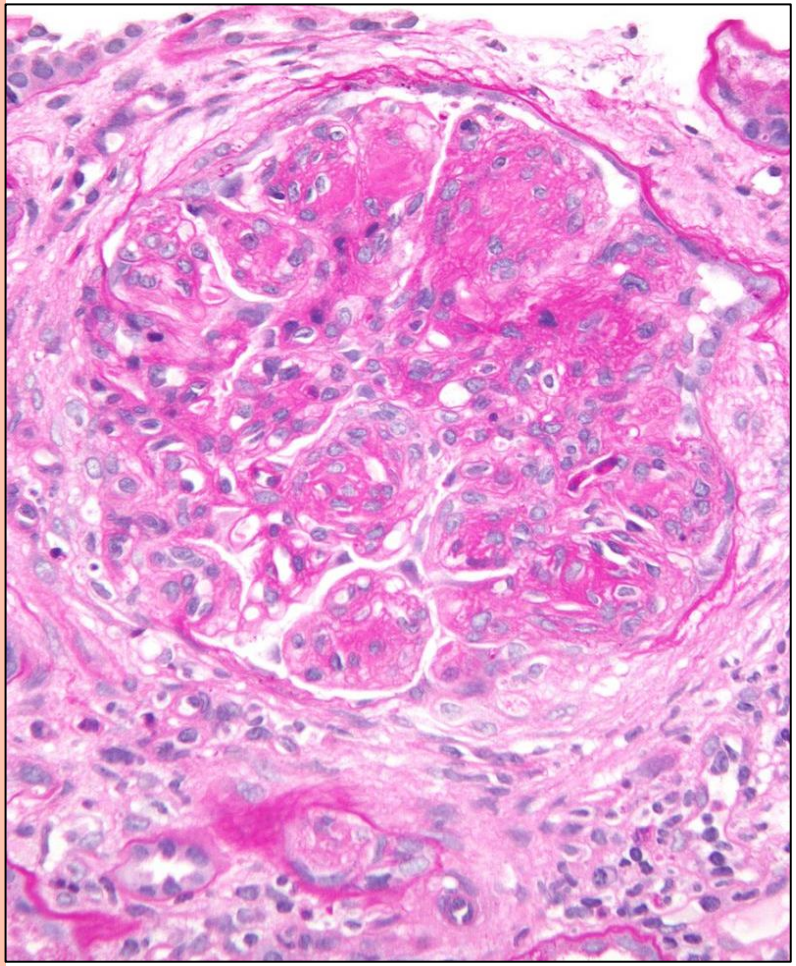
diffuse glomerulonephritis a severe form of glomerulonephritis with proliferative changes in **more than half the glomeruli**, frequently with epithelial crescent formation and **necrosis**; it is often seen in cases of advanced systemic lupus erythematosus.

IgA glomerulonephritis IgA nephropathy.

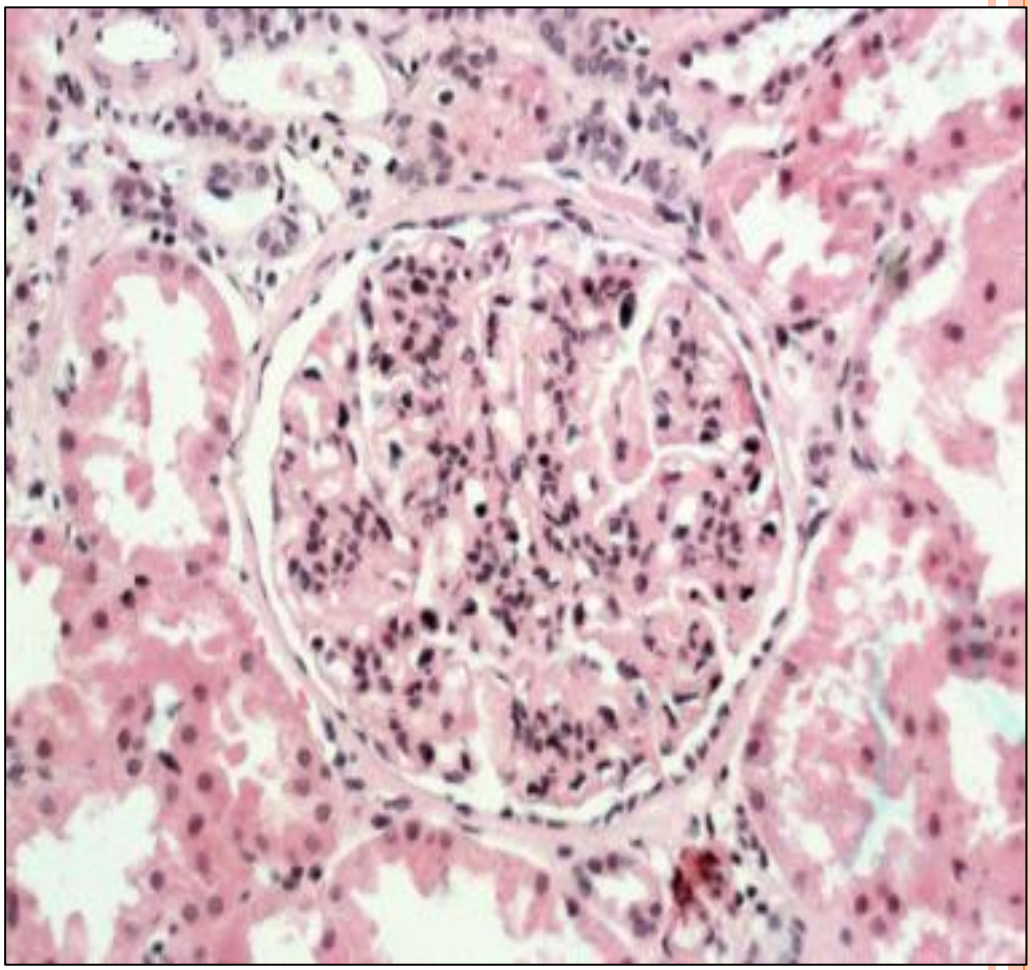
lobular glomerulonephritis (**membranoproliferative glomerulonephritis**) a chronic glomerulonephritis characterized by **mesangial cell proliferation** and **irregular thickening of the glomerular capillary wall**.



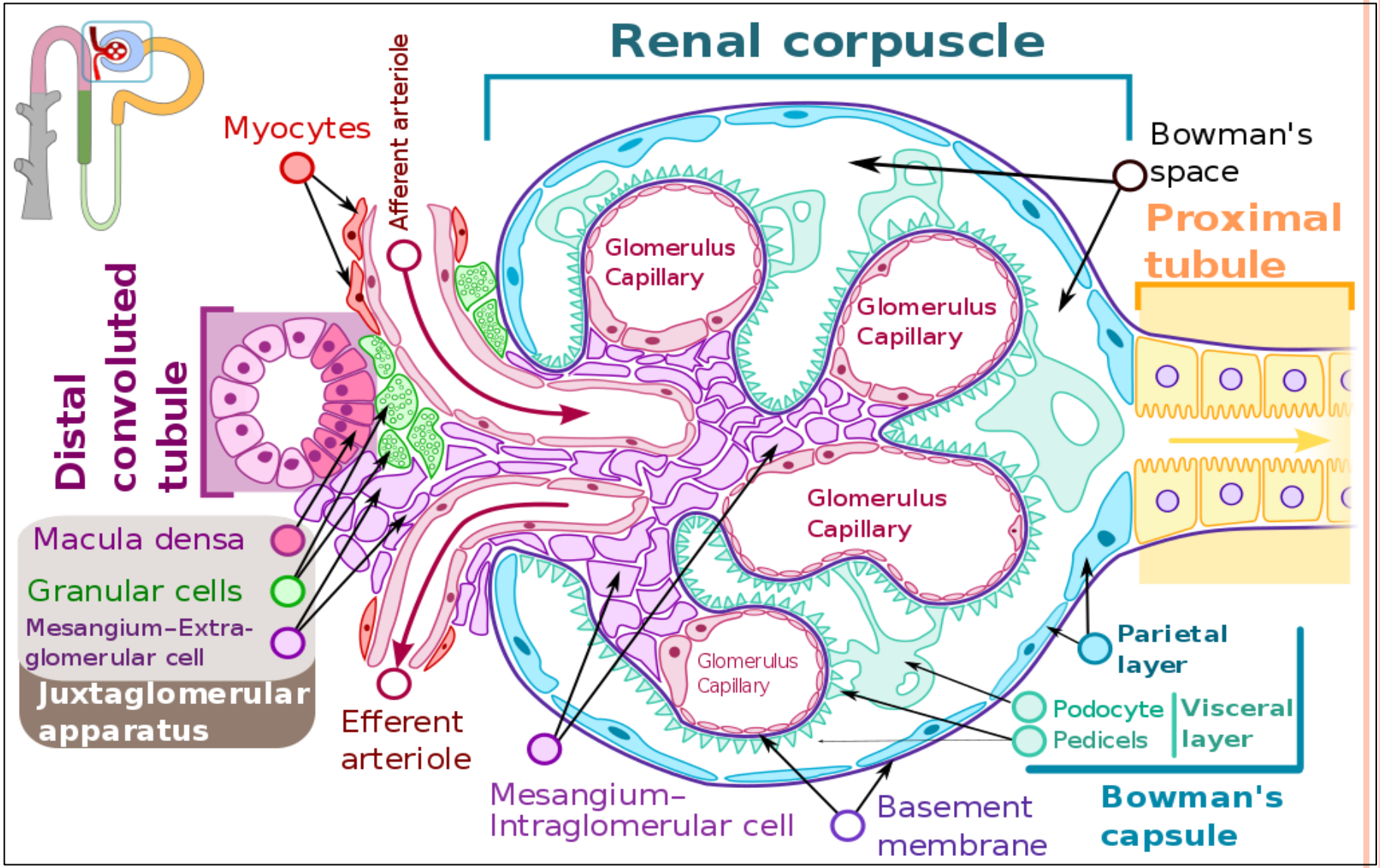
mesangiocapillary glomerulonephritis (membranoproliferative glomerulonephritis) charchertized histologically by profuse epithelial proliferation, often with epithelial crescents; principal signs are anuria, proteinuria, hematuria, and anemia.



Very high magnification of membranoproliferative glomerulonephritis. PAS stain. The most common cause of MPGN is hepatitis C.



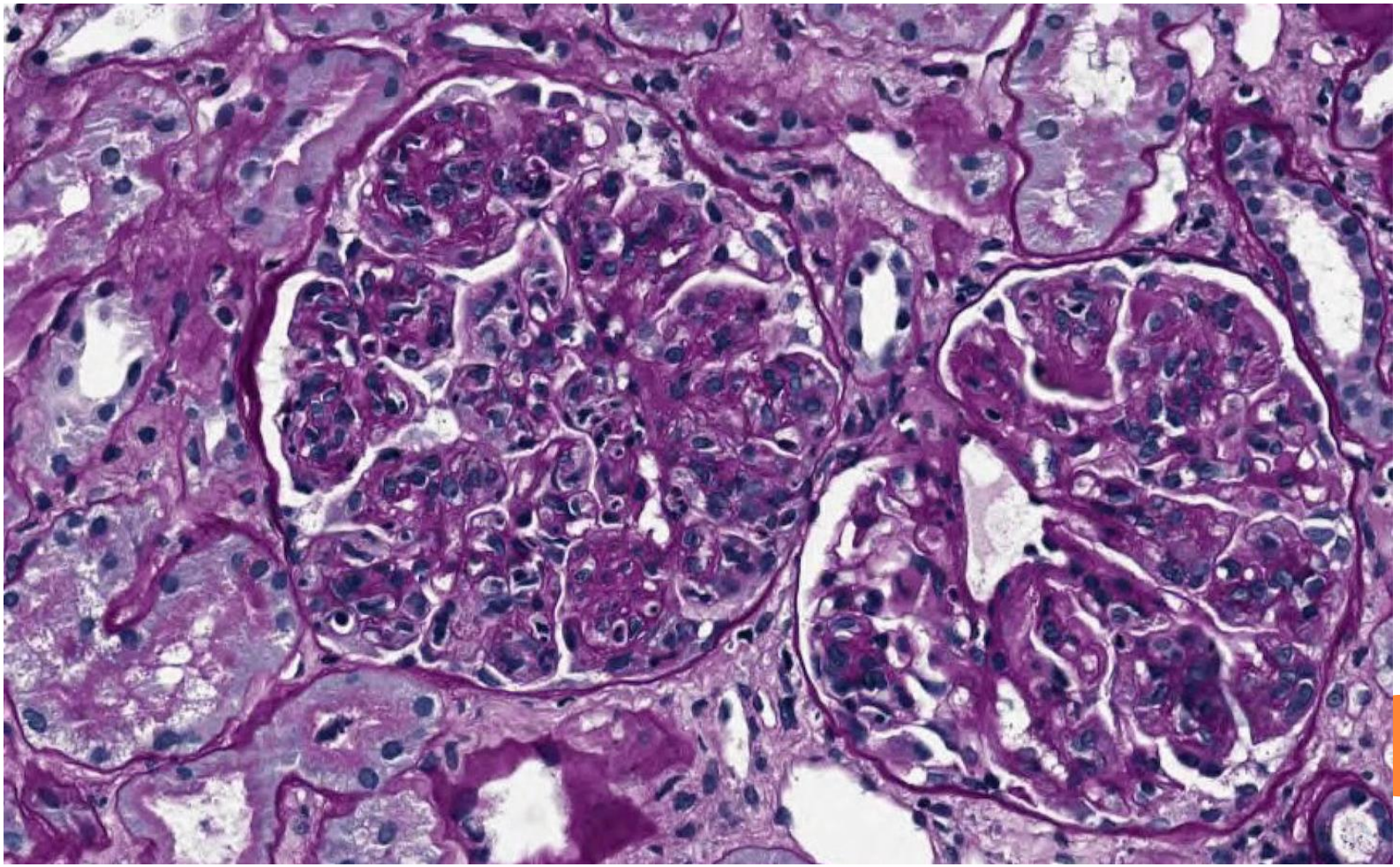
Membranoproliferative glomerulonephritis (MPGN) type I. Glomerulus with lobular accentuation from increased mesangial cellularity. A segmental increase occurs in the mesangial matrix, and the peripheral capillary walls are thickened .



Renal corpuscle. Membranoproliferative glomerulonephritis involves deposits at the intraglomerular mesangium which leads to "splitting" of the glomerular basement membrane.

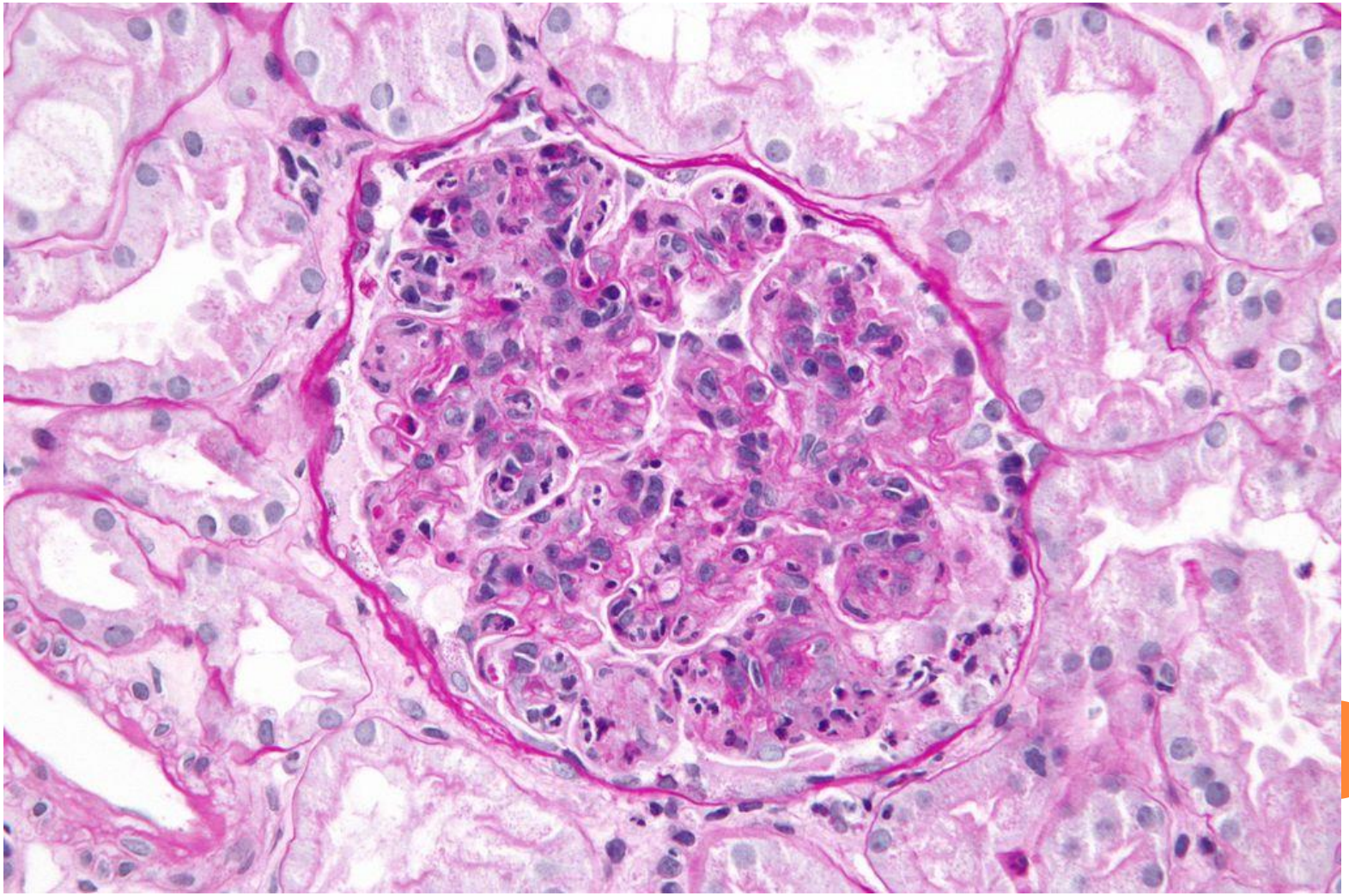
membranous glomerulonephritis

a form characterized by proteinaceous deposits on the glomerular capillary basement MEMBRANE or by thickening of the membrane, with circulating antigen-antibody COMPLEXES indicating immune complex disease; it may be secondary to any of numerous other conditions. In some cases it may develop into the nephrotic syndrome. Called also membranous nephropathy.



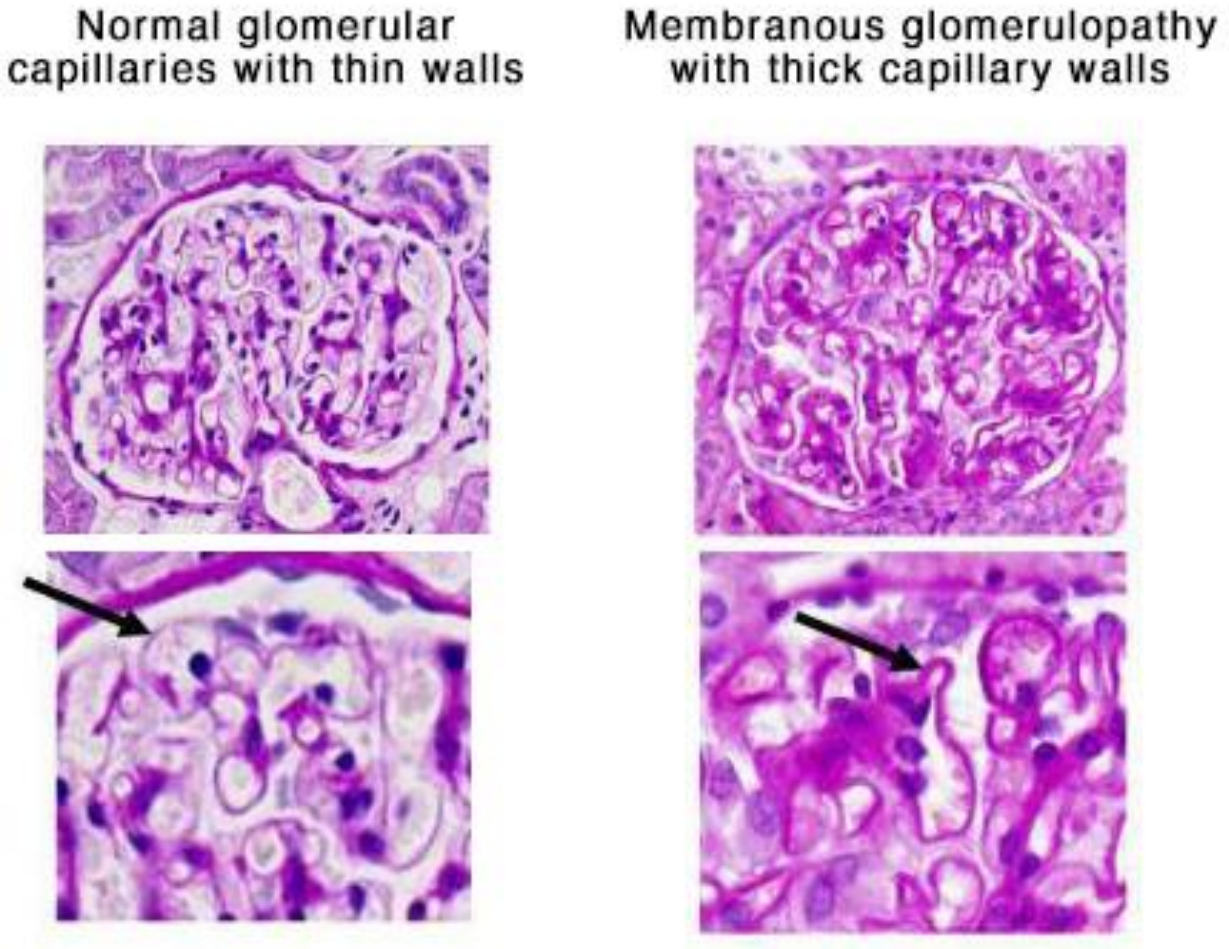
PROLIFERATIVE GLOMERULONEPHRITIS

Proliferative glomerulonephritis is a form of immunecomplex glomerular disease characterized by increased cellularity of the glomerular tufts caused by proliferation of glomerular endothelial, epithelial, and mesangial cells and an influx of neutrophils and other leukocytes and involves both the capillary loops and the mesangium .



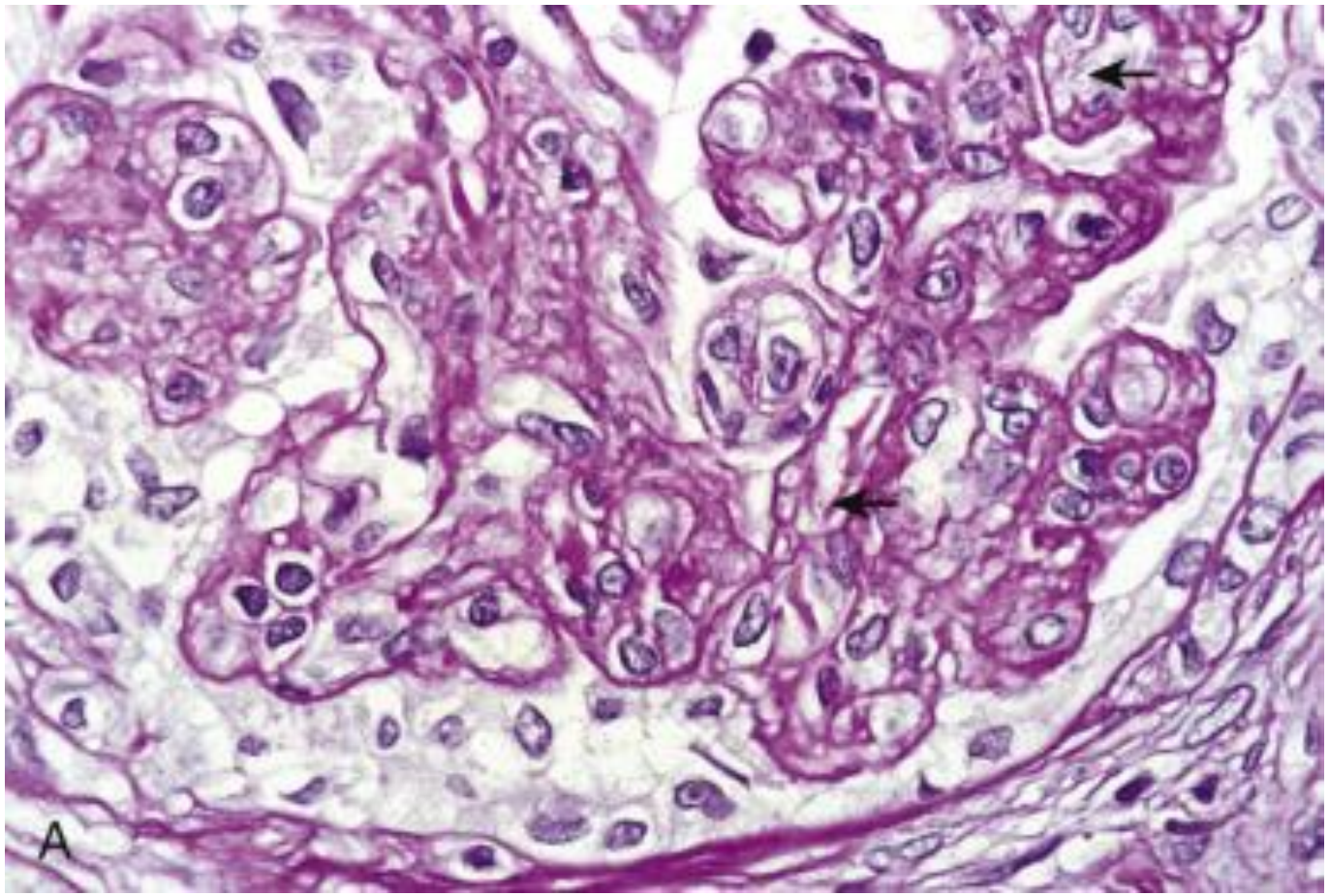
MEMBRANOUS GLOMERULONEPHRITIS

Membranous glomerulonephritis is characterized by diffuse glomerular capillary basement membrane thickening because of the presence of subepithelial immunoglobulin deposits, as the predominant change . This is characterized by increased deposition of (periodic acid-Schiff) positive material and a lesser amount of fibrosis.



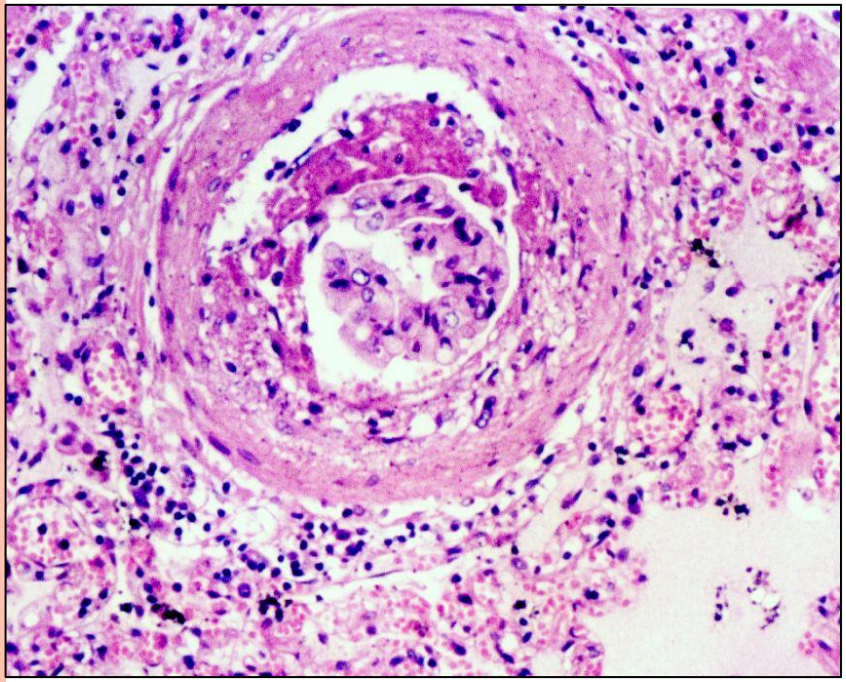
MEMBRANOPROlIFERATIVE GLOMERULONEPHRITIS

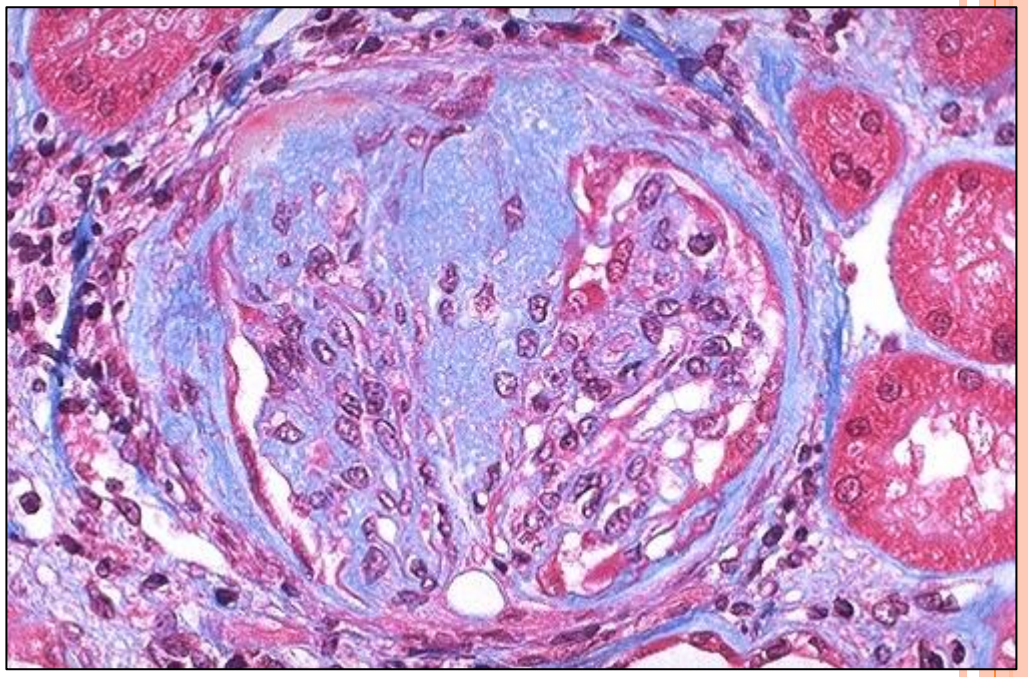
Membranoproliferative glomerulonephritis (mesangioproliferative, mesangiocapillary) is characterized by hypercellularity following proliferation of glomerular cells and thickening of the capillary basement membrane and mesangium.



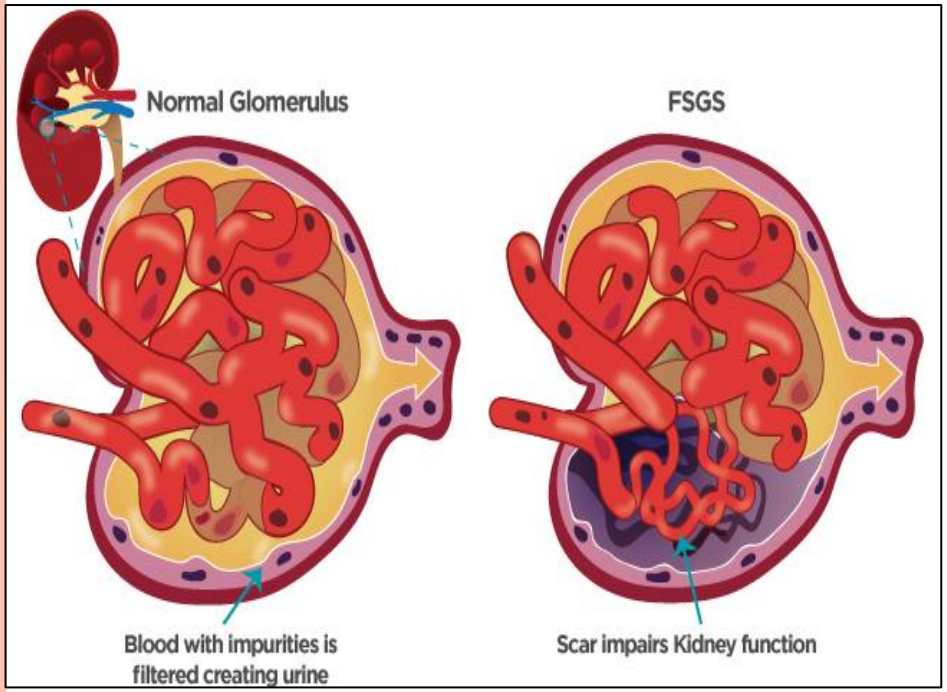
GLOMERULOSCLEROSIS

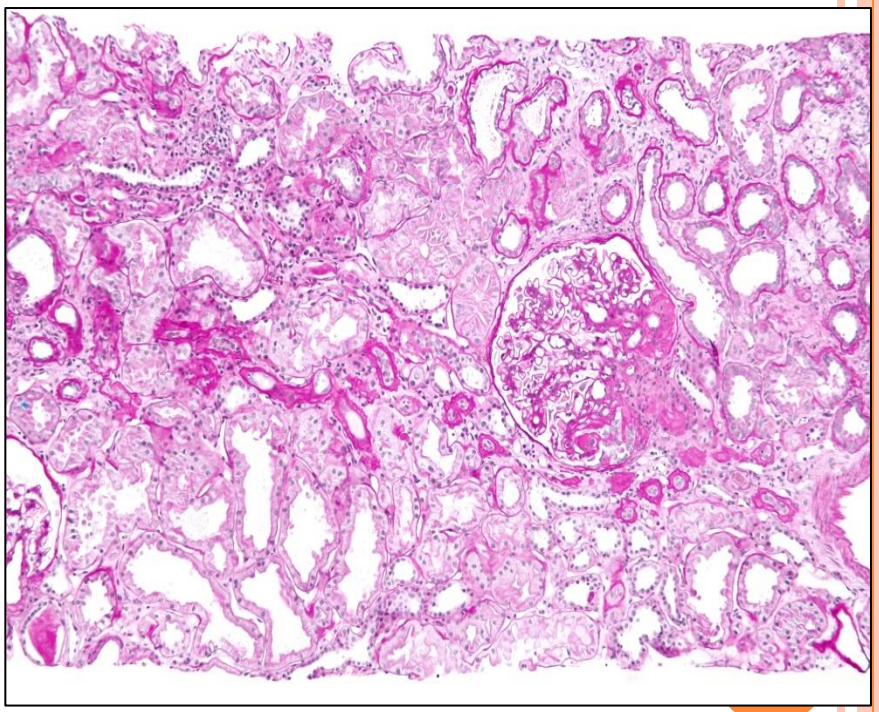
In chronic glomerulonephritis, severely affected glomeruli shrink and become hyalinized because of an increase in both fibrous connective tissue and mesangial matrix and a loss of glomerular capillaries.
These glomeruli are hypocellular and nonfunctional. This process is referred to as glomerulosclerosis.





Glomerulosclerosis can be diffuse, involving all glomeruli, or multifocal. In addition, glomerulosclerosis can involve a whole glomerular tuft (global) or only portions of the tuft (segmental) thus appearing as a nodular or segmental hyalinized thickening in affected glomeruli.
The resulting hypoxia is responsible for tubular epithelial cell death via apoptosis and results in tubular atrophy and flattening of the remaining tubular epithelium. In addition, chronic proteinuria often accompanies glomerulosclerosis and has been reported to stimulate tubular epithelial cell loss through apoptosis.





Focal Segmental Glomerulosclerosis (FSGS)

Numerous factors accelerate glomerulosclerosis include the following:

1. Unrestricted protein in the diet

2. Increased glomerular capillary pressure in functional glomeruli

3. Cytokines

4. Platelet-derived growth factors which

A. Alter cellular components of the functional glomerular tufts

B. Cause hypertension and transglomerular hyperfiltration with resultant damage to endothelium

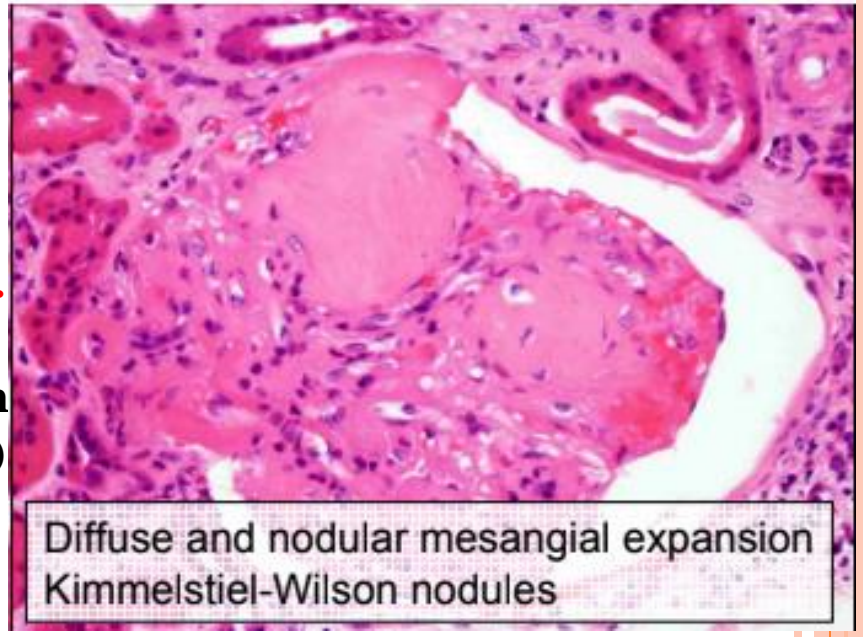
C. Activate mesangial cells to proliferate

D. Increase mesangial matrix production

E. Accelerate visceral epithelial cell loss

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 eosinoph glycoprotein material (hyaline material)** is deposited in the glomerular mesangium.



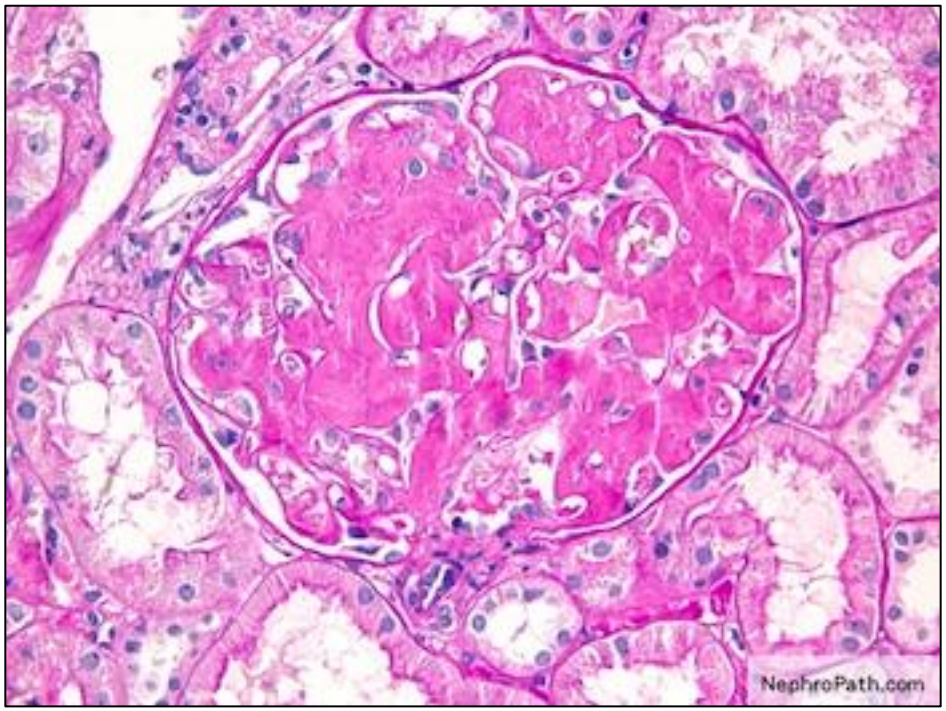
Diffuse and nodular mesangial expansion
Kimmelstiel-Wilson nodules

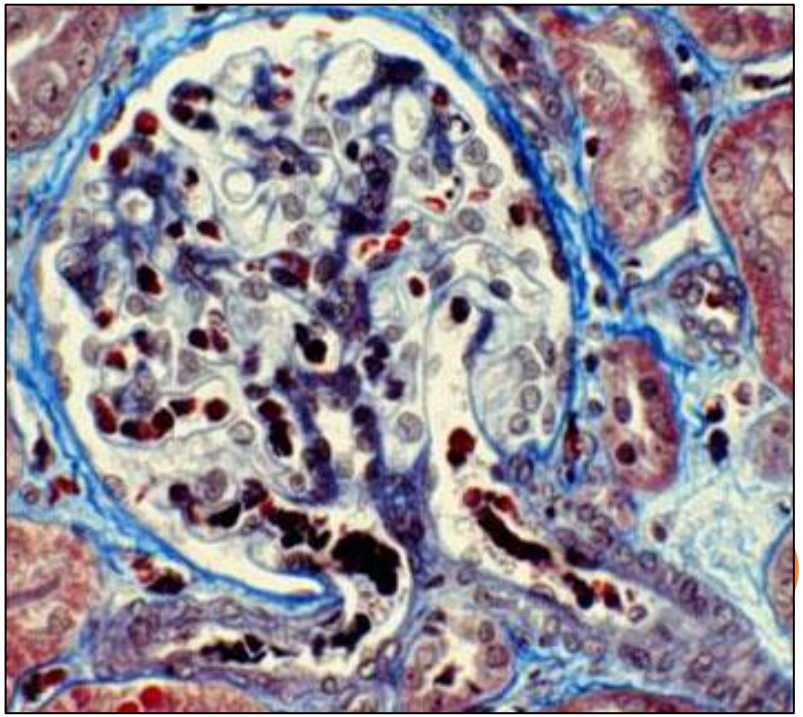
GLOMERULAR AMYLOIDOSIS

Amyloid, an **insoluble fibrillar protein** is produced after incomplete proteolysis of several soluble amyloidogenic proteins.

Amyloid deposits in patients with **plasma cell myelomas or other B-lymphocyte dyscrasias** (called Ai amyloidosis) are composed of fragments of the light (L) chains of immunoglobulins. **Glomeruli** are the most common renal sites for deposition of amyloid in most domestic animal species.

Renal amyloidosis commonly occurs in association with other diseases, particularly **chronic inflammatory or neoplastic diseases**. In a recent study, 23% of dogs that presented with **proteinuria** had renal amyloidosis. In cattle, renal amyloidosis is nearly always due to chronic systemic infectious disease.

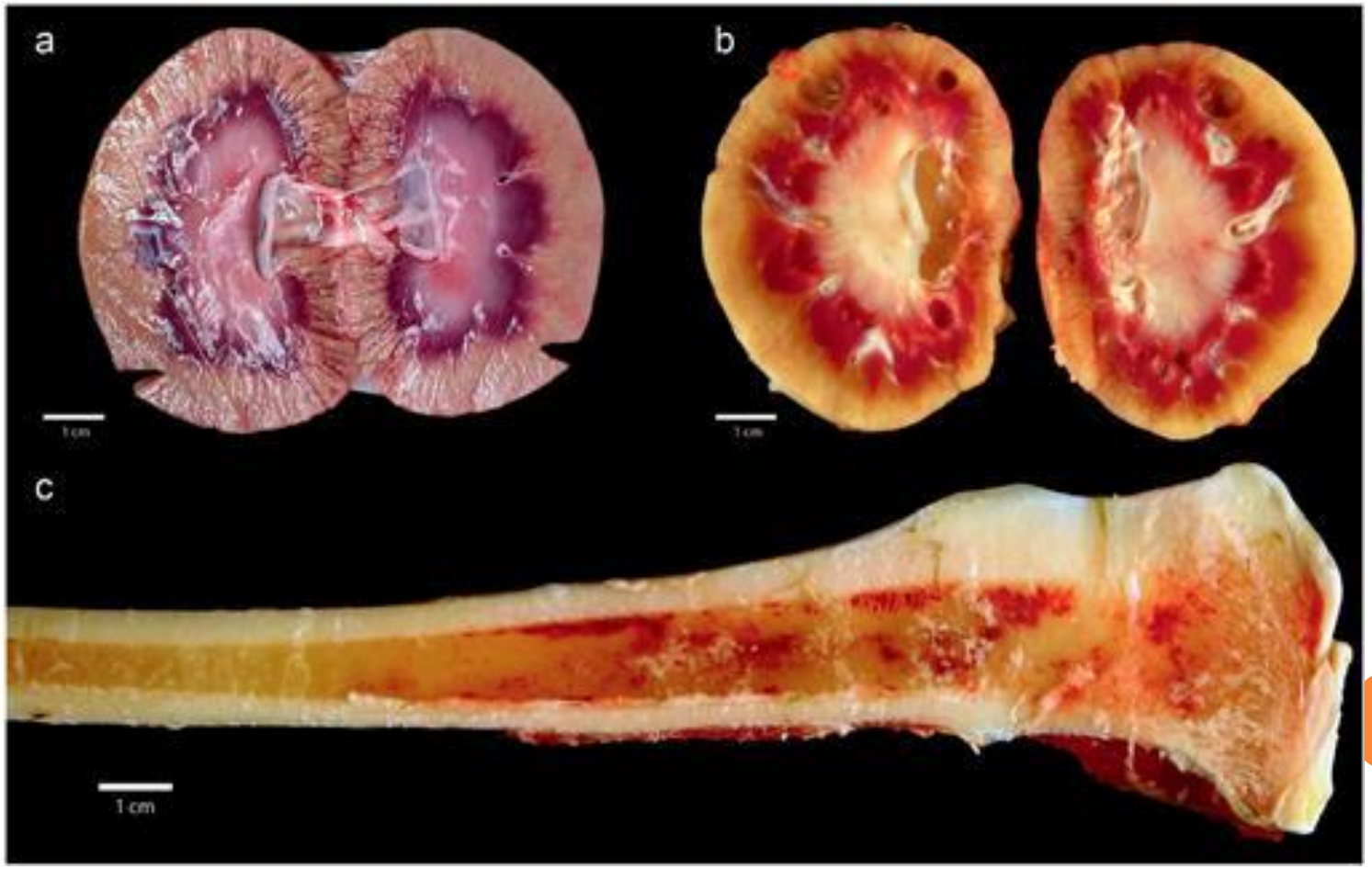




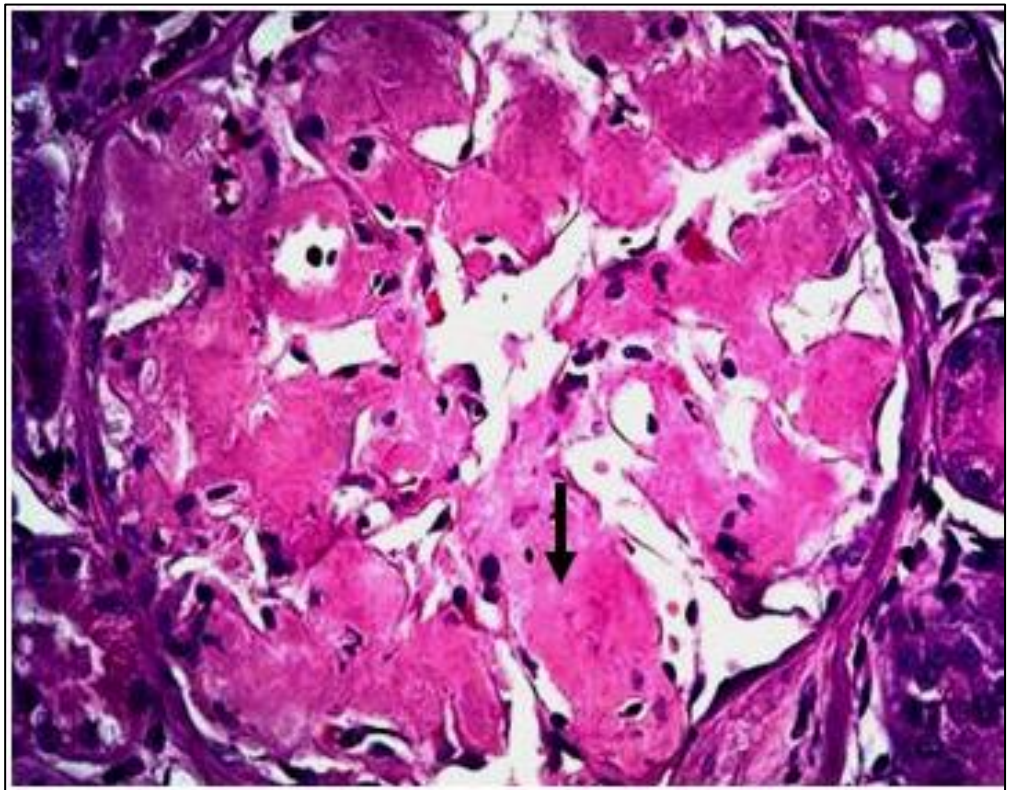
Glomerular amyloidosis like immunecomplex glomerulonephritis, result in the **nephrotic syndrome**
(proteinuria, hypoproteinemia, albuminuria, oedema, lipidurea and hypercholesterolemia).
Long-standing glomerular amyloidosis results in diminished **renal blood flow** through the glomeruli which lead to **renal tubular atrophy**, **degeneration**, diffuse **fibrosis** and in severe cases, **renal papillary necrosis**.

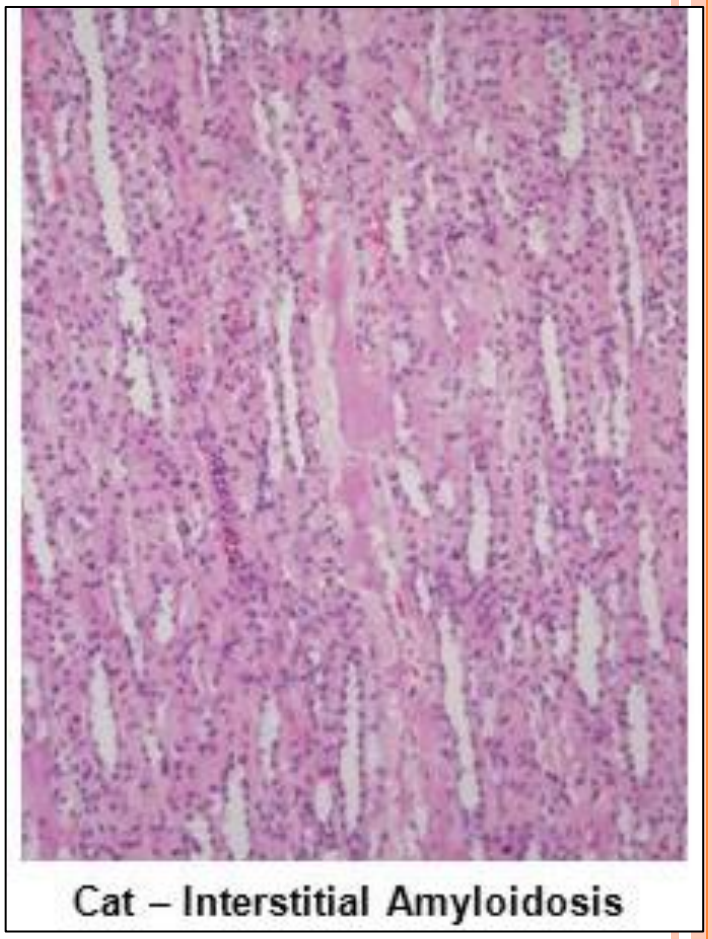
Grossly:
Kidneys affected with glomerular amyloidosis are often:
*enlarged,
*pale,
*increased in consistency,
*have a smooth to finely granular capsular surface
Amyloid-laden glomeruli may be visible grossly as:
fine **translucent dots on the capsular surface**

Similarly, the cut surface of the cortex can have a finely granular appearance. 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 exposed to dilute sulfuric acid . This technique provides a rapid presumptive diagnosis of renal amyloidosis.



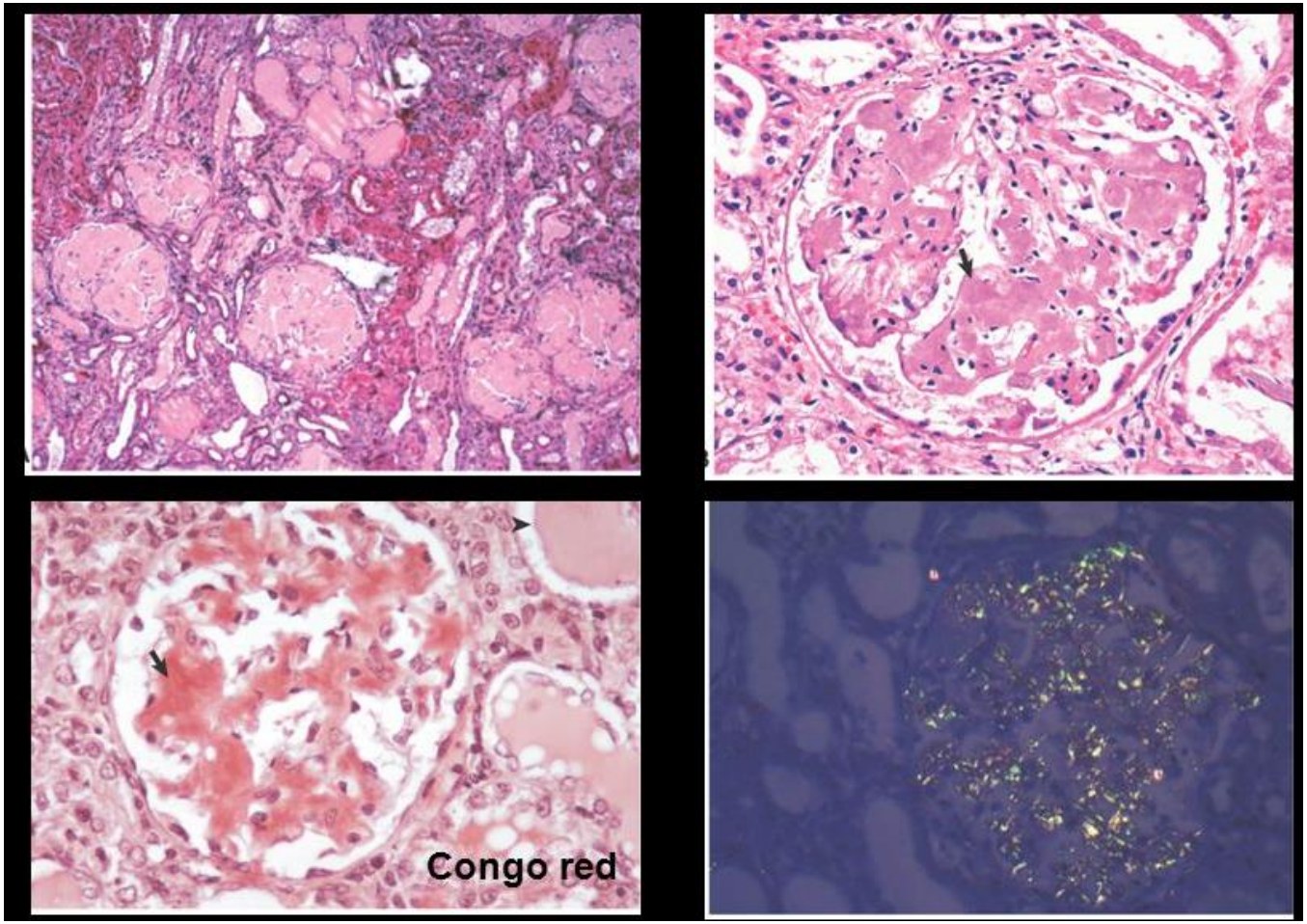
Microscopically,
glomerular amyloid is deposited in both the mesangium and subendothelial locations. Amyloid is relatively **acellular** and can accumulate segmentally within **glomerular tufts**; thus a portion of the **normal glomerular architecture** is replaced by **eosinophilic, homogeneous to slightly fibrillar material** .
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**.


Dog - Glomerular Amyloidosis


Cat – Interstitial Amyloidosis

Amyloid can be present in **renal tubular basement membranes**, and these membranes are **hyalinized and thickened**. Additionally, in cases of glomerular amyloid deposition, secondary changes may be present in renal tubules, which are usually **markedly dilated**, have variably **atrophic epithelium**, and contain **proteinaceous and cellular casts**.

Amyloid is confirmed microscopically by staining with **Congo red stain** . When viewed with polarized light, amyloid has a green birefringence .



DISEASES OF THE TUBULES AND INTERSTITIUM

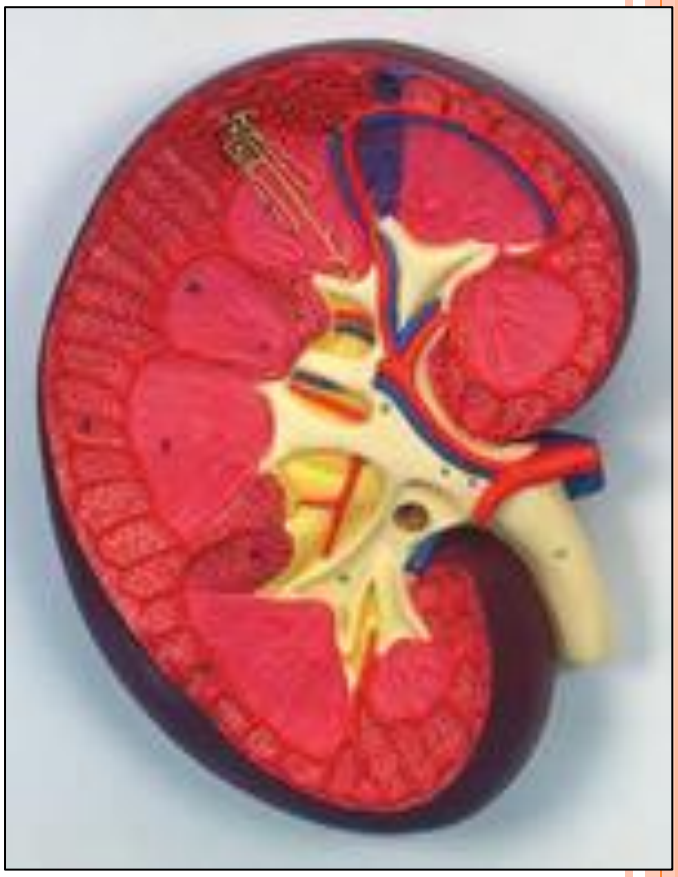
AZOTEMIA AND UREMIA

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**.

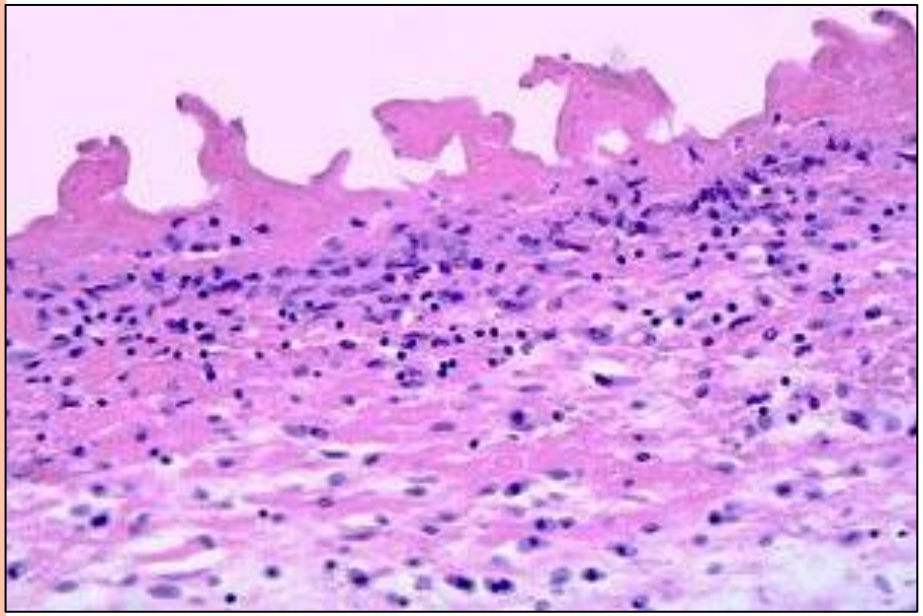
Renal failure can result in the following:

1. Intravascular accumulation of other metabolic wastes, such as guanidines, phenolic acids, and large molecular weight alcohols (example: myoinositol)
2. Reduced blood pH (metabolic acidosis)
3. Alterations in plasma ion concentrations, particularly potassium, calcium, and phosphate
4. Hypertension

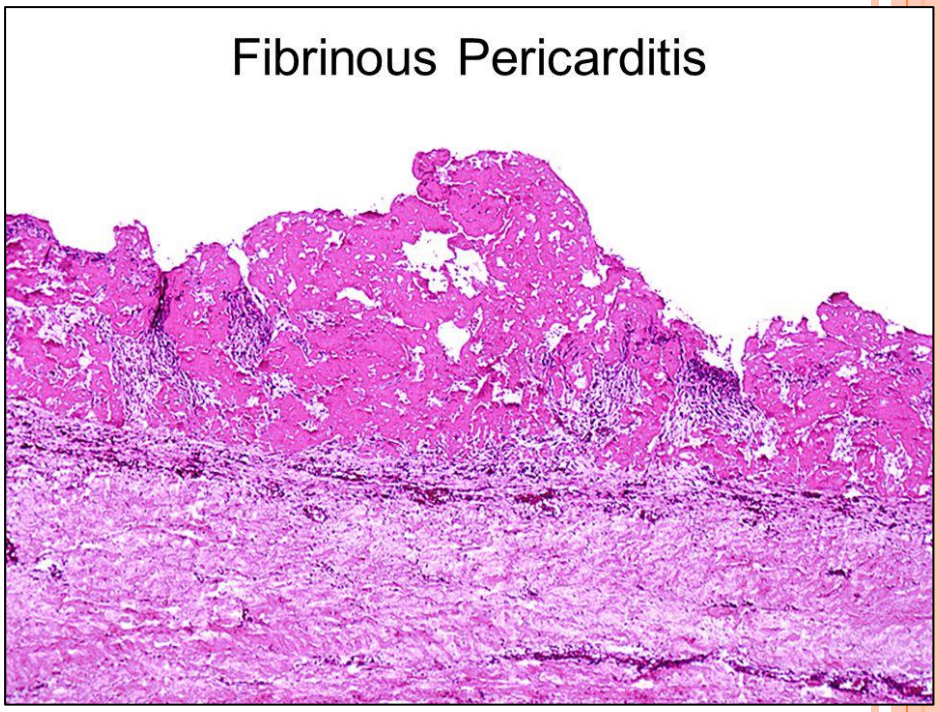


AZOTEMIA

The result of renal failure is a toxicosis called **uremia**. Uremia can therefore be defined as a syndrome associated with **multisystemic** lesions and clinical signs because of renal failure. Nonrenal lesions of uremia identified clinically or at necropsy are useful indicators of renal disease. The severity of nonrenal lesions of uremia is dependent on the length of time that the animal has survived in the uremic state. Therefore in acute renal failure, nonrenal lesions are few, whereas in chronic renal failure many lesions can be present.



Uremic pericarditis



Typically, lesions can be attributed to either of the following:

1. **Endothelial degeneration and necrosis**, resulting in **vasculitis** with secondary **thrombosis** and **infarction** in a variety of tissues

2. Caustic injury to epithelium of the oral cavity and stomach secondary to the production of large concentrations of **ammonia** following splitting of salivary or gastric urea by bacteria.

Systemic lesions of uremia include the following:

1. Ulcerative and necrotic **stomatitis**
2. Ulcerative and hemorrhagic **gastritis**
3. Ulcerative and hemorrhagic **colitis**
4. **Fibrinous pericarditis**
5. Diffuse pulmonary edema.

This lesion is called **uremic pneumonitis**.

6. **Mucoarteritis**

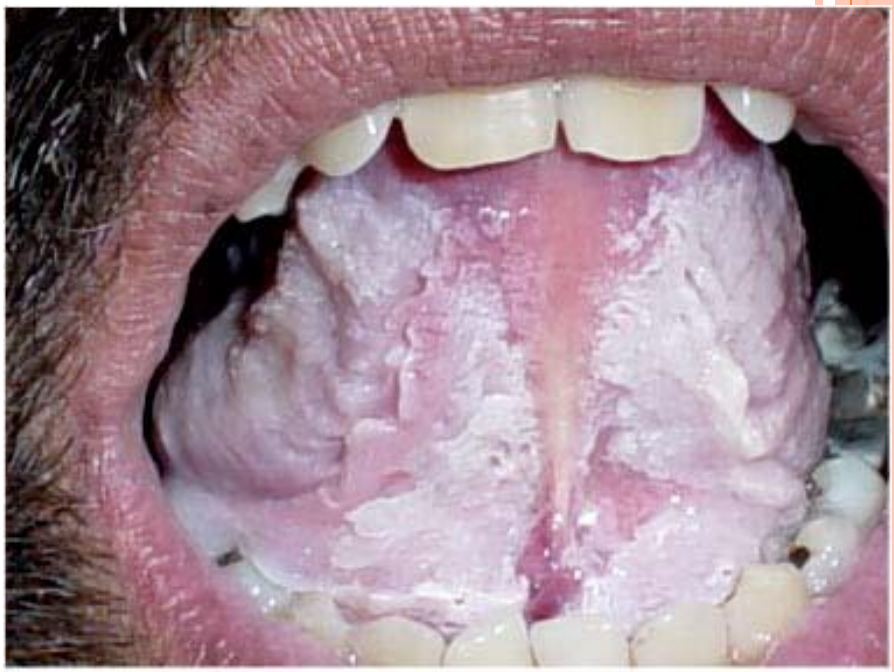
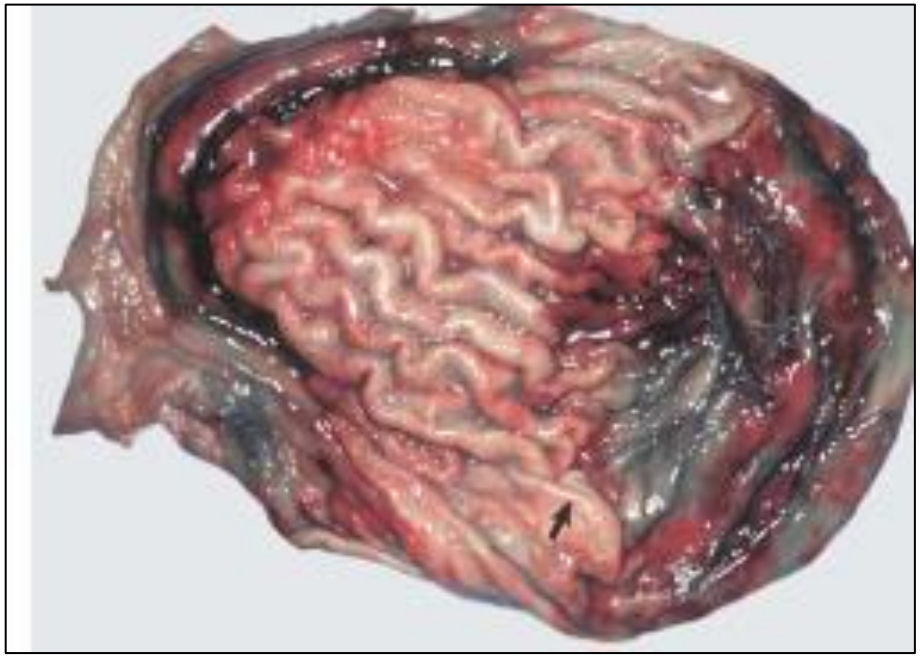


Figure 1 - Adherent white patch on ventral surface of tongue and floor of the mouth.



Uremic gastritis

Uremic glossitis

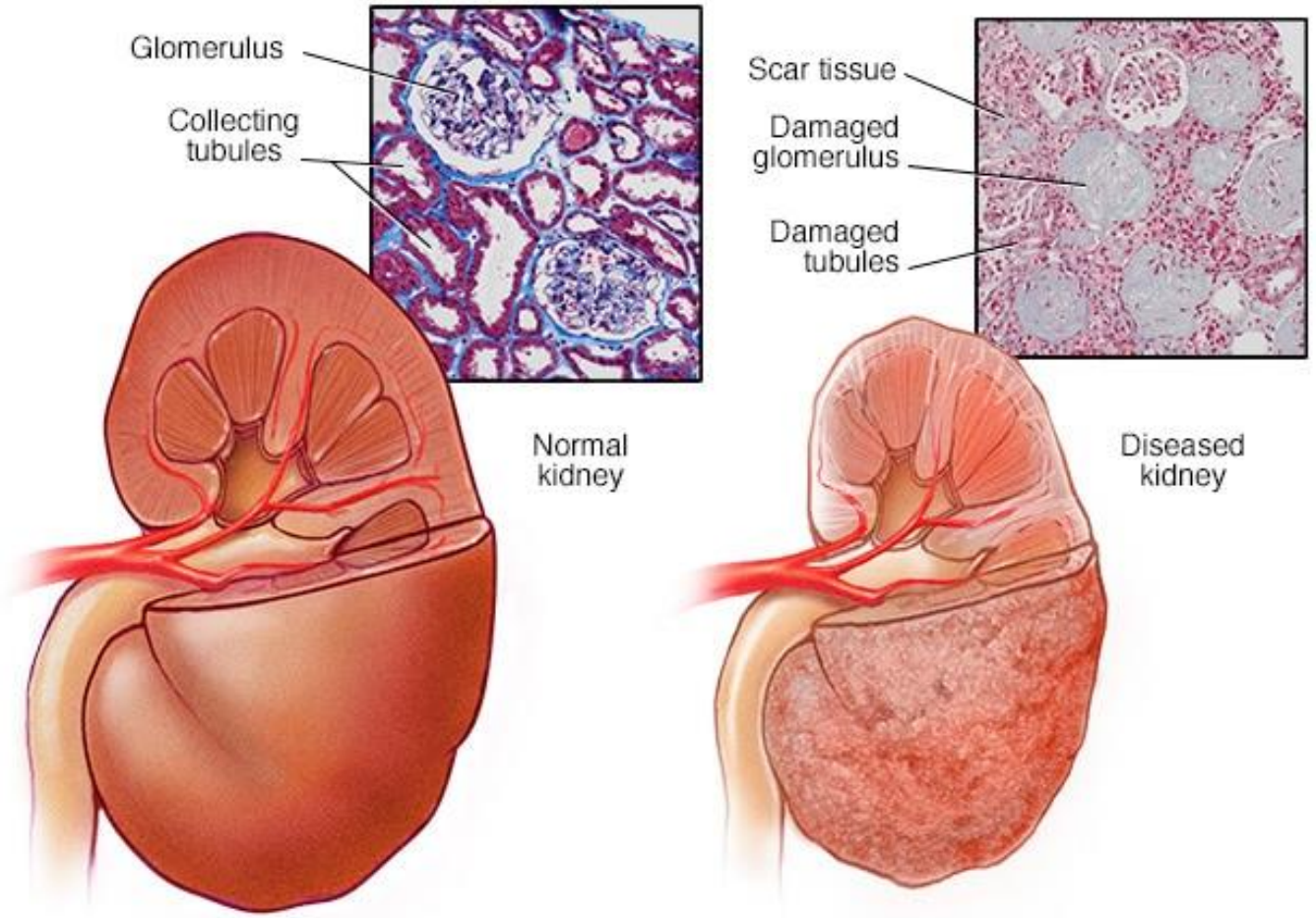
- Relatively common lesion associated with renal failure in dogs and less commonly in cats
- Clinical signs
  - Cyanotic buccal mucosa
  - Fetid ulceration of tongue
    - Margins of ulcer swollen

Chronic renal failure often results in hematologic and biochemical alterations. In the diseased kidney,

A, There is accentuation of the gastric urgae and calcification in the deep mucosa.

B, The mucosa has laminar **mineralization of gastric glands**. von Kossa stain.

Most animals in renal failure have **hyperphosphatemia** and low to normal calcium levels, 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 below:

1. 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.

2. 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.

3. Reduced ionized serum calcium stimulates parathyroid hormone secretion, causing calcium release from the readily **mobilizable calcium** stores in the **bone** and from **osteoclastic bone** resorption.

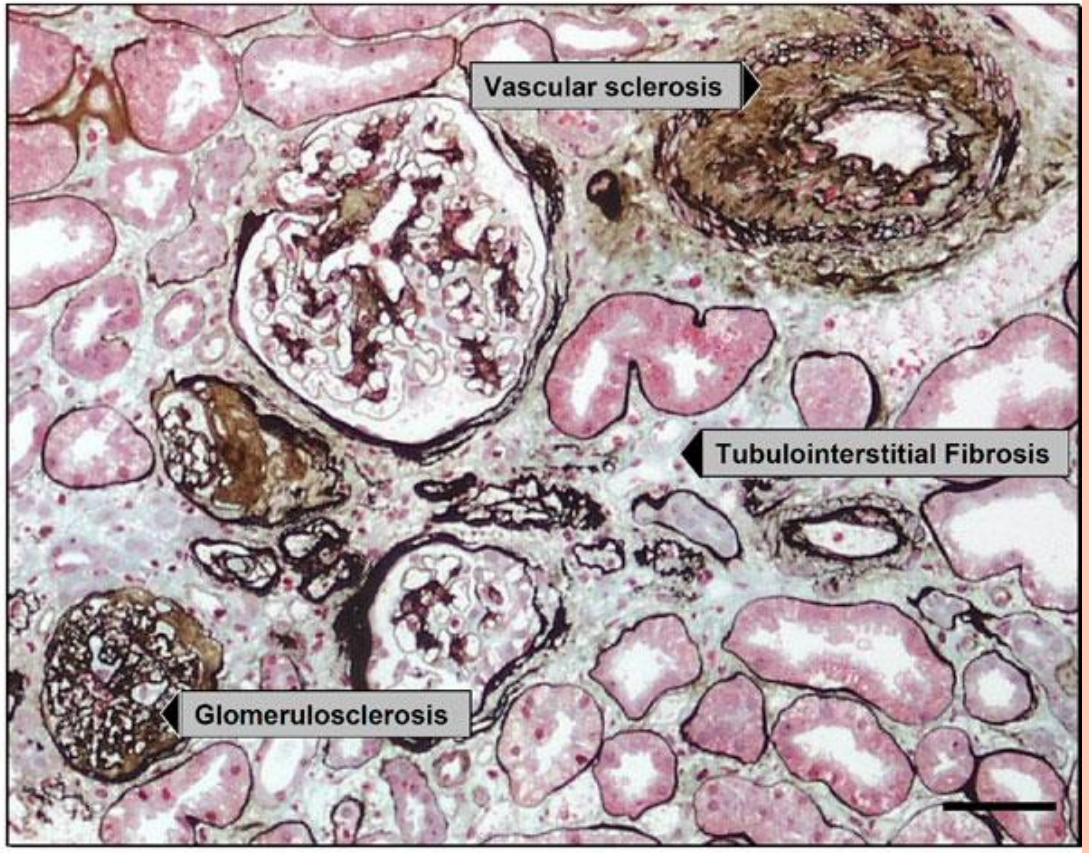
4. These changes in **calcium-phosphorus metabolism** are made more severe by the reduced ability of the diseased kidneys to hydroxylate 25-hydroxycholecalciferol to the more active 1,25-dihydroxycholecalciferol **(calcitriol**), resulting in **decreased intestinal absorption of calcium**.

5. **Calcitriol production** is further **inhibited** by hyperphosphatemia.

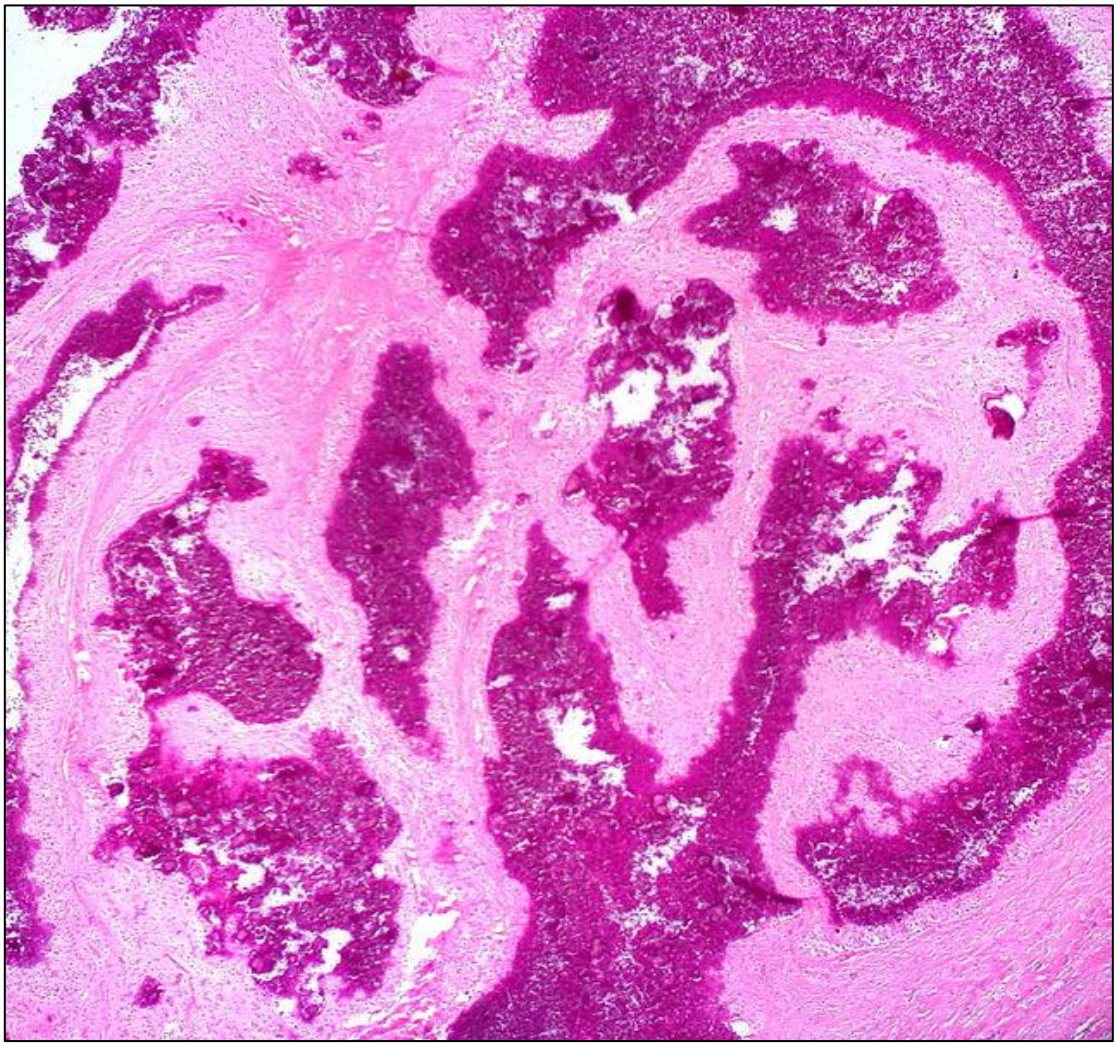
6. In addition, **calcitriol** normally **suppresses parathyroid hormone secretion**; therefore **reduced calcitriol** production further **increases parathyroid hormone secretion**. With time, these events lead to parathyroid chief cell hyperplasia (renal secondary **hyperparathyroidism**), fibrous osteodystrophy (**renal osteodystrophy**), and soft tissue **calcification**.

7. Renal secondary hyperparathyroidism is further thought to perpetuate and enhance renal disease by stimulating nephrocalcinosis , 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.

8. Soft tissue calcification associated with uremia occurs in numerous sites and represents both **dystrophic and metastatic calcification.**

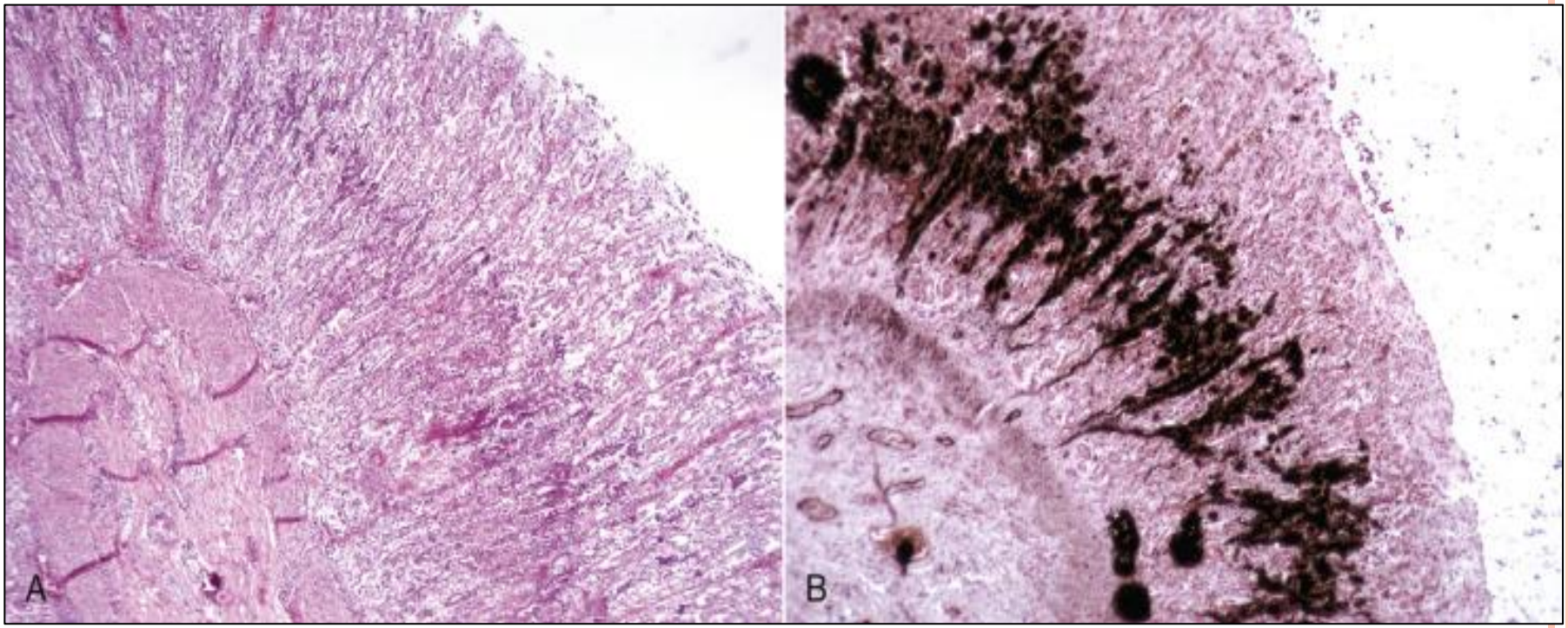


A characteristic lesion of uremic mineralization. particularly in dogs, is calcification of the subpleural connective tissue of the cranial intercostal spaces (subpleural calcinosis).



Calcinosis of Chronic Renal Failure

These lesions are **white-gray granular pleural thickenings** with **a horizontal "ladderlike" 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 occur occasionally in conjunction with the lesions of uremic pneumonitis.



Uremic Calcification, Stomach, Dog. A band of calcification is in the middle of the gastric mucosa. **A**, The calcium salts are basophilic (stained blue with hematoxylin). H&;E stain. **B**, The calcium salts are black with the von Kossa technique for mineralization.

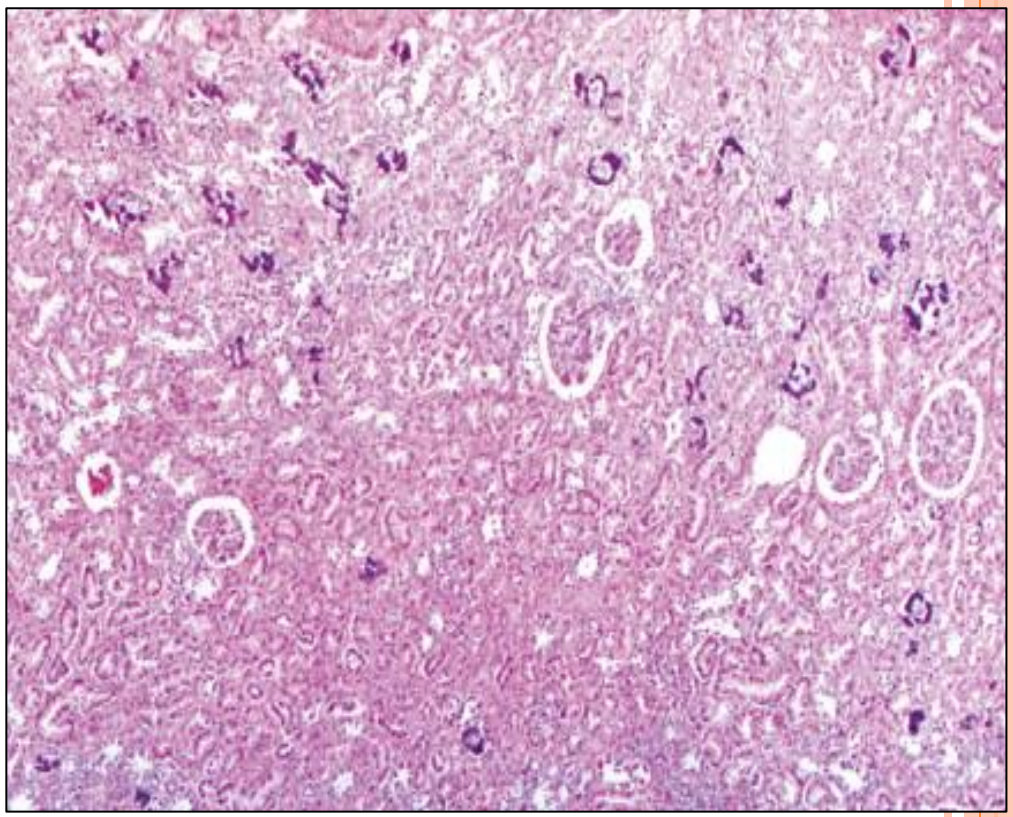
Microscopically:

*The **alveolar septa are calcified** and can focally rupture. causing small **emphysematous bullae**.

*Calcification occurs in the kidneys. The kidneys can be **gritty** when cut because of calcification of **tubular basement membranes**, **Bowman's capsules**, and necrotic tubular epithelium.

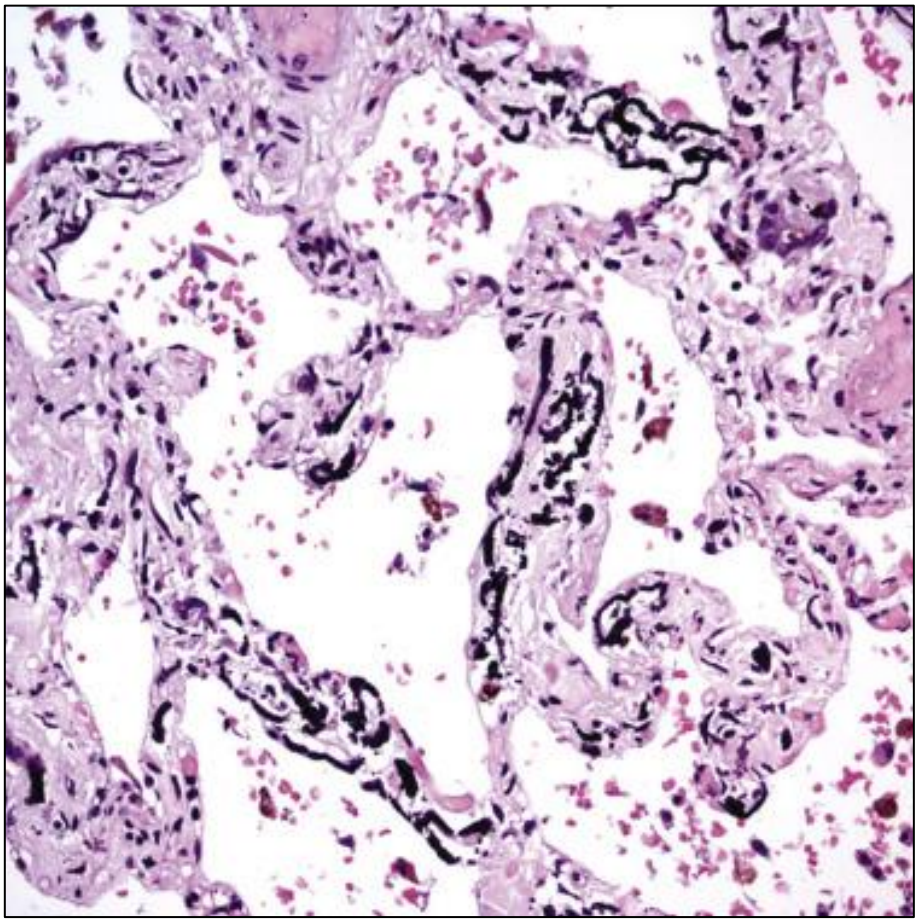
*The gastric wall can be **gritty** when cut because of calcification of the mucosa, and the submucosal **arterioles**.

Necrotic arterioles (uremic vasculitis) throughout the body are particularly susceptible to ***dystrophic calcification*** following uremic injury.

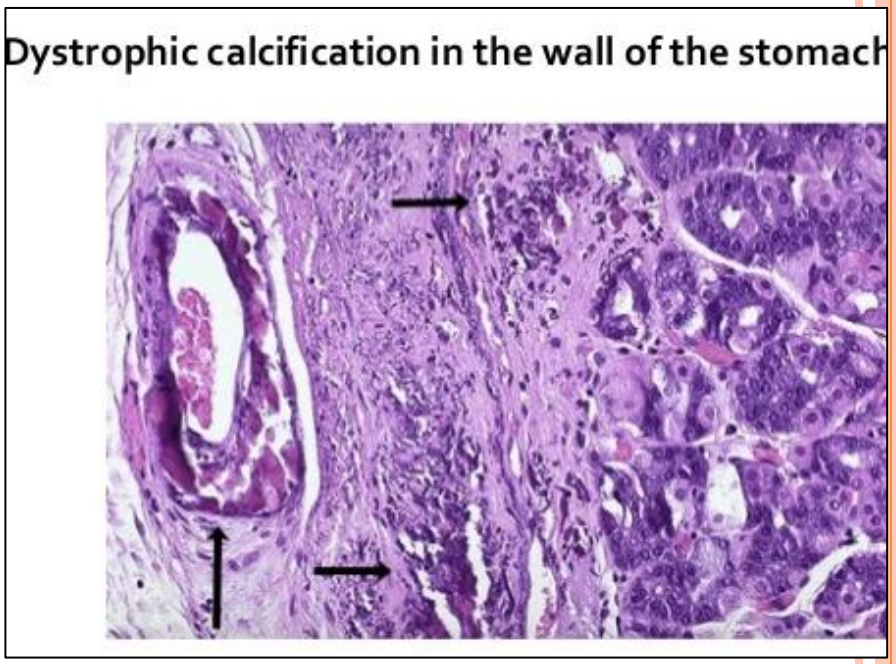


Photomicrograph of the kidney in a patient with prolonged hypercalcemia resulting from a parathyroid adenoma. Extensive calcium deposits are seen in relation to the proximal tubules.

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.



Metastatic calcification. Calcium is present as dark, basophilic fibrils within the alveolar walls and vessels in this lung



Lecture 2

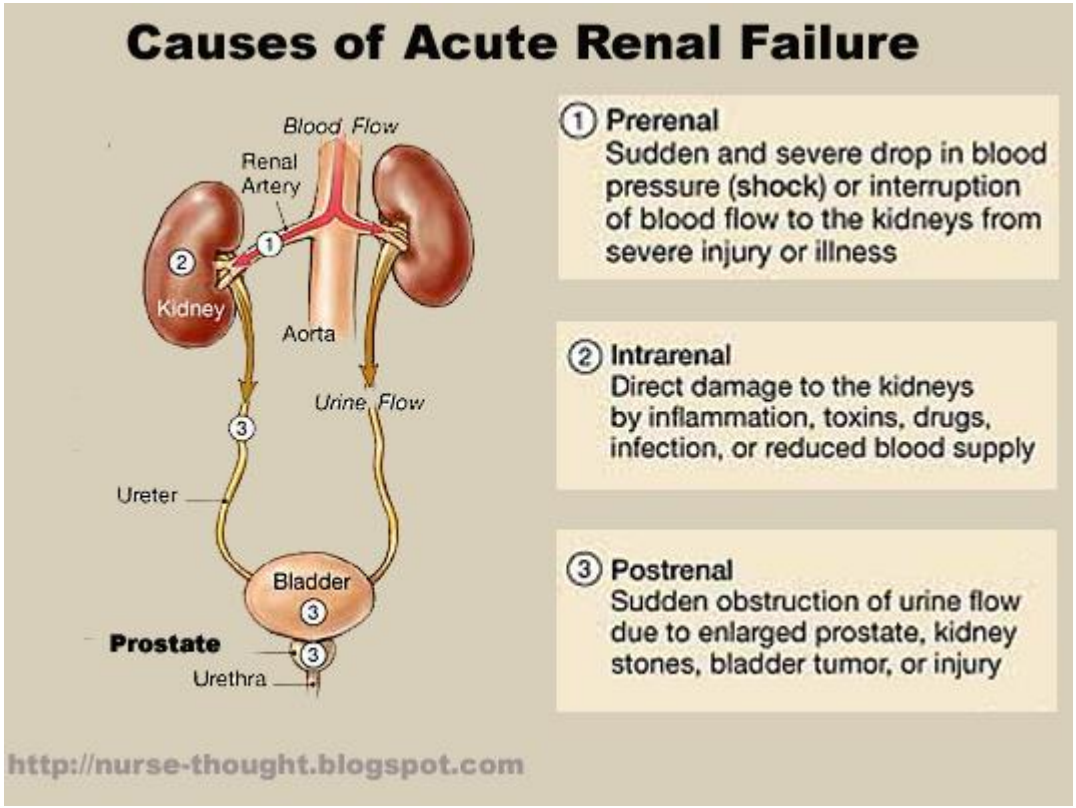
ACUTE RENAL FAILURE

When renal functional capacity is abruptly impaired (loss of 75%), 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, are duction in glomerular blood flow consequently reduces the blood supply to the tubules.

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). Prerenal and intrarenal factors are most responsible for episodes of acute renal failure, with prerenal azotemia and ischemic tubular damage actually being a continuum.

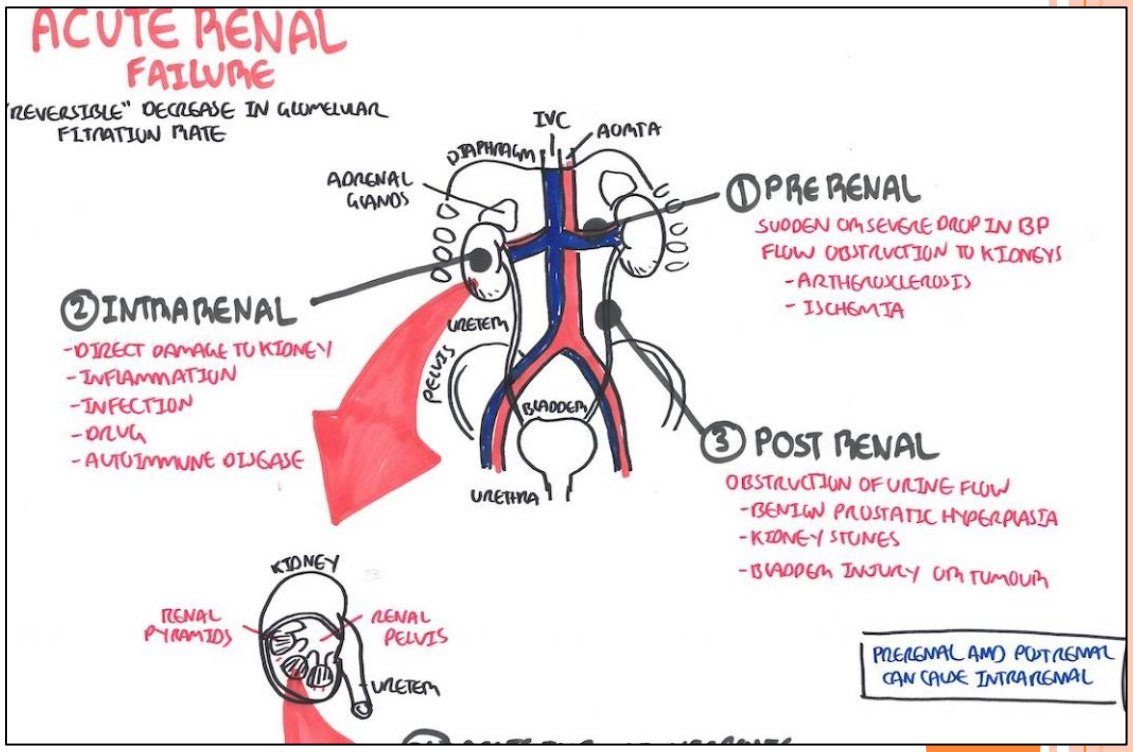


Intrarenal disease can target tubules by three main mechanisms:

1. Ascending disease, such as pyelonephritis
2. Intraluminal toxic metabolites
3. Ischemia Postrenal obstructive diseases will be discussed in the lower urinary tract section. 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:

1. Decreased ultrafiltration
2. Intratubular obstruction
3. Fluid back leak
4. Intrarenal vasoconstriction



These can occur following many insults, including the following:

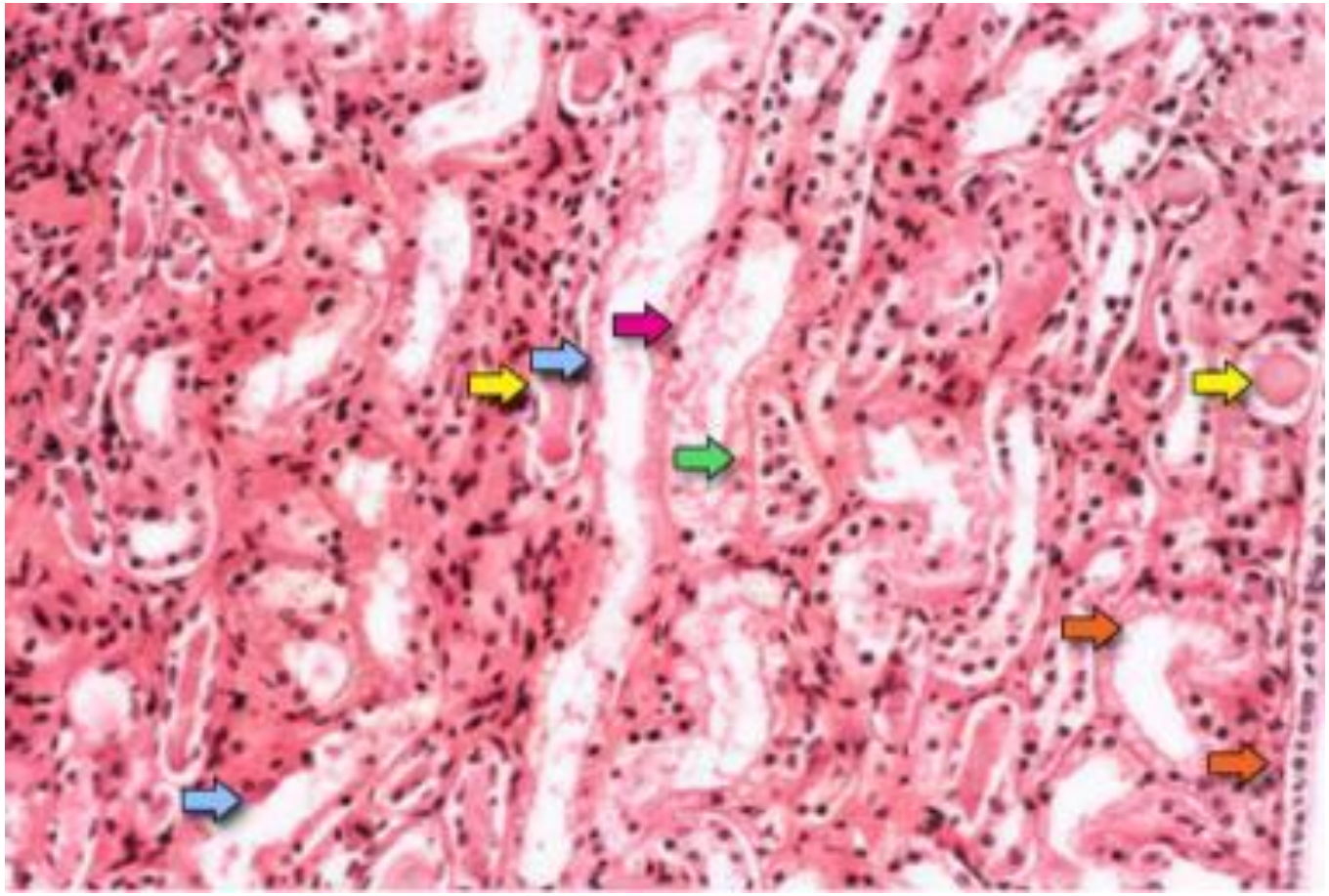
1. Decreased renal perfusion
2. Decreased glomerular filtration
3. Ischemic tubular damage
4. Toxictubular damage
5. Obstructive renal tubular damage
6. Tubulointerstitial inflammation, edema, or fibrosis

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 damage to the renal tubular epithelial cells or ischemia.

Nephrotoxins can directly damage renal epithelial cells, particularly those of the proximal convoluted tubules. Additionally, reactive metabolites can cause renal tubular epithelial necrosis following reabsorption or diffusion, respectively. Additionally, many of these metabolites can indirectly stimulate vasoconstriction and ischemia, which further compromises renal function.

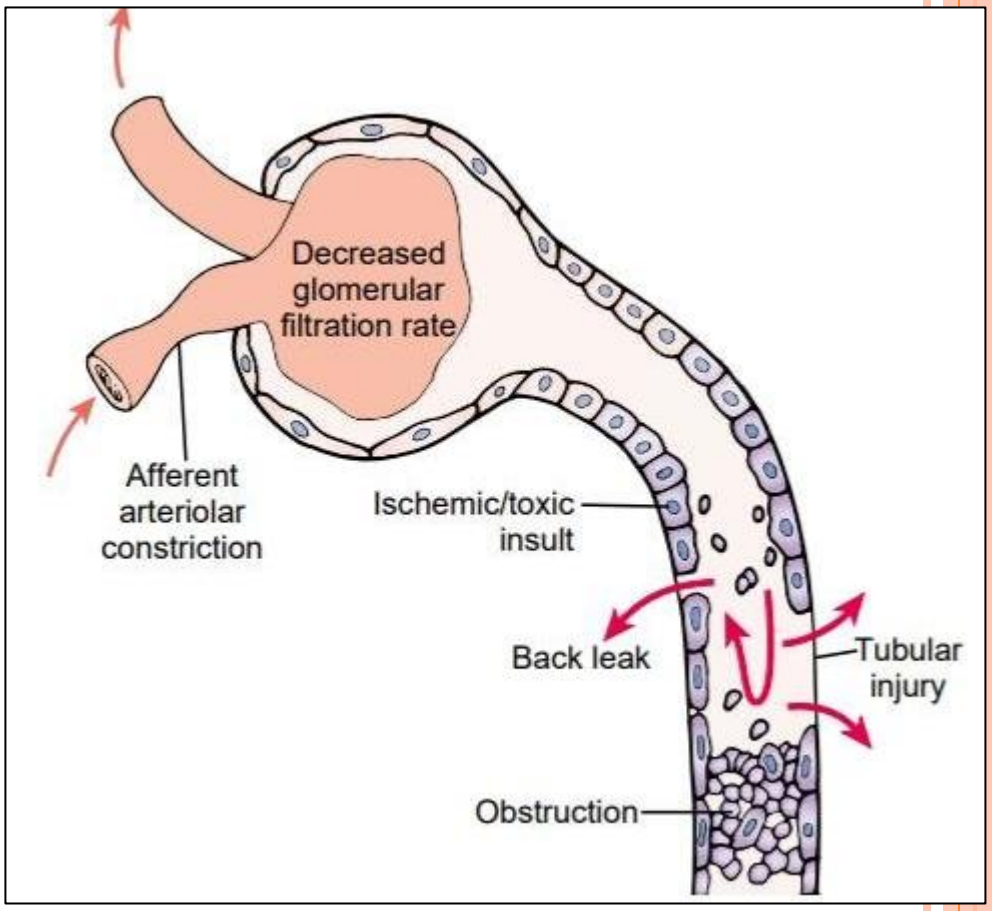
In nephrotoxin-associated ischemia, one of the first events in renal tubular cell damage is altered ion transport at the luminal surface. This process results in decreased sodium absorption and increased sodium ions in the lumens of the distal tubules, which stimulate the renin-angiotensin mechanism, causing vasoconstriction and reduced blood flow that result in ischemia and tubular cell damage.



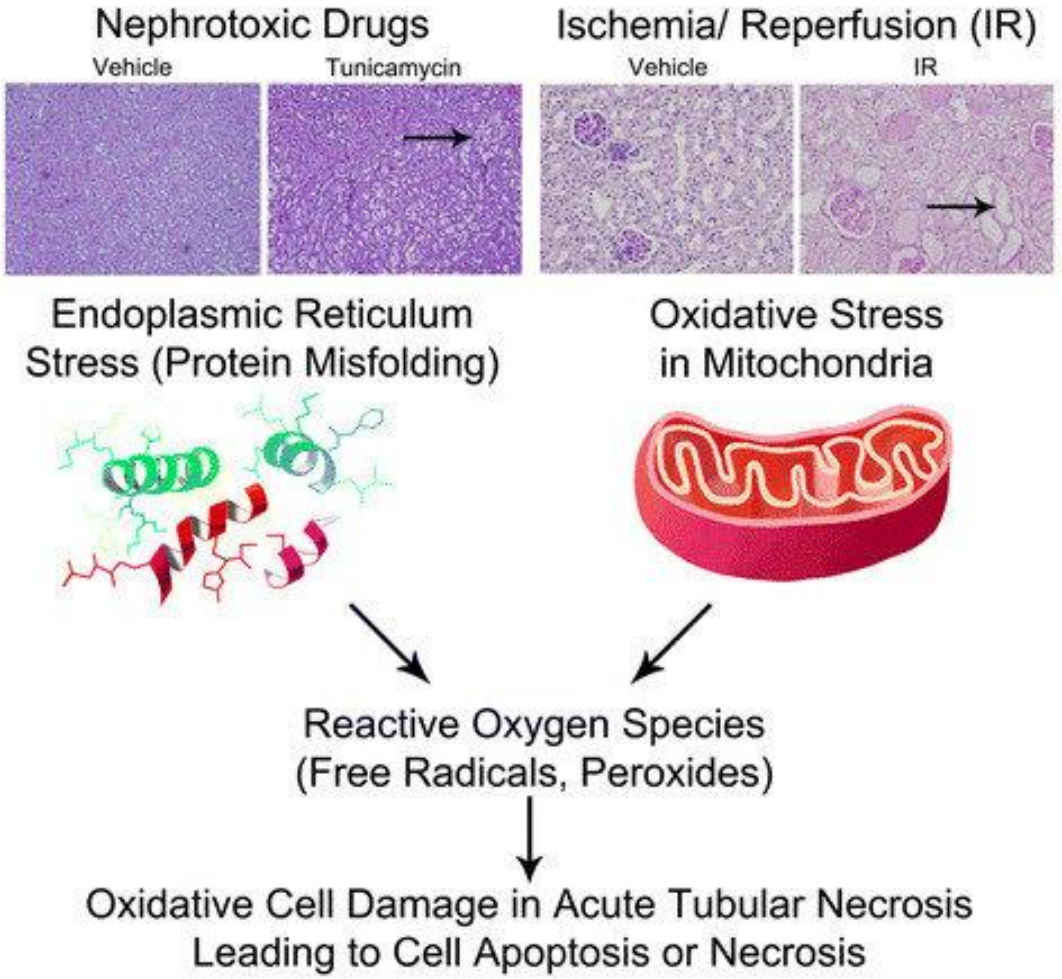
Photomicrograph of a renal biopsy spcimen shows renal medulla, which is compose mainly of renal tubules. Features suggesting acute tubular necrosis are the patchy or diffuse denudation of the renal tubular cells with loss of brush border (blue arrows); flattening of the renal tubular cells due to tubular dilation (orange arrows); intratubular cast formation (yellow arrows); and sloughing of cells, which is responsible for the formation of granular casts (red arrow). Finally, intratubular obstruction due to the denuded epithelium and cellular debris is evident (green arrow); note that the denuded tubular epithelial cells clump together because of rearrangement of intercellular adhesion molecules

Nephrotoxins usually do not damage the tubular basement membranes, and thus regeneration (repair) of tubules can occur . The intact basement membrane acts as a scaffold over which regenerating epithelial cells may slide.

Exposure to a variety of nephrotoxin, either from the **vasculature** (including certain chemicals or excessive metabolites, such as glycogen or fat) or from the **tubular lumen** (including certain antibiotics [aminoglycosides], pigments [hemoglobin], metals [lead], or chemicals [ethylene glycol-induced calcium oxalate crystals]), cause cells to undergo degeneration followed by necrosis and sloughing 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.



Proximal tubular epithelium has a microvillous border, which amplifies absorptive surface area and cellular junctional complexes that structurally polarize the cell such 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 following ischemic insult include

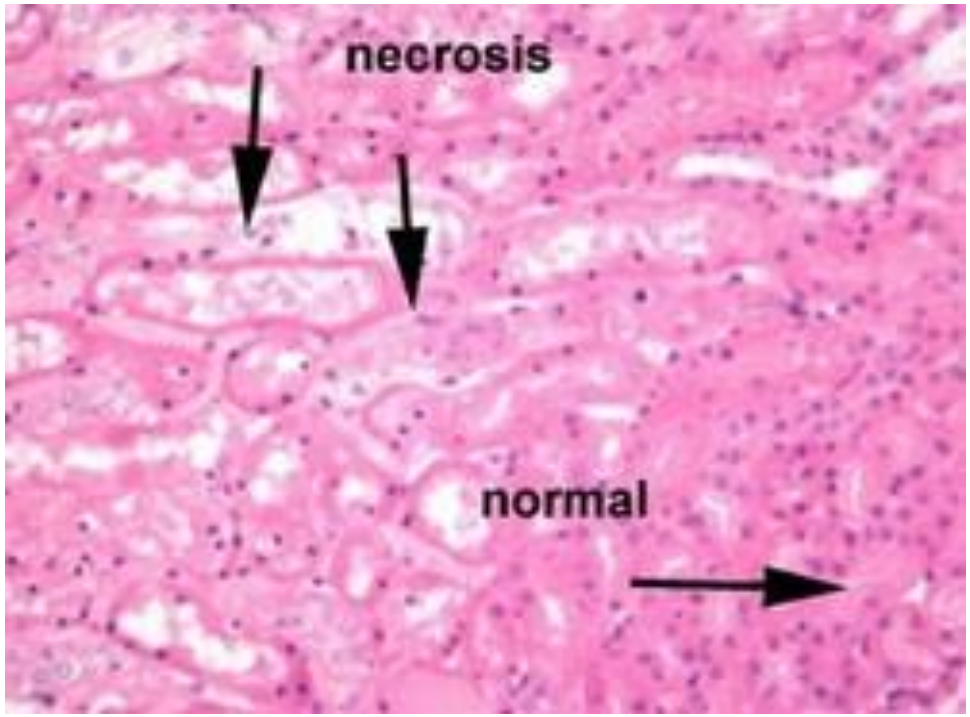
formation of apical blebs,

loss of brush border,

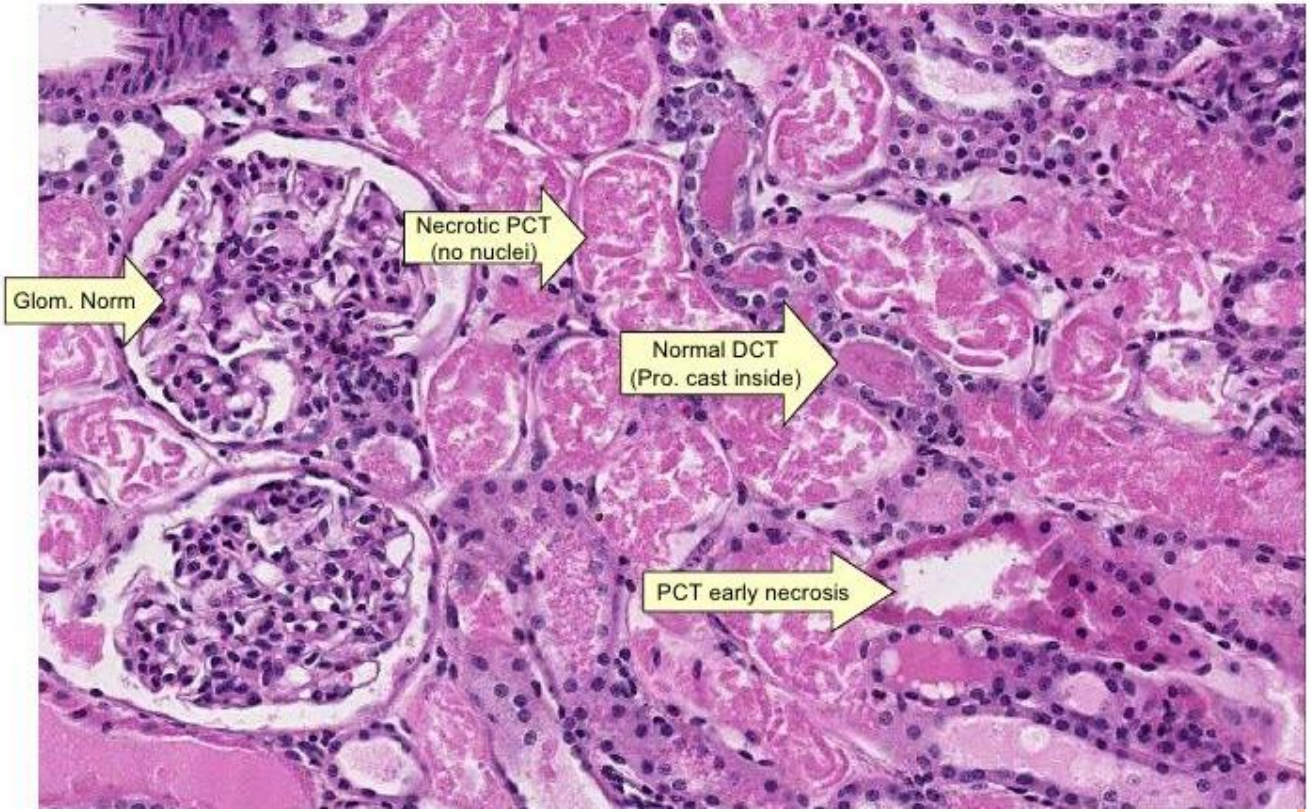
loss of cellular polarity,

disruption of tight junctions,

and sloughing of cells, **which result in intratubular cast formation .**

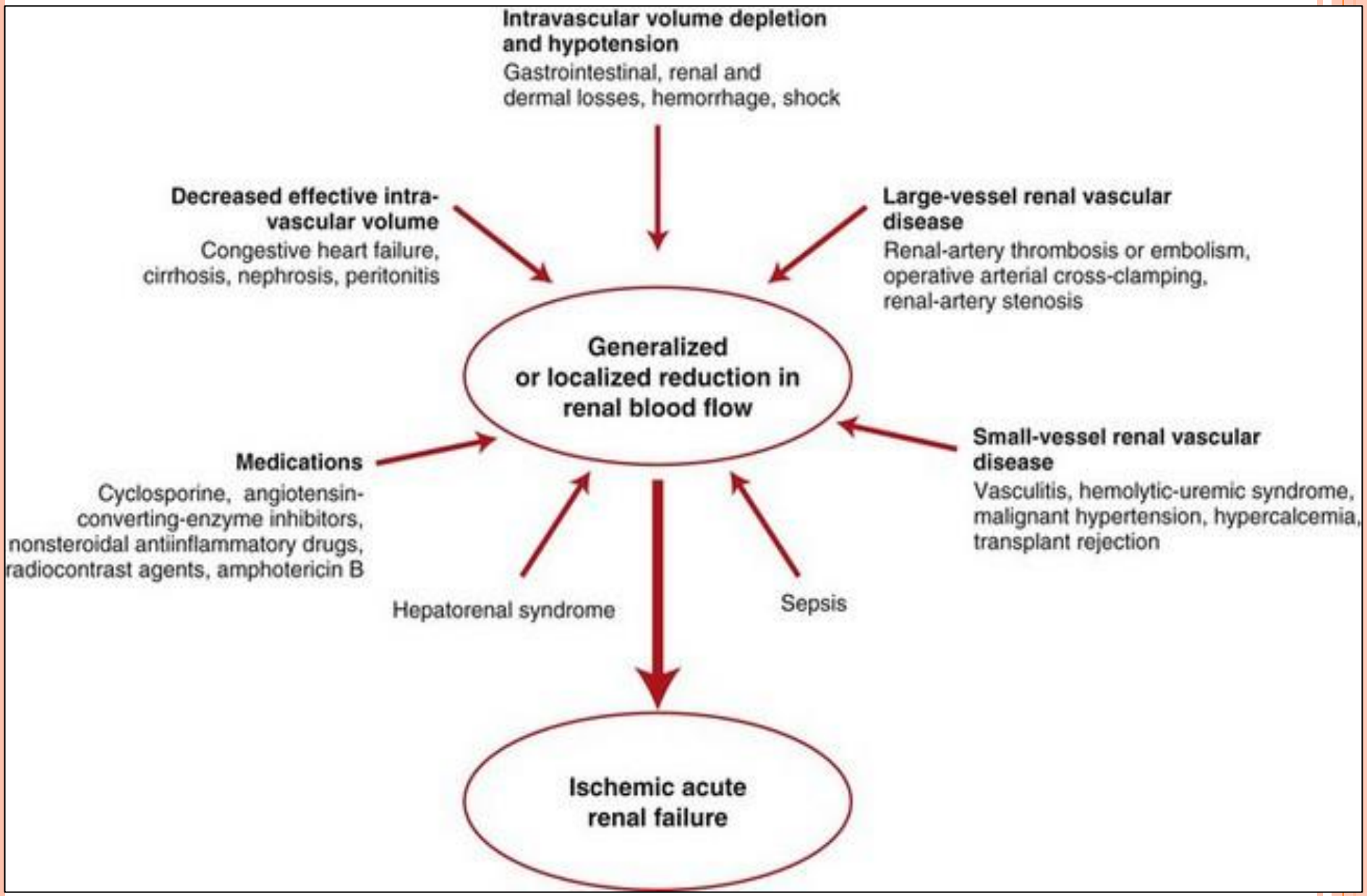


Damage to the cellular cytoskeleton modifies cell polarity, cell-to-cell interactions and cell-matrix interactions. Cells are attached to each other by junctional complexes, tight junctions and adherens junctions, and to the extracellular matrix by integrins. Several mechanisms contribute to tight junction 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 following alteration of the actin cytoskeleton and redistribution of integrins to the apical cell surface, such that cell desquamation occurs. The former results in deranged sodium handling by the proximal tubular cell.

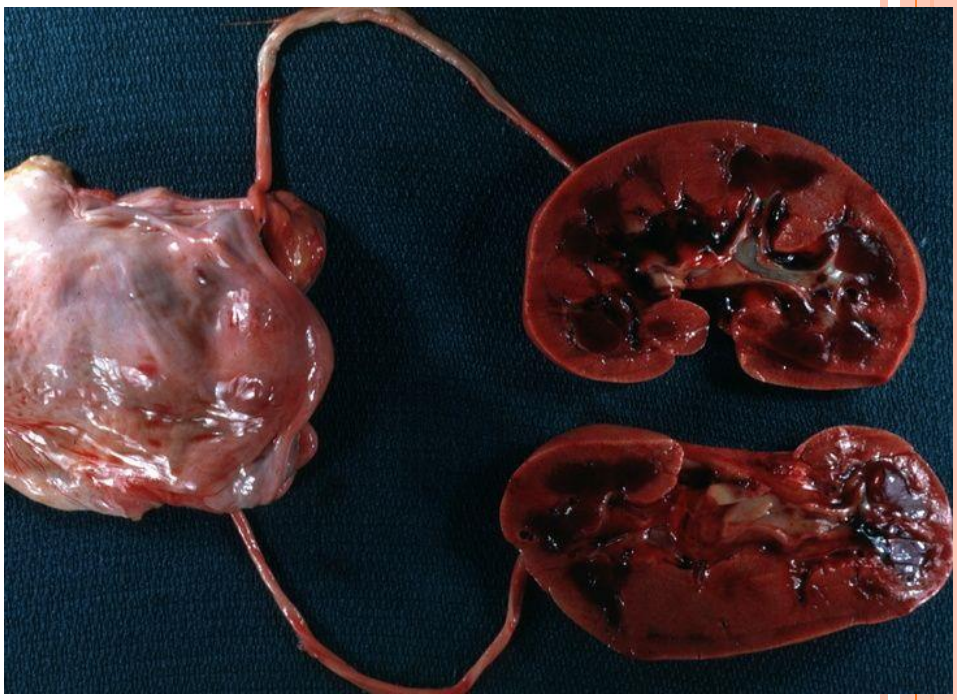


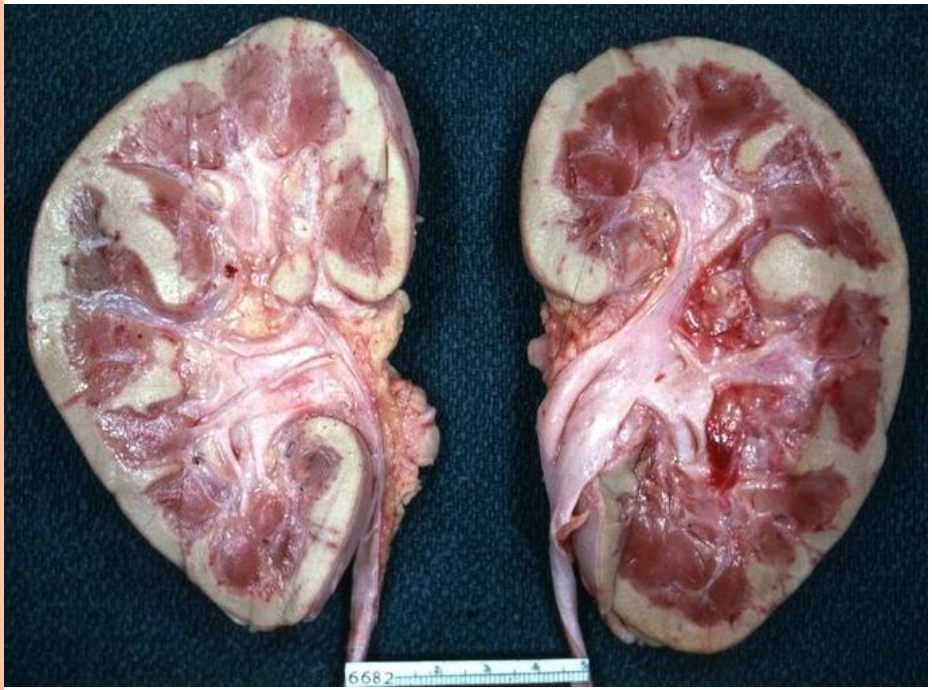
Animals with severe tubular necrosis have vascular derangements include:

1. Afferent arteriolar constriction
2. Efferent arteriolar dilation
3. Loss of autoregulation of renal blood flow



On gross necropsy, 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. The medulla is either pale or diffusely congested.

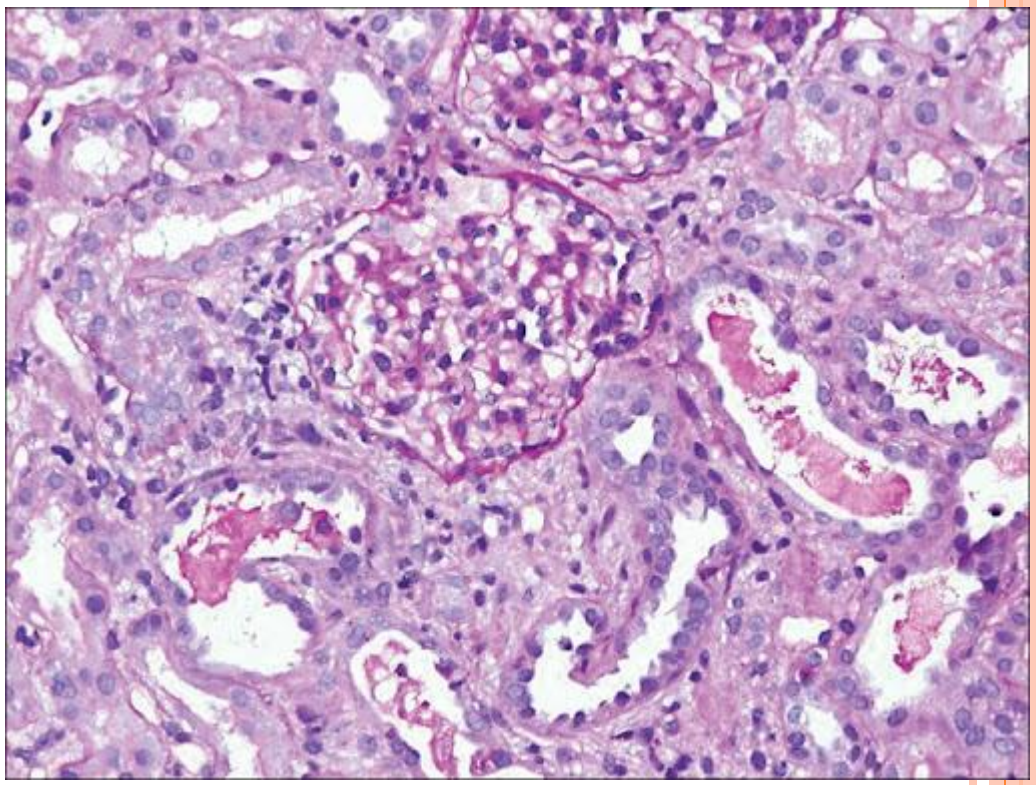




The microscopic appearance of kidneys with acute tubular necrosis can be variable, depending on the following:

1. The severity of the injury
2_ The duration of exposure to the damaging agent
3. The length of time between the injury and death. 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. Initially, proximal tubular epithelium is swollen, and the cytoplasm is vacuolated or granular and intensely eosinophilic, all features indicative of coagulation necrosis. 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.



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:

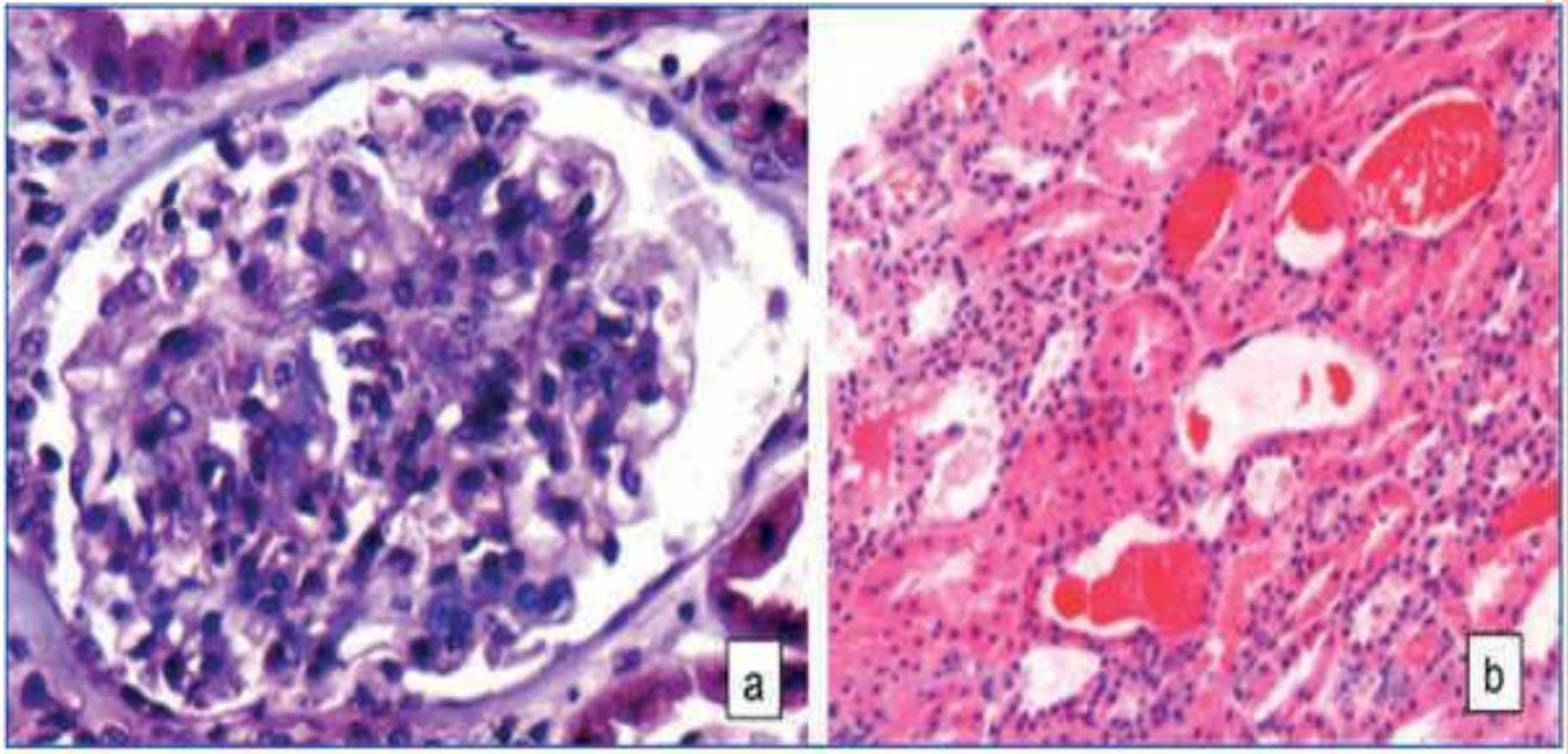
1. Leakage of tubular ultrafiltration from damaged tubules across disrupted basement membranes into the renal interstitium
2. Intratubular obstruction resulting from sloughed necrotic epithelium The latter mechanism is less well accepted,

but both mechanisms result in decreased glomerular fIltration rate. The balance of this section will deal with specific disease processes that produce acute tubular necrosis and include the following:

- Pigments
- Hemoglobin/myoglobin
- Bile/bilirubin
- Heavy metals
- Antibiotics
- Aminoglycosides
- Oxytetracycline
- Amphotericin B
- Sulfonamides
- Monensin
- Nonsteroidal antiinflammatory drugs
- Fungal toxins
- Plant toxins
- Antifreeze (ethylene glycol)
- Vitamins
- Hydrocarbons
- Bacterial toxins

A set of events leading to ischemic tubular necrosis frequently occurs in hypoperfused kidneys complicated by hemoglobinuria or myoglobinuria. Hemoglobinuria accompanies episodes of hemoglobinemia seen secondary to severe intravascular hemolysis as observed in the following:

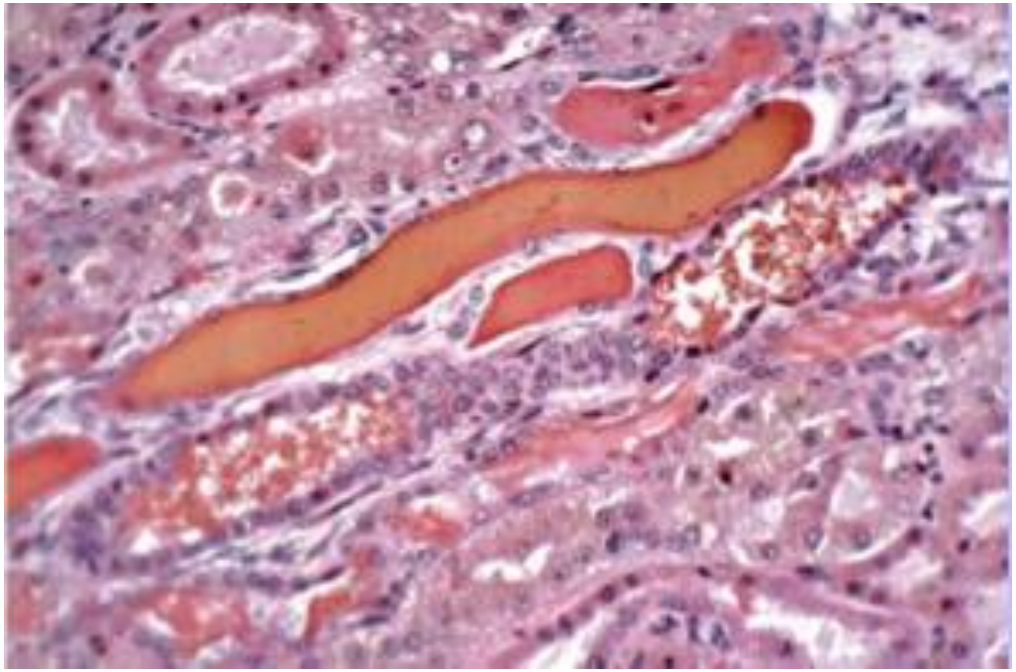
1. Chronic copper toxicity in sheep
2. Leptospirosis or babesiosis in cattle
3. Red maple toxicity in horses
4. Babesiosis or autoimmune hemolytic anemia in dogs



Myoglobinuria accompanies acute rhabdomyolysis as occurs in any extreme necrosis of muscle as seen with the following:

1. Azoturia
2. Severe direct trauma to muscle

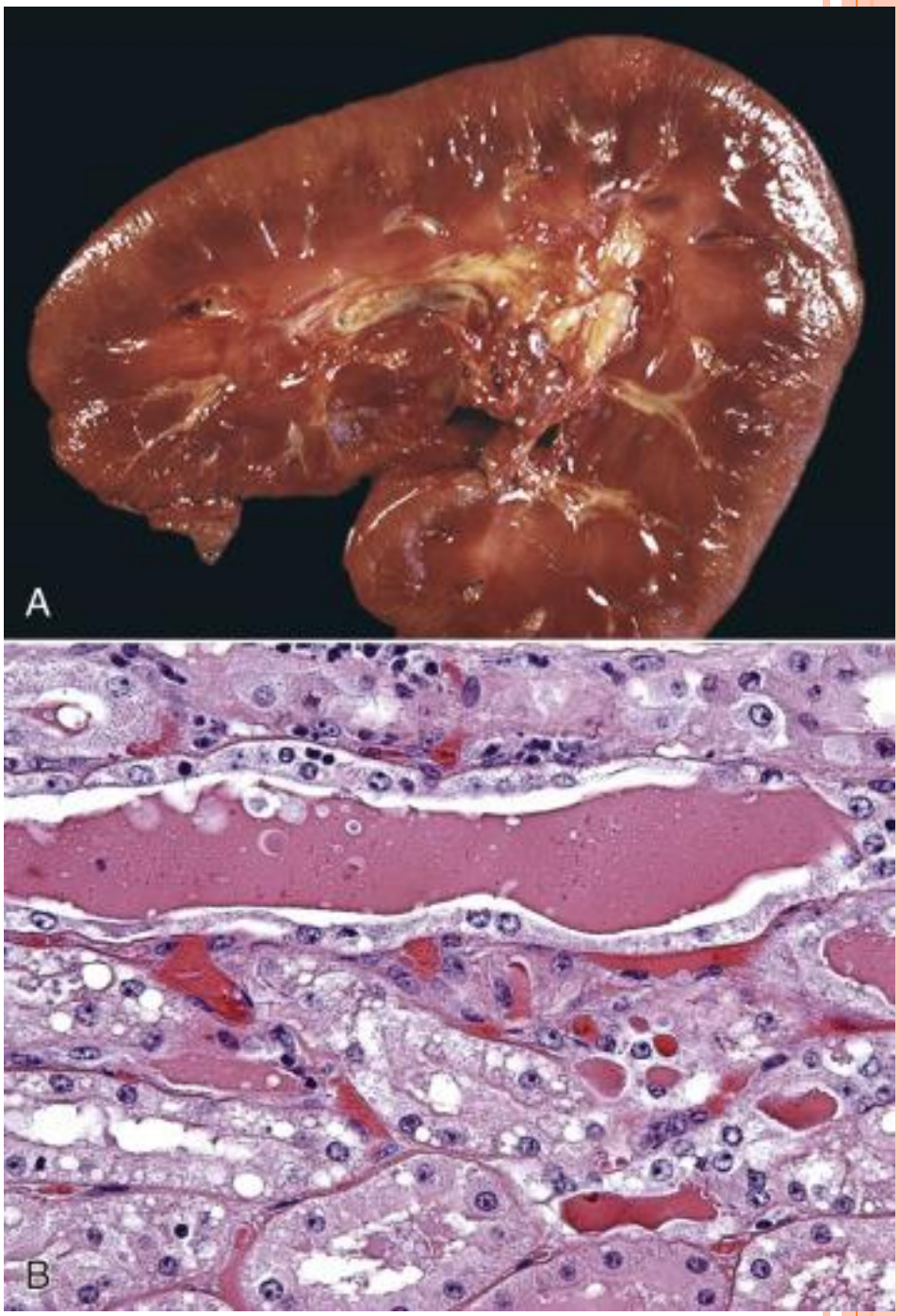
In these diseases, serum concentrations of hemoglobin or myoglobin are increased. These products pass into the glomerular filtrate, producing greatly increased intraluminal concentrations that cause hemoglobinuric nephrosis or myoglobinuric nephrosis.



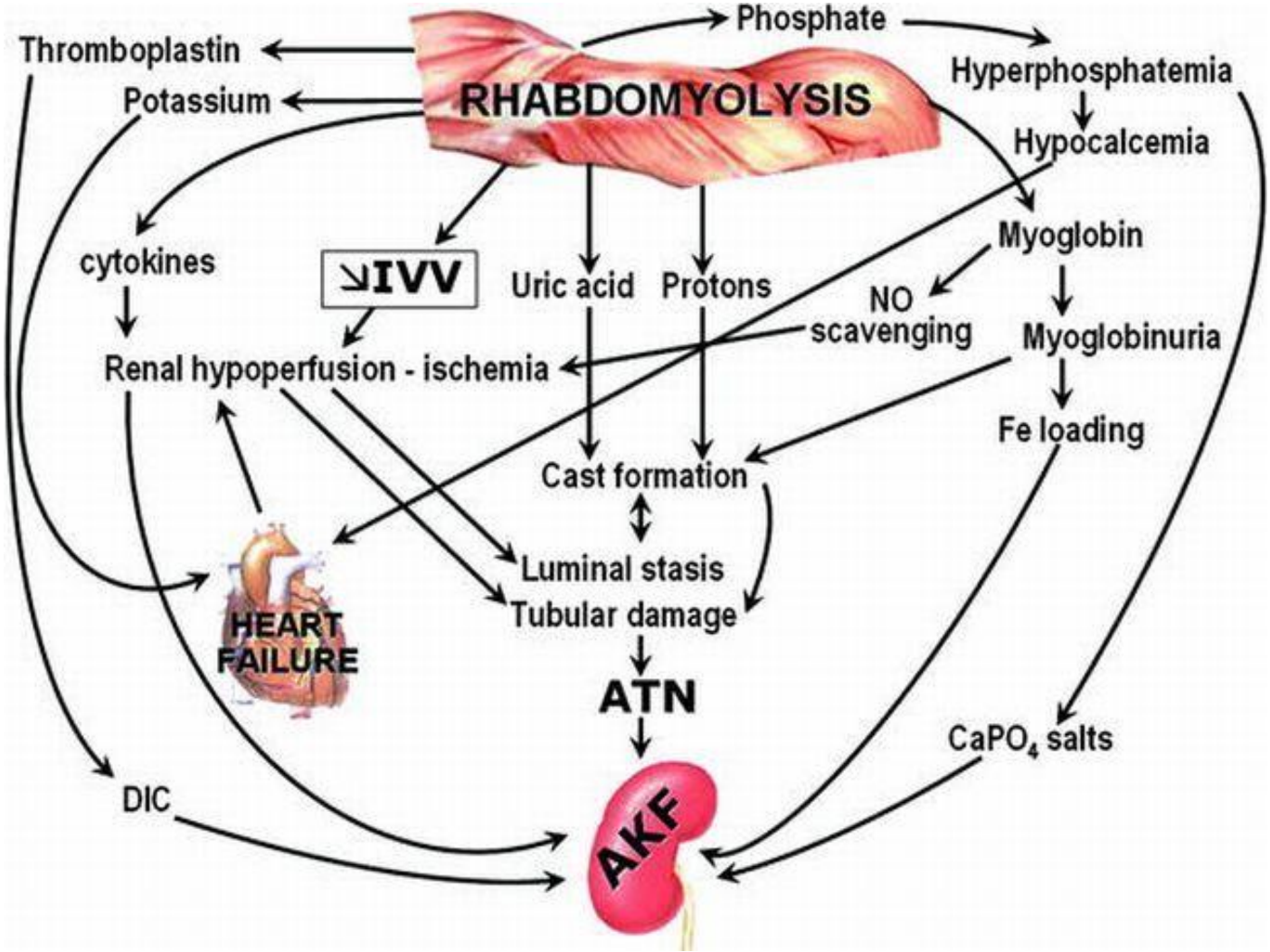
hemoglobinuric nephrosis

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.
(

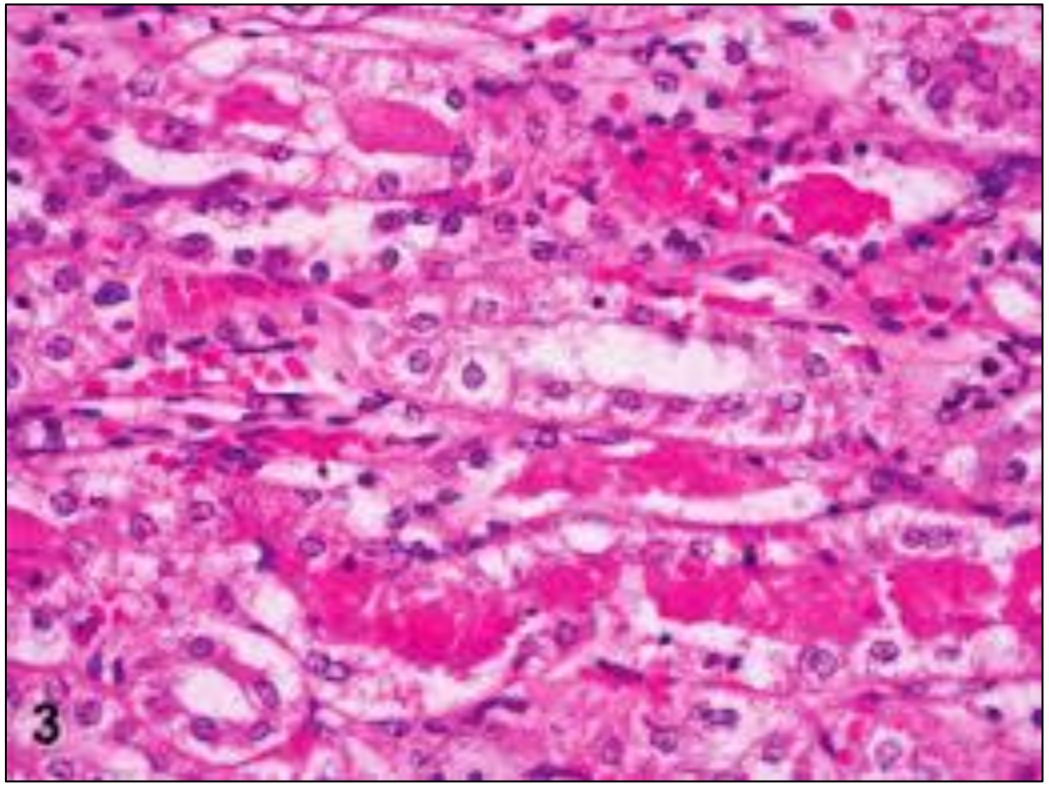


Hemoglobin and myoglobin are not nephrotoxic in themselves, and intravenous infusions of these compounds into healthy animals produce no recognizable lesions. However, large concentrations of hemoglobin or myoglobin in the glomerular filtrate can increase the tubular necrosis that occurs as a result of renal ischemia.



At necropsy, the renal cortices of animals with severe hemoglobinuria or myoglobinuria are diffusely stained red-brown to blue-black and have intratubular hemoglobin or myoglobin casts.

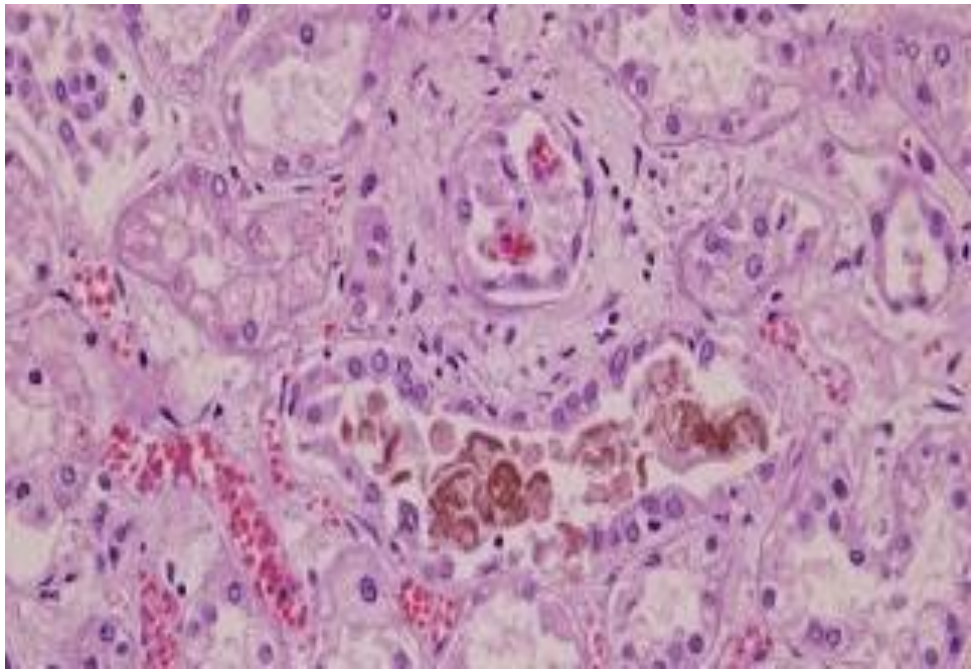
These hemoglobin casts appear as a red-black stippling of the external surface and continue into the cortex as radially oriented, dark red streaks. The medulla is diffusely dark red or has patchy red streaks. Classically, kidneys from sheep with chronic copper toxicity are diffusely, uniformly and strikingly blue-black and described as "gunmetal blue.".



Kidney: Intratubular pigmented casts associated with tubular epithelial cells swelling (hematoxylin and eosin method).

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 .

Also, increased serum concentrations of bilirubin, as in young lambs, calves, and foals with immature hepatic conjugating mechanisms, can be associated with cellular swelling, degeneration, and brown-green pigmentation of the proximal tubular epithelial cells. The term **cholemic nephrosis** has been applied to this lesion;

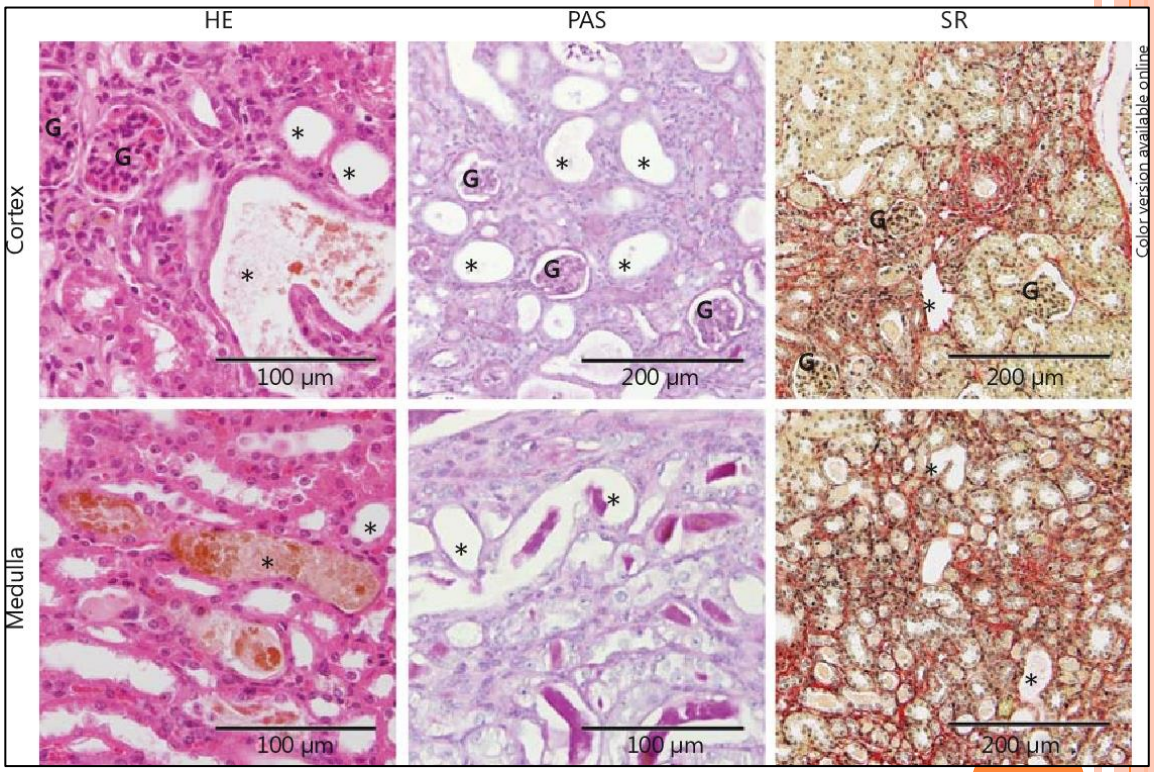


cholemic nephrosis: The green discoloration of this kidney at autopsy is because of the conversion of bilirubin to biliverdin after formalin fixation. The renal pyramids show a darker green color as the concentration of bilirubin is higher in these regions compared with the cortex. Linear green streaks consistent with bile casts can also be seen throughout the cortex and medulla

Acute tubular necrosis, when seen in association with severe bilirubinemia, the so-called hepatorenal syndrome, probably is not due to bile acid or bilirubin retention , but to ischemia from prerenal causes, such as constriction of renal vessels related to shock or catecholamine release.

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), impure petroleum distillates, and other environmental contaminants.



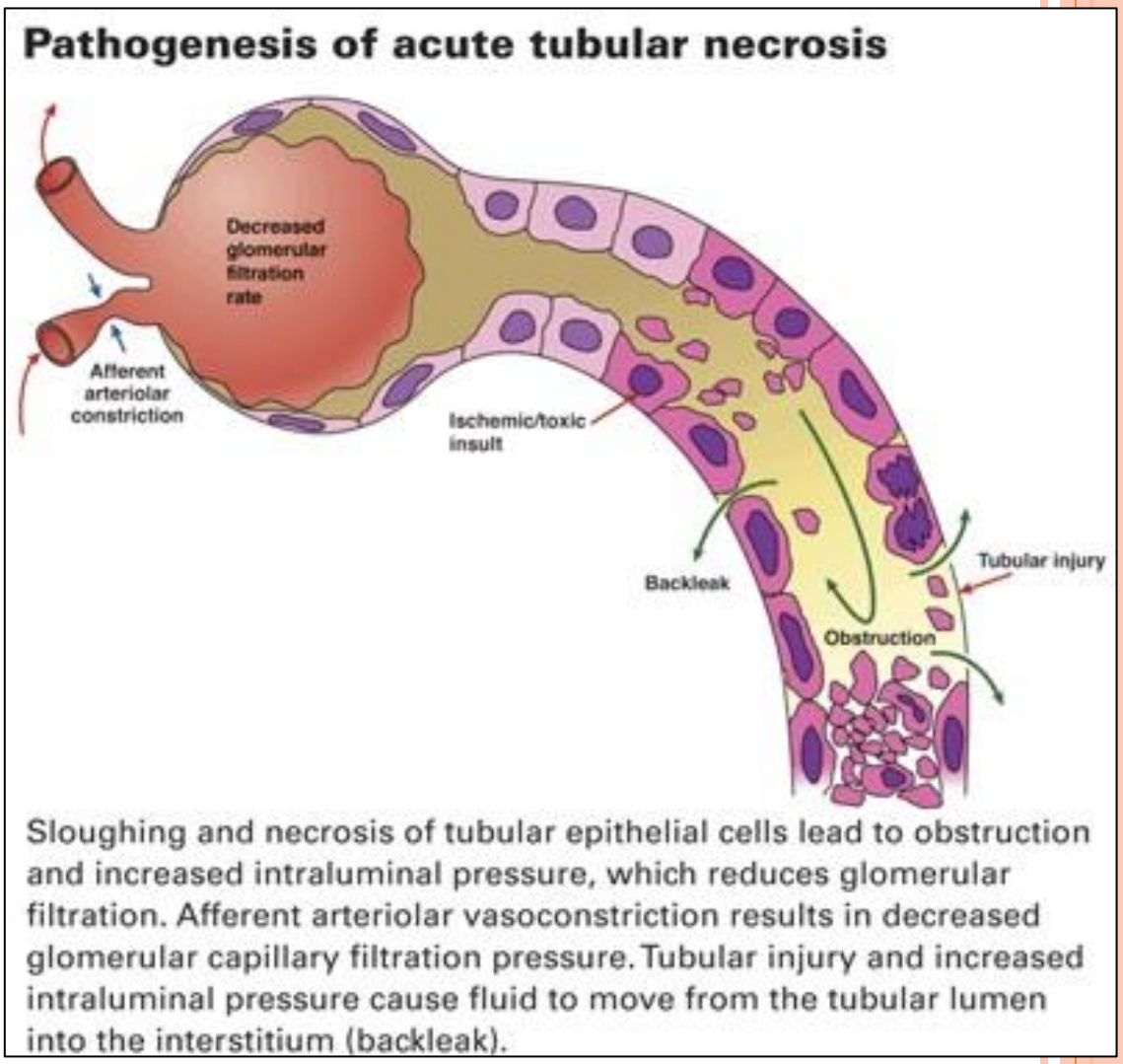
Hematoxylin and eosin (HE), PAS and Sirius red (SR)-stained kidney sections of 8-week common bile duct-ligated mice show pronounced tubulointerstitial fibrosis with dilated tubules (asterisks) and intraluminal brownish (HE; color in online version only) or PAS-positive casts. G = Glomeruli.

Acute tubular necrosis is due to the following:

1. Damage to membranes of proximal convoluted tubular epithelial cells
2. 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 enter the proximal tubular cells both from the luminal side, and from the peri tubular side, Mercuric ions become concentrated in the rough endoplasmic reticulum and Cause early tubular changes That include loss of brush Borders and dispersion of ribosomes.

These changes are followed by mitochondrial swelling and cellular death. Recently, cadmium has been reported to cause cell death in proximal convoluted tubules by apoptosis.

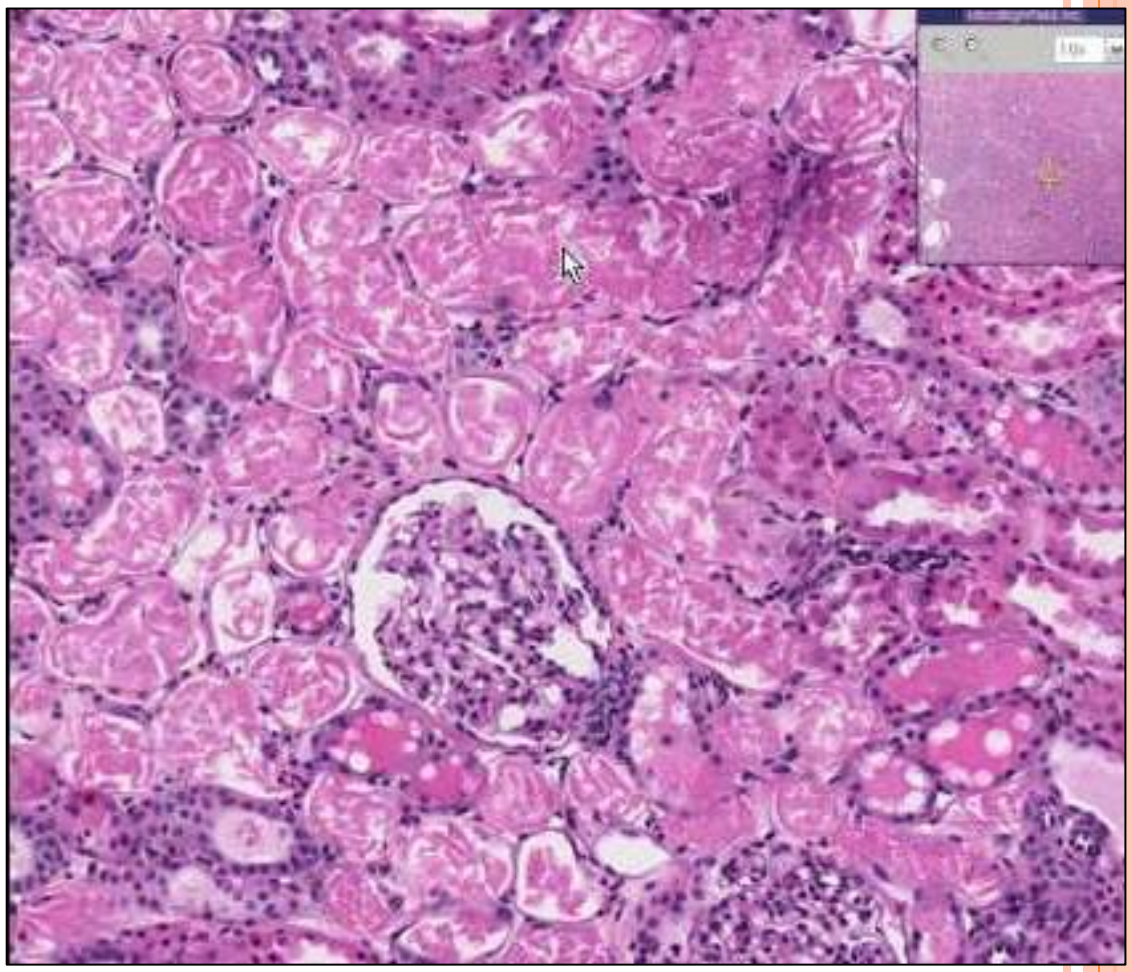


The specific metal involved in toxic tubular injury cannot be identified by the renal lesions alone. The exception is lead toxicity, in which the endothelial and epithelial cells of affected glomeruli and tubules, respectively, sometimes have acid-fast intranuclear inclusions composed of lead-protein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

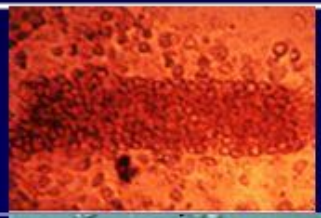
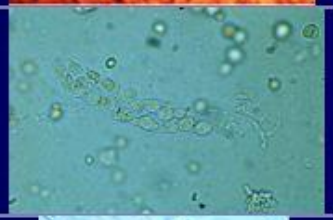
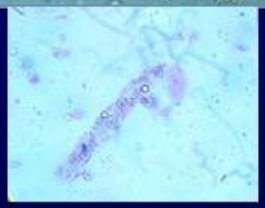
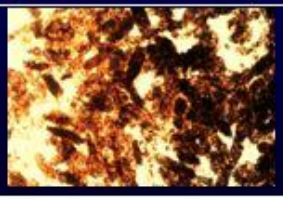
Certain pharmaceutical agents are nephrotoxic and cause acute tubular necrosis when administered at excessive doses or too frequently.

Cisplatin, a platinum containing cancer chemotherapeutic agent, causes tubular necrosis by:

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



Assessing patient with acute renal failure
Urinary Casts

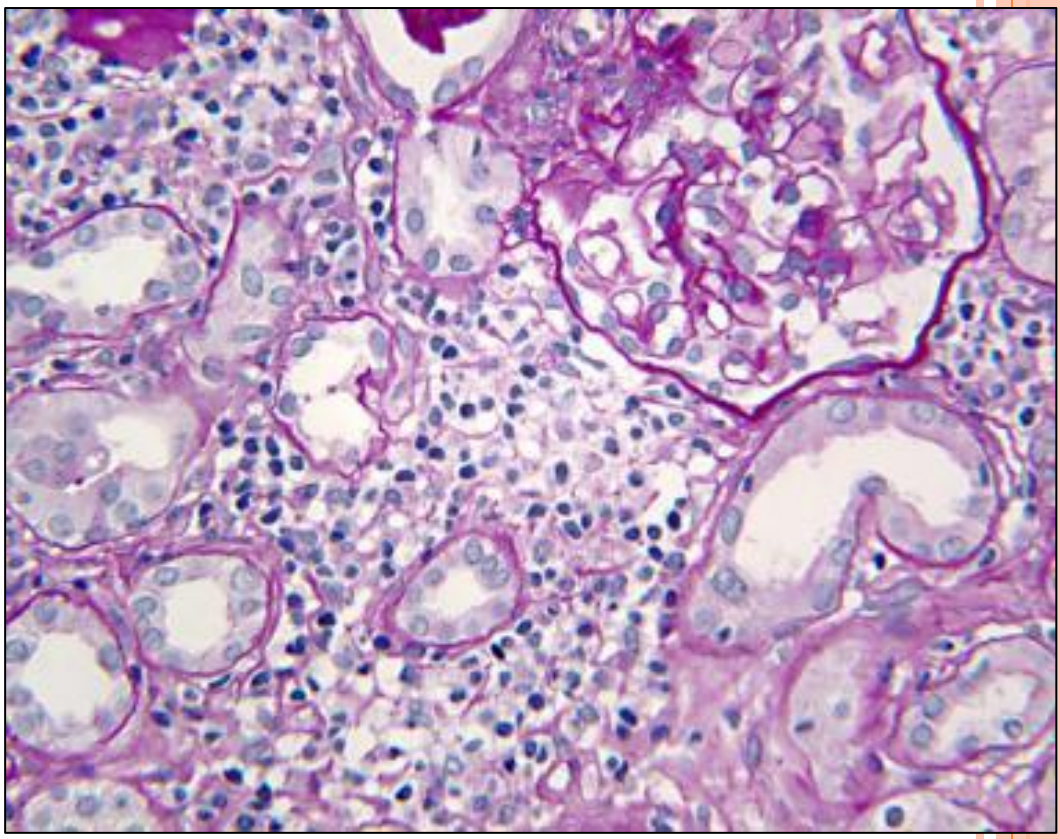
Red cell casts	Glomerulonephritis Vasculitis	
White Cell casts	Acute Interstitial nephritis	
Fatty casts	Nephrotic syndrome, Minimal change disease	
Muddy Brown casts	Acute tubular necrosis	

TUBULOINTERSTITIAL NEPHRITIS

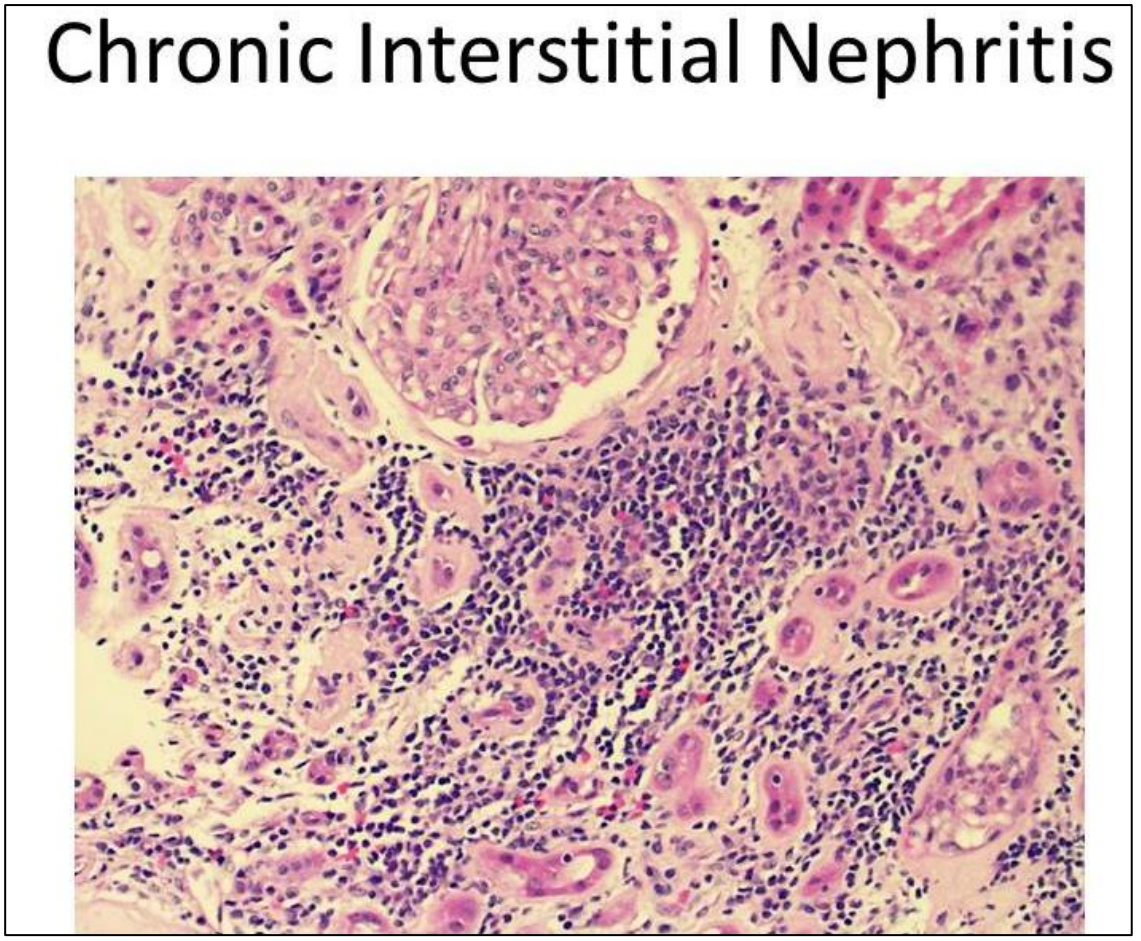
Bacterial infection of the pelvis with tubulointerstitial extension is referred to as pyelonephritis. Because of differences in pathogenesis, lesion distribution, and microscopic appearance, pyelonephritis is considered a separate entity from interstitial nephritis.

While interstitial inflammation, mounted against the veins, arteries, lymphatics, or connective tissues, appears to be the primary lesion, it has traditionally been called interstitial nephritis and may be of infectious or noninfectious cause and 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.

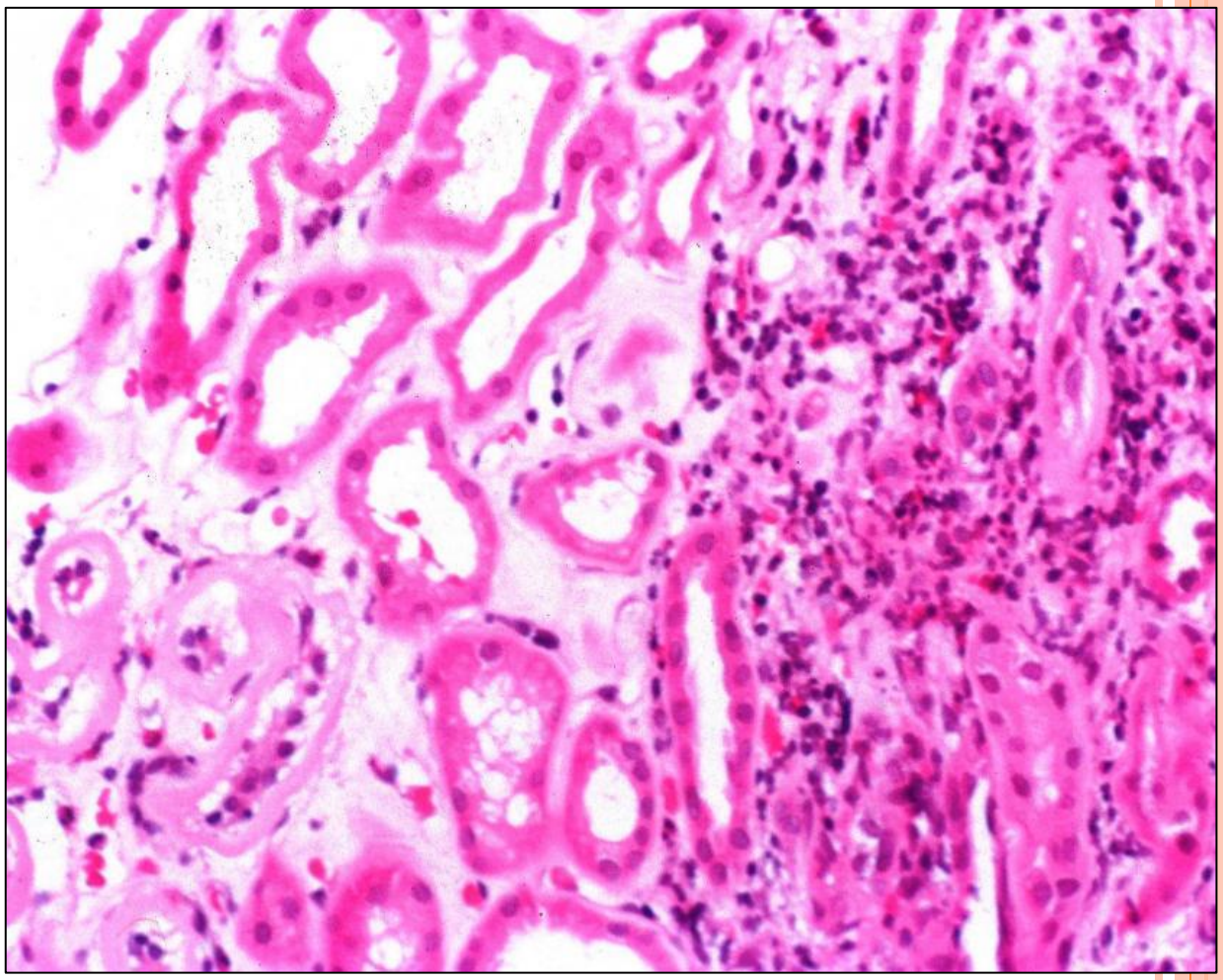


More recently, the term tubulointerstitial nephritis has been used to characterize a group of inflammatory diseases that involve the interstitium and tubules. Acute tubulointerstitial disease includes a group of processes namely, acute tubular necrosis, bilateral renal cortical necrosis, papillary necrosis, and acute interstitial nephritis. Tubulointerstitial nephritis can result .from bacterial or viral septicemias, in which these infectious agents first infect the kidney tubules and then incite an inflammatory response in the interstitium .



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 agents such as leptospira , adenoviruses, or herpesviruses.

Chronic tubulointerstitial nephritis 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, variable degrees of tubular and glomerular atrophy and/or sclerosis, and compromised nephron function.

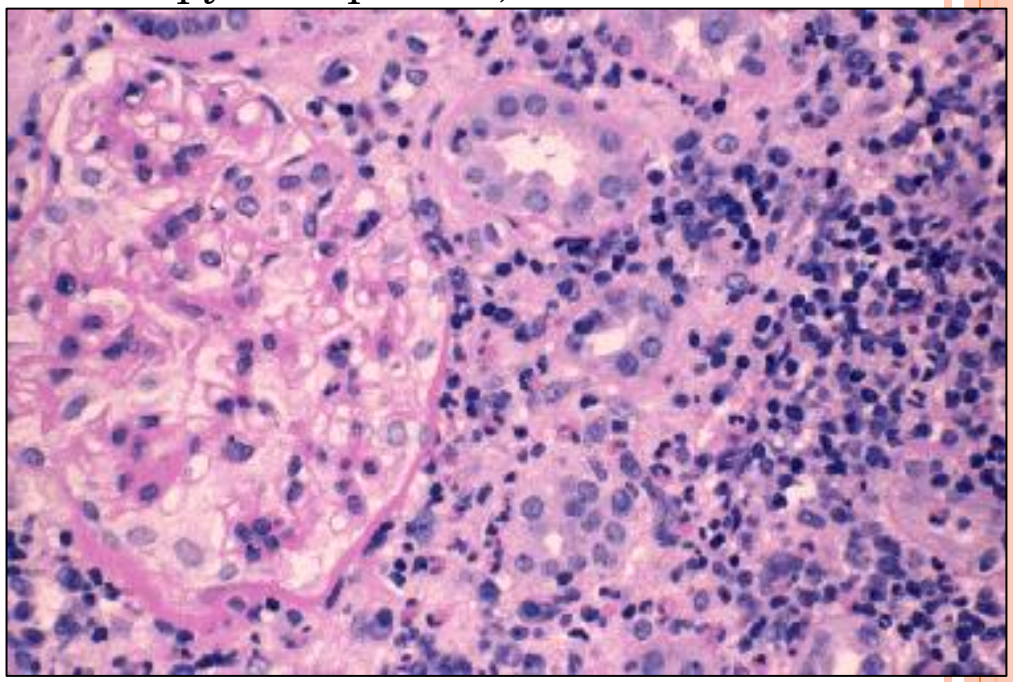


Three theories on the cause of chronic tubulointerstitial nephritis are:

(1) focal acute interstitial nephritis

(2)chronic glomerulonephritis (GN) or chronic pyelonephritis; or

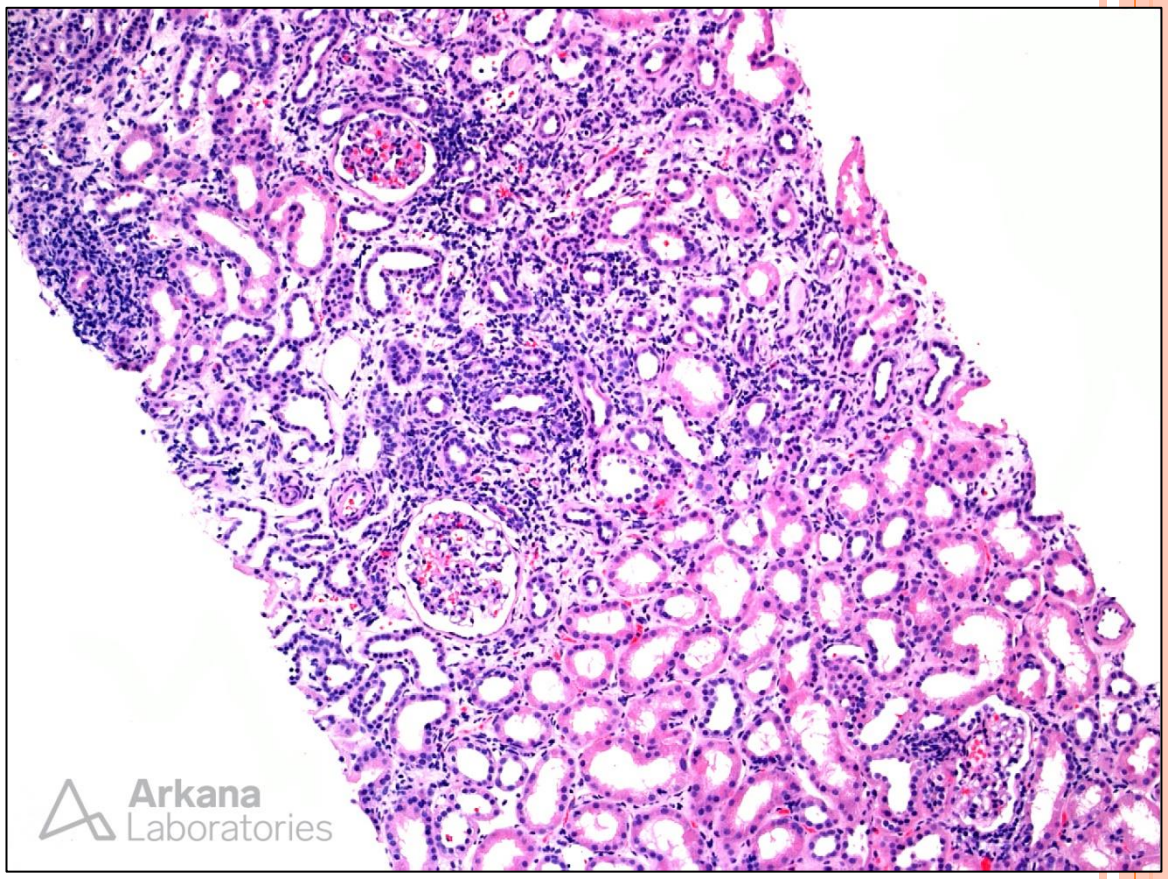
(3) immune-mediated
damage to the renal tubules
And interstitium.



The pathogenesis of leptospirosis:

Following exposure to the organism, leptospiremia occurs and then organisms:

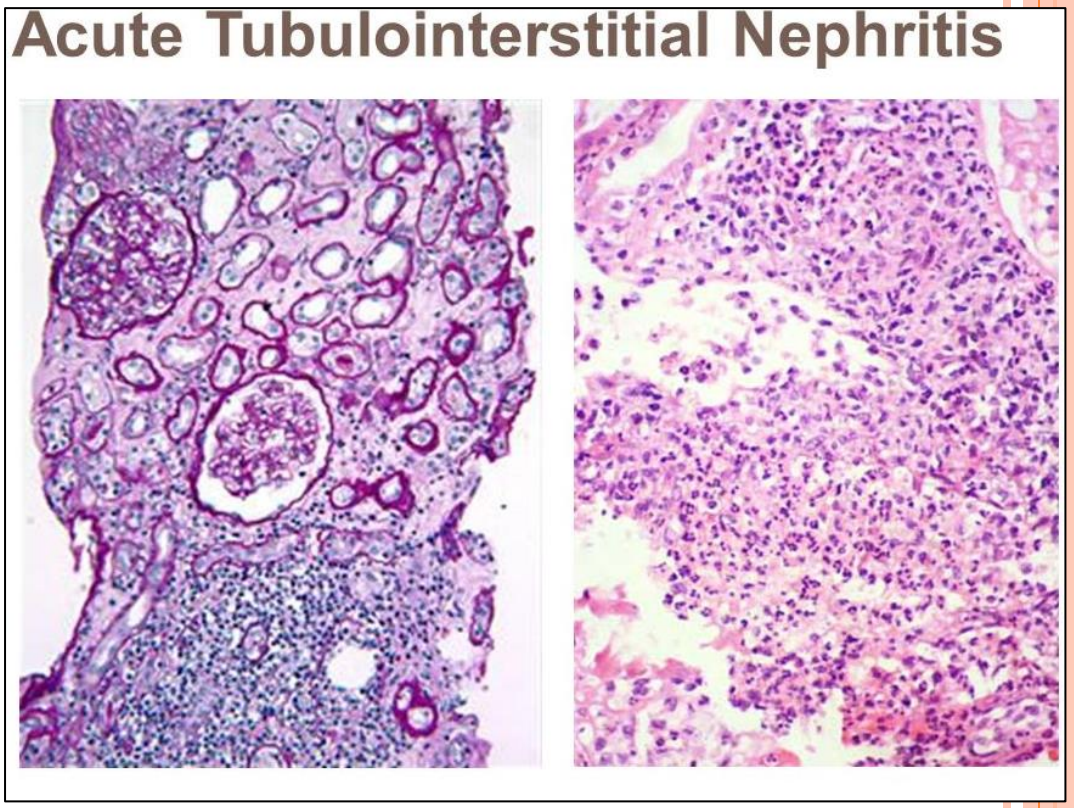
1. Localize in the renal interstitial capillaries
2. Migrate through vascular endothelium
3. Persist in the interstitial spaces
4. Migrate via the lateral intercellular junctions of tubular epithelial cells to reach renal tubular lumina
5. Associate with epithelial microvilli
6. Persist within phagosomes of the epithelium of the proximal and distal convoluted tubules
7. 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



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:

1. Localization of virus in the glomeruli
2. Production of a transient immune-complex glomerulonephritis
3. Recovery from the acute phase
4. Onset of the systemic immune response
5. Disappearance of virus from the glomeruli only to reappear in tubular epithelial cells as basophilic I/N inclusions
6. Persistence of virus in tubular epithelium for weeks to months
7. Production of tubular epithelial necrosis as a result of viral-induced cytolysis
8. Production of chronic lymphocytic, plasmacytic, and less commonly histiocytic interstitial nephritis .

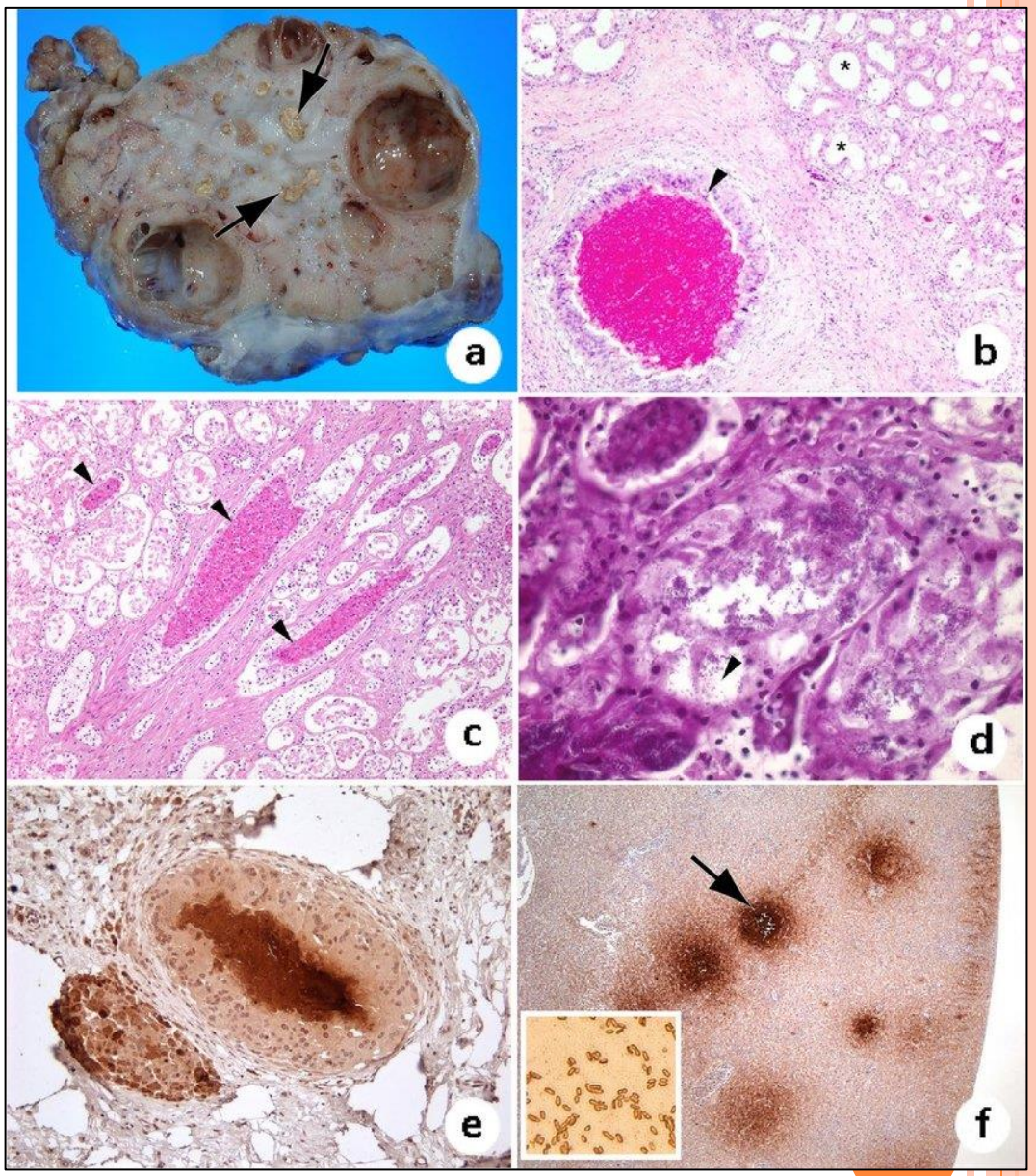


GRANULOMATOUS NEPHRITIS

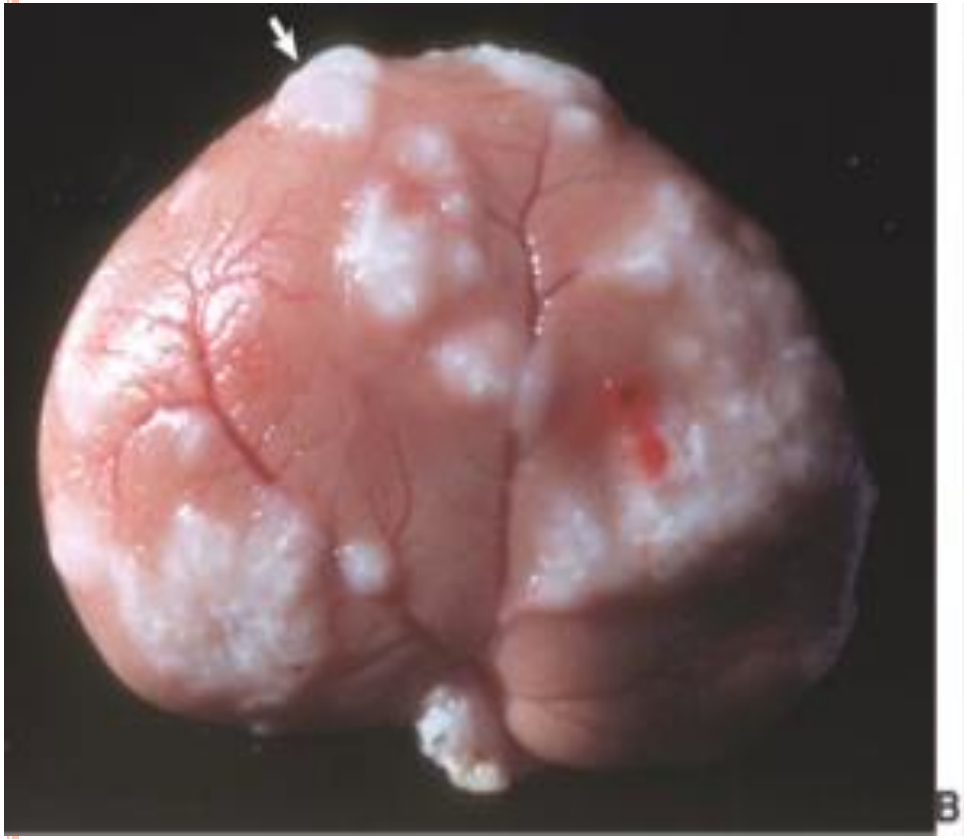
Granulomatous nephritis is a tubulointerstitial disease that often accompanies chronic systemic diseases that are characterized by multiple granulomas in various organs.

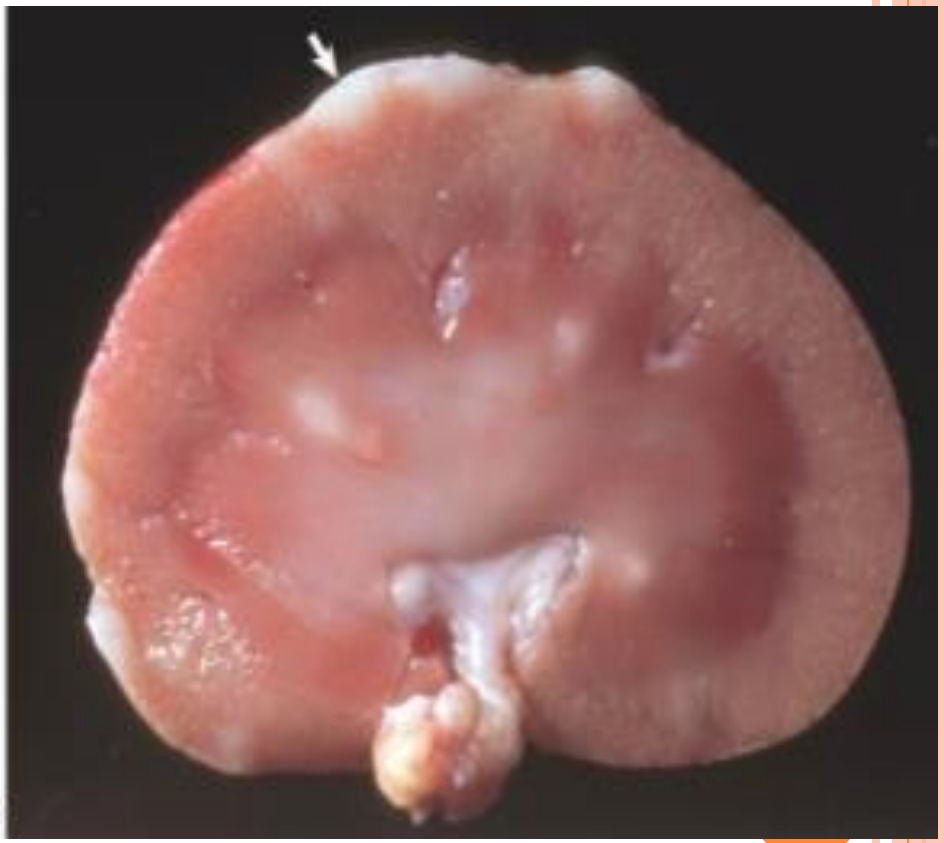
In domestic animals, granulomatous nephritis has been associated with a variety of infectious agents, including viruses (feline coronavirus), bacteria (mycobacteria), fungi (Aspergillus sp.), and parasites (Toxocara sp.).

(a) Extensive fibrosis in the kidney of stranded turtle; note variably sized caseous nodules (granulomas) on cut surface (arrow). (b) Renal granuloma (arrowhead); note core of necrotic material surrounded by macrophages, including multinucleated giant cells, and a broad zone of fibrosis. There is secondary dilation of the surrounding renal tubules (asterisks). (c) Heterophils infiltrate multiple renal tubules (arrowheads). There is detachment of the renal epithelium and other artifacts resulting from autolysis. (d) Numerous gram-negative bacilli (arrowhead) within areas of nephritis from which S. Typhimurium was isolated. (e) Immunohistochemistry staining of renal granuloma with anti-Salmonella antibodies; note brown reactivity at the center of granulomas. (f) Positive control liver from a cattle egret with multifocal necrosis from which S. Typhimurium was cultured; note S. Typhimurium-positive foci (arrow). Inset: Pure culture of S. Typhimurium bacteria staining positive with anti-S. Typhimurium antibody



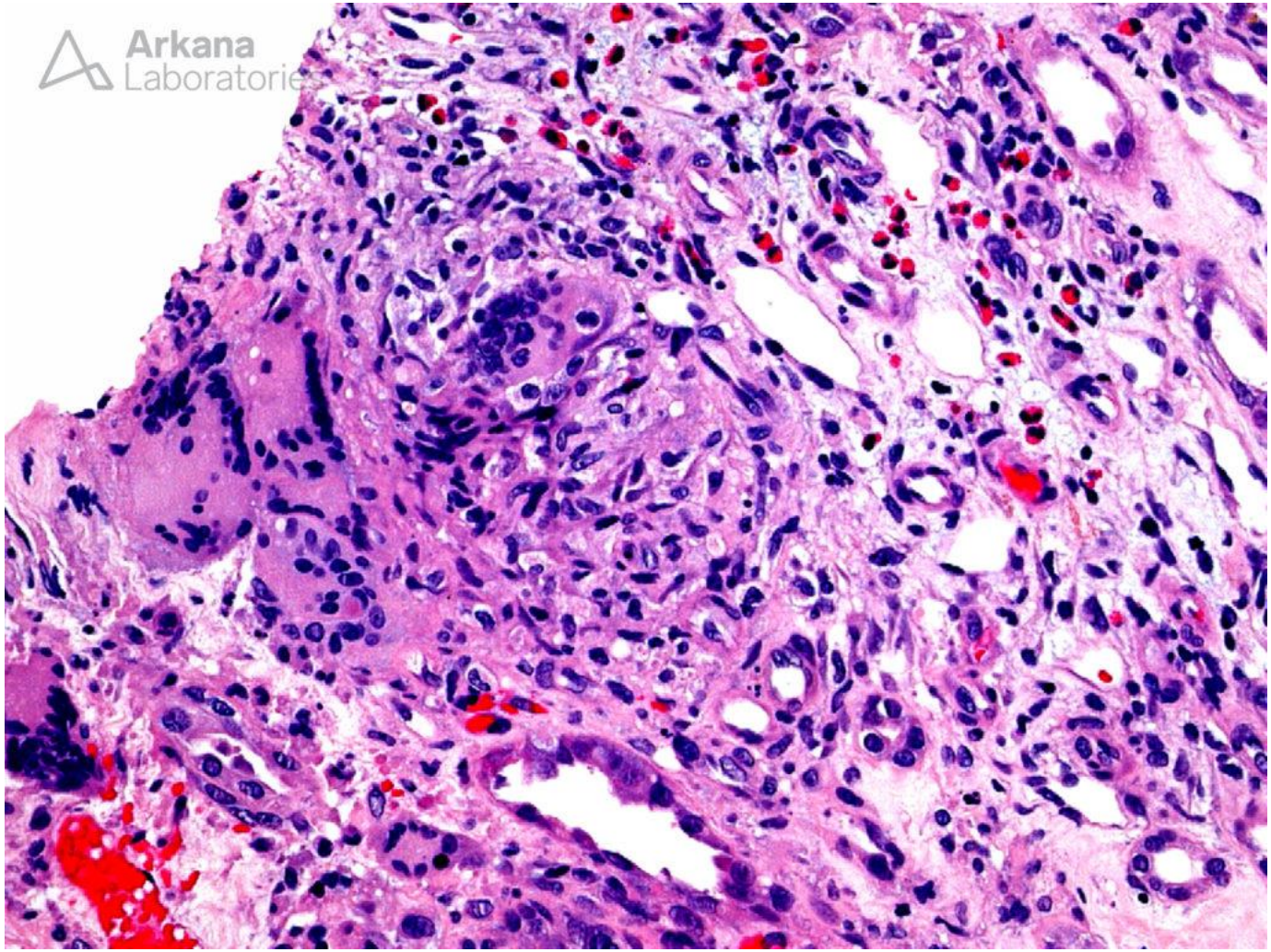
grossly visible granulomas are randomly scattered throughout the kidneys, but especially in the cortex.
The renal lesions are characterized grossly by multiple, large, irregular, pale gray subcapsular cortical foci that are firm and granular on a cut surface.
These lesions are somewhat circumscribed and bulge from the capsular surface.





Microscopically, extensive accumulations of macrophages interspersed with lymphocytes, plasma cells, and neutrophils (pyogranulomas) surround foci of necrotizing fibrinoid vasculitis

lesions are characterized by central foci of necrosis surrounded by epithelioid macrophages, variable minerals, and giant cells that contain acid-fast bacteria.



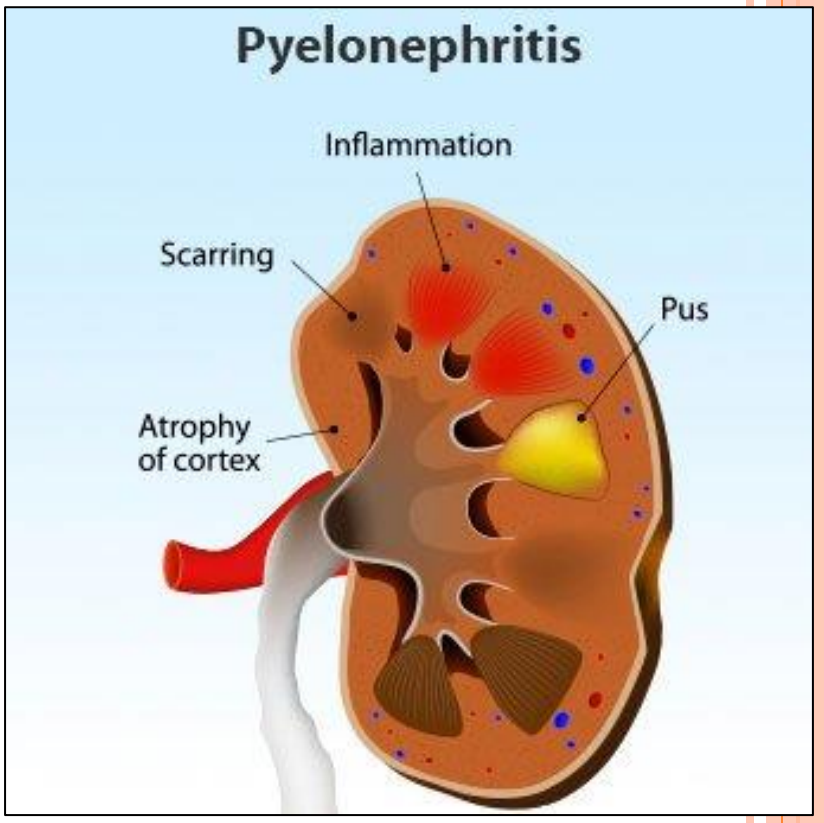
DISEASES OF THE RENAL PELVIS
PYELONEPHRITIS

Although pyelitis refers to inflammation of the renal pelvis, pyelonephritis is inflammation of both the renal pelvis and renal parenchyma and is an excellent example of suppurative tubulointerstitial disease.

Each disease usually originates as an extension of a bacterial infection affecting the lower urinary tract that ascends the ureters to the kidneys and establishes an infection in the pelvis and inner medulla.

Rarely, pyelonephritis can result from descending bacterial infections, wherein bacterial infection of the kidneys occurs via the hematogenous route, that is, 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.



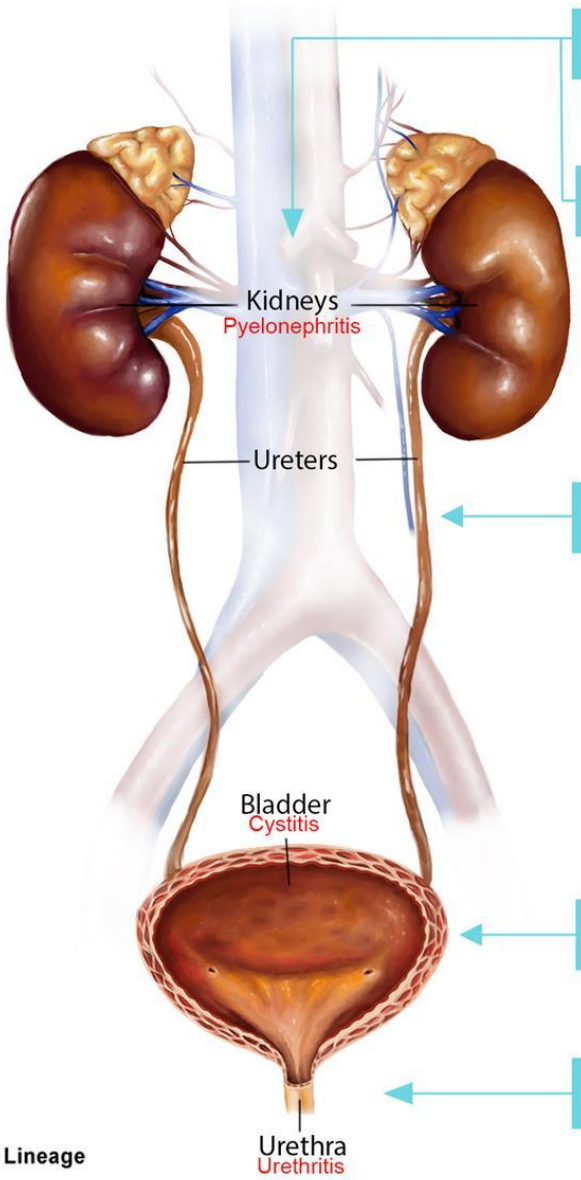
The pathogenesis of ascending pyelonephritis depends on the abnormal reflux of bacteria-contaminated urine from the lower tract to the renal pelvis and collecting ducts (vesicoureteralreflux).

Normally, little vesicoureteral reflux occurs during micturition. Vesicoureteral reflux occurs more readily when pressure is increased within the urinary bladder, as with urethral obstruction.

Bacterial infection of the lower urinary tract can enhance vesicoureteral reflux by several other mechanisms:

1. When the bladder wall is inflamed (cystitis), the normal competency of the vesicoureteral valve can be compromised, allowing greater opportunity for urine to reflux.
2. Endotoxin, liberated from gram-negative bacteria infecting the ureter and bladder, can inhibit normal ureteral peristalsis, increasing reflux.

Pathogenesis of Urinary Tract Infections



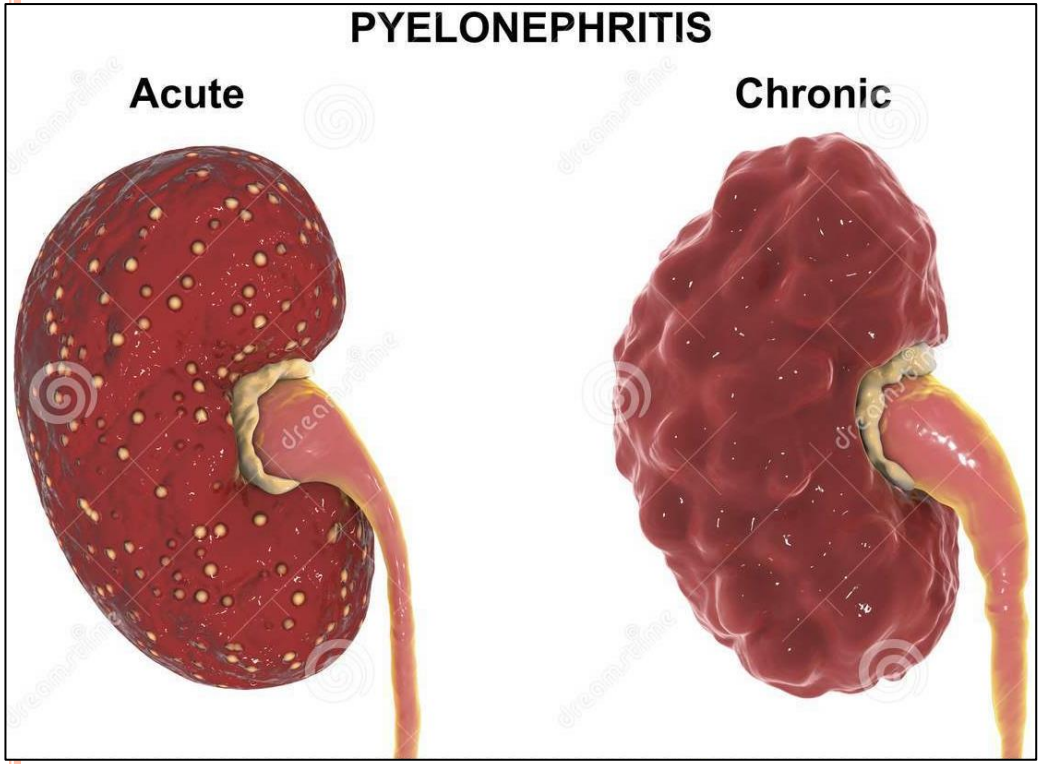
Acute kidney injury
- Continuous inflammatory response results in interstitial edema, interstitial nephritis, and ultimately acute kidney injury (AKI)

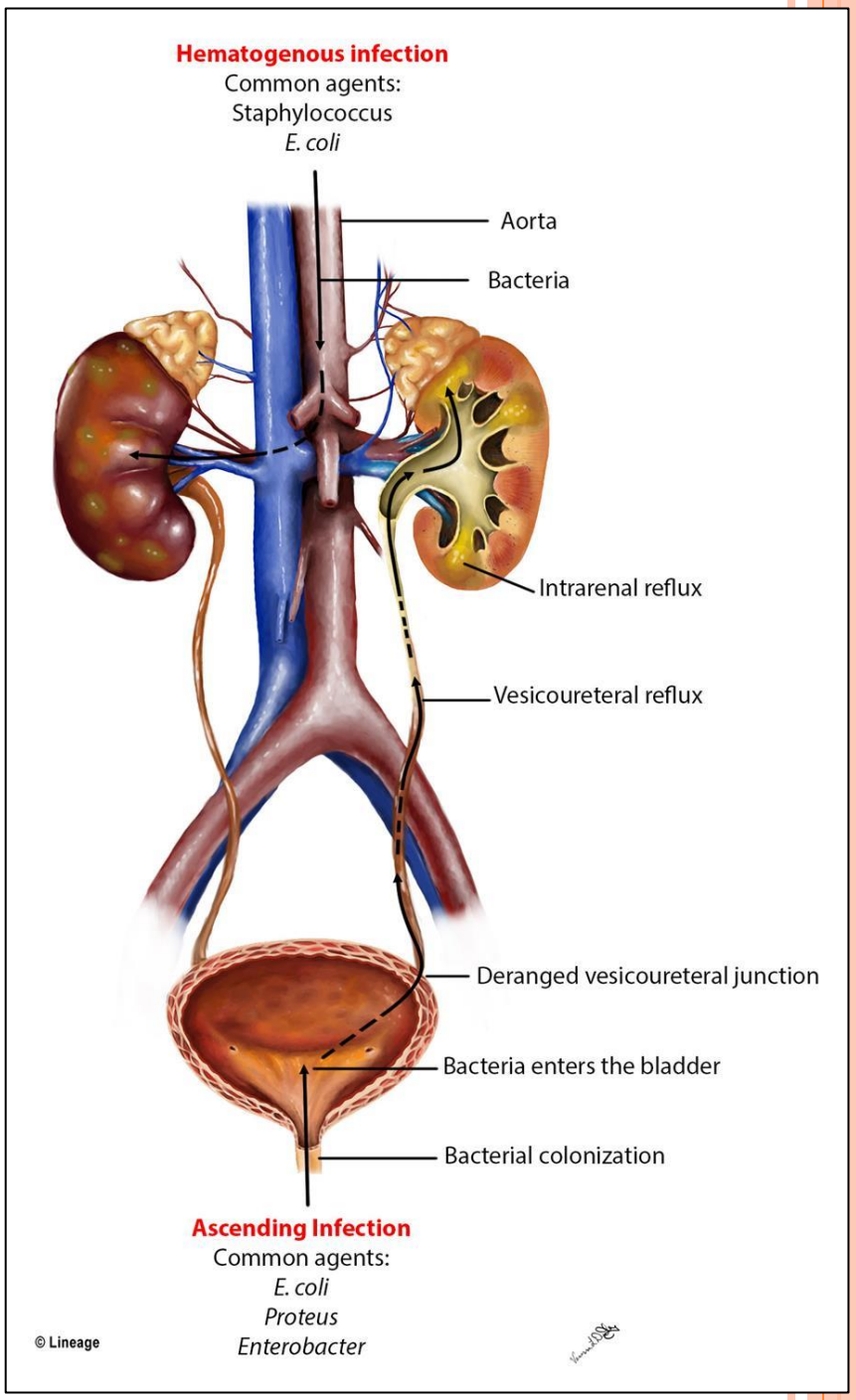
Pyelonephritis
- Bacterial ascension or hematogenous spread infects the renal parenchyma and results in pyelonephritis

Ascension
- Sufficient bacterial colonization can lead to bacterial ascension through the ureters

Uroepithelium penetration
- Bacterial fimbriae allows for attachment and penetration of bladder epithelial cells

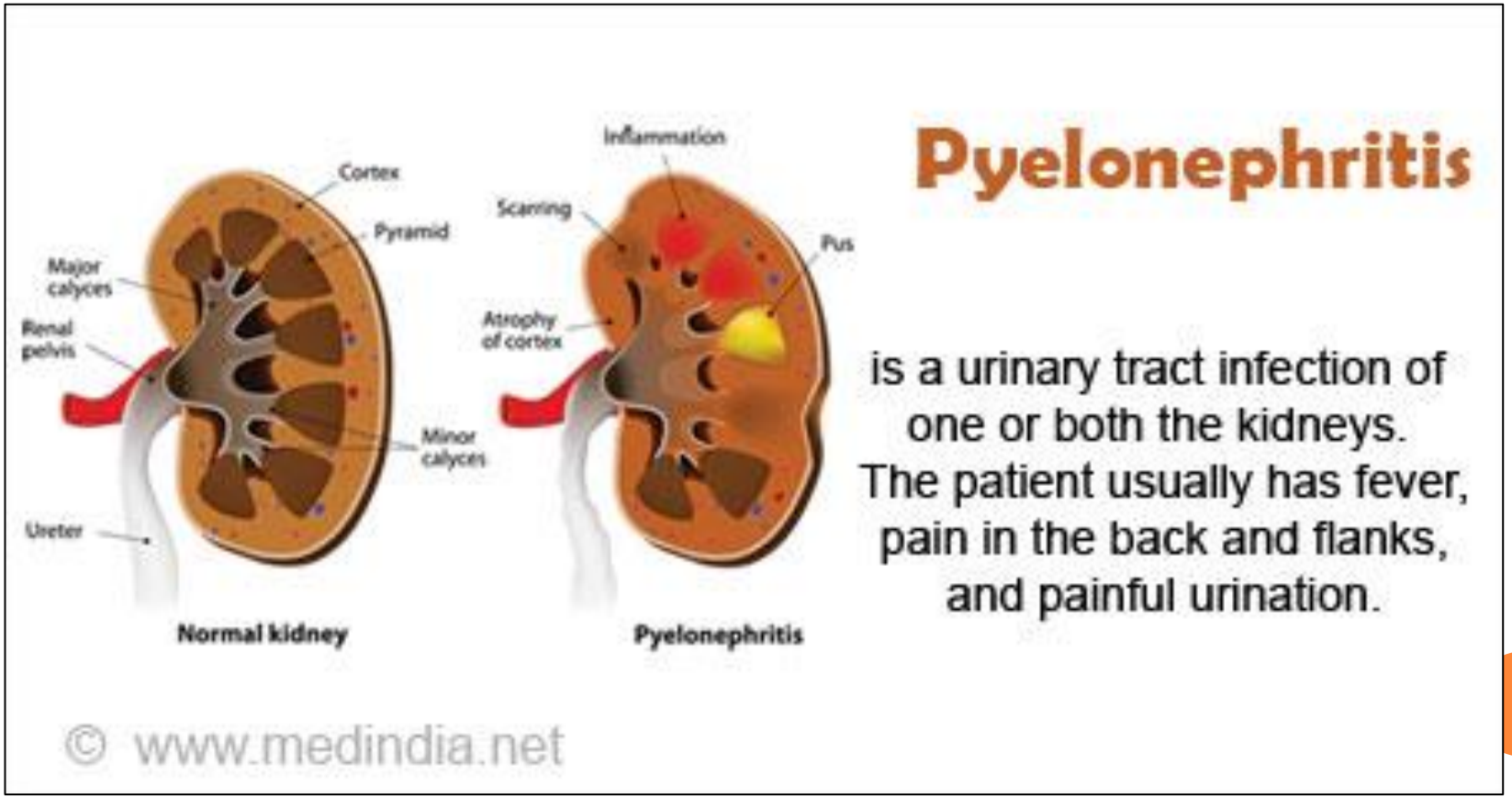
Colonization
- Bacterial colonization in the periurethra allows for ascension via the urethra


PYELONEPHRITIS
Acute
Chronic


Hematogenous infection
Common agents:
Staphylococcus
E. coli
Aorta
Bacteria
Intrarenal reflux
Vesicoureteral reflux
Deranged vesicoureteral junction
Bacteria enters the bladder
Bacterial colonization
Ascending Infection
Common agents:
E. coli
Proteus
Enterobacter
© Lineage

The urinary tract has a number of protective features in place to help prevent bacterial colonization and these include the following:

1. Mucoproteins in the surface urothelial mucosal lining that prohibit bacterial adherence.
2. Sloughing of superficial urothelial cells to minimize surface colonization
3. Goblet cell metaplasia
4. Phagocytosis by superficial mucosal urothelial cells

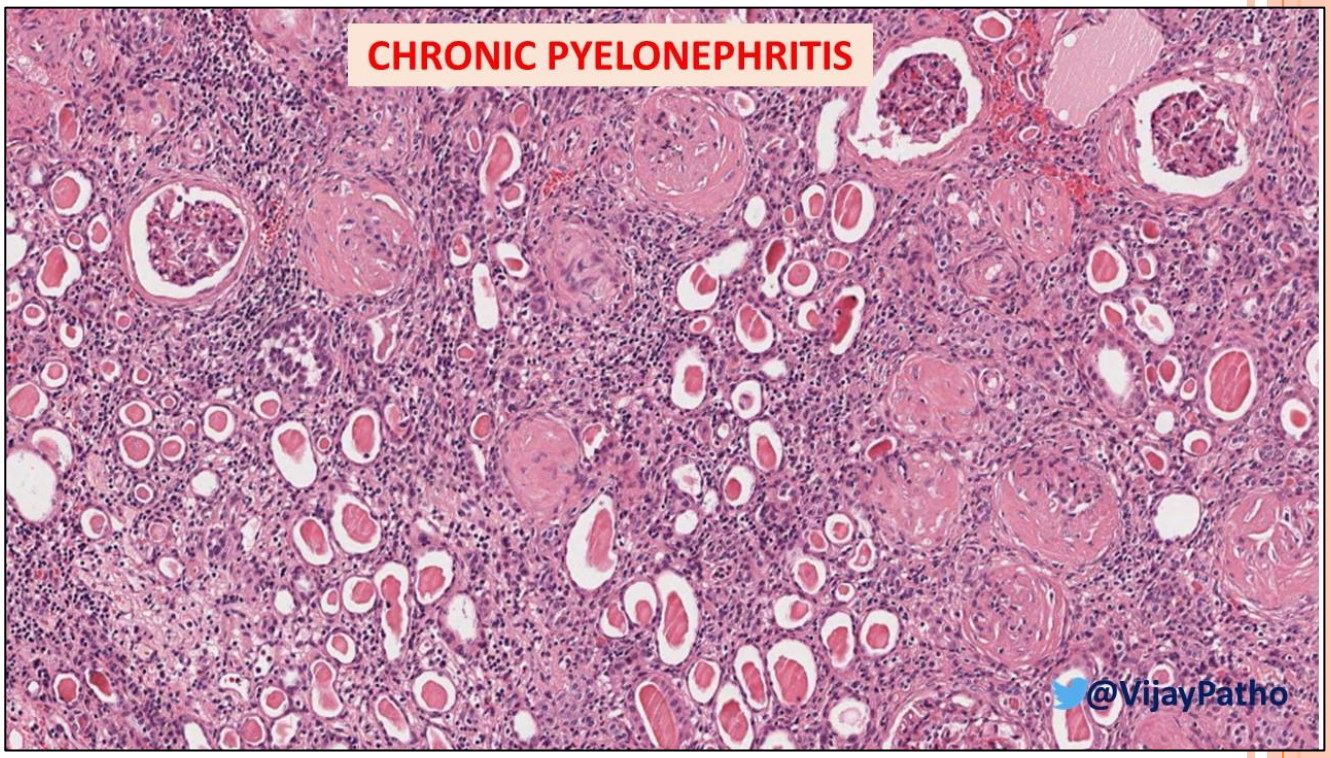


Bacteria that colonize the pelvis can readily infect the inner medulla. The medulla is highly susceptible to bacterial infection because of the following:

1. Its poor blood supply
2. Its great interstitial osmolality that inhibits neutrophil function
3. Its large ammonia concentration that inhibits complement activation.

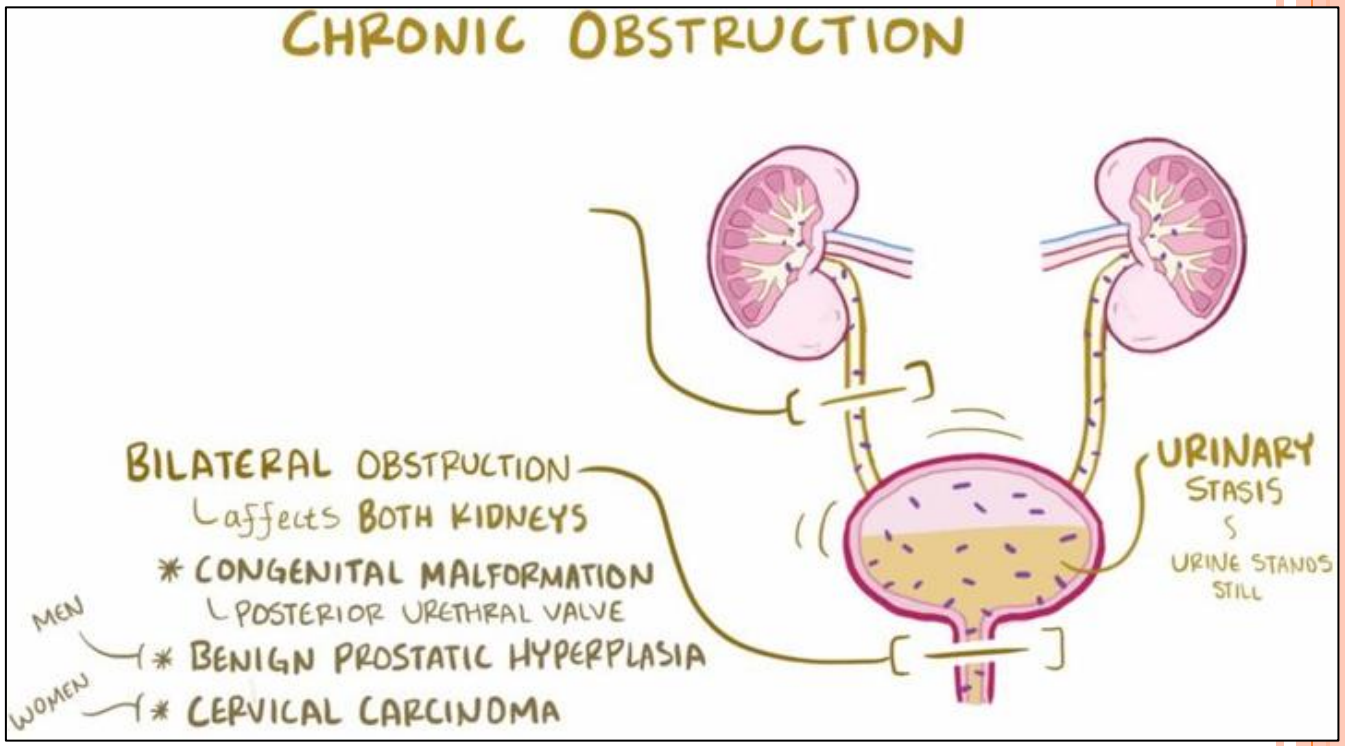
Thus bacteria can infect and ascend collecting ducts, cause tubular epithelial necrosis and hemorrhage, and incite a notable inflammatory response.
Bacterial infection can progressively ascend within tubules and the interstitium until the inflammatory lesions extend from pelvis to capsule.

Chronic pyelonephritis may result from infection superimposed on conditions that result in recurrent obstructive disease or reflux (reflux nephropathy).
Recurrent infections lead to recurrent bouts of inflammation that result in 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 a-hemolysin, adhesins, and P fimbria, is one of the most common causes of lower urinary tract disease and pyelonephritis. Proteus sp., Klebsiella sp., Staphylococcus sp., Streptococcus sp., and Pseudomonas aeruBinosa are also common causes of lower urinary tract infection and pyelonephritis in all species. Corynebacterium renale and Eubacterium (Corynebacterium) suis are specifically pathogenic for the lower urinary tract of cattle and pigs, respectively, and are common causes of pyelonephritis. Recent or multiple catheterizations may be a predisposing factor.

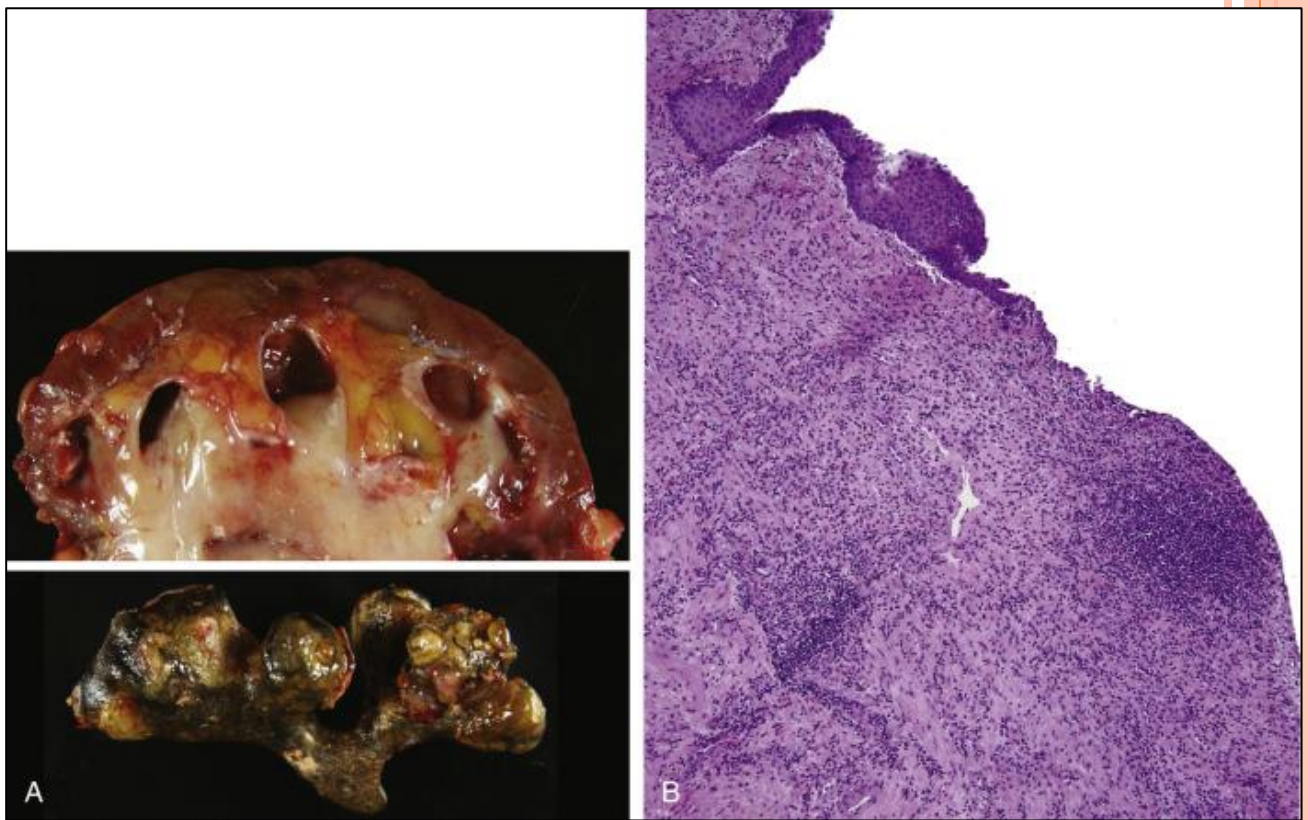


A gross diagnosis of pyelonephritis is accomplished by recognizing the existence of pelvic inflammation with extension into the renal parenchyma .

Pyelonephritis can be unilateral, but it is often bilateral and most severe at the renal poles.

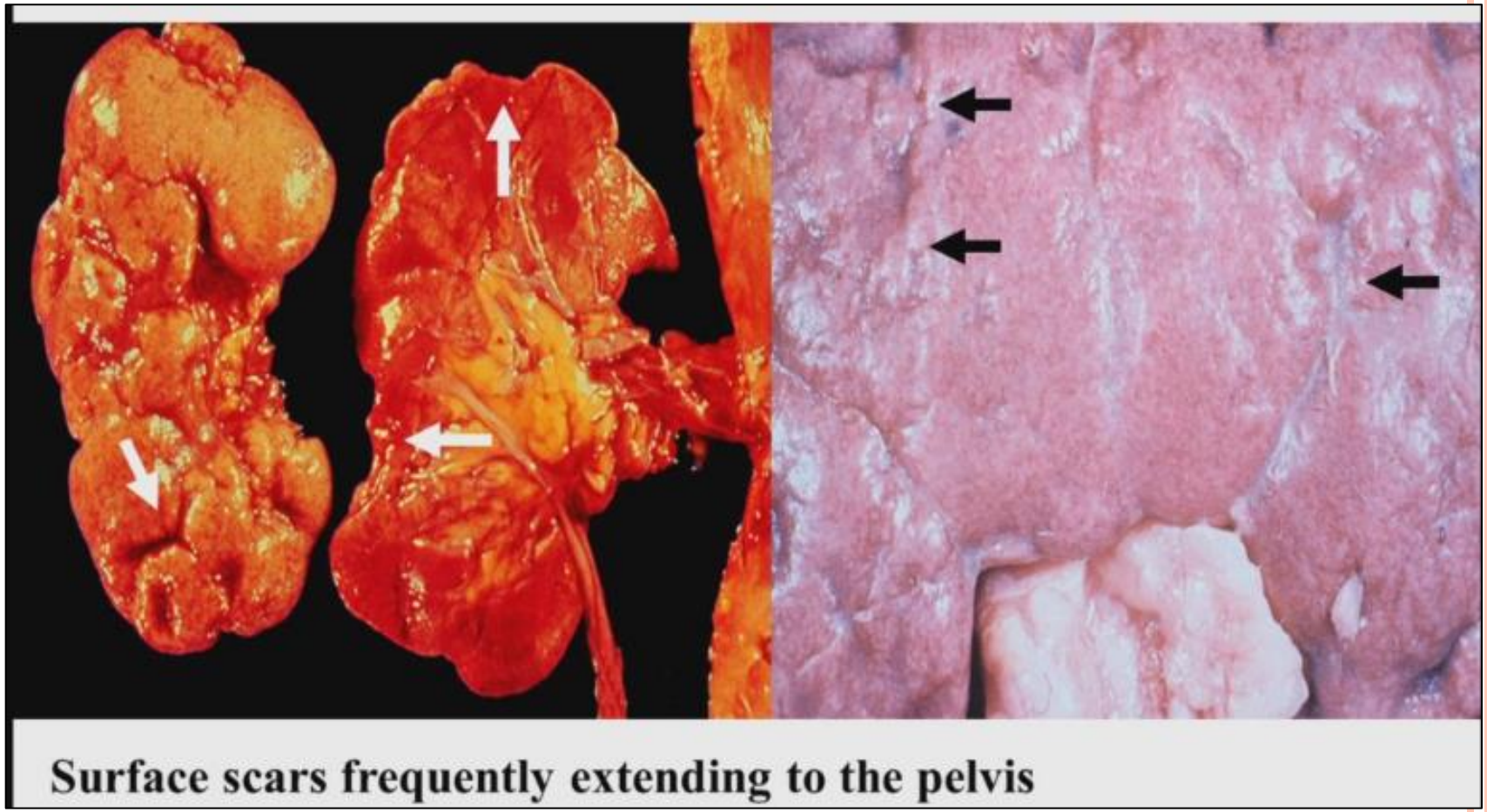
The pelvic and ureteral mucous membranes can be acutely inflamed, thickened, reddened, roughened or granular, and coated with a thin exudate. The pelvis and ureters can be markedly dilated and have purulent exudate in the lumina.

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 .



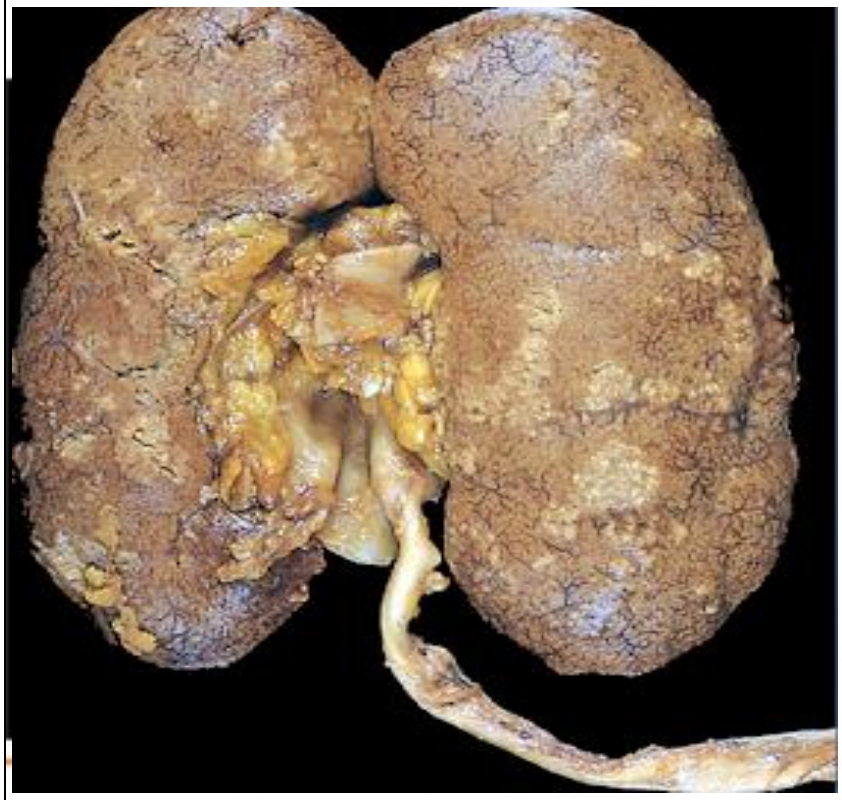
Occasionally, inflammation extends through the surface of the kidneys to produce extensive subcapsular inflammation and localized peritonitis. The renal lesions of chronic pyelonephritis, in which an active bacterial infection exists, include most of the elements of acute inflammation described previously 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.

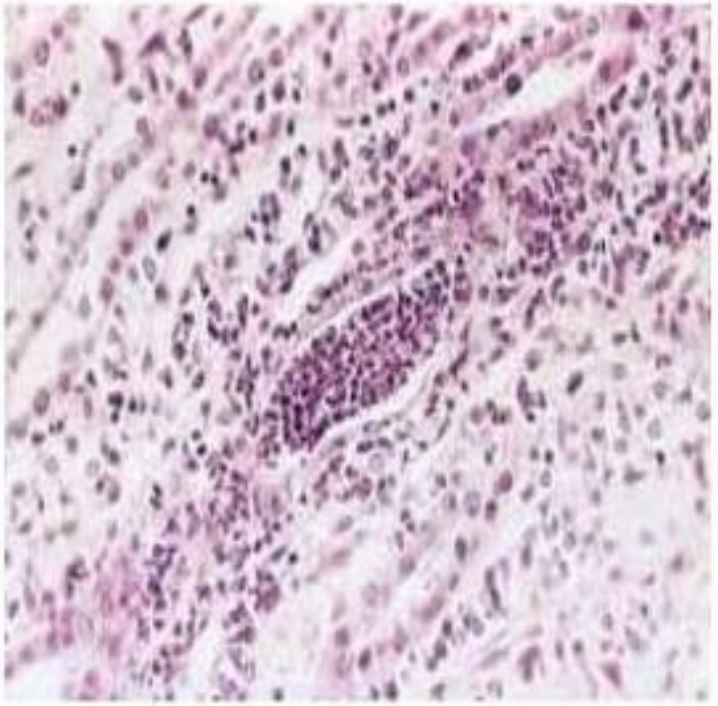


Surface scars frequently extending to the pelvis

ACUTE PYELONEPHRITIS



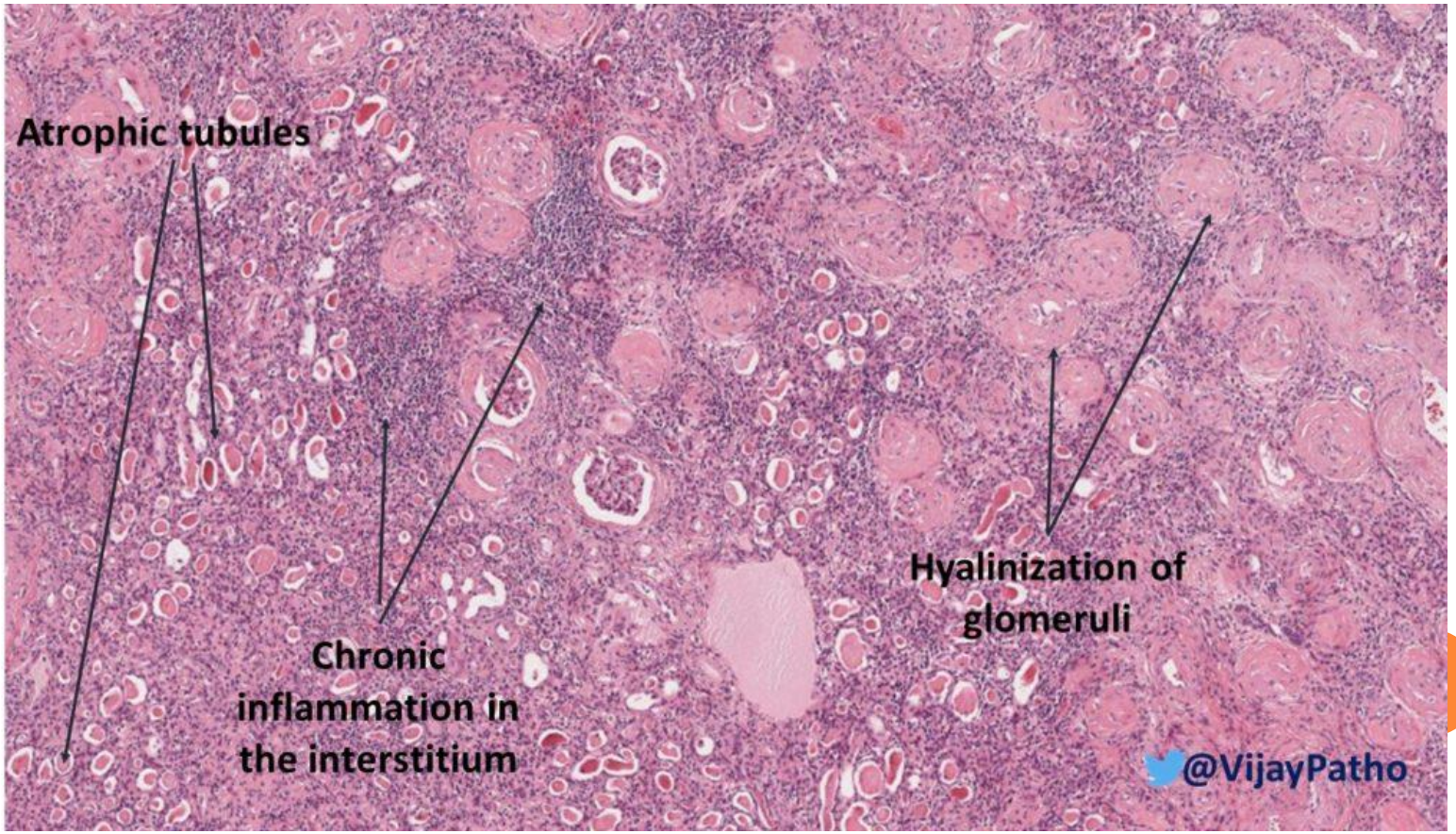
Cortical surface exhibits grayish white areas of inflammation and abscess formation

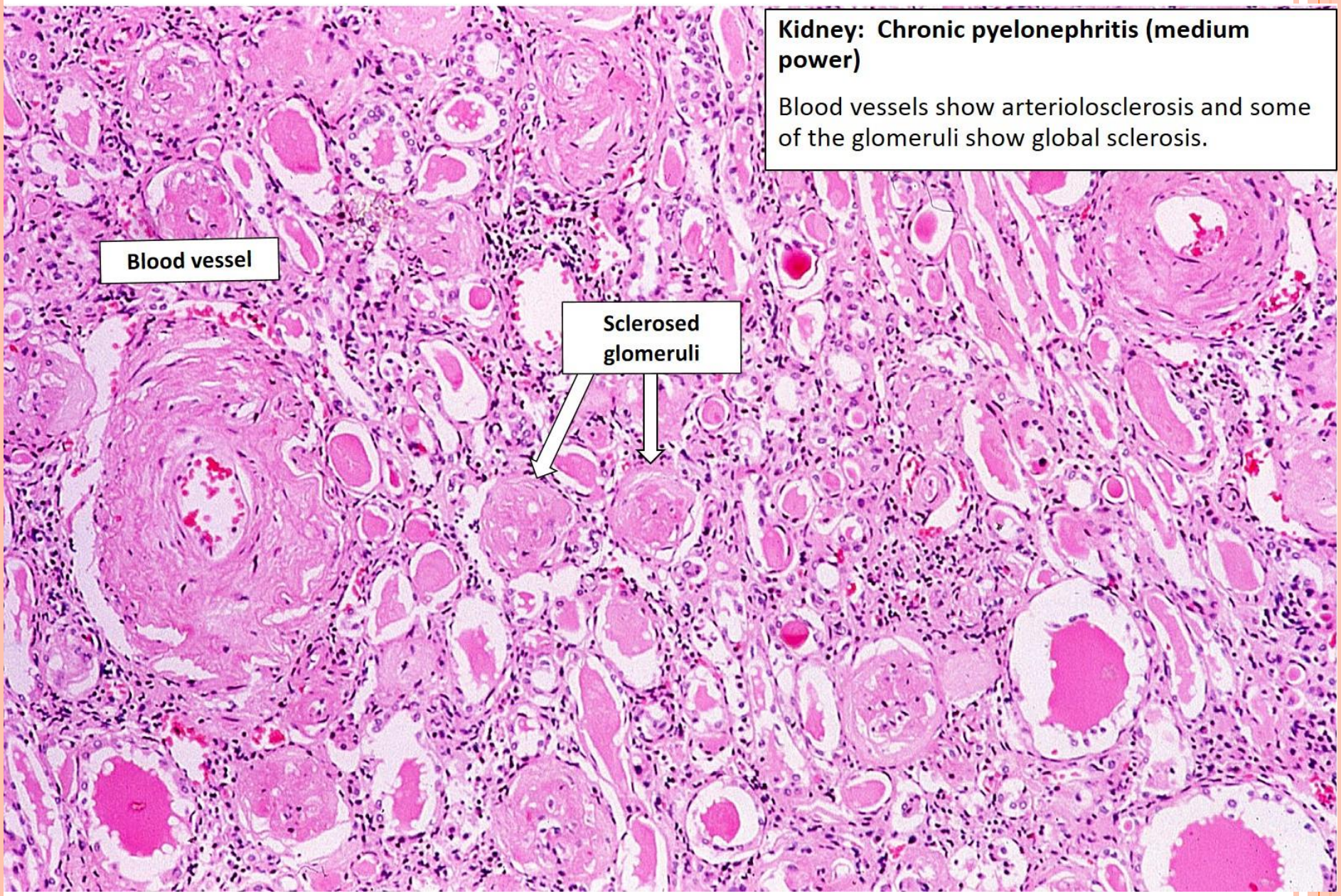


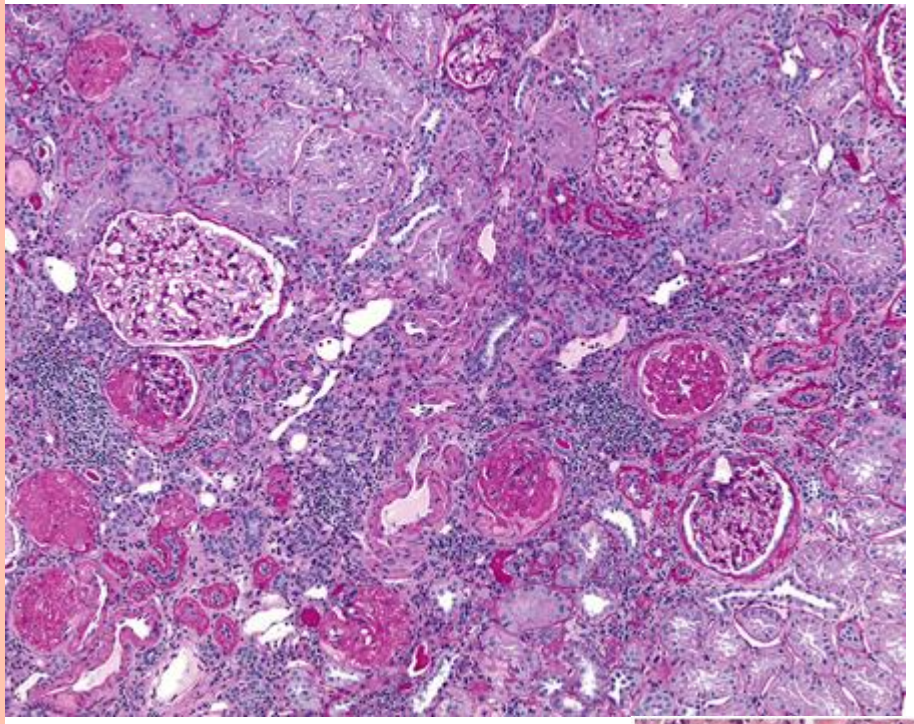
Acute pyelonephritis marked by an acute neutrophilic exudate within tubules and the renal substance.

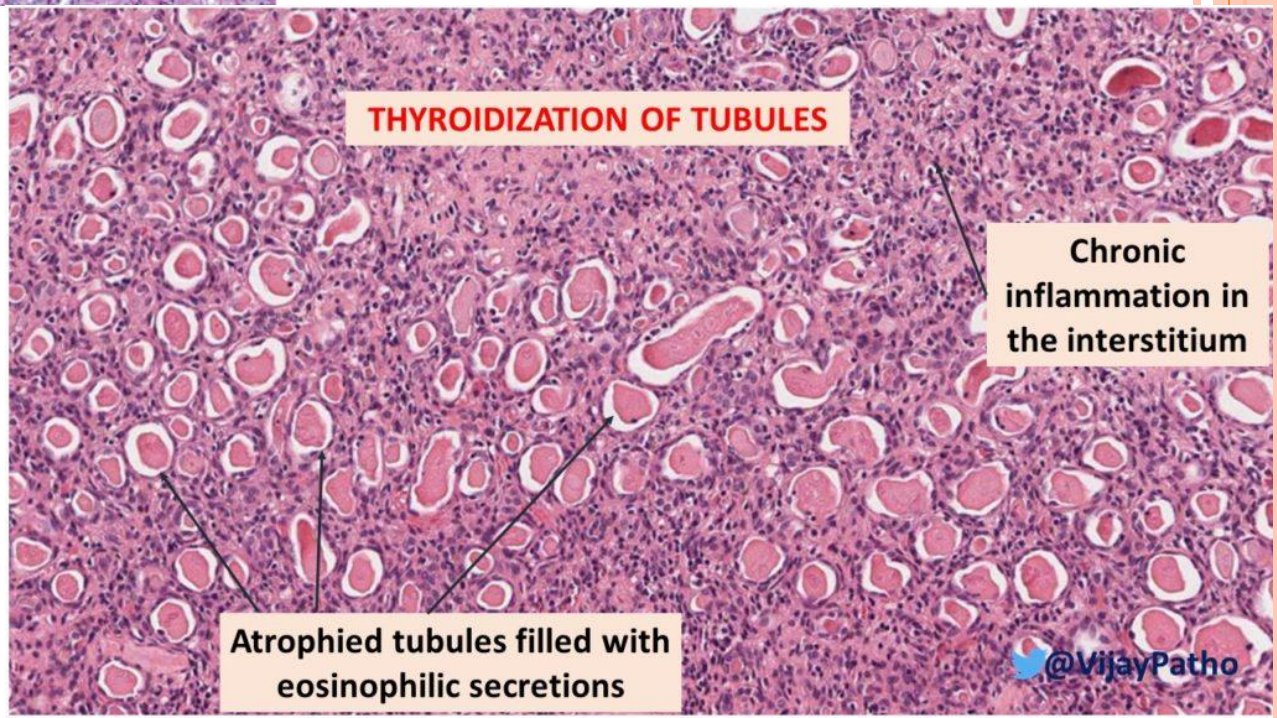
Microscopically the most severe acute lesions of pyelonephritis are usually in the inner medulla. The transitional epithelium is usually focally or diffusely necrotic and desquamated. Necrotic debris, fibrin, neutrophils, and bacterial colonies can be adherent to the denuded surface.

Medullary tubules are notably dilated, and their lumina contain neutrophils and bacterial colonies. Focally the tubular epithelium is necrotic. An intense neutrophilic infiltrate, present in the renal interstitium, can be accompanied by notable interstitial hemorrhages and edema . Chronic lesions have severe fibrosis.




Kidney: Chronic pyelonephritis (medium power)
Blood vessels show arteriolosclerosis and some of the glomeruli show global sclerosis.
Blood vessel
Sclerosed glomeruli




THYROIDIZATION OF TUBULES
Chronic inflammation in the interstitium
Atrophied tubules filled with eosinophilic secretions
@VijayPatho

HYDRONEPHROSIS

Hydronephrosis refers to dilation of the renal pelvis because of obstruction of urine outflow and is principally caused by a slow or intermittent increase in pelvic pressure.

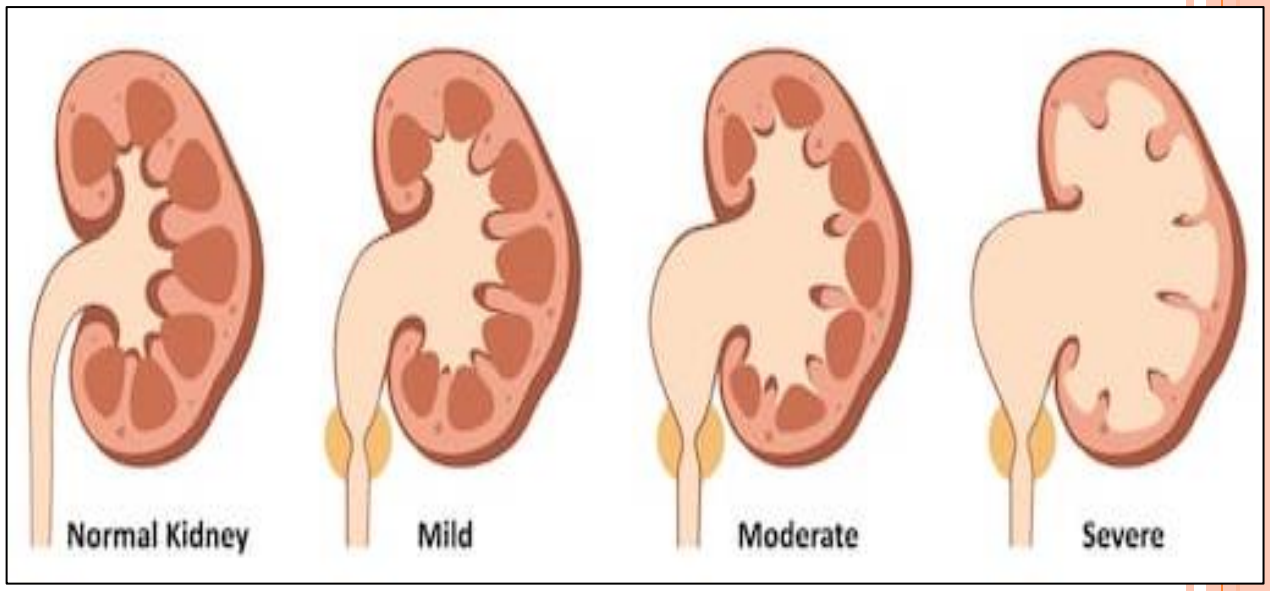
Abrupt increases in pressure, such as those associated with inadvertent surgical ligation of a ureter, more commonly result in a decline in filtration rate in the affected kidney and a lesser propensity to develop hydronephrosis.

Obstruction leading to hydronephrosis can occasionally be caused by congenital malformation of the ureter, vesicoureteral junction, or urethra or from congenitally malpositioned kidneys with secondary kinking of the ureter.

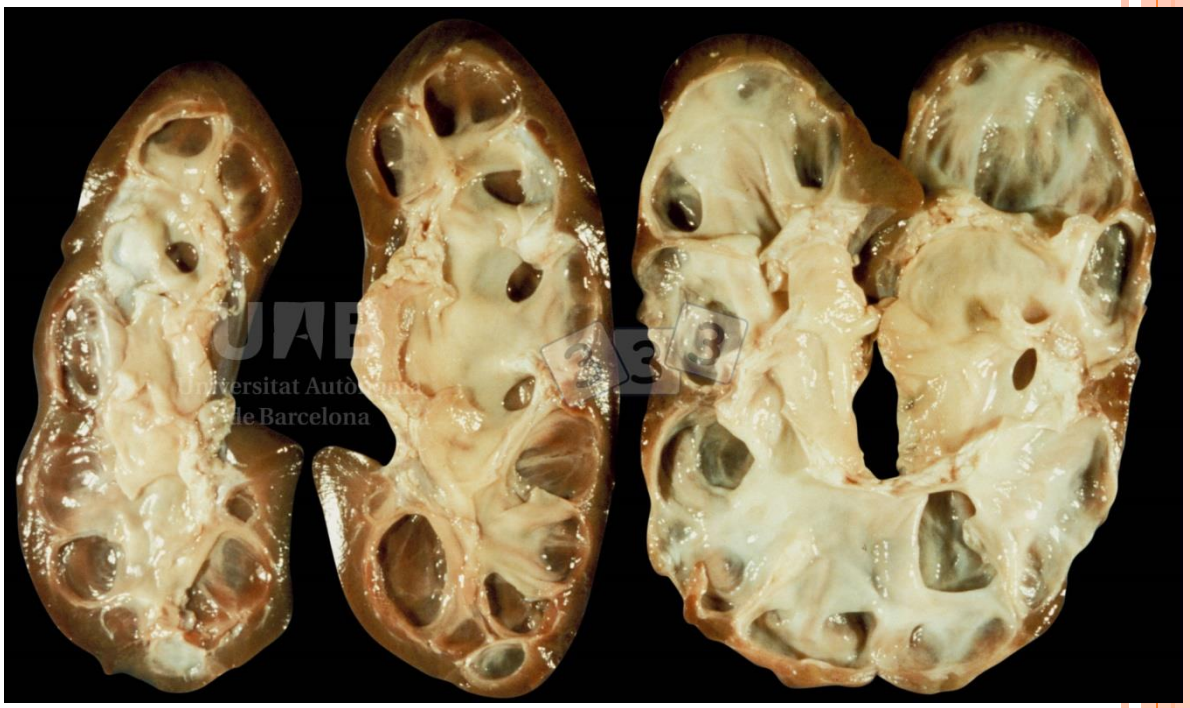
The more common causes of hydronephrosis are as follows:

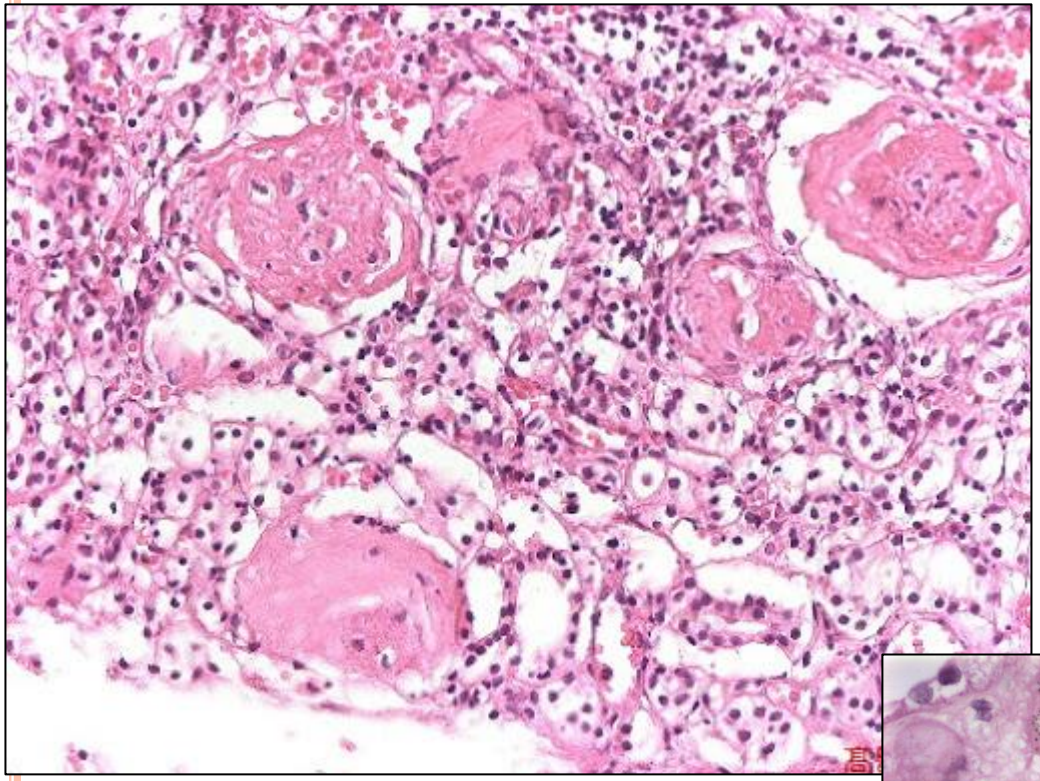
1. Ureteral or urethral blockage due to urinary tract calculi.
2. Chronic inflammation
3. Ureteral or urethral neoplasia
4. Neurogenic functional disorders

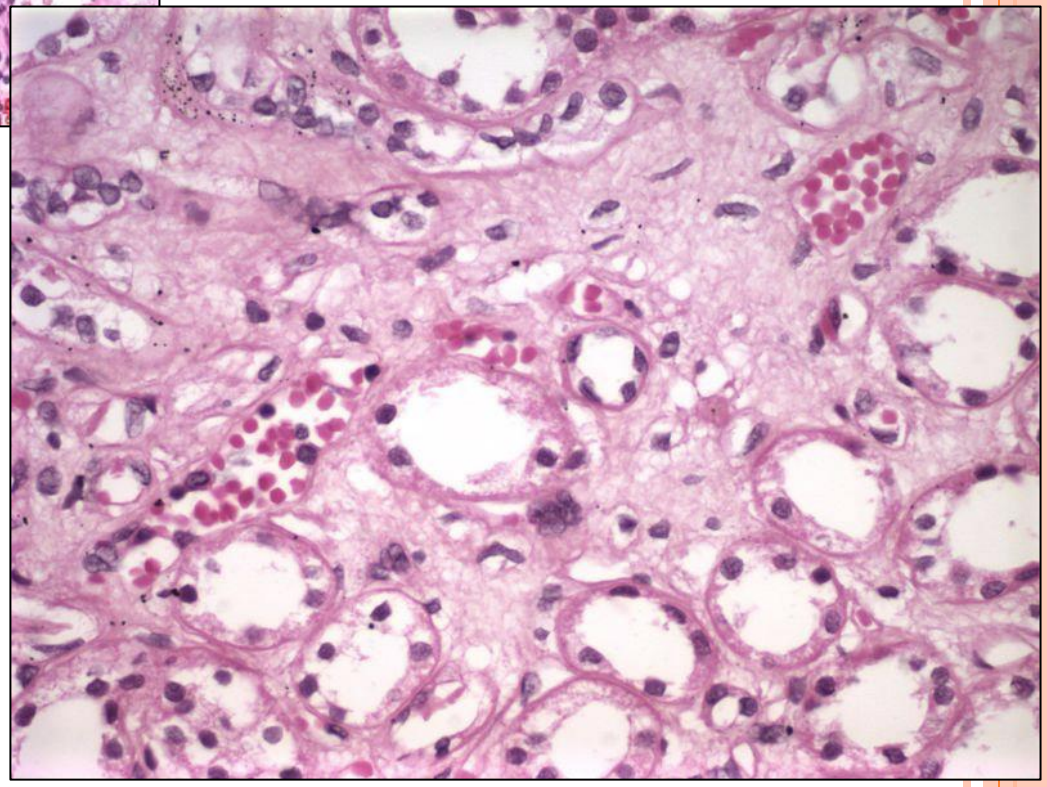
Hydronephrosis occurs in all domestic animals. Depending on the location of the obstruction, hydronephrosis can be unilateral (ureteral) or bilateral.



Early changes of hydronephrosis include dilation of the pelvis and when pelvic dilation is progressive, the kidney is enlarged and rounder than normal.
Interstitial vascular obstruction from compression produces an expanding front of medullary and later cortical ischemia and necrosis. The 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-thick), fluid-filled sac. This sac is lined by flattened transitional epithelium. Occasionally, a severely hydronephrotic kidney becomes contaminated by bacteria and the thin-walled sac becomes filled with pus instead of urine. This lesion, referred to as **pyonephrosis**, is likely the result of blood-borne bacteria lodging in a hydronephrotic kidney.







CIRCULATORY DISTURBANCES

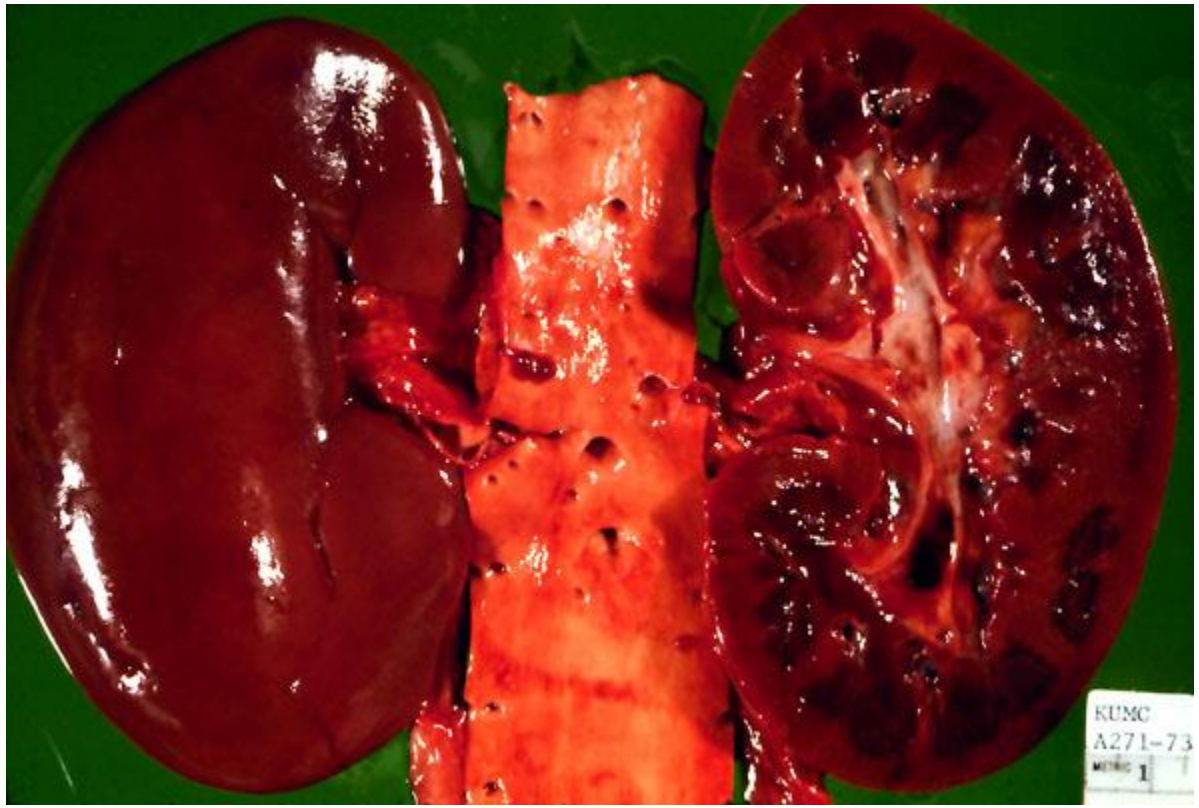
HYPEREMIA AND CONGESTION

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:

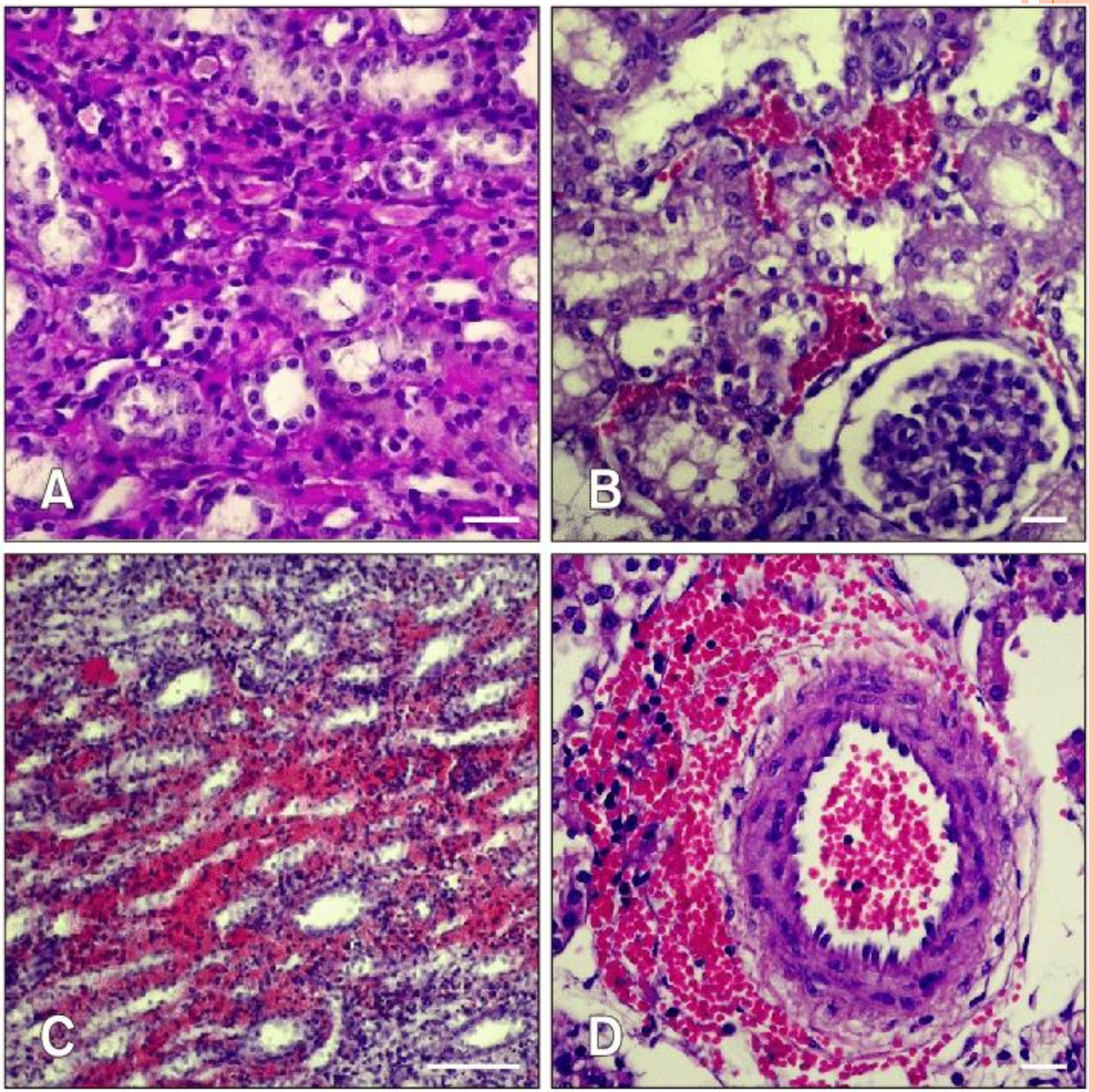
1. Physiologic
2. Passive
3. Secondary to hypovolemic shock
4. Secondary to cardiac insufficiency
5. Hypostatic



Hyperemic kidneys are darker red than normal, swollen, and ooze blood from the cut surface. Congested kidneys are dark purple and ooze blood from the cut surface due to the accumulation unoxygenated blood in the renal venous system.

At necropsy, unilateral renal hypostatic congestion is present in animals that die in lateral recumbency, following 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

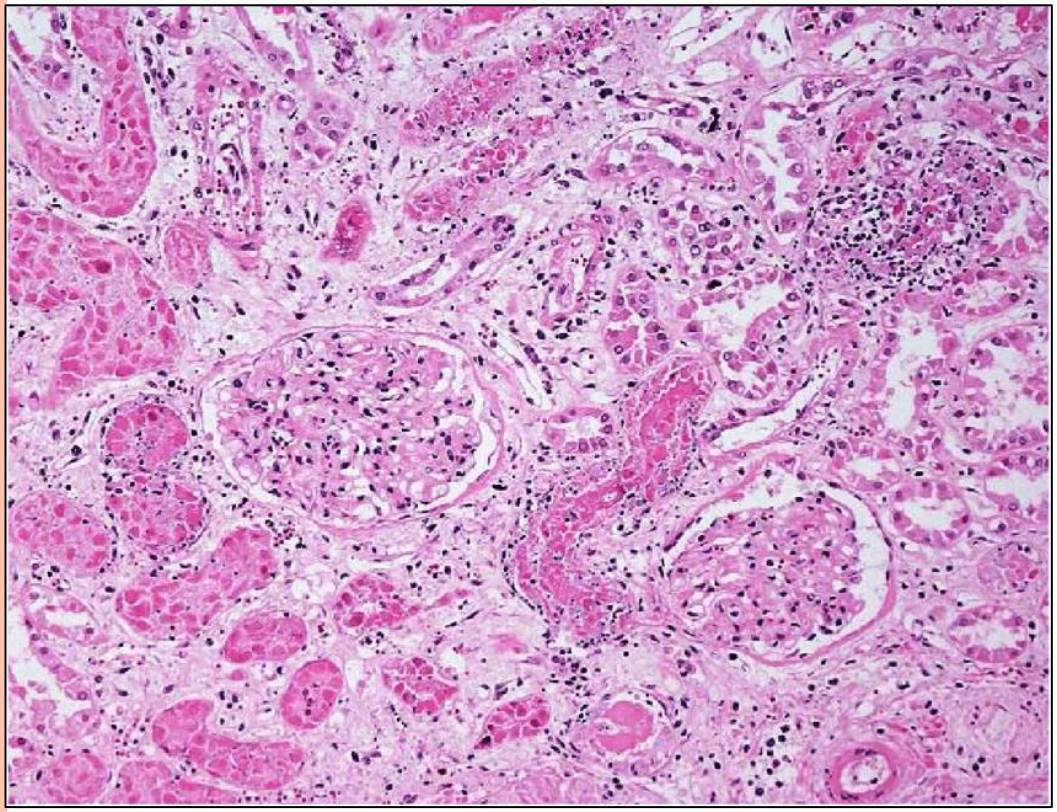


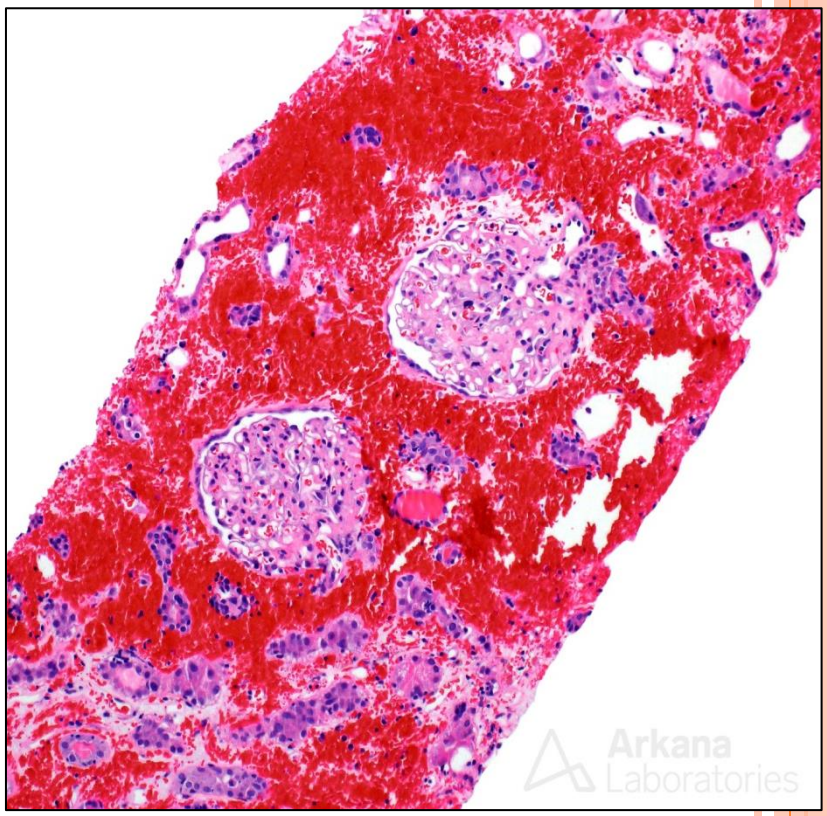
Edema (A), congestion (B), hemorrhage (C) and hyperemia (D)

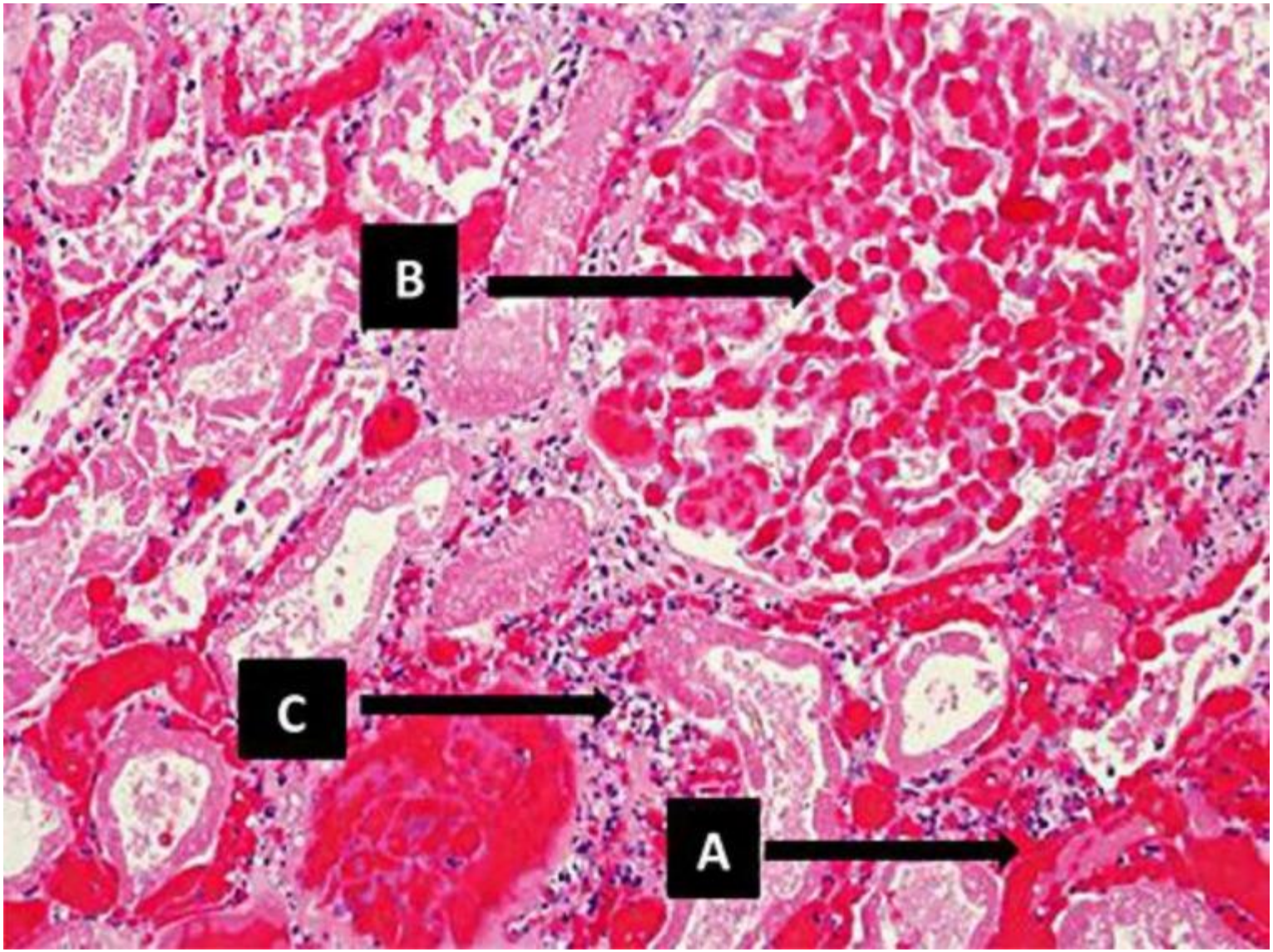
HEMORRHAGE AND THROMBOSIS

Hemorrhage occurs when red blood cells extend beyond the vessel walls, it can result from direct trauma, renal biopsy, and systemic bleeding disorders. Subcapsular and renal cortical hemorrhages occur in association with septicemic diseases, vasculitis, vascular necrosis, thromboembolism.

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), erysipelas, streptococcal infections, salmonellosis, and other embolic bacterial diseases . Valvular endocarditis can predispose to renal thromboembolic damage in any species.





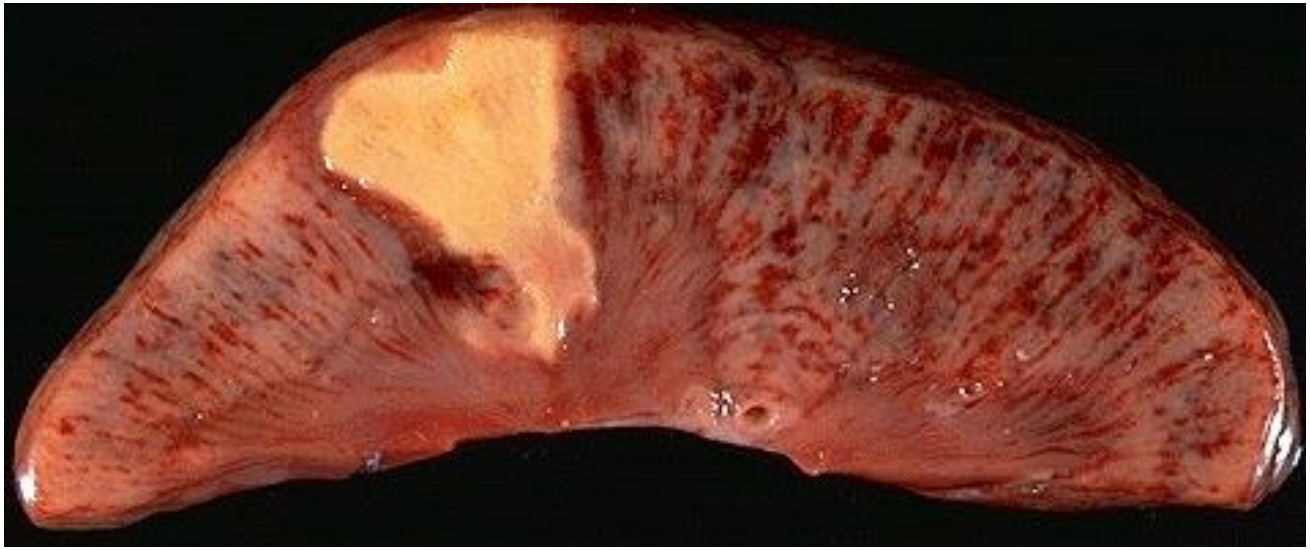


The renal cortex demonstrates extensive coagulative necrosis and interstitial hemorrhage (A). Renal tubules are necrotic and there is marked glomerular congestion (B). A reactive acute inflammatory infiltrate is present within the interstitium (C).

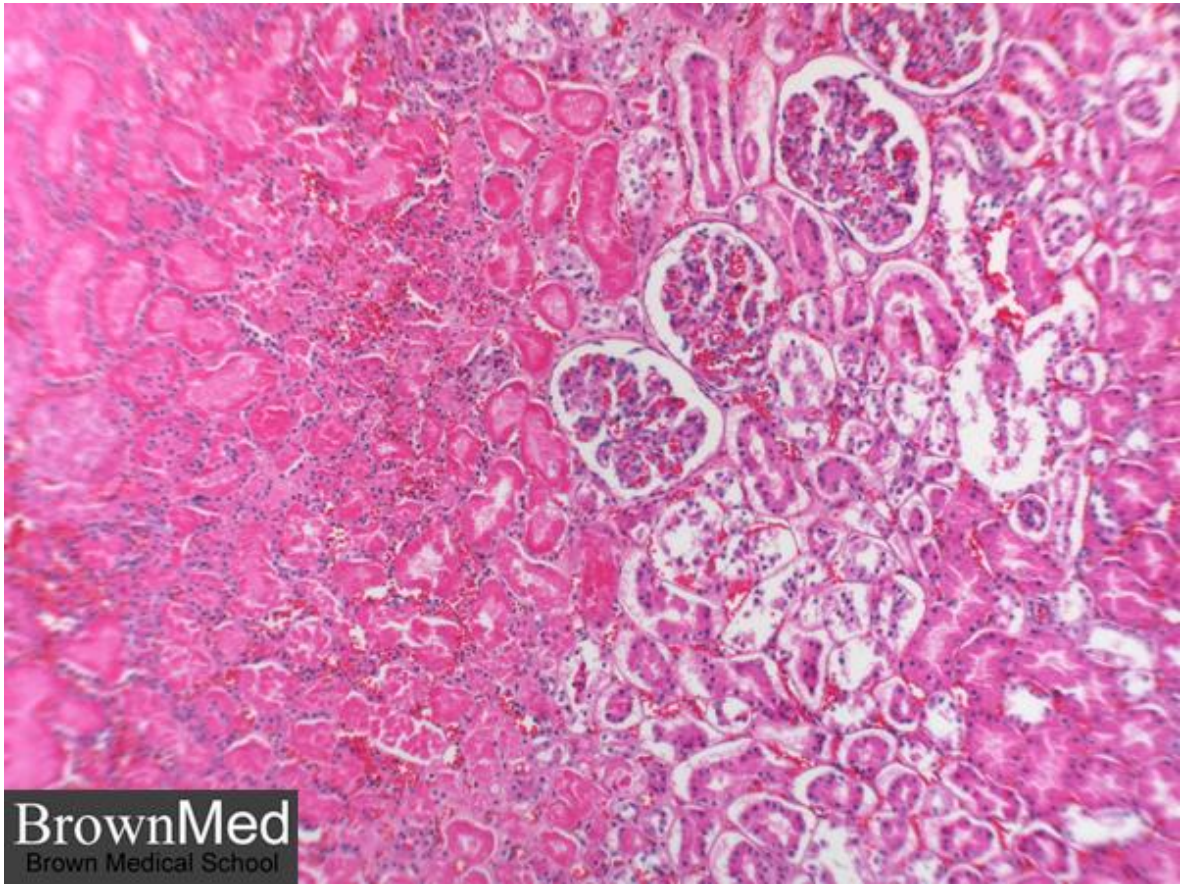
INFARCTION

Renal infarcts are areas of coagulative necrosis that result from the local ischemia of vascular occlusion and usually are due to thromboembolism secondary to valvu1ar endocarditis; endarteritis from parasitic diseases, such as heart worm or strongyles; mural thrombosis (atherosclerotic plaque); or aseptic emboli (neoplastic emboli).

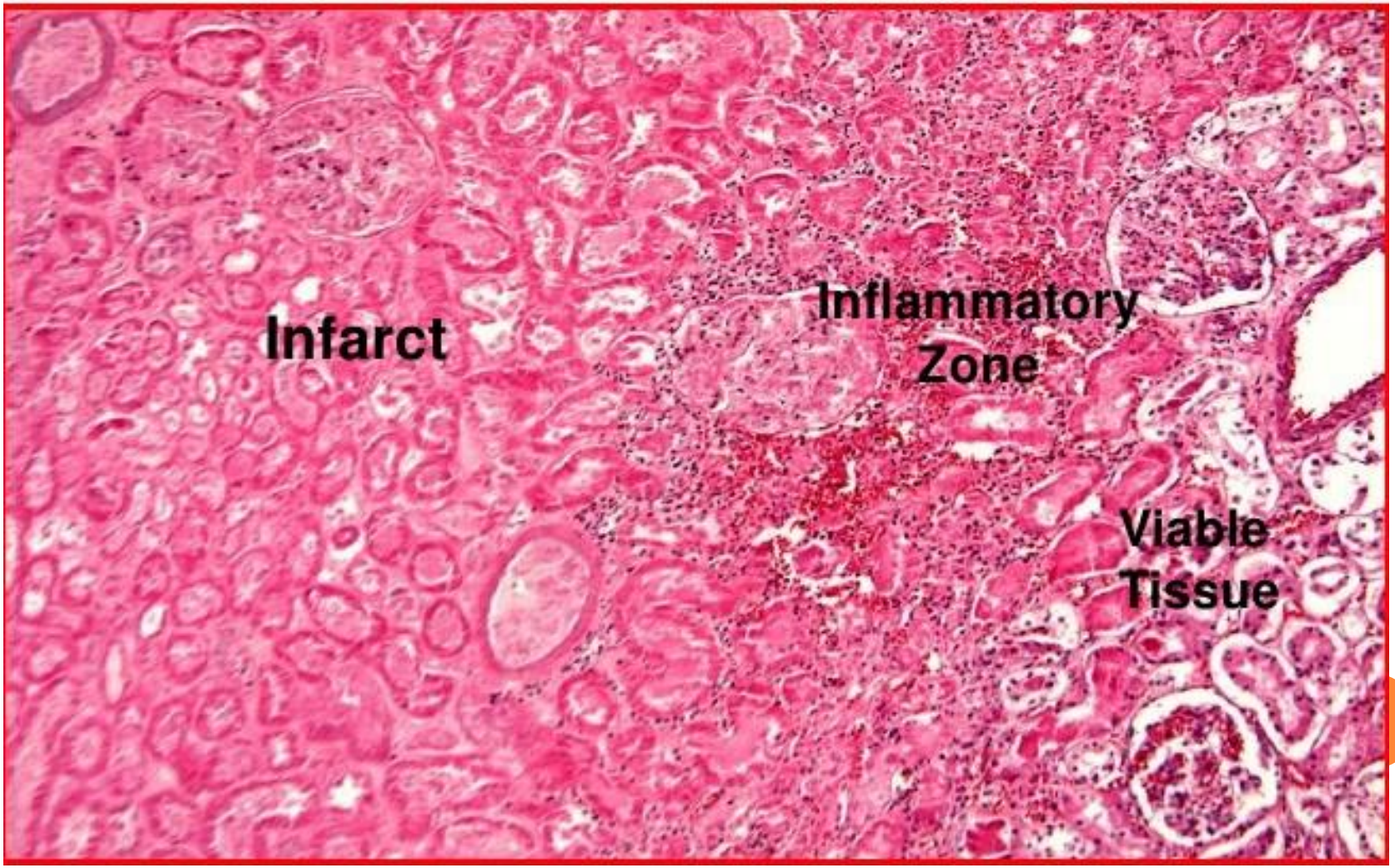
Grossly, renal infarcts appear red or pale white depending on several factors, including the interval after infarcts that are initially slightly swollen and red because of hemorrhage and which later become pale yellow-gray within 2 to 3 days because of lysis of erythrocytes and loss of hemoglobin . Initially, large infarcts develop when an embolus lodges in the interlobular artery closer to its origin from the arcuate artery. These larger infarcts have a central area of pallor (coagulative necrosis) and are usually surrounded by a peripheral red zone of congestion and hemorrhage along with a pale margin because of a surrounding zone of leukocytes



Because of the loss of parenchyma, healing infarcts are depressed below the cortical surface, and later become pale and shrunken as a result of fibrosis.
Infarcts are often wedge-shaped in a cross section of kidney, with the base against the cortical surface and the apex pointing toward the medulla, conforming to a zone of cortical parenchyma supplied by the obstructed interlobular artery. Infarcts can involve the cortex only or the cortex and medulla depending on the size of the occluded vessel and the site of obstruction. For example, thrombosis of an arcuate artery, which supplies both cortex and medulla, would result in an infarct involving the cortex and extending partway into the medulla .



Microscopically, in an acute infarct, nephrons (including tubules, glomeruli, and interstitium) in the central zone of the infarct become necrotic ,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.



DISEASES OF THE LOWER URINARY SYSTEM

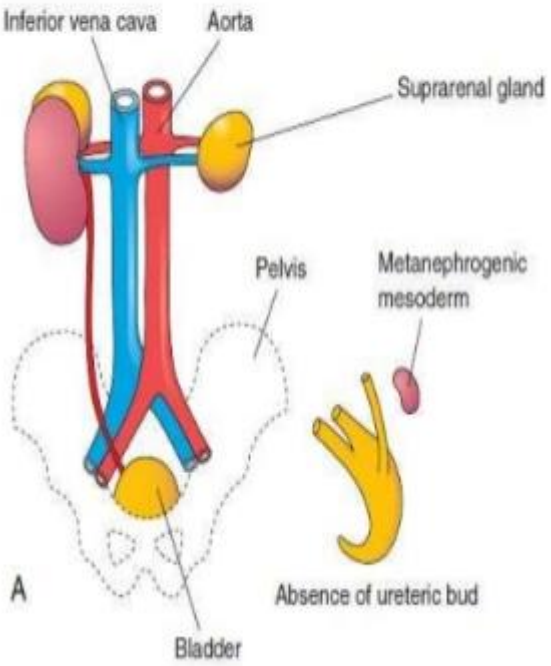
DEVELOPMENTAL ANOMALIES

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 due to failure of the ureteral bud to form, and may be unilateral or bilateral. Both conditions are rare. If these defects occur alone, then there is disruption of urinary flow from the kidney to the urinary bladder, resulting in obstructive diseases such as hydronephrosis.

Renal Agenesis

- Renal Agenesis (absence): Can be unilateral or bilateral
- Renal agenesis results when the ureteric buds do not develop or the primordia (stalks of buds) of the ureters degenerate.
- Failure of the ureteric buds to penetrate the metanephrogenic blastema results in failure of kidney development



OBSTRUCTIVE DISEASES

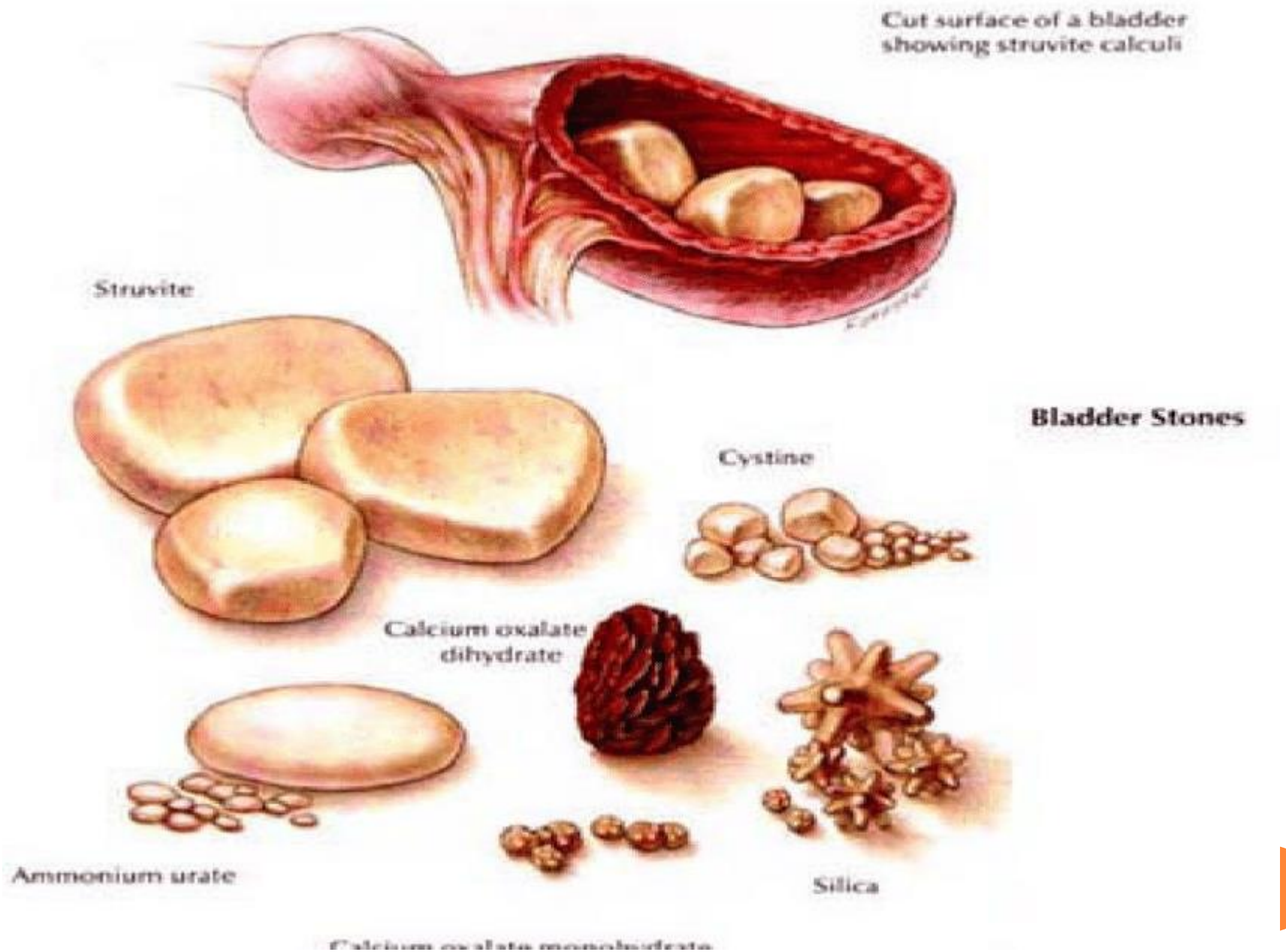
UROLITHIASIS

Urinary calculi (uroliths) are concretions formed anywhere in the urinary collecting system.

Uroliths are commonly found in the ureter, and are among the most important urinary tract problems of domesticated animals.

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 ("stone"),an outer shell, and surface crystals.

These calculi predispose affected animals to pyelitis and pyelonephritis. Urinary bladder calculi can be single or multiple, variable in size (2 mm to 10 cm), and sometimes are composed of a fine, sandlike material, which causes cloudy urine Calculi can have smooth or rough surfaces; and may be solid, soft, or friable. Calculi vary in color depending on their composition, it 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), depending on their composition.


Cut surface of a bladder showing struvite calculi
Struvite
Bladder Stones
Cystine
Calcium oxalate dihydrate
Ammonium urate
Silica

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

1. Calculus precursors material in urine in quantities sufficient to be precipitated.
2. Substance is metabolized in an unusual way, as is uric acid in Dalmatian dogs.
3. Substance may be processed abnormally by the kidney (hereditary defects), as with cystine or xanthine.
4. Abnormally high levels of a substance are encountered in the diet, such as the following:

a. Silicic acid in native pastures
b. Phosphate in milo or sorghum products (struvites)
c. Estrogens in subterranean clover (clover stones [benzocoumarin] or carbonates)
d. Magnesium in commercial dry cat food
e. Oxalate in oxalate-accumulating plants (oxalates)

5. Abnormally low levels of a substance are encountered in the diet, such as the following: a. Vitamin A (equivocal evidence that vitamin A deficiency may produce metaplastic change in the urinary tract epithelium that creates a nidus of calculus formation following sloughing of epithelium)

INFLAMMATORY DISEASES

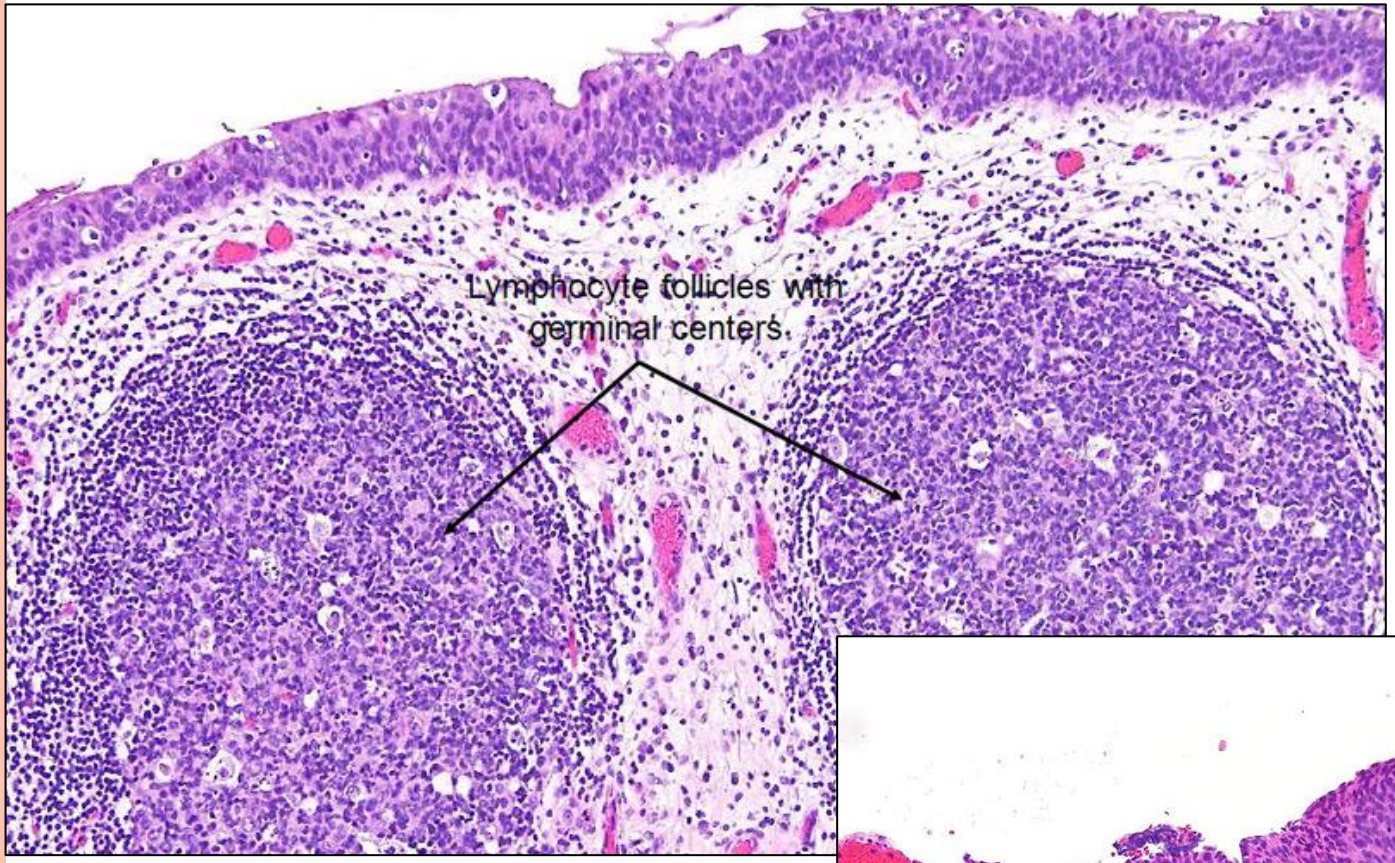
ACUTE CYSTITIS

Inflammation of the urinary bladder (cystitis) is common in domestic animals. The causes of acute cystitis are varied; however, for all animal species, bacterial infection is the most common cause. Cystitis may be acute or chronic. Normally the bladder is resistant to infection, and contaminating bacteria are quickly eliminated by the normal flow of normal urine. Predisposition to urinary tract infection (UTI) occurs when there is stagnation of urine because of obstruction.

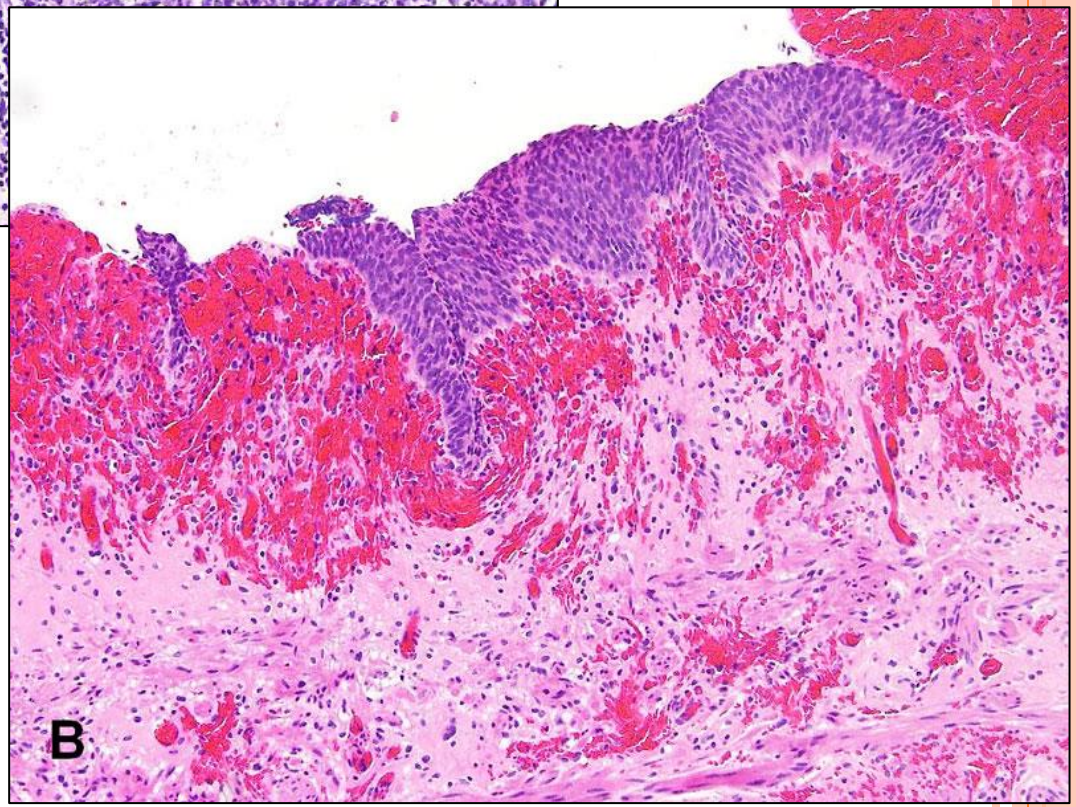
Other risk factors for UTI include: catheterization, vaginoscopy, vaginitis, prolonged administration of medications such as antibiotics that induce bacterial resistance.

Bacterial cystitis is more common in females because their relatively short urethra provides a shorter barrier to ascending infections than the longer, narrow diameter of the male urethra.

The bacterial species most commonly associated with cystitis are uropathogenic Escherichia coli in all animal species; Corynebacterium renale in cattle; Eubacterium (Corynebacterium) suisin pigs;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.



Follicular cystitis



Haemorrhagic cystitis

CHRONIC CYSTITIS

Chronic cystitis presents as several forms based on the pattern and type of inflammatory response noted. These forms include diffuse, follicular, and polypoid variants. Diffuse variants reveal an irregularly reddened and usually thickened mucosa. There is some epithelial desquamation, and the submucosa is heavily infiltrated with mononuclear inflammatory cells; there are few neutrophils. In addition, there is often connective tissue thickening of the submucosa and hypertrophy of the muscularis layer.