Renal Pathology

By

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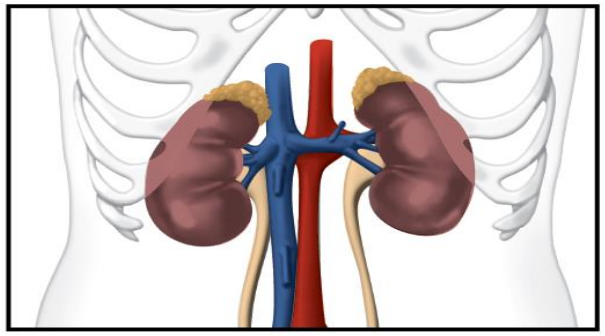
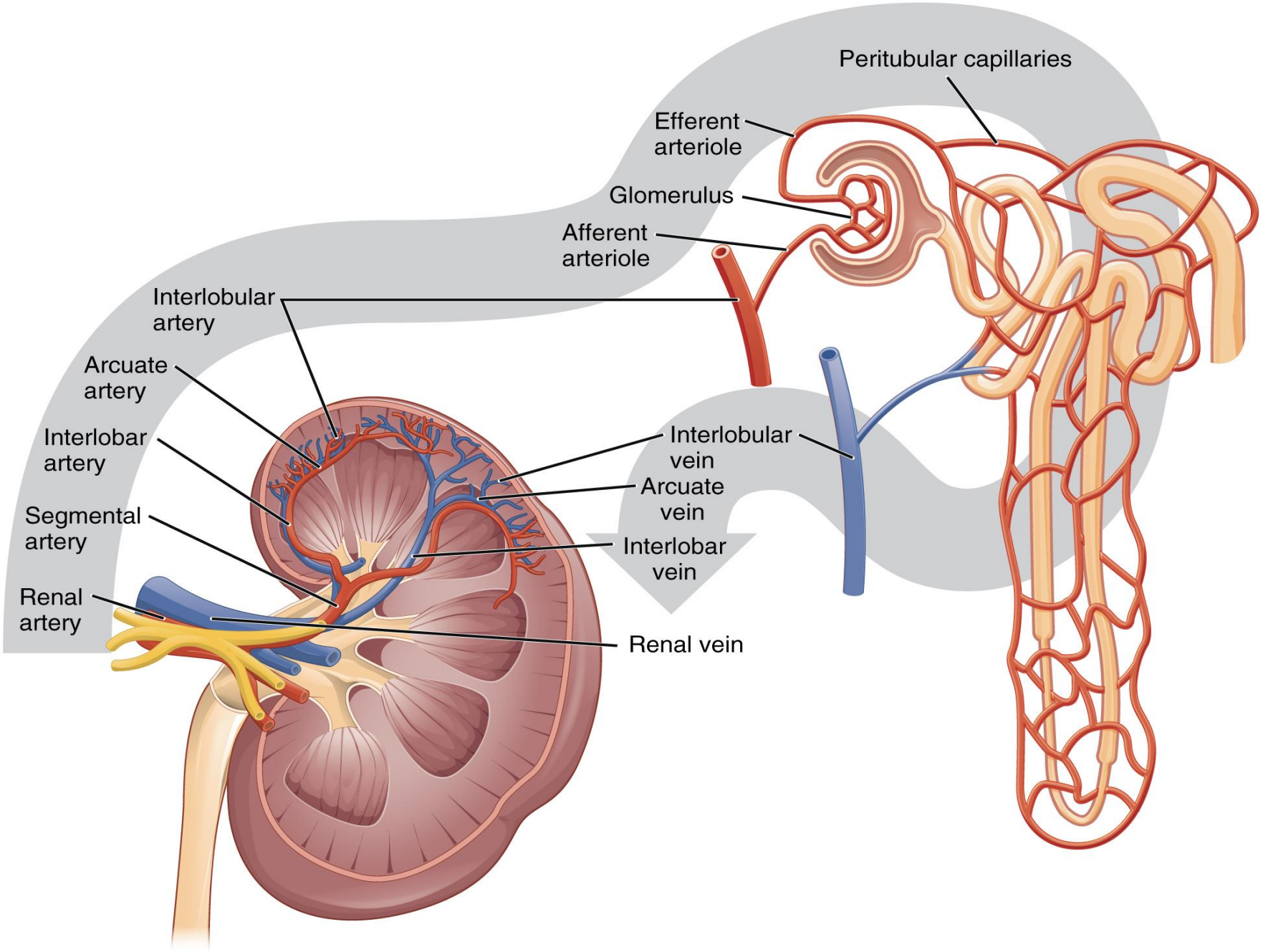
Pathologist

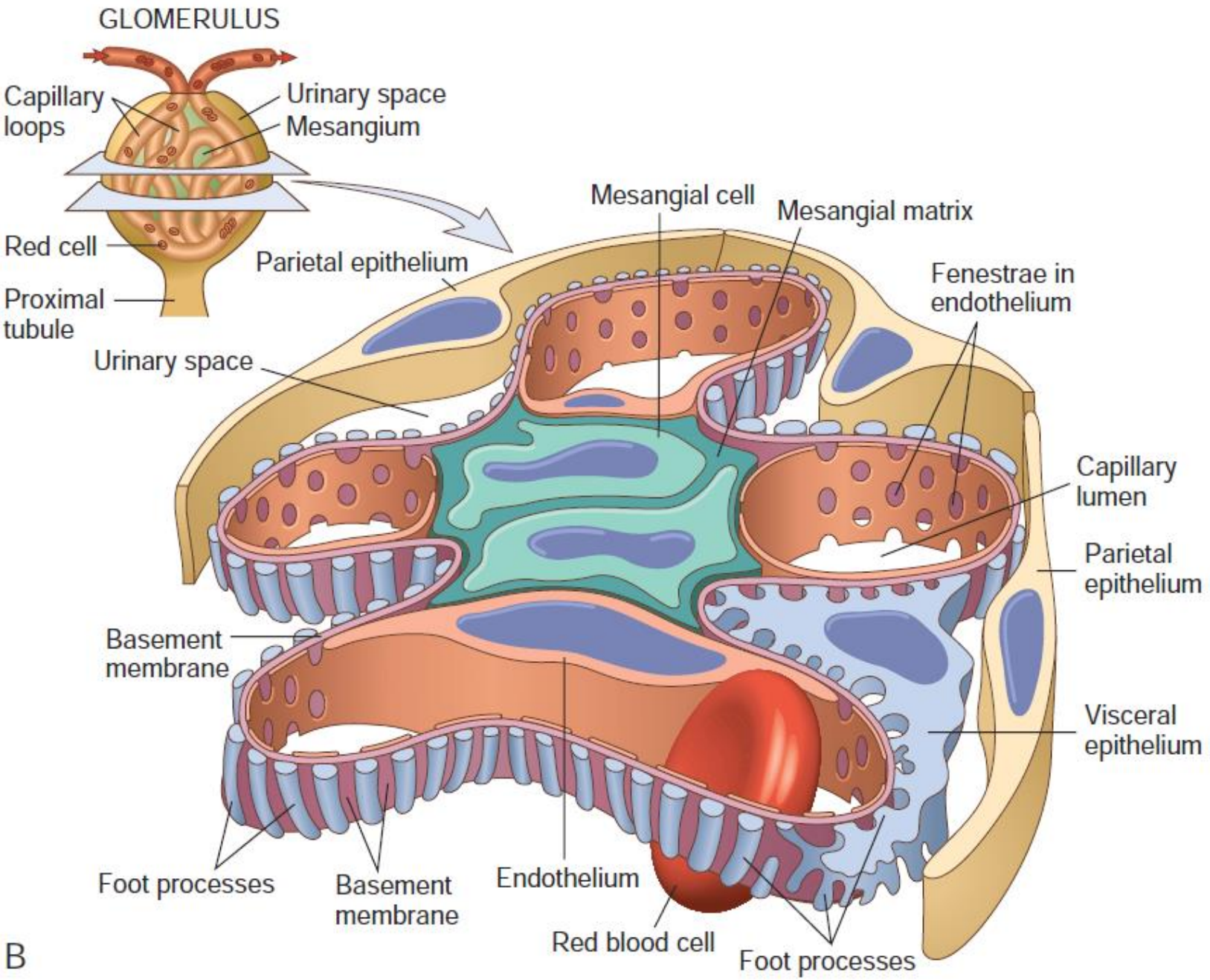
What is a human but an ingenious machine designed to turn, with "infinite artfulness, the red wine of Shiraz into urine?" So said the storyteller in Isak Dinesen's Seven Gothic Tales. More accurately but less poetically, human kidneys serve to convert more than 1700 L of blood per day into about 1 L of a highly concentrated fluid called urine.

Review of anatomy



Renal hilum
Renal vein
Renal nerve
Renal artery
Renal medulla
Ureter
Capsule
Minor calyx
Major calyx
Renal pelvis
Pyramid
Papilla
Renal column
Renal cortex


Peritubular capillaries
Efferent arteriole
Glomerulus
Afferent arteriole
Interlobular artery
Arcuate artery
Interlobar artery
Segmental artery
Renal artery
Interlobular vein
Arcuate vein
Interlobar vein
Renal vein


GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Mesangial cell
Mesangial matrix
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Basement membrane
Endothelium
Red blood cell
Foot processes
B

Key points

A ***glomerular basement membrane*** **(GBM)** is composed of;

1. A thick electron-dense central layer, the Lamina densa, and
2. Thinner electron-lucent peripheral layers,
   - Lamina rara interna
   - Lamina rara externa.

- The GBM consists of **collagen (mostly type IV**), laminin, polyanionic proteoglycans (mostly heparan sulfate), fibronectin, entactin, and several other glycoproteins.

- **Type IV collagen** forms a network suprastructure to which other glycoproteins attach.

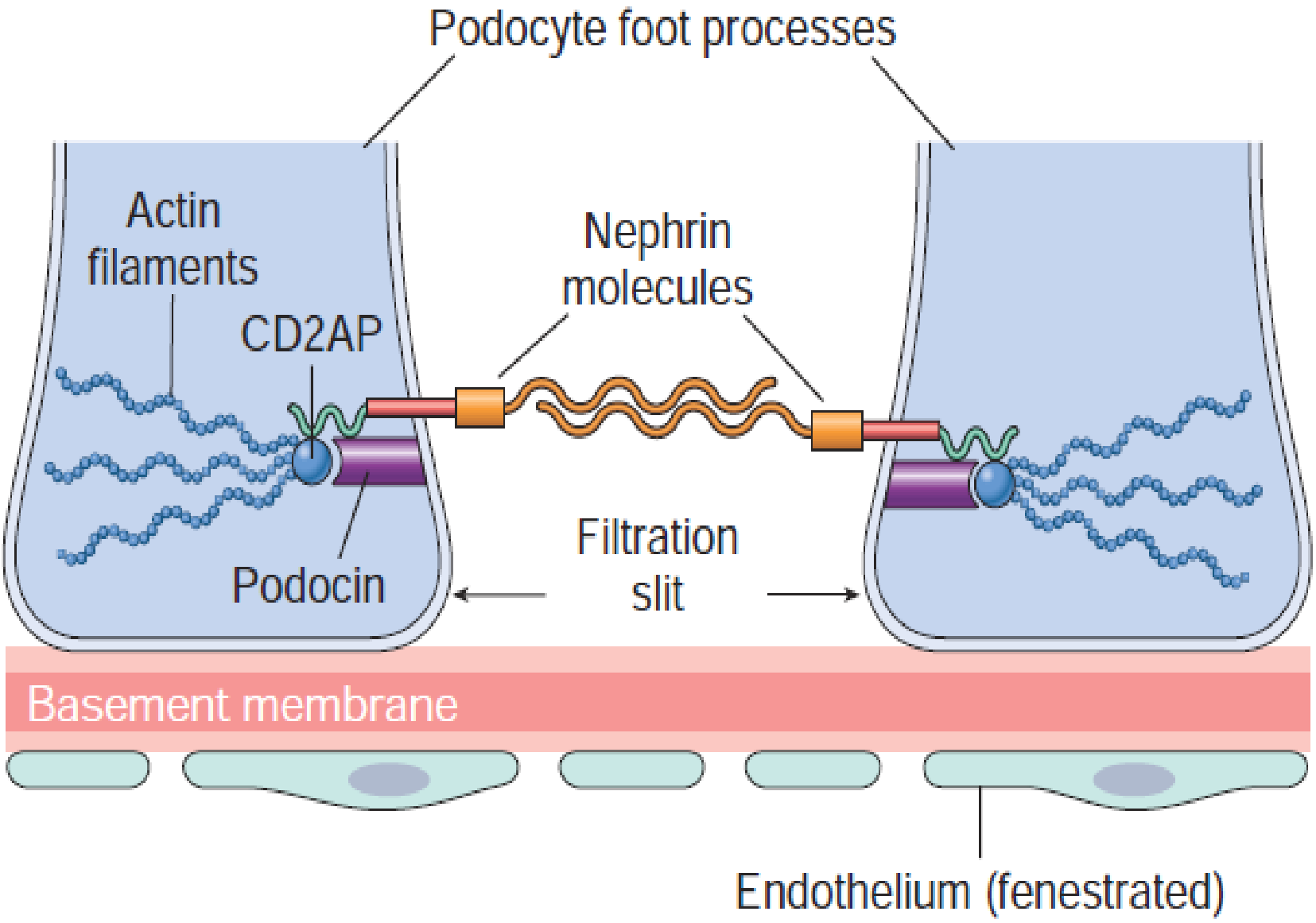
- The building block (monomer) of this network is a triple-helical molecule composed of one or more of six types of α chains (α1 to α6 or COL4A1 to COL4A6).

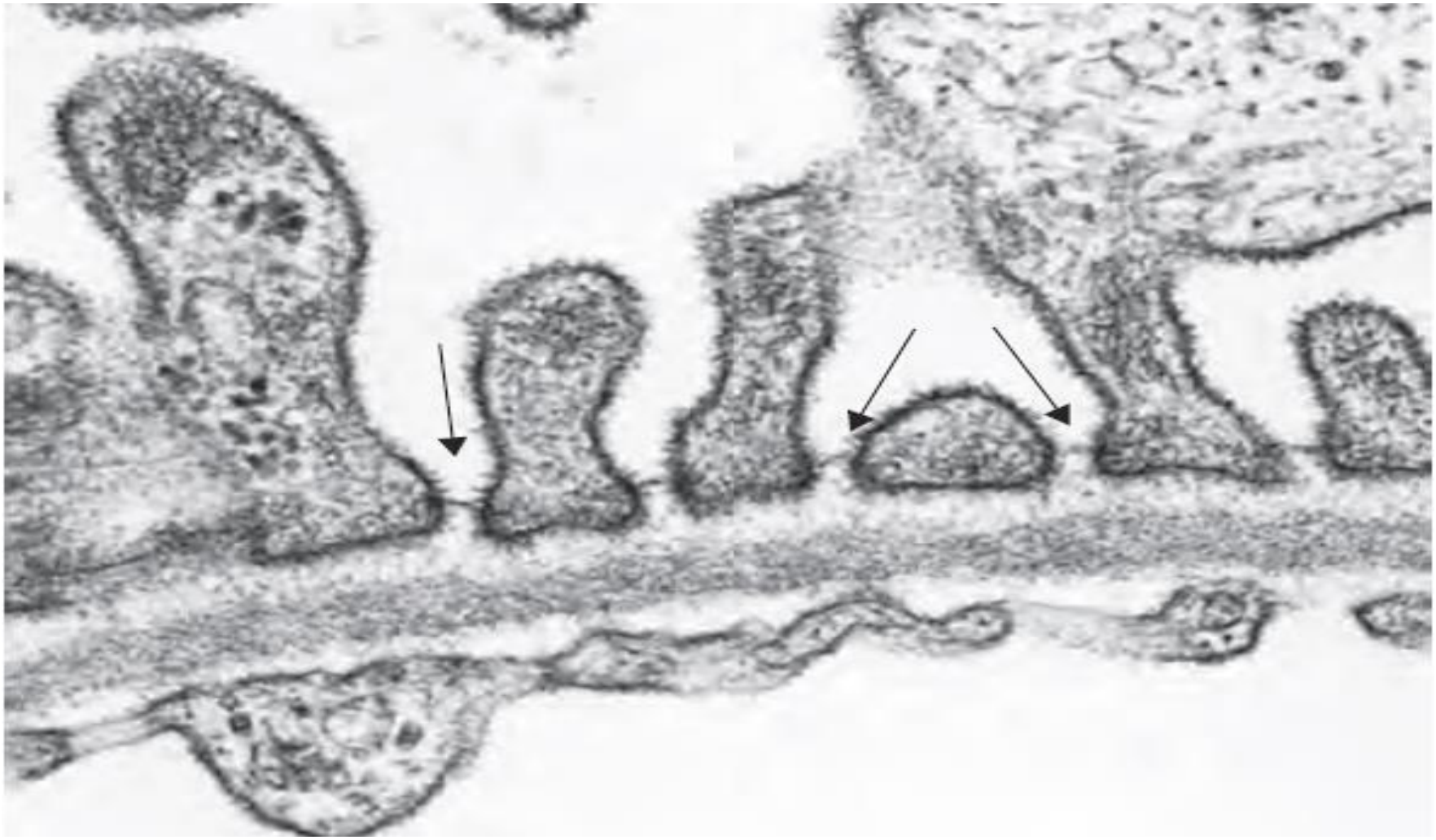
- **The visceral epithelial cell is important for the maintenance of glomerular barrier function; its slit diaphragm presents a size-selective distal diffusion barrier to the filtration of proteins, and this cell type is largely responsible, under normal circumstances, for synthesis of GBM components.**

- **Nephrin** is a transmembrane protein with a large extracellular portion made up of immunoglobulin (Ig)-like domains.

- Nephrin molecules extend toward each other from neighboring foot processes and dimerize across the slit diaphragm.

- Within the cytoplasm of the foot processes, nephrin forms molecular connections with **podocin, CD2-associated protein, and ultimately the actin** cytoskeleton of the visceral epithelial cells.


Podocyte foot processes
Actin filaments
CD2AP
Nephrin molecules
Podocin
Filtration slit
Basement membrane
Endothelium (fenestrated)



Glomerular filter consisting *(from bottom to top)* of fenestrated endothelium, basement membrane, and foot processes of epithelial cells. Note the filtration slits *(arrows)* and diaphragm between the foot processes. Note also that the basement membrane consists of a central lamina densa, sandwiched between two looser layers, the lamina rara interna and lamina rara externa.

Classification of kidney diseases

- **kidney diseases affect the four basic morphologic components:**
  - **Glomeruli**
  - **Tubules**
  - **Interstitium**
  - **Blood vessels**
- This approach is useful because the early manifestations of disease affecting each of these components tend to be distinct.

- Others are; **cystic diseases** and **renal transplant pathology**

Glomeruli

Clinical Manifestations of Glomerular Diseases

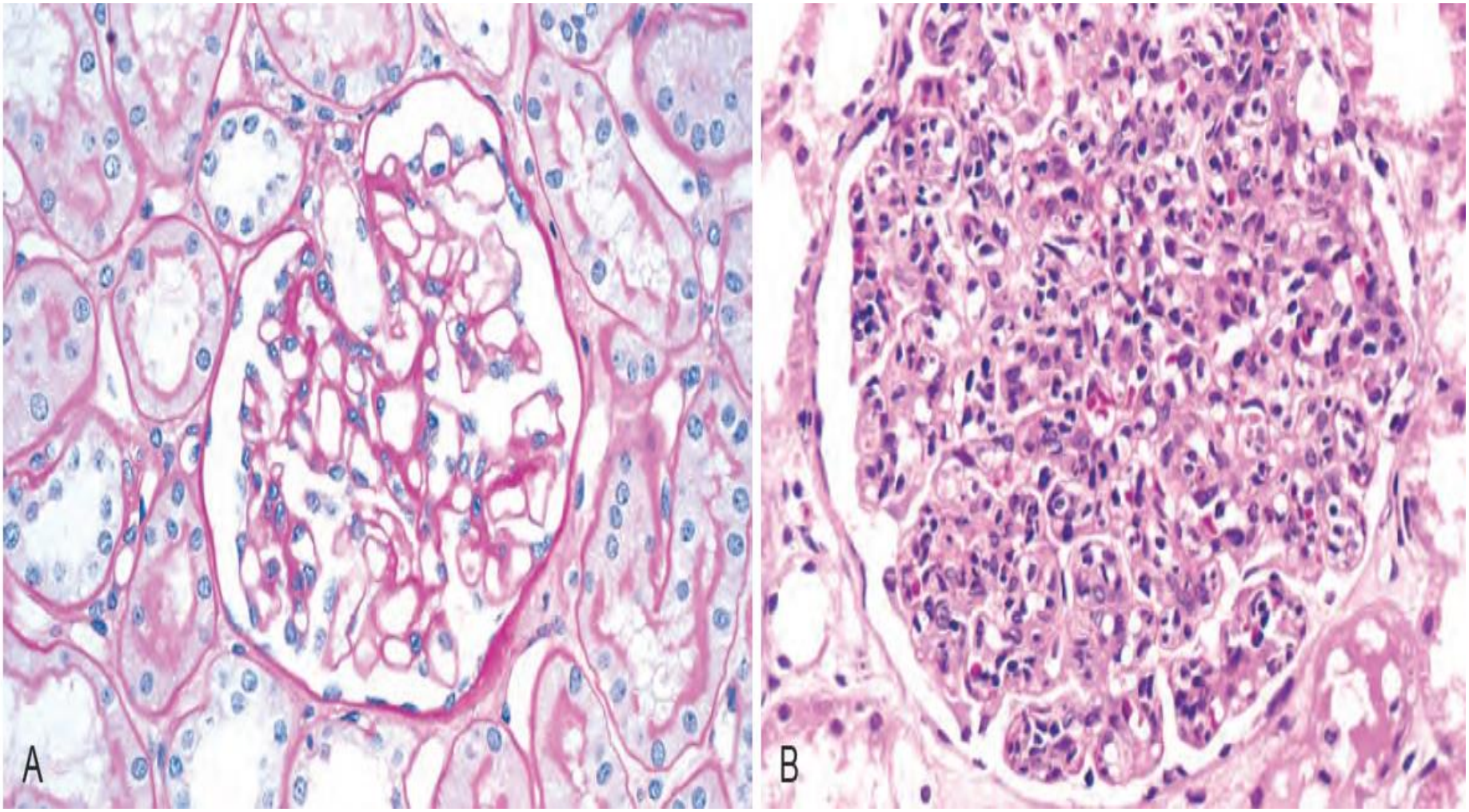
Syndrome	Manifestations
Nephritic syndrome	Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension
Rapidly progressive glomerulonephritis	Acute nephritis, proteinuria, and acute renal failure
Nephrotic syndrome	>3.5 g/day proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria
Chronic kidney disease	Azotemia → uremia progressing for months to years
Isolated urinary abnormalities	Glomerular hematuria and/or subnephrotic proteinuria

Pathologic Responses of the Glomerulus to Injury

Hypercellularity

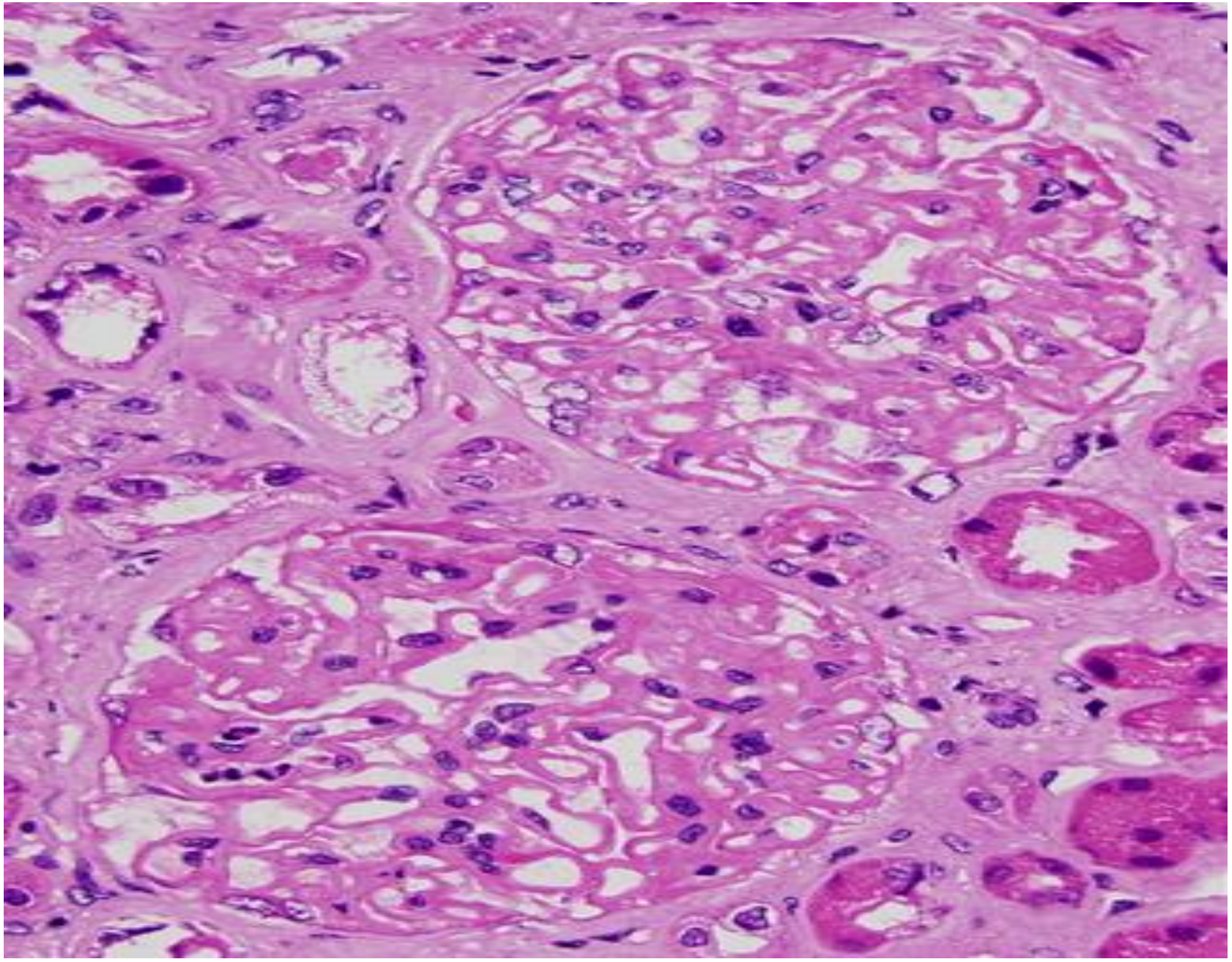
- Proliferation of **mesangial** or **endothelial cells**.

- Infiltration of **leukocytes**.
  - The combination of infiltration of leukocytes and swelling and proliferation of mesangial and/or endothelial cells is often referred to as **endocapillary proliferation.**
- Formation of crescents.
  - These are accumulations of cells composed of **proliferating glomerular epithelial cells** and **infiltrating leukocytes**.


A
B

Basement Membrane Thickening

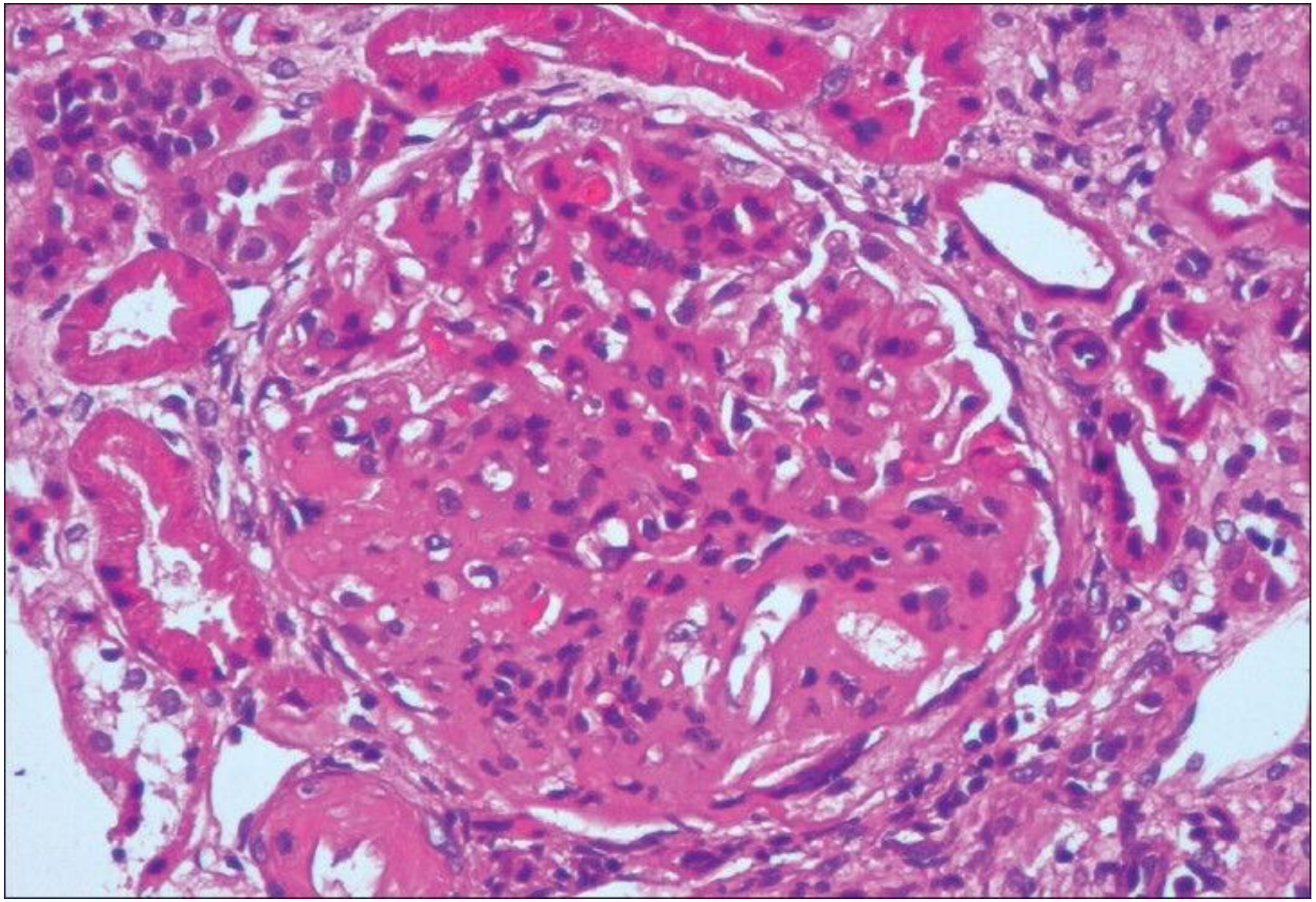
- By light microscopy, this change appears as thickening of the capillary walls, best seen in sections stained with periodic acid–Schiff (PAS).
- This can be due to;
  - **Deposition of amorphous electron-dense material**
  - **Increased synthesis** of the protein components of the basement membrane, as occurs in diabetic glomerulosclerosis.
  - **Formation of additional layers of basement membrane matrices**, which most often occupy subendothelial locations.



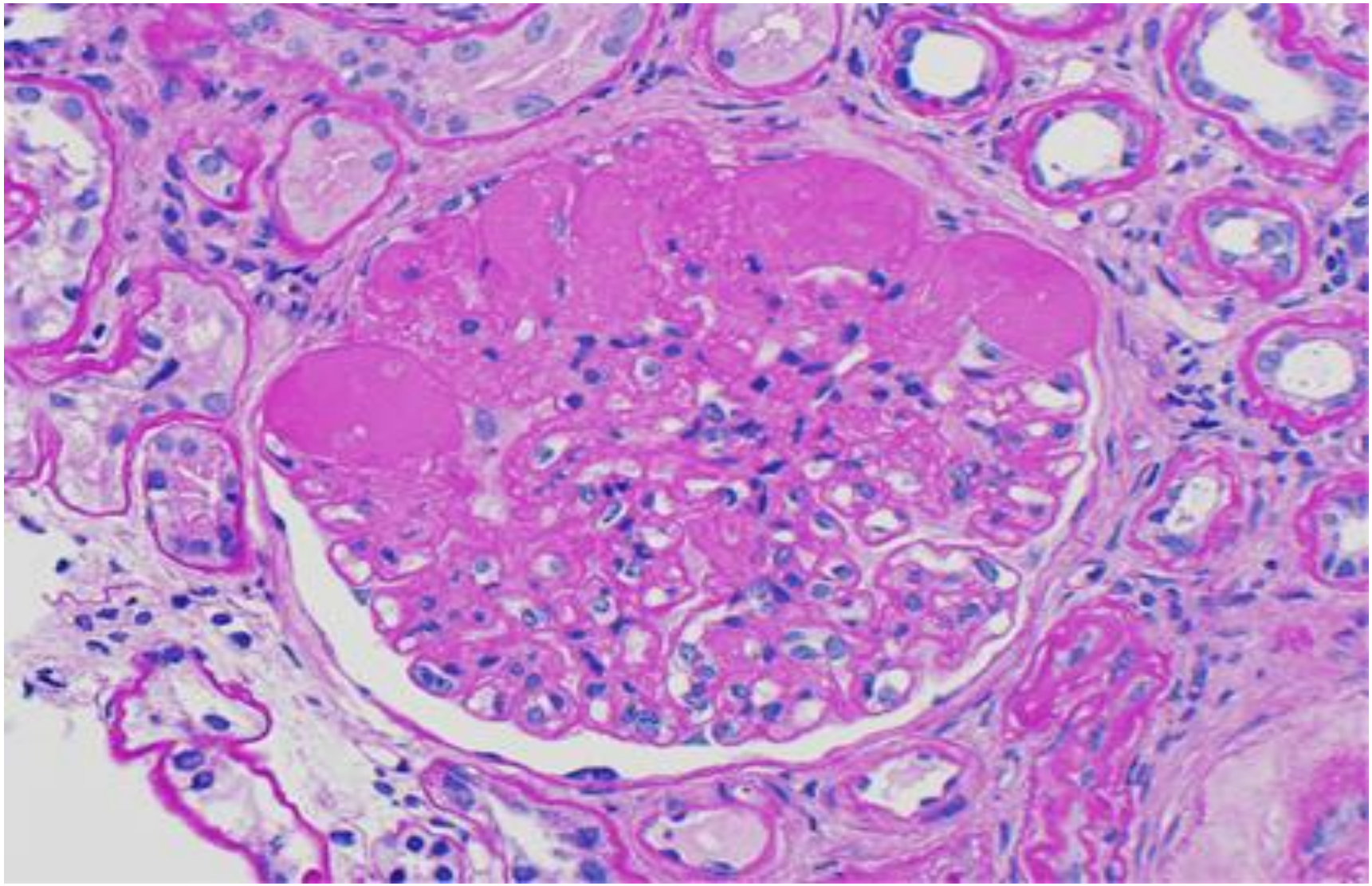
Hyalinosis and Sclerosis

- **Hyalinosis,** as applied to the glomerulus, denotes the accumulation of material that is homogeneous and eosinophilic by light microscopy.
  - Hyaline is an extracellular, amorphous material composed of plasma proteins that have insudated from the circulation into glomerular structures.
  - Hyalinosis is usually a consequence of endothelial or capillary wall injury and typically the end result of various forms of glomerular damage.

- **Sclerosis** is characterized by deposition of extracellular collagenous matrix.



Diabetic glomerulosclerosis with global mesangial sclerosis (H and E, ×400)



This glomerulus shows a lesion of segmental sclerosis with prominent luminal hyalinosis and adhesion to Bowman's capsule (periodic acid-Schiff, × 400)

Pathogenesis of Glomerular Injury

- Antibody-mediated injury is an important mechanism of glomerular damage, mainly via complement- and leukocyte-mediated pathways.

- The most common forms of antibody-mediated glomerulonephritis are caused by the formation of immune complexes, which may involve either endogenous antigens (e.g., PLA2R in membranous nephropathy) or exogenous antigens (e.g., microbial).

- Immune complexes show a **granular pattern** of deposition by immunofluorescence.

- Autoantibodies against components of the GBM are the cause of anti–GBM antibody–mediated disease, often associated with severe injury. The immunofluorescence pattern of antibody **deposition is linear.**

- Activation of the **alternative complement pathway** is an important mechanism of injury in C3 glomerulopathies that include dense deposit disease and C3 glomerulonephritis.

- **Soluble inflammatory mediators**, such as cytokines, chemokines, growth factors, eicosanoids, nitric oxide, and activated coagulation factors, also contribute to the glomerular injury.

- **Epithelial cell (podocyte) injury** induced by antibodies, toxins, cytokines, infections, and poorly characterized circulating factors is a **common manifestation of various forms of glomerular diseases**.

- **Progressive glomerular injury** can be the result of either primary or secondary glomerular injuries, of diseases that are either **renal limited or systemic**, and of diseases that initially involve renal structures other than glomeruli.

- Progressive injury ensues from a **cycle of glomerular and nephron loss, compensatory changes that lead to further glomerular injury and glomerulosclerosis,** and eventually **ESRD.**

- Progressive glomerular injury is accompanied by **chronic injuries to other renal structures**, typically manifest as **tubulointerstitial fibrosis**.

Glomerular Lesions Associated With the Nephrotic Syndrome

Minimal Change Disease

Clinical

- The most common cause of the nephrotic syndrome in children
- Mild periorbital edema, prior to the rapid onset of the nephrotic syndrome
- Proteinuria is “selective” or composed primarily of albumin
- Microscopic hematuria is rare; hypertension is unusual
- MCD in adults has been associated with various drugs (i.e., NSAIDs)

Pathogenesis

- Podocyte foot process injury due to circulating factor/s produced by T lymphocytes that damage one or more elements of the glomerular permeability barrier responsible for the proteinuria seen in this condition.

- Patients with MCD did show T-cell subset abnormalities, and elevated levels of interleukin-13 (IL-13) were demonstrated during relapses.

- IL-13 has been shown to increase the expression of CD80 in podocytes.

- CD80, in turn, has been identified in the urine of patients of MCD and appears to be a potential diagnostic biomarker.

Microscopic

- Light microscopy
  - The glomeruli, tubules, and interstitium appear normal
- Immunofluorescence microscopy
  - Usually negative, mesangial IgM may occasionally be present
- Electron microscopy
  - Diffuse effacement of the epithelial cell (podocyte) foot processes is the sole abnormality
- **Differential Diagnosis**
- An early membranous lesion may look normal in light microscopy
- Undersampled focal segmental glomerulosclerosis (where segmental scars are not present in the biopsy) may look identical to MCD.

Focal Segmental Glomerulosclerosis (FSGS)

Clinical

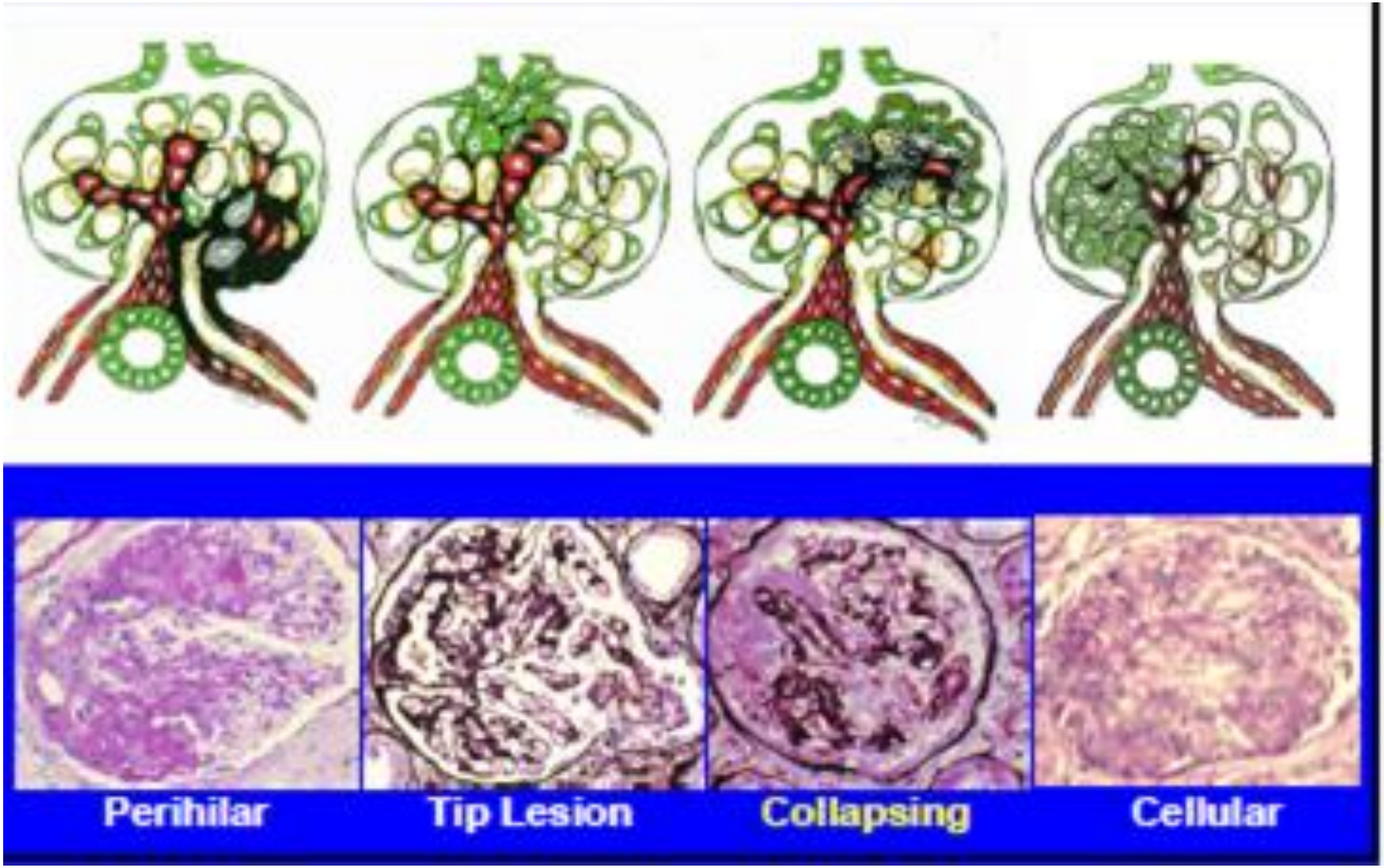
- Focal segmental glomerulosclerosis may be primary (idiopathic) or secondary to a number of etiologic agents, including
  - Unilateral renal agenesis
  - Renal ablation
  - Sickle cell disease
  - Morbid obesity (with or without sleep apnea)
  - Reflux nephropathy
  - HIV nephropathy
- Idiopathic FSGS is the most common cause of nephrotic syndrome in African Americans
- Secondary FSGS usually does not present with the full nephrotic syndrome

- As the name implies, this lesion is characterized by sclerosis of **some, but not all, glomeruli** (thus, it is focal); and in the **affected glomeruli, only a portion of the capillary tuft is involved** (thus, it is segmental).

- Five hierarchical histologic subtypes have been described (**Columbia classification of FSGS**).
  - Collapsing variant,
  - “Tip” lesion,
  - Cellular variant,
  - Perihilar lesion,
  - FSGS-NOS (not otherwise specified) variant.

Variant	Histologic feature	Clinical features/prognosis	Progression to ESKD, %
Collapsing	Podocyte hyperplasia collapsing glomerular tuft	Worst prognosis. Usually presents with abrupt onset of severe nephrotic syndrome. Predominant in black race. Poor response to steroids	~70
Cellular	Podocyte hyperplasia, endocapillary proliferation. Usually severe foot process effacement	Early stage in the evolution of FSGS. Least common variant. Usually primary FSGS, but could be seen in other forms of FSGS	~30
Perihilar	Segmental sclerosis at the vascular pole	Most common in adaptive FSGS. Usually presents with subnephrotic proteinuria or nephrotic-range proteinuria and normal serum albumin	30–50
Tip lesion	Segmental sclerosis at the proximal tubular pole	Best prognosis. Usually primary. Most common in white patients, frequently responds to steroids. May present reversible AKI at presentation	5–20
Classic (NOS)	Segmental sclerosis, not meeting the definition of the other variants	Most common subtype, could be found in any form of FSGS	30–40

FSGS, focal segmental glomerulosclerosis.


Perihilar
Tip Lesion
Collapsing
Cellular

Pathogenesis

- The pathogenesis of primary FSGS is unknown, but it appears to be the result of **circulating "permeability" factor(s),** possibly a lymphokine or a cytokine.

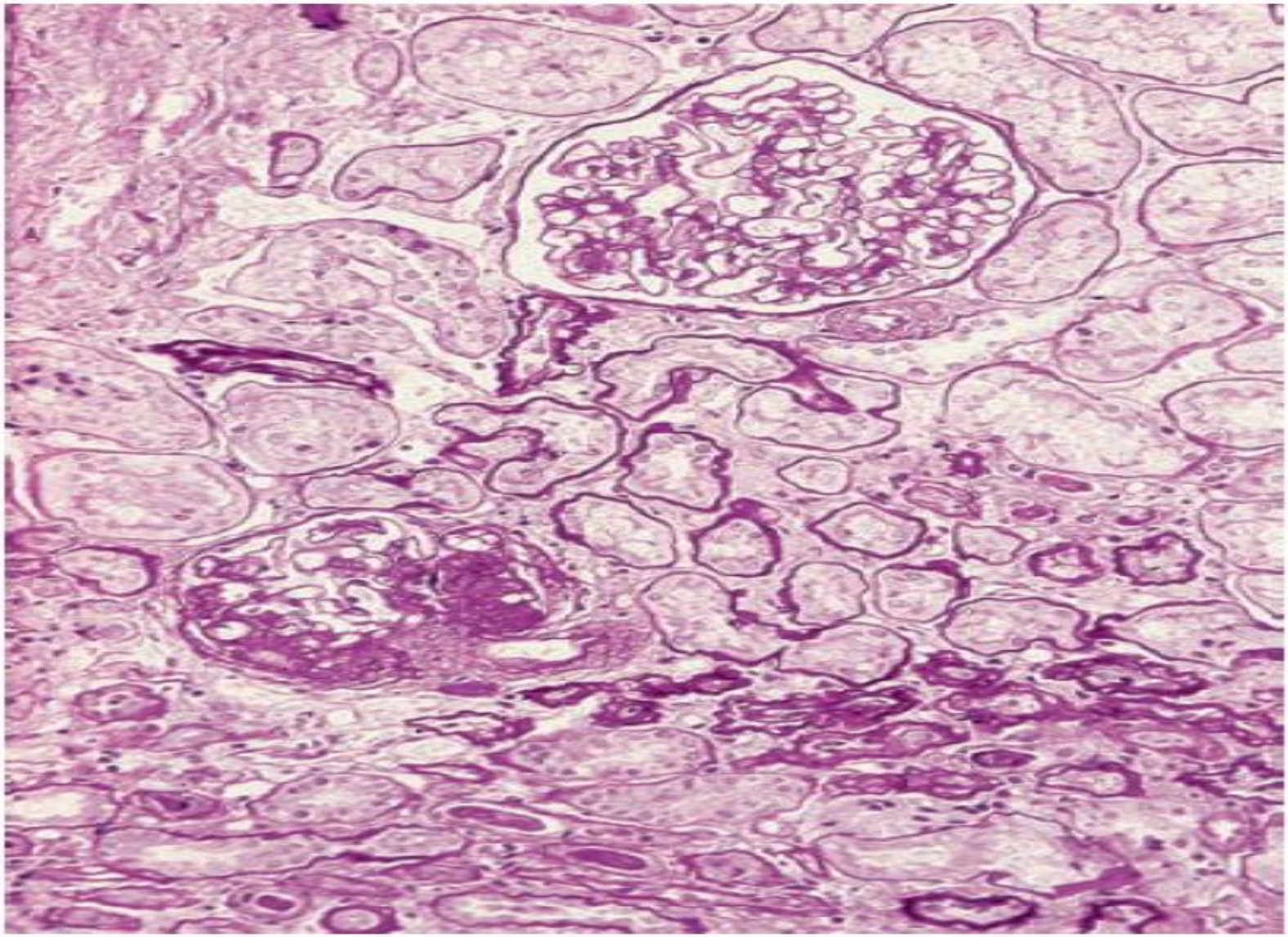
- Mutations of the ***NPHS 1*** **genes** give rise to *congenital nephrotic syndrome* of the Finnish type, producing a minimal change disease–like glomerulopathy with extensive foot process effacement.

- Mutations in the ***NPHS2*** **gene** which encodes the protein product *podocin* result in a syndrome of steroid-resistant nephrotic syndrome of childhood onset.

- Mutations in the gene encoding the podocyte actin-binding protein **α-actinin 4** underlie some cases of autosomal dominant FSGS.

- Mutations in the gene encoding **TRPC6** (transient receptor potential calcium channel-6) have been found in some kindreds with adult-onset FSGS.

- Recent studies have established a strong association between apolipoprotein L1 ***(APOL1)*** **gene** and FSGS in blacks.



Biopsy From a Patient With Focal and Segmental Glomerulosclerosis. One of the glomeruli shows segmental sclerosis, while the other appears unremarkable. Tubular atrophy is also seen (periodic acid–Schiff stain; PAS).

Collapsing Glomerulopathy

- Collapsing glomerulopathy is a clinically and pathologically distinct variant of FSGS that is characterized by the widespread collapse of glomerular capillary loops, and predominance in blacks attributable to the *APOL1* risk alleles.

- An idiopathic form of collapsing FSGS has poor prognosis with rapid loss of renal function and virtually no response to immunosuppressive therapy.

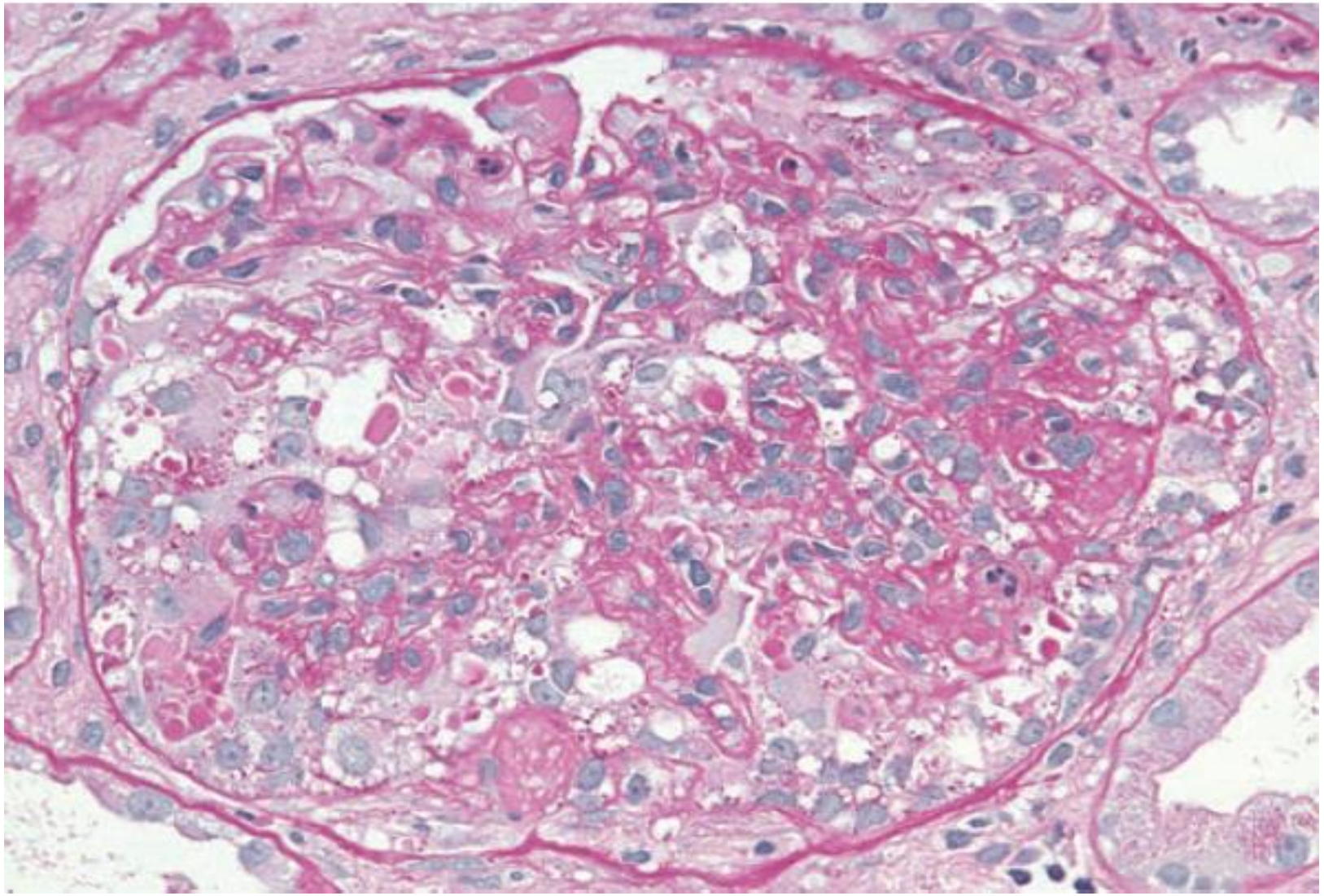
- This variant of FSGS constitutes about 80%–85% of the glomerular changes reported in HIV-infected patients.
- Collapsing glomerulopathy has also been reported in association with some;
  - Autoimmune diseases,
  - Lymphoproliferative disorders,
  - Drugs such as bisphosphonates and interferons,
  - Non-HIV viral infections, such as
    - Hepatitis C,
    - Cytomegalovirus, and
    - Parvovirus B19.

Histology

- Predominantly collapsing type of focal glomerulosclerosis that is segmental and often global.

- The segmental sclerosis is characterized by localized hypertrophy and hyperplasia of the epithelial cells overlying the collapsed segment.

- The presence of even a single glomerulus with collapsing FSGS lesion is adequate for this diagnosis.



Collapsing variant of focal segmental glomerulosclerosis lesion is characterized by the retracted glomerular basement membrane and hyperplastic overlying podocytes obliterating the Bowman space. The podocytes have prominent cytoplasm protein droplets (PAS).

Membranous Glomerulonephritis

- MGN is a glomerular disease of diverse etiology characterized by subepithelial immune complex deposits and variable basement membrane thickening, without infiltration by inflammatory cells.
- The majority of cases are primary.

- Over 85% of cases of secondary MGN are caused by infection, neoplasia, or SLE.

- The most common causes worldwide are malaria and schistosomiasis.

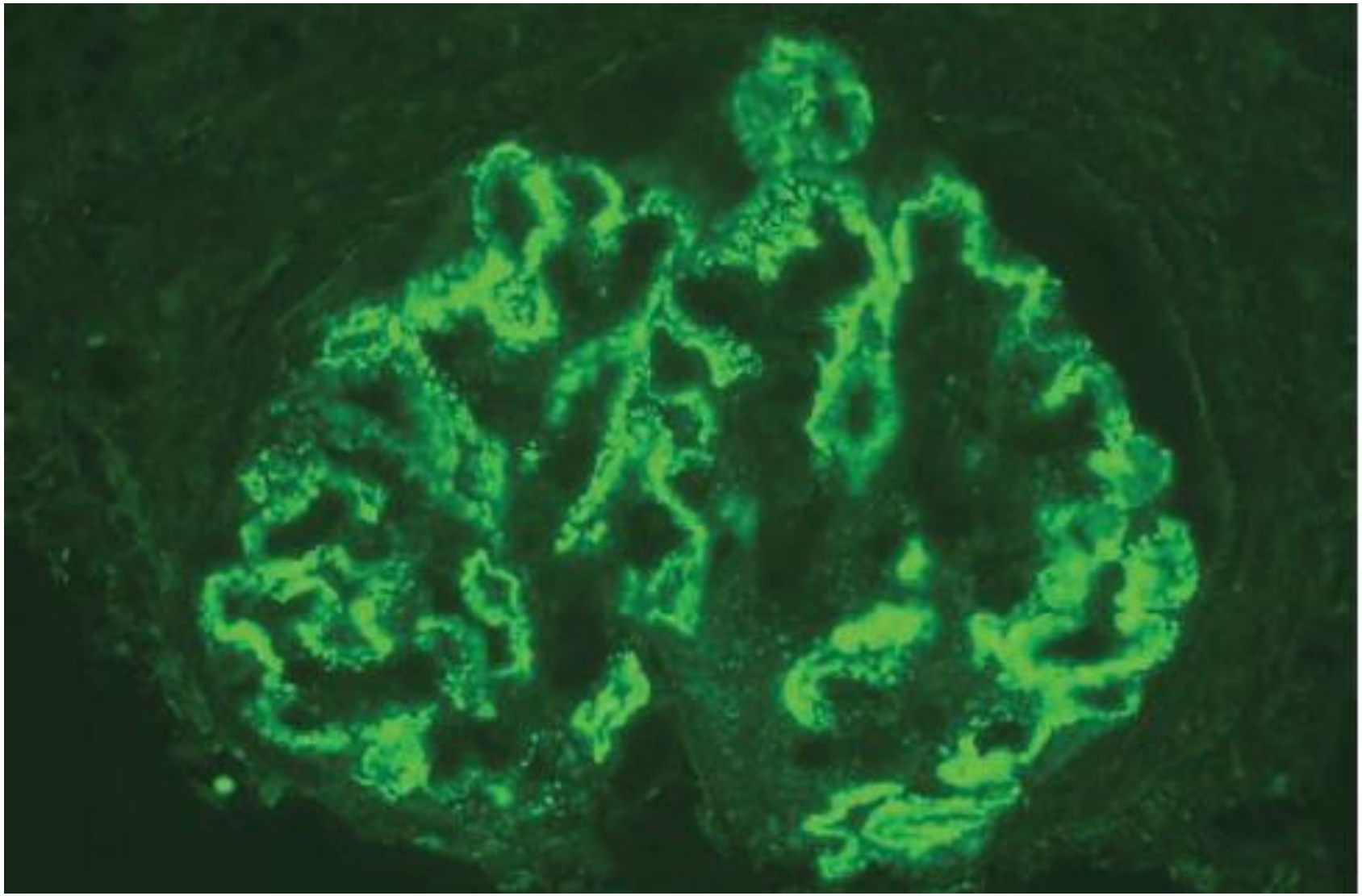
Pathogenesis

- **Immune complexes are formed *in situ* by the binding of circulating antibodies with antigens that are normally present in the glomerulus or with extrinsic antigens that have previously been planted as free antigens in the subepithelial area**.

- Primary MGN patients have autoantibodies directed against **PLA2R** expressed in podocytes and proximal tubules.

- These circulating **PLA2R autoantibodies are IgG4 subtype** and the plasma levels correlate with disease activity.

- Conditions associated with secondary MGN include;
  - **Chronic infections** (E.g hepatitis B antigens (HBsAg, HBcAg, and HBeAg), virus-liken particles (hepatitis C)
  - **Neoplasms**
  - **Autoimmune diseases** (SLE, rheumatoid arthritis, IgG4-related systemic disease), drugs, and
  - **Sarcoidosis**
  - **Drugs**(Nonsteroidal antiinflammatory drugs, penicillamine, gold, lithium, mercury, captopril, and anti-tumor necrosis factor agents).



Diffuse granular capillary wall staining with antibody to PLA2R supports a diagnosis of primary membranous nephropathy (anti-PLA2R).

Diabetic Nephropathy

- Diabetic nephropathy is a clinical syndrome characterized by persistent proteinuria, hypertension, and progressive decline in renal function.

Pathogenesis

- Persistent hyperglycemia causes accumulation of advanced glycosylated end products in various organs including kidney with resultant injury, tissue remodeling, and extracellular matrix deposition.

- It also causes defects in mitochondrial electron transport, increased production of reactive oxygen species, and increased oxidative stress.

- Many cellular proteins, including GBM collagen and matrix proteins, are affected.

- The most striking lesions are found in the glomeruli and blood vessels including;
  - **Diffuse glomerulosclerosis**
  - **Nodular glomerulosclerosis**
  - **Insudative lesions** (fibrin caps, capsular drops, and arteriolar hyalinosis).

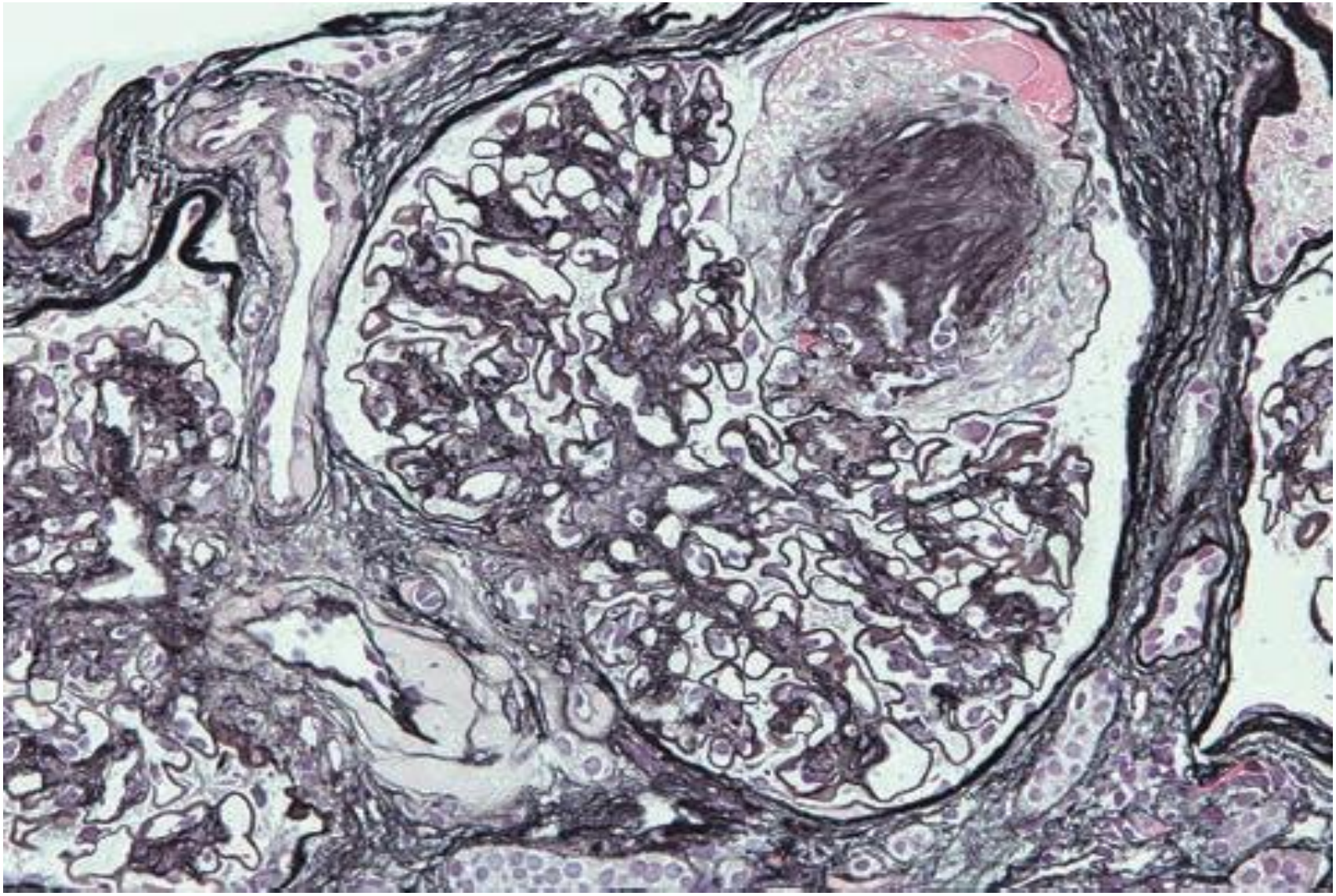
- **Diabetic glomerulosclerosis** is the general term for all of these lesions, and they are considered to be an expression of the microangiopathy.

- **Diffuse glomerulosclerosis**, the most common lesion in diabetic nephropathy, is characterized by a diffuse increase in the mesangial matrix and thickening of the capillary walls.
- **Nodular glomerulosclerosis (Kimmelstiel–Wilson lesion)** It consists of **large acellular nodules located in the intercapillary regions** that vary in size and are eosinophilic, argyrophilic, and PAS positive and blue with trichrome stain.

Insudative lesions

- Ultrastructurally, they are seen to be masses of electron dense material, often containing lipid droplets.

- This insudative lesion, known as hyalinosis, can affect the afferent and efferent arterioles and may ultimately replace the smooth muscle cells.



Diabetic glomerulosclerosis with segmental mesangial Kimmelstiel–Wilson nodule and adjacent microaneurysm. Other mesangial areas have mild diffuse mesangial sclerosis. Arteriolar hyaline insudation is seen near the vascular pole (methenamine silver stain).

Congenital Nephrotic Syndrome

- The term congenital nephrotic syndrome encompasses a heterogeneous group of conditions but is reserved for patients who present clinical symptoms of nephrotic syndrome at birth or within the first 3 months of life.

- Two distinct inherited types have been recognized:
  1. **Congenital nephrotic syndrome of the Finnish type**
  2. **Diffuse mesangial sclerosis (DMS).**

- Neither form responds to steroids or immunosuppressive therapy, and renal transplantation is the only way to prolong and improve the quality of life.

Congenital Nephrotic Syndrome of the Finnish Type

- It is a rare autosomal recessive disease caused by mutations of the *NPHS1* gene located on chromosome 19q13.1.

- More than **70 mutations in *NPHS1* gene** have been identified worldwide, and majority are frameshift mutations (Fin-major) leading to complete absence of nephrin expression and an early onset severe nephrotic syndrome with rapid progression to end-stage kidney disease.

- The disease manifests in the fetal stage with heavy proteinuria in utero.

- At birth, the patients have large placentas, proteinuria, edema, and a high susceptibility to infections.

- Premature birth, mild abnormalities in face and limbs, and poor somatic development are common findings.

- The nephrotic syndrome often makes its appearance during the **first days of life** and **does not respond to steroid therapy**.

- The disease is progressive during the first 2 years of life, and kidney transplantation is the only successful life-saving treatment.

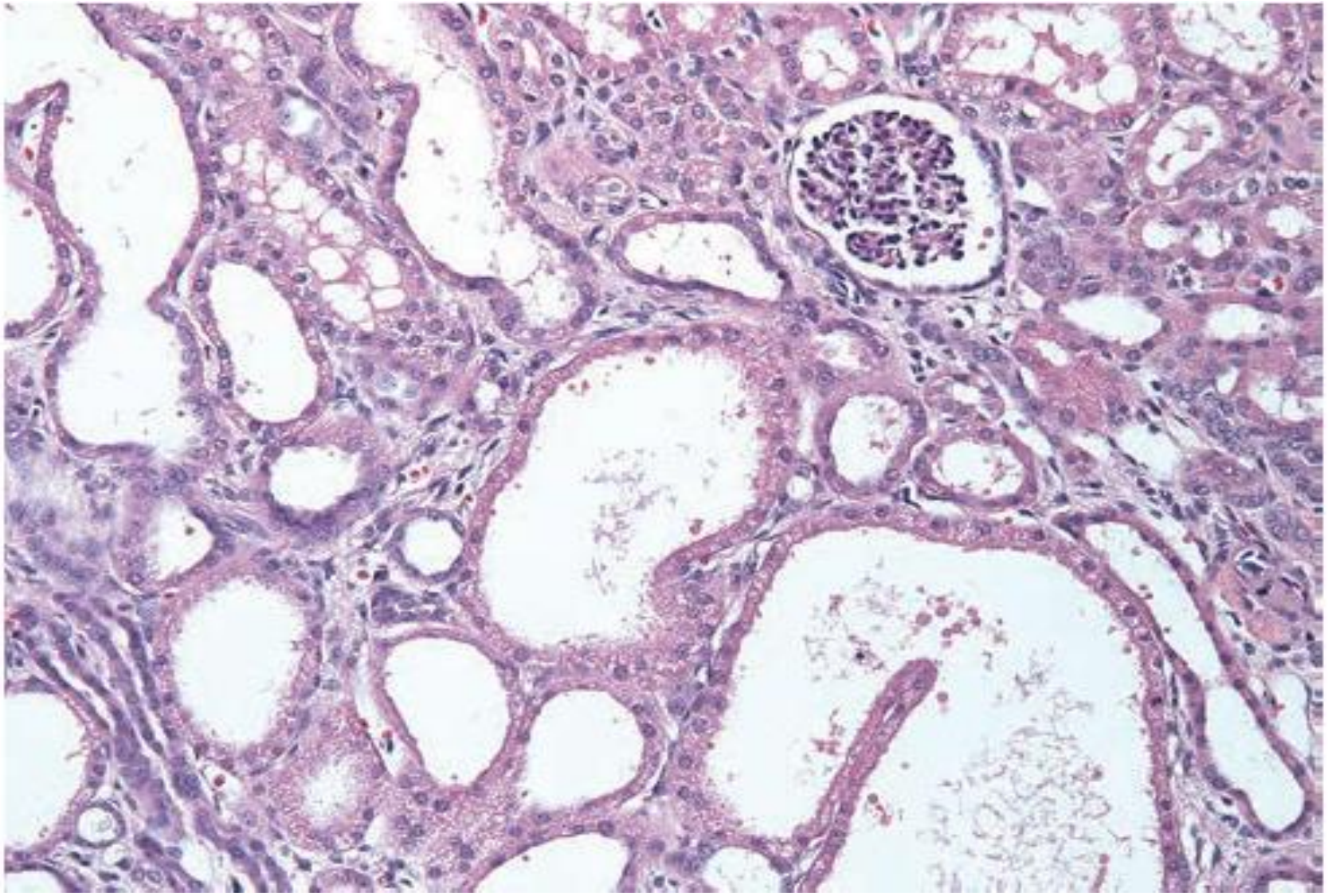
Light microscopy.

- The most striking histologic feature is ectasia of the proximal and distal tubules with flattening of the tubular epithelium

- The glomeruli show minimal changes early on but subsequently develop varying degrees of mesangial proliferation, sclerosis, and dilation of the Bowman space.

- Obliteration of epithelial foot processes and other podocyte changes seen in MCD are observed by **electron microscopy**.

- **Immunofluorescence** is usually negative for immunoglobulins and complement components.



Microcystic dilation of proximal tubules and interstitial scarring in a 1-year-old child with congenital nephrotic syndrome, Finnish type.

Glomerular Lesions Associated With the Syndrome of Acute Nephritis

- Patients with this syndrome present with **hematuria, azotemia, oliguria, and mild to moderate hypertension**.

- Urinalysis reveals an “active” sediment, which consists of the presence of **red blood cells, leukocytes, and red blood cell casts.**

- Proteinuria is common but is rarely in the nephrotic range.

- Edema, when present, is usually mild and is frequently manifested by facial puffiness.

- As with the nephrotic syndrome, the **histopathologic lesions that can give rise to this clinical presentation are varied.**

Diffuse Endocapillary Proliferative Glomerulonephritis

- Diffuse endocapillary (or intracapillary) proliferative glomerulonephritis is a term used to describe lesions characterized by both mesangial and endothelial proliferation.

- Although this category has become virtually synonymous with acute poststreptococcal glomerulonephritis, it may occur after infections caused by other;
  - Bacteria,
  - Viruses
  - Parasites

Acute Poststreptococcal Glomerulonephritis

- Poststreptococcal glomerulonephritis is primarily a disease of childhood, usually occurring between the ages of 5 and 15 years, but it can affect individuals of any age.

- Males are affected more commonly than females, with a ratio of 2 : 1.

- In the classic form, the disease occurs within 1–4 weeks after infection with a nephritogenic strain of group A β-hemolytic streptococci

- The principal serotypes implicated in glomerulonephritis are streptococci of group M types 12, 4, 1, and 49.

- poststreptococcal glomerulonephritis is an immune complex disease, and the main target antigens implicated thus far include “streptococcal pyrogenic exotoxin B” (SPEB) and “nephritis associated plasmin receptor.”

- SPEB is a cationic protein that co-localizes in the subepithelial deposits and both antigens promote plasmin activity, contributing to glomerular tissue injury.
- In addition, the circulating antigen-antibody complexes deposit in subendothelium, activate the alternative and possibly lectin complement pathway, and trigger an inflammatory response.

- Antibodies to certain streptococcal antigens, such as antistreptolysin O (ASO), are elevated, but this finding may not be helpful in diagnosis due to the ubiquitous nature of streptococcal infections.

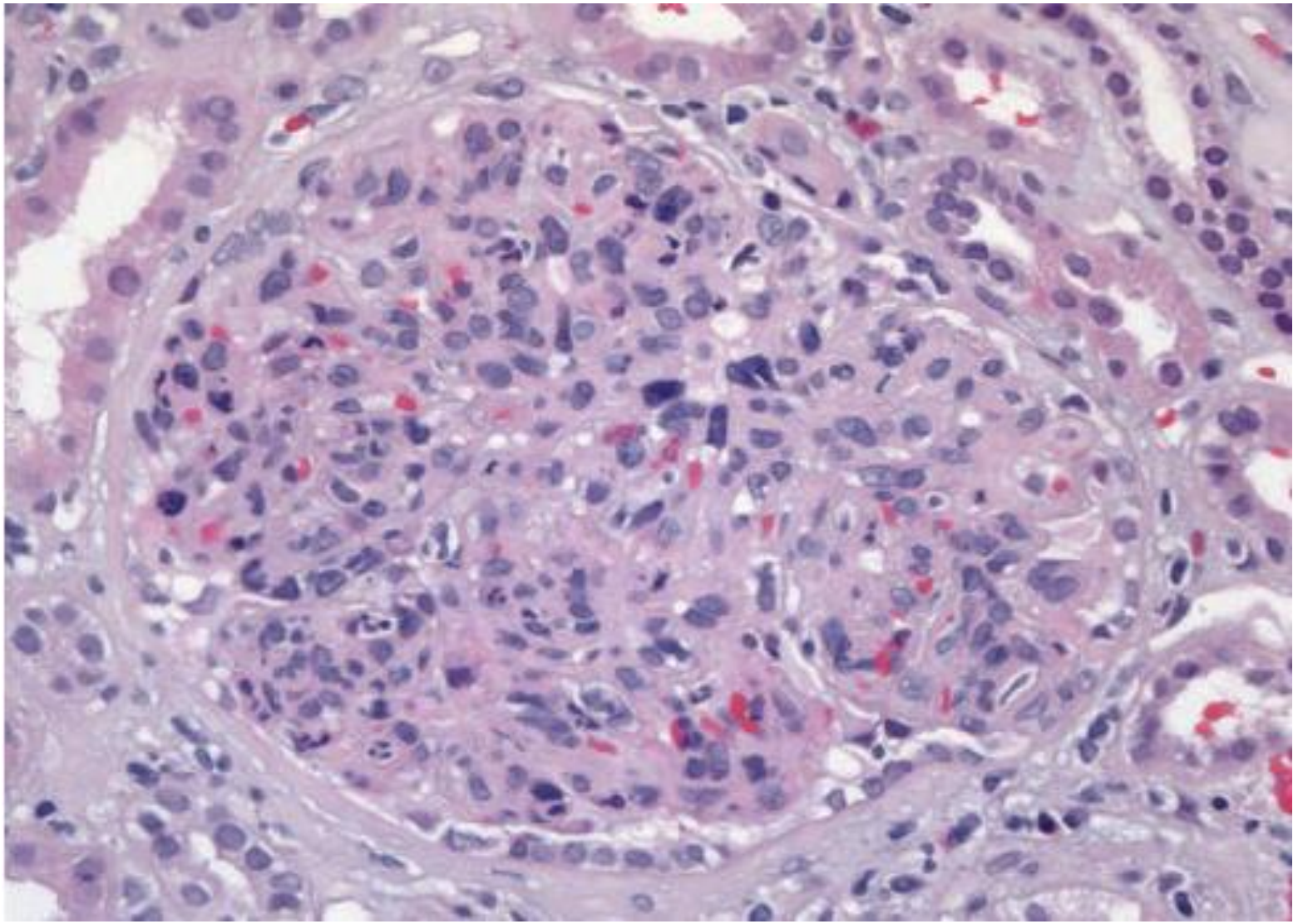
Light microscopy

- Diffuse enlargement of the glomerular tufts that tend to narrow the Bowman space.

- Glomerular intracapillary cellularity is increased due to mesangial proliferation

- Proliferating and swollen endothelial cells.

- Infiltration of leukocytes



Diffuse Proliferative Glomerulonephritis. There is marked hypercellularity due to an increase in mesangial and endothelial cells and infiltration by inflammatory cells.

IgA-Dominant Staphylococcal Infection-Associated Glomerulonephritis

- Staphylococcal infection-associated glomerulonephritides are more common in the elderly population (over 60 years of age) with comorbidities such as diabetes mellitus, drug abuse, alcoholism, and malignancy.

- The underlying infection is typically ongoing (rather than “post-infection”) and is often brought to attention by the kidney disease.

- The characteristic feature of this entity is IgAdominant or co-dominant immune deposits that are seen in addition to C3.

Pathogenesis

- *S. aureus* enterotoxins and possibly other antigens function as "superantigens," meaning ,**capable of binding directly to the major histocompatibility complex (MHC) class II molecules on antigen presenting cells without the required intracellular antigen processing to form receptor-fitting peptides**.

- These superantigens bind to T-cell receptors, causing massive T-cell activation, proliferation, and cytokine release.

- These events in turn trigger polyclonal B-cell activation with subsequent production of polyclonal IgA and IgG.

Light microscopy

- Mild mesangial hypercellularity to diffuse endocapillary proliferation with accompanying acute tubular injury and interstitial inflammation.

Electron microscopy

- The electron-dense deposits are primarily in the mesangium and paramesangium,
- The subepithelial “humps,” the hallmark of infection-related glomerulonephritis, are seen in less than 50% of patients. When present, these subepithelial deposits are often smaller and less “hump”-like.

Diffuse Mesangioproliferative Glomerulonephritis

- Diffuse proliferation of the mesangial cells and matrix without significant involvement of capillary walls or lumina occurs in a variety of renal diseases, including;
  - IgAN,
  - HSP,
  - SLE, and
  - Resolving stage of postinfectious glomerulonephritis.

- Only IgAN is discussed in this section.

IgA Nephropathy

- IgAN (previously called Berger disease) is defined by the predominant deposition of IgA in the glomerular mesangium

- The familial forms of IgAN follow autosomal dominant transmission with incomplete penetrance.

- The diagnosis of IgAN is primarily based on the demonstration of IgA deposits in the mesangium, a feature seen in association with several conditions.

Box 23.5 Entities associated with secondary IgA nephropathy

Liver diseases

Alcoholic cirrhosis, viral hepatitis, toxic liver disease, cystic fibrosis

Gastrointestinal diseases

Crohn disease, ulcerative colitis, celiac disease

Infectious diseases

HIV infection, tuberculosis, brucellosis, leprosy, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Clostridium difficile*, *Yersinia enterocolitica*

Rheumatologic diseases

Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Behçet disease, Reiter syndrome

Neoplastic diseases

Various carcinomas, including squamous cell carcinomas, small cell lung carcinoma, renal cell carcinoma, and a variety of adenocarcinomas, non-Hodgkin lymphoma, polycythemia vera, mycosis fungoides/Sézary syndrome

Skin diseases

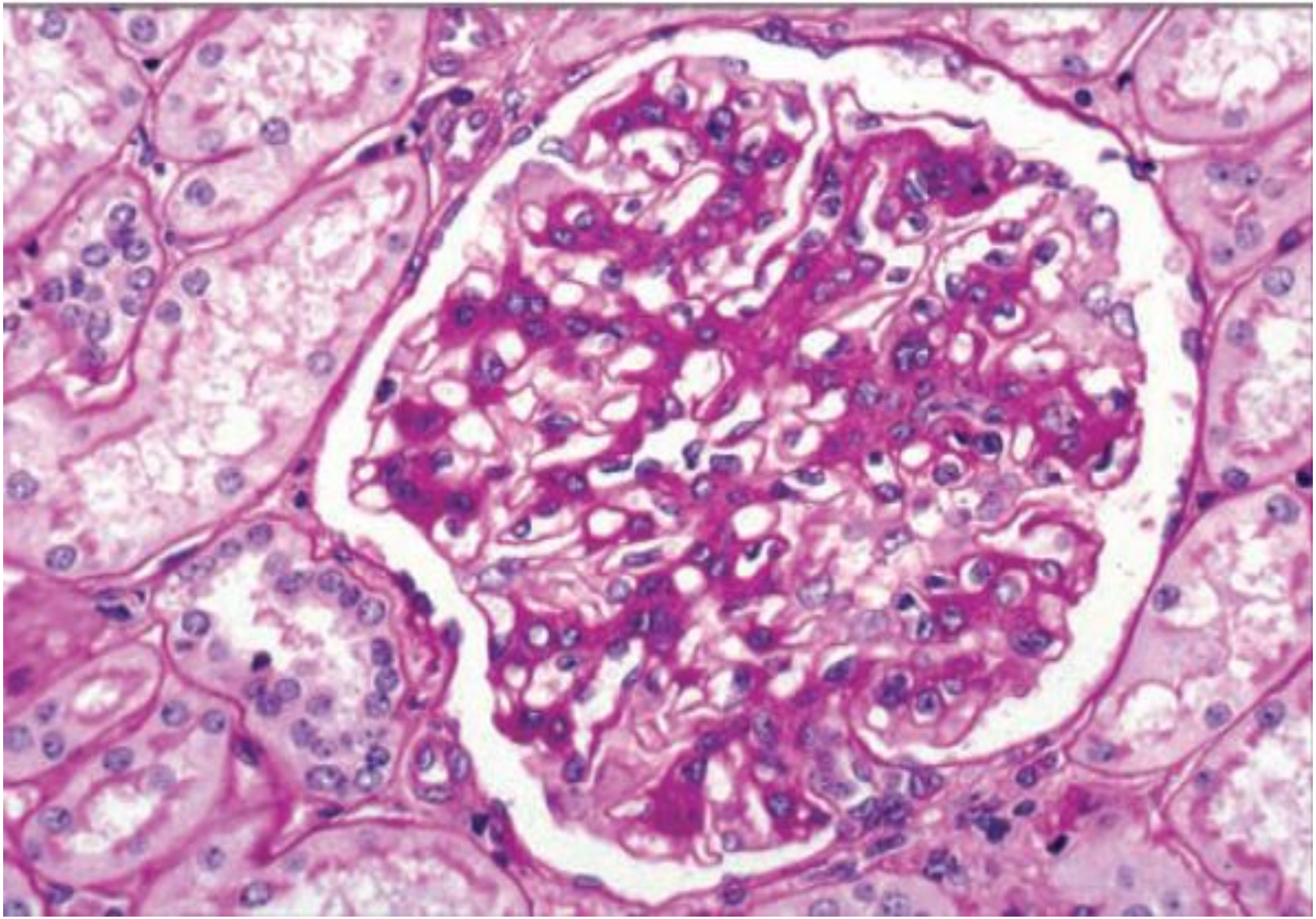
Dermatitis herpetiformis, psoriasis

Miscellaneous diseases

Sarcoidosis, silicosis, bronchiolitis obliterans, uveitis with retinal vasculitis

- IgAN results from the deposition of circulating immune complexes in the glomerular mesangium, leading to the activation of the complement cascade via the alternative pathway.

- The deposited IgA in idiopathic form is predominantly aberrantly glycosylated polymeric IgA1.



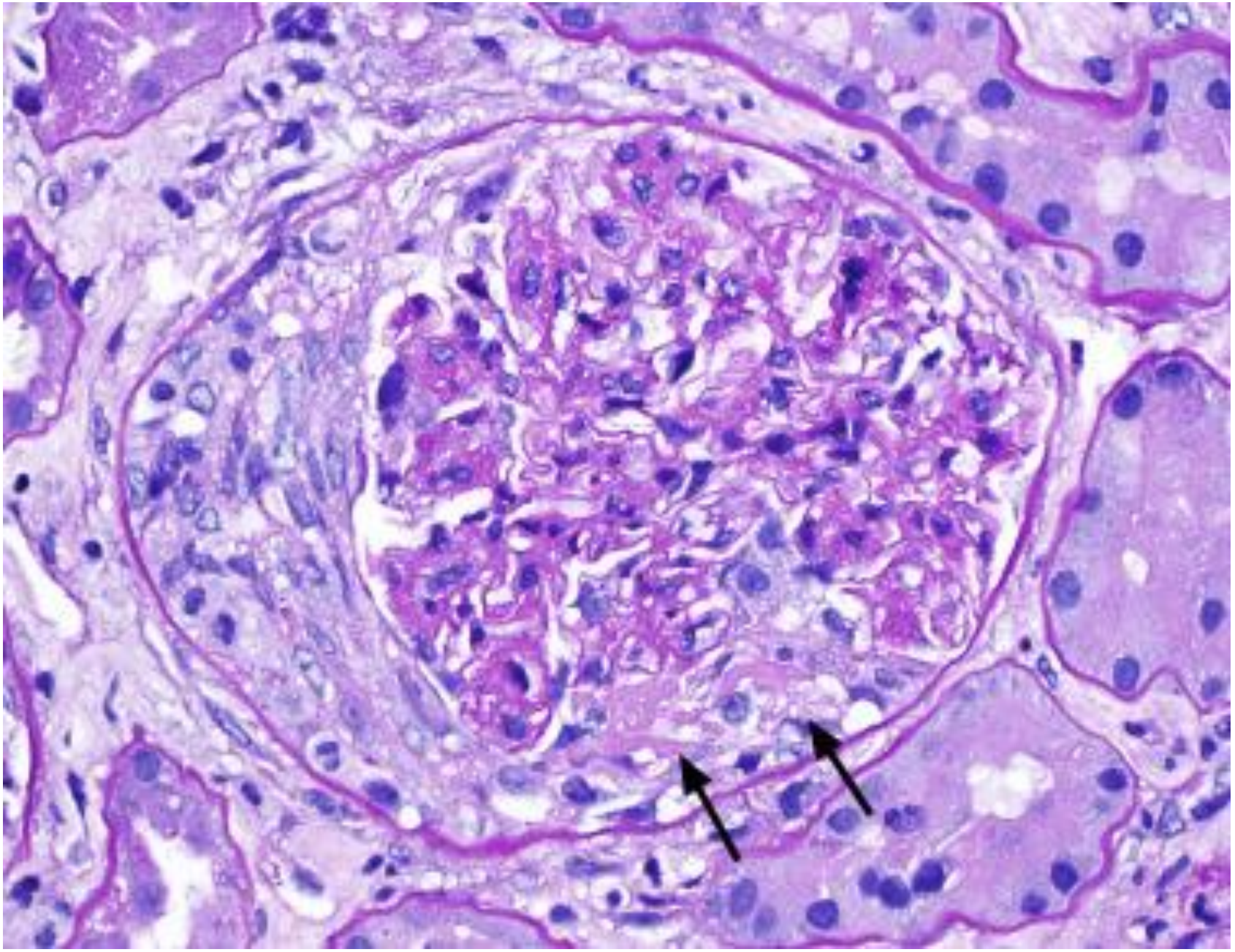
Mesangial enlargement with increase in mesangial matrix and cellularity in IgA nephropathy (PAS).

Crescentic Glomerulonephritis

- *Crescentic glomerulonephritis* is a histopathologic term used to designate a severe form of glomerulonephritis in which 50% or more of the glomeruli are involved by epithelial crescents.

- It is associated with a clinical syndrome known as rapidly progressive glomerulonephritis that is characterized by the rapid and progressive loss of renal function accompanied by hematuria, red cell casts in urine, variable degrees of proteinuria, and severe oliguria.

- Untreated, this disease can result in death within weeks.



Antiglomerular Basement Membrane Disease

- This form of glomerulonephritis is characterized by the immunofluorescent demonstration of linear deposits of IgG and, in many instances, C3 along the GBM.

- It can occur as a renal-limited disease or as a pulmonary renal syndrome induced by a cross reaction of the anti-GBM antibodies with pulmonary basement membranes **(Good pasture syndrome)**.

- Patients with Good pasture syndrome present with **glomerulonephritis and pulmonary involvement, which is more often in the form of severe pulmonary hemorrhage.**

- A preceding upper respiratory infection has been documented in about one-fourth of these patients.

- Pulmonary hemorrhage has also been observed after exposure to various inhalants, particularly hydrocarbons and there is an association with cigarette smoking.

- The principal antigen to which anti-GBM antibodies react is localized to the carboxyl terminus of the NC1 domain of the α3 chain of type IV collagen (**Good pasture epitope).**

- **Genetic predisposition** may play a role, and there is a strong association between certain HLA class II antigens and risk of developing anti-GBM nephritis.

- Up to one-third of the patients with anti-GBM disease have circulating ANCA, especially with specificity for myeloperoxidase (MPO).

- The presence of ANCA in patients with anti-GBM disease is associated with small vessel vasculitis in various organs in addition to lung and kidney.

Lupus Nephritis

- SLE is a multisystem, autoimmune disease with a broad range of clinical presentation that has a high morbidity and mortality.

- Serum antinuclear antibodies (ANAs) are detected in over 95% of patients and their presence is a sensitive marker of SLE, while anti-double-stranded DNA and anti-Sm antibodies are more specific markers.

- There is a genetic predisposition for developing SLE.

- The immune deposits in the kidney (and elsewhere) are derived from either circulating complexes or from an *in situ* combination of antigen and antibody.

- Immune-complex deposition is the most common form of glomerular injury.

- Microscopic hematuria is almost always present, but rarely does it develop in isolation; macroscopic hematuria is rare.

- The pathologic findings of lupus nephritis are extremely diverse and may occur in all four renal compartments: **glomeruli, tubules, interstitium, and blood vessels.**

- **Standardized histologic classification** of lupus nephritis developed by the **International Society of Nephrology (ISN)/Renal Pathology Society (RPS)** provides clear definitions for diagnostic categories based on quantitative assessment of individual histologic lesions.

International Society of Nephrology/Renal Pathology Society classification of lupus nephritis

CLASS	PATHOLOGY DIAGNOSIS	DESCRIPTION
I	Minimal mesangial LN	Normal by LM, mesangial deposits by IF and EM
II	Mesangial proliferative LN	Mesangial proliferation on LM, mesangial deposits by IF and EM
III	Focal LN (<50% of glomeruli)	Active or chronic lesions by LM in <50% glomeruli, usually subendothelial (in addition to mesangial) deposits by IF and EM
III (A)	Active lesions	Active lesions include endocapillary proliferation, cellular crescents, karyorrhexis/necrosis, neutrophils, and wire loops
III (A/C)	Active and chronic lesions	
III (C)	Chronic lesions	Chronic lesions include segmental or global glomerulosclerosis attributable to LN, and fibrous crescents
IV	Diffuse LN (≥50% of glomeruli)	Active or chronic lesions by LM in >50% glomeruli, usually subendothelial (in addition to mesangial) deposits by IF and EM
IV (A)	Active lesions	Subclassification of active lesions as S (segmental) or G (global) based on extent of glomerular tuft affected
IV (A/C)	Active and chronic lesions	
IV (C)	Chronic lesions	Subclassification of chronic lesions as S (segmental) or G (global) based on extent of glomerular tuft affected
V	Membranous LN	Subepithelial deposits present by LM, IF, and EM; can co-exist with class III or IV
VI	Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)	Global glomerulosclerosis attributable to LN

EM, Electron microscopy; *IF*, immunofluorescence microscopy; *LN*, lupus nephritis.

Tubulointerstitial diseases

- 2 major groups of processes
  - A) ischemic or toxic tubular injury (AT Necrosis)
  - B) inflammatory reactions (tubulointestitial nephritis)

A) Acute tubular necrosis

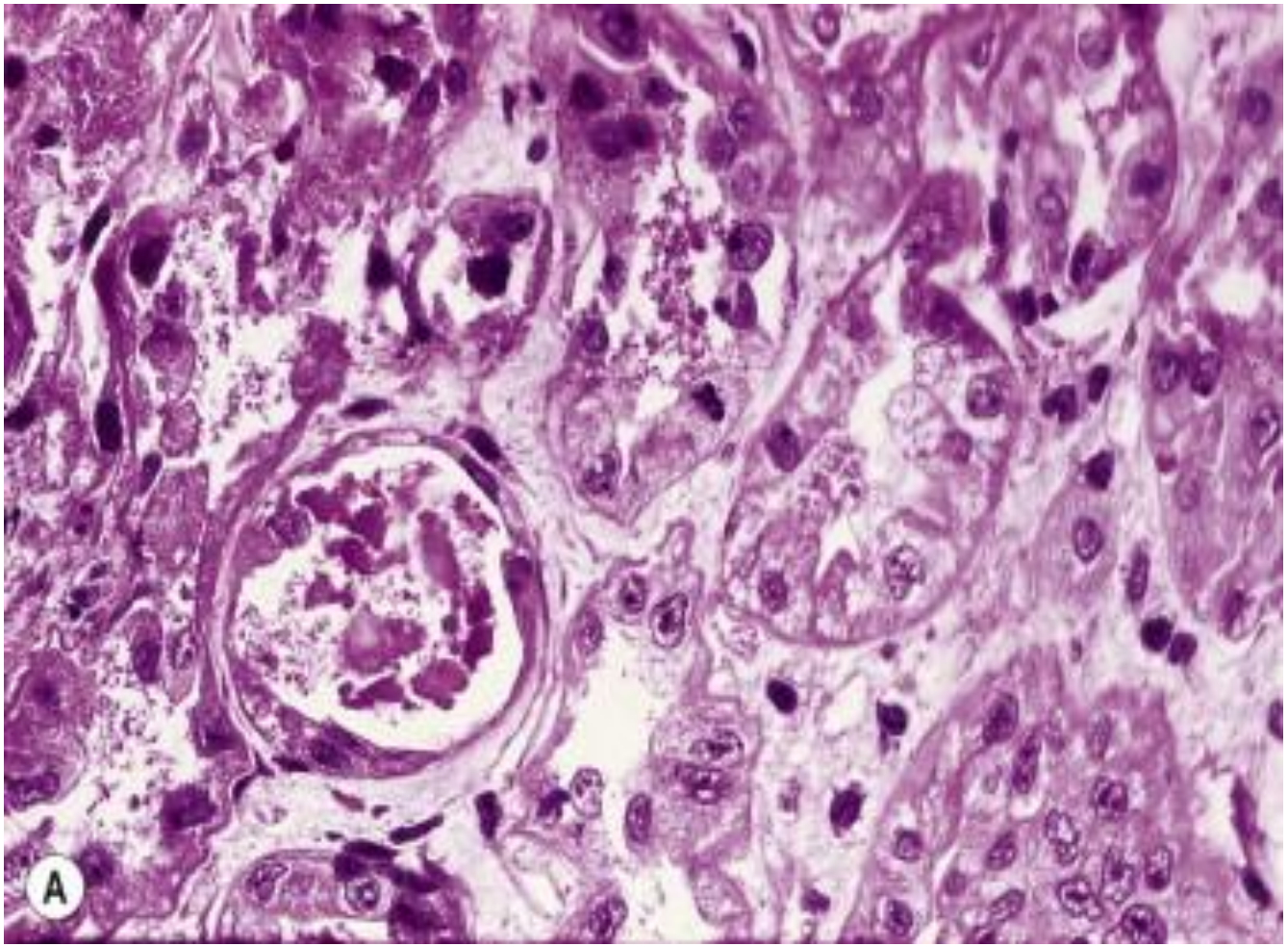
- Clinicopathologic syndrome characterised by acute suppression of renal function accompanied by morphologic evidence of tubular epithelial cell injury
- 2 subtypes
  - Ischemic=> hypoperfusion
  - Toxic=> eg

- c/f
  - Rapid increase in serum creatinine
  - Oliguria
  - Anuria
- Urinalysis-sloughed degenerated epithelial cells and granular casts

- Microscopy
  - Single cell necrosis with desquamation
  - Loss of proximal tubule brush border
  - Tubular dilatation
  - Pigmented (brown) casts in distal tubules
  - Crystals in distal tubules and collecting ducts
  - Mild interstitial edema and inflammation
  - Accumulation of leukocytes in the vasa recta of outer medulla

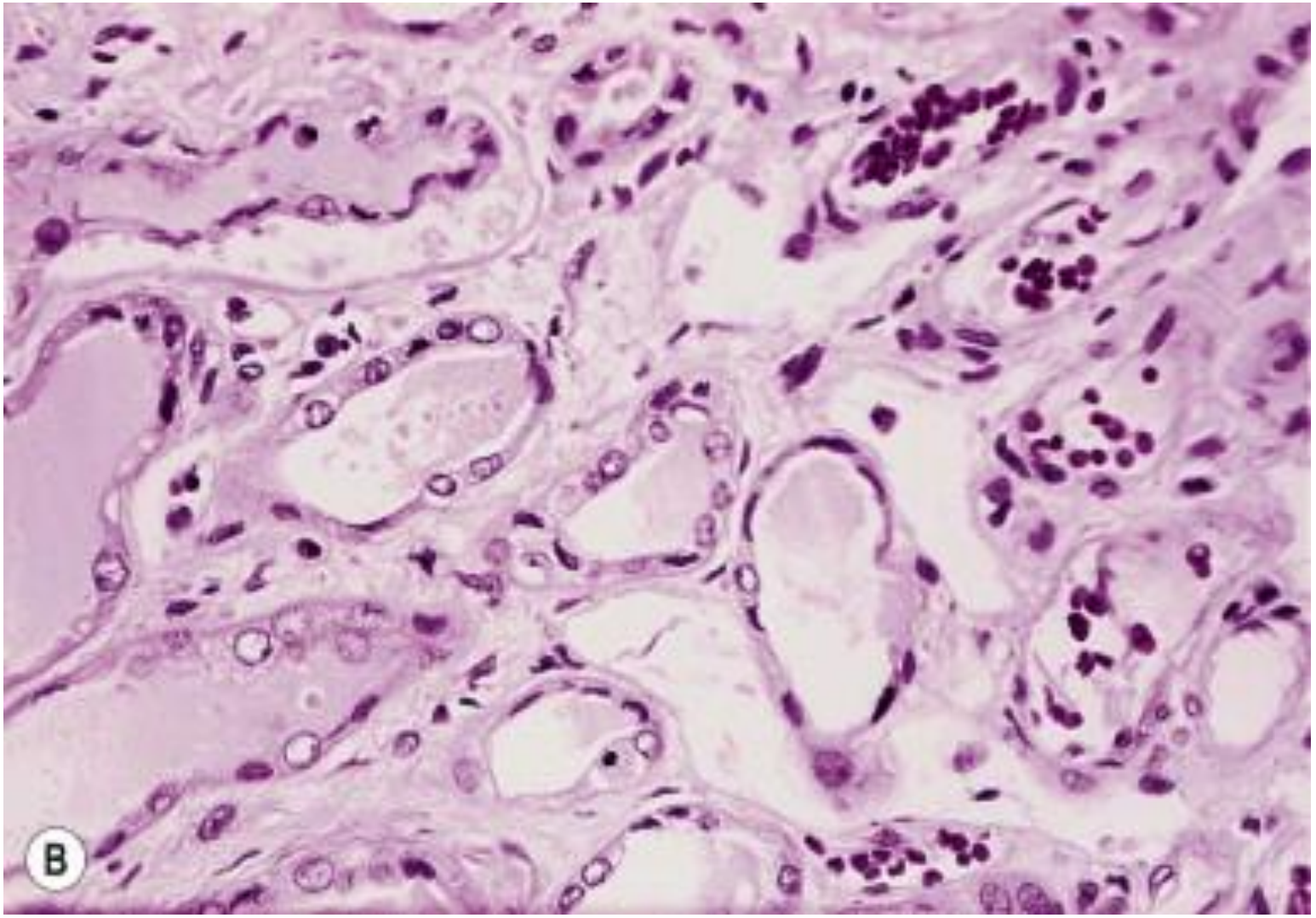
Acute tubular necrosis.

There is focal necrosis and desquamation of the cells into the tubular lumen



- After initial injury evidence of tubular regeneration can be seen;
  - Flattened epithelium with dilation of tubular lumen
  - Presence of large nuclei with prominent nucleoli
  - Mitotic activity
- Kidney injury molecule- 1

The tubules are dilated and lined by flattened epithelium.



B) Tubulointerstitial nephritis

- Heterogeneous group of conditions that primarily affect the renal interstitium and tubules.
- Is causes of renal failure in abt 20-40% of pts with end stage renal dz.
- Different etiologies

- Infections
  - Acute pyelonephritis
    - Ascending or hematogenous infection
    - Bacteria, fungi
  - Chronic pyelonephritis
    - Non obstructive (reflux associated)
    - Obstructive
    - Xanthogranulomatous
    - malakoplakia

- Obstructive uropathy
  - Hydronephrosis without infection
  - Hydronephrosis with infection
  - Reflux associated nephropathy
- Allergic tubulointerstitial nephritis
  - Drug induced
    - Antibiotics, diuretics, NSAIDS
    - Associated with systemic vasculitis
    - Lupus associated
    - Antitubular basement membrane

- Toxic tubulointerstitial nephritis
  - Drug induced
    - Aminoglycosides
    - Cyclosporine
    - Lithium
    - Analgesics
  - Heavy metals toxicity
    - Cisplatin
    - Lead, mercury, etc
  - Other
    - Radiation, sarcoid, idiopathic

- Manifestations include;
  - Impaired concentrating ability
  - Impaired ability to secrete acid
  - Reduced Na reabsorption
  - Hyperkalemia
  - Azotemia
- Symptoms, acute or chronic

Acute infectious pyelonephritis

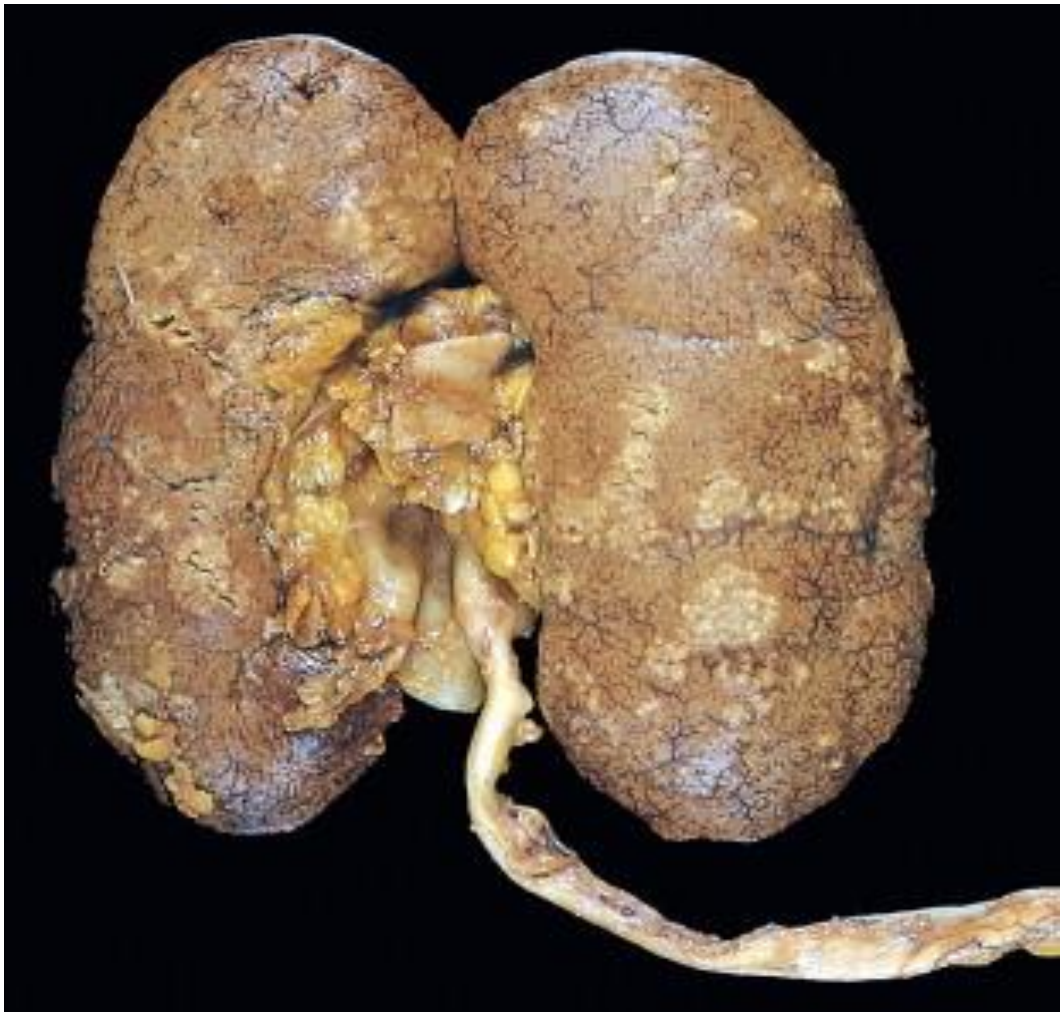
- 3 peaks
  - Infancy and early childhood
  - Women of child bearing age
  - Men/women > 60yrs
- Associated with;
  - Congenital or aquired obstructive lesions of LUT
  - Conditions related to residual urine retention in the bladder

- Etiology
  - Ascending infection
    - G –ve organisms normally present in intestinal tract
      - E. coli
      - Klebsiella
      - Enterobacter
  - Hematogenous infection
    - Stap. Aureus
    - Fungal organisms, candida and aspergillus
    - Esp in immunocompromised states

- Gross
  - Kidney- enlarged
  - Microabscesses in cortex and studding the subcapsular surface of kidney
  - Pus filled collecting ducts that extend into the underlying medulla
  - Dilated pelvicaliceal system and renal papillae are diffusely blunted, with inflammed lining mucosa

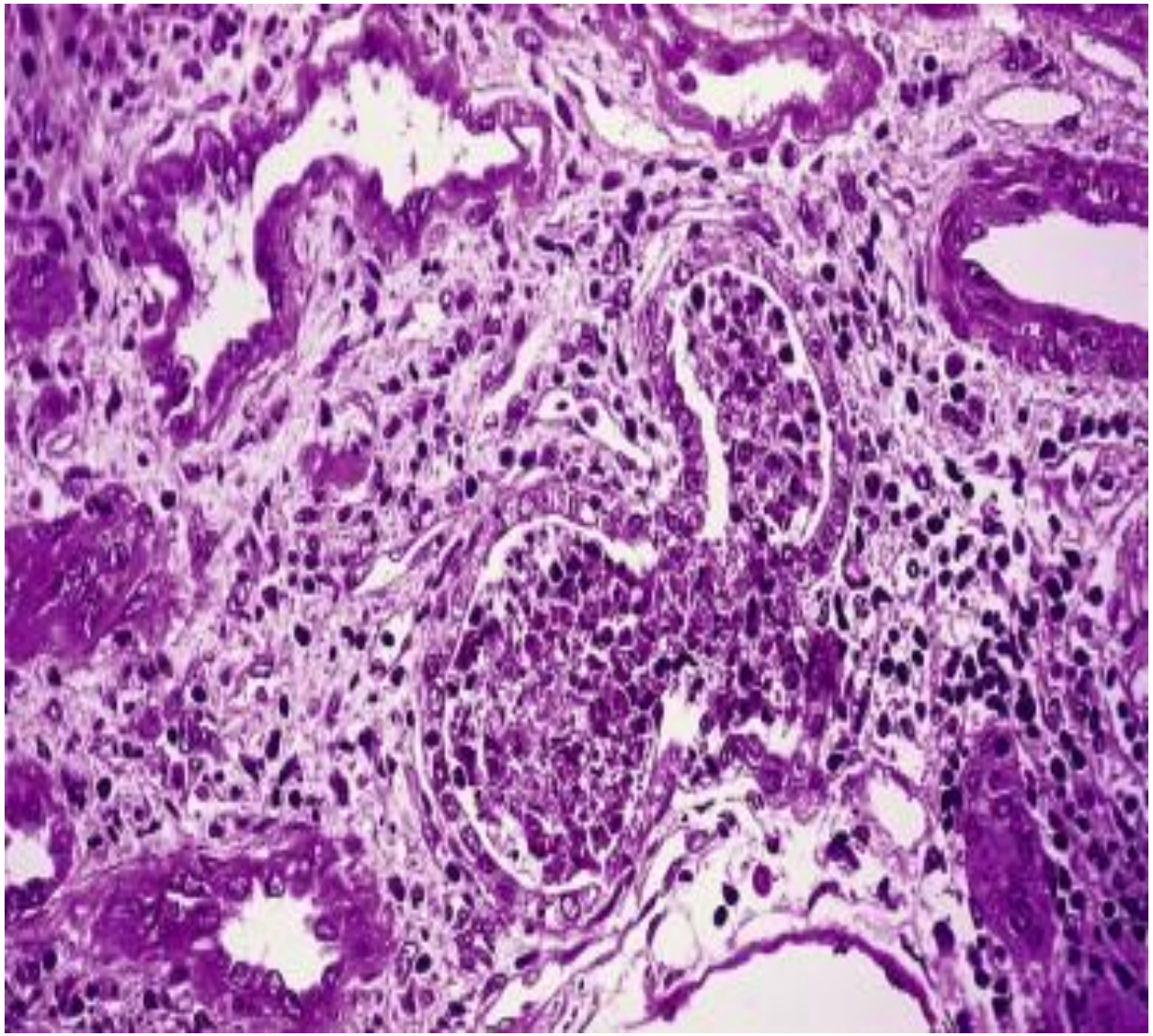
Acute pyelonephritis.

Cortical surface shows grayish white areas of inflammation and abscess formation

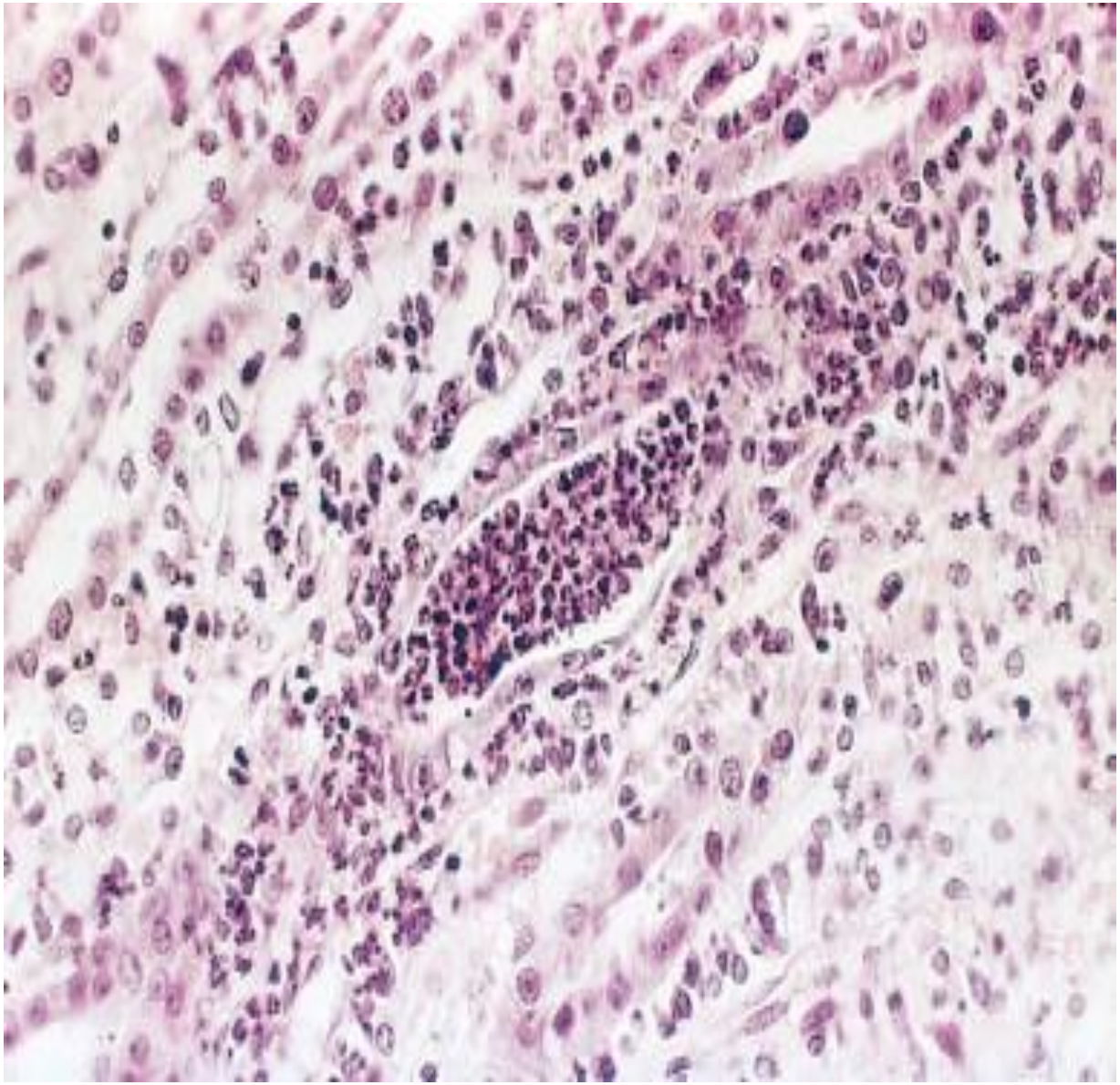


- Microscopy
  - Dense interstitial and intratubular infiltrate of acute inflammatory cells with tubular distruction

There is acute inflammatory infiltrate in the interstitium and tubular lumina



Acute pyelonephritis marked by an acute neutrophilic exudate within tubules and interstitial inflammation



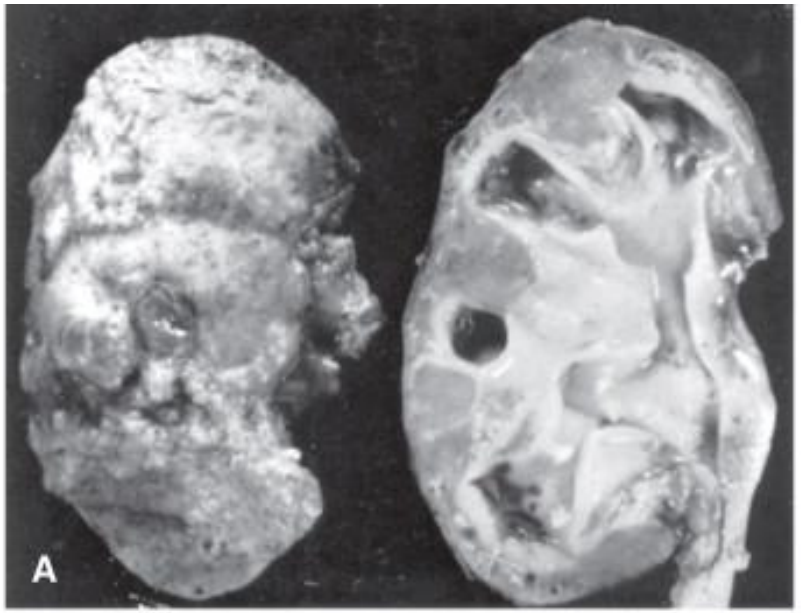
Chronic pyelonephritis

- Chronic obstructive pyelonephritis
    - Ureter obstruction by calculi, tumour, or extrinsic pressure
- Chronic non obstructive pyelonephritis (reflux nephropathy)
    - Results from reflux of urine from bladder into the ureter and renal pelvis

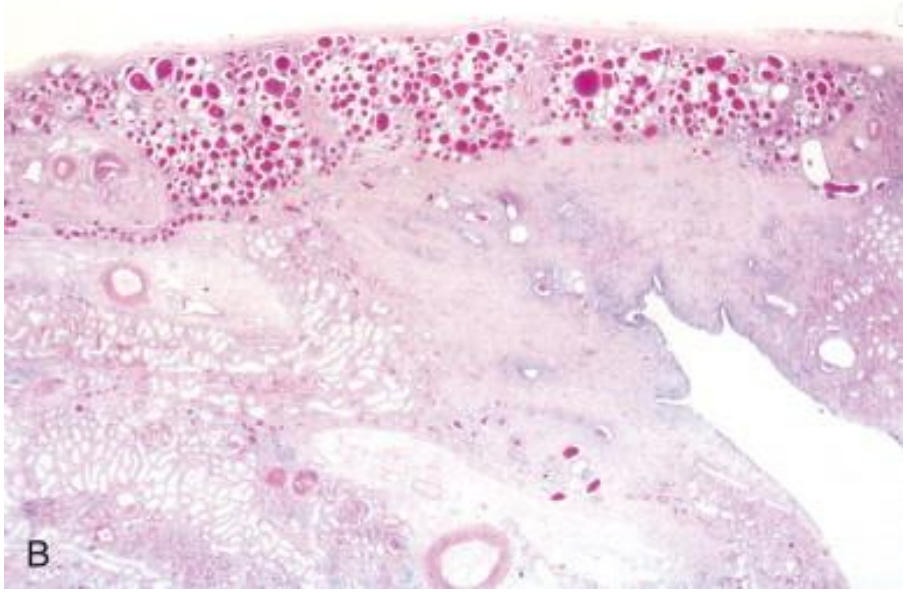
- Gross
  - Focal coarse fibrosis of parenchyma over dilated calyces
  - scaring is more prominent and extensive at poles of kidney=> reflux nephropathy

Chronic pyelonephritis.

The surface *(left)* is irregularly scarred. The cut section *(right)* reveals characteristic dilation and blunting of calyces. The ureter is dilated and thickened, a finding that is consistent with chronic vesicoureteral reflux.



Low-power view showing a corticomedullary renal scar with an underlying dilated deformed calyx. Note the thyroidization of tubules in the cortex.

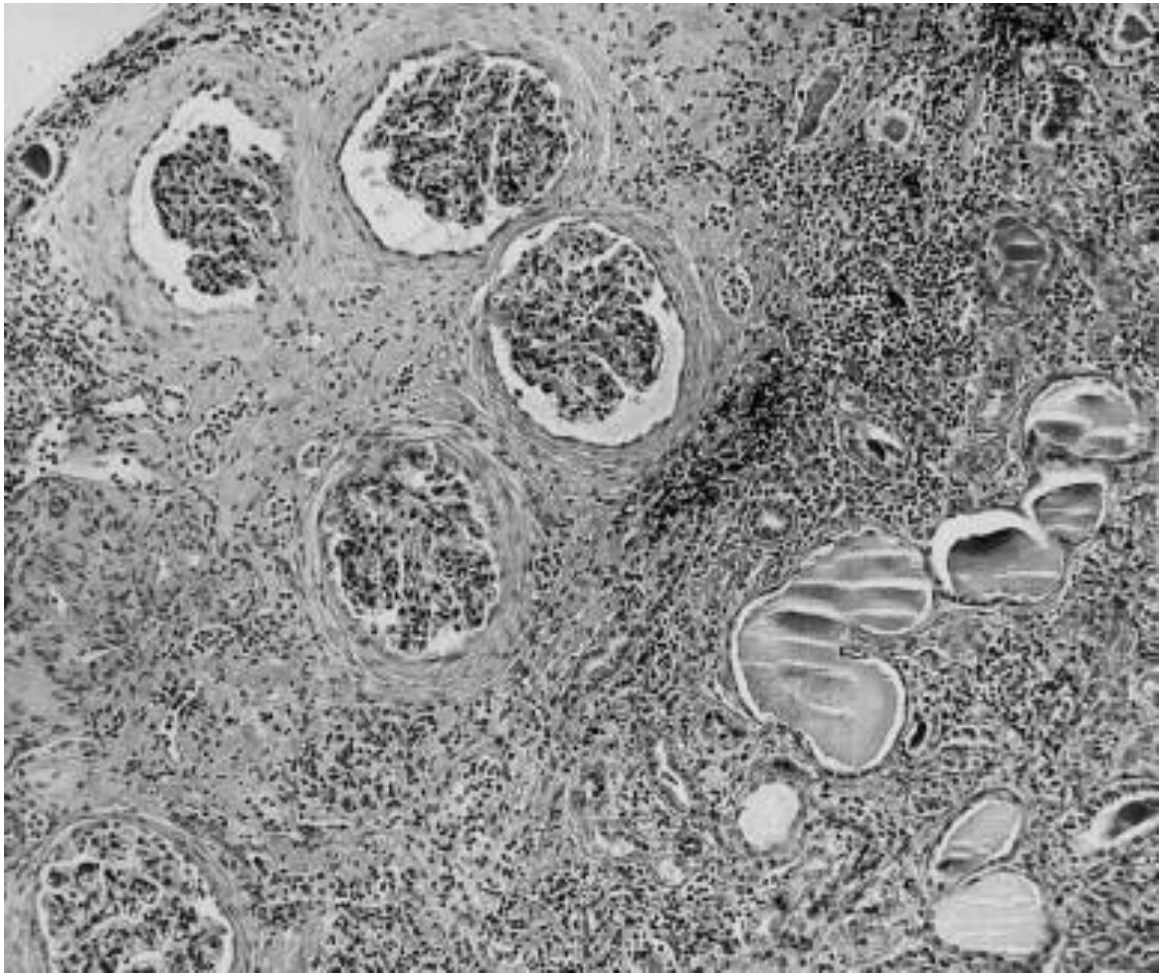


- Microscopy
  - Tubular damage
  - Interstitial inflammation-lymphocytes,histiocytes and plasma cells
  - Fibrosis
  - Tubules are atrophic or dilated, and lined by flattened epithelium and filled with colloid casts(thyroidization)
  - Tamm-Horsfall protein-in interstitium=> small bodies of amorphous fibrillary material-PAS +
  - +/- periglomerular fibrosis
  - +/-Focal and segmental sclerosis and hyalinosis=>ischemic changes

Nephrectomy specimen from a patient with obstructive hydronephrosis

There is interstitial scarring with periglomerular fibrosis and mononuclear inflammatory cell infiltration

The tubules are atrophic and contain hyaline casts.

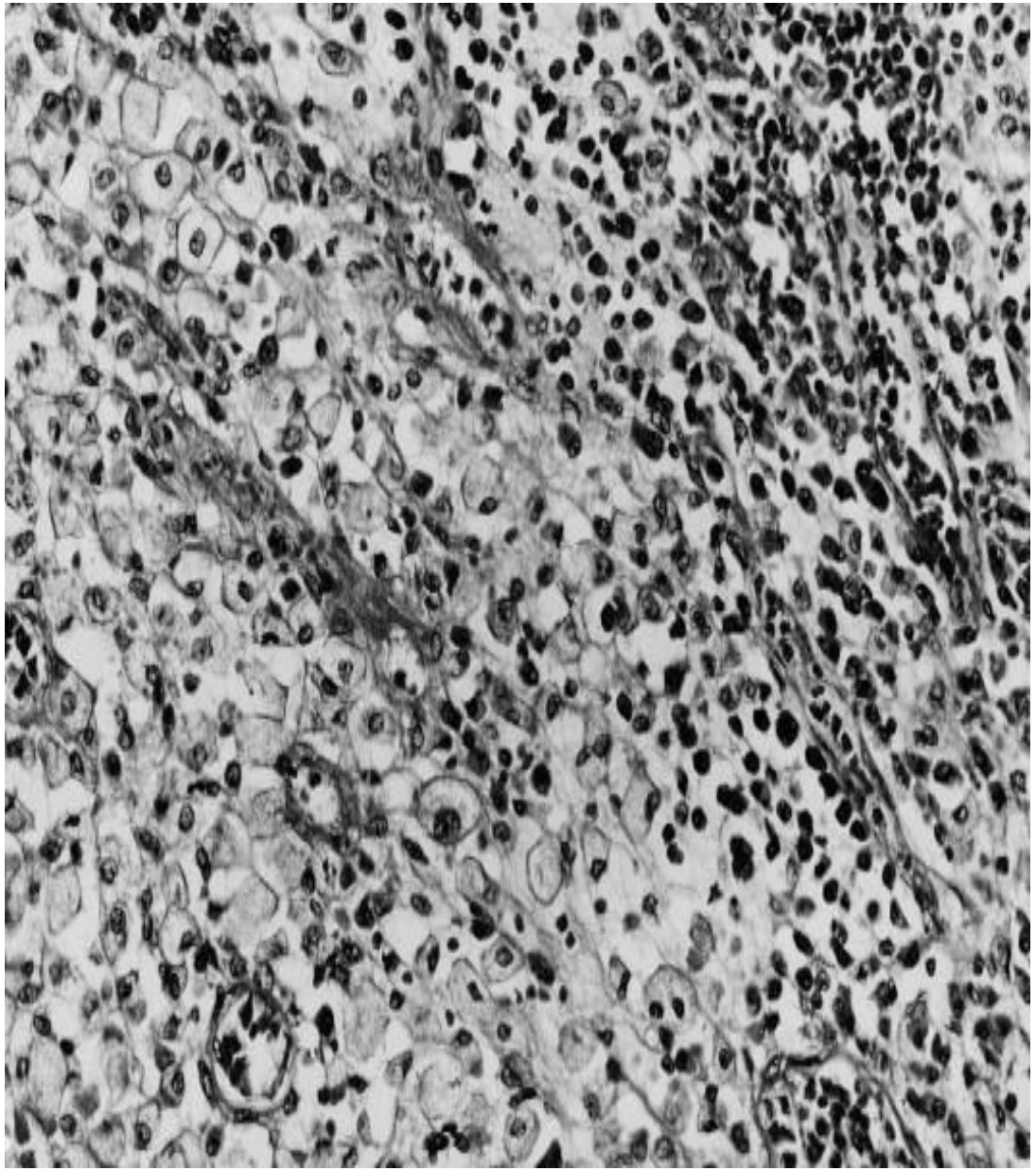


- **Xanthogranulomatous pyelonephritis**
  - Uncommon
  - Distinct type of chronic infectious pyelonephritis
  - Yellow, lobulated masses diffusely replace the renal architecture
  - Usu unilateral
  - Any age
  - F:M 2:1
  - Urinary obstruction usu caused by stone
  - Mass occupying nature= ? Renal cell ca

- Microscopy
  - Diffuse granulomatous inflammatory infiltrate (foamy macs + multinucleated giant cells+ lymphocytes, plasma cells, neutrophils)
- E. coli is usu etiological agent
- Others, proteus mirabilis and s. aureus

Foamy histiocytes in xanthogranulomatous pyelonephritis

Lymphocytes and plasma cells are also present.

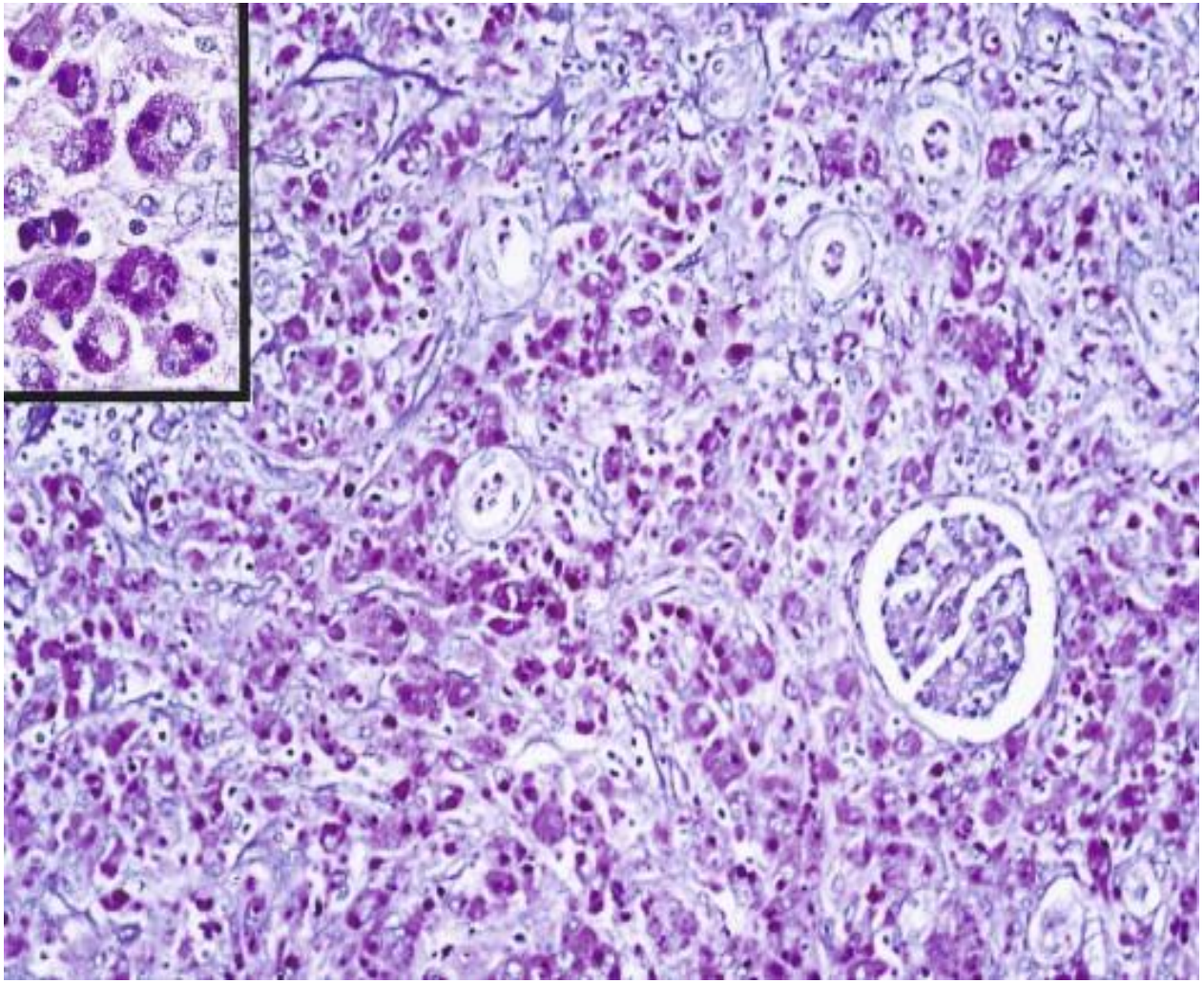


- Malakoplakia
  - Rare
  - Inflammatory reaction
  - Caused by enteric bacteria
  - Gross + microscopy; like xanthogranulomatous pyelonephritis
  - Distinctive **Michaelis-Gutmann bodies** in histiocytes and extracellularly in the stroma=PAS +

Nephrectomy specimen from a patient with malakoplakia

The interstitium is infiltrated by numerous macrophages with granular cytoplasm.

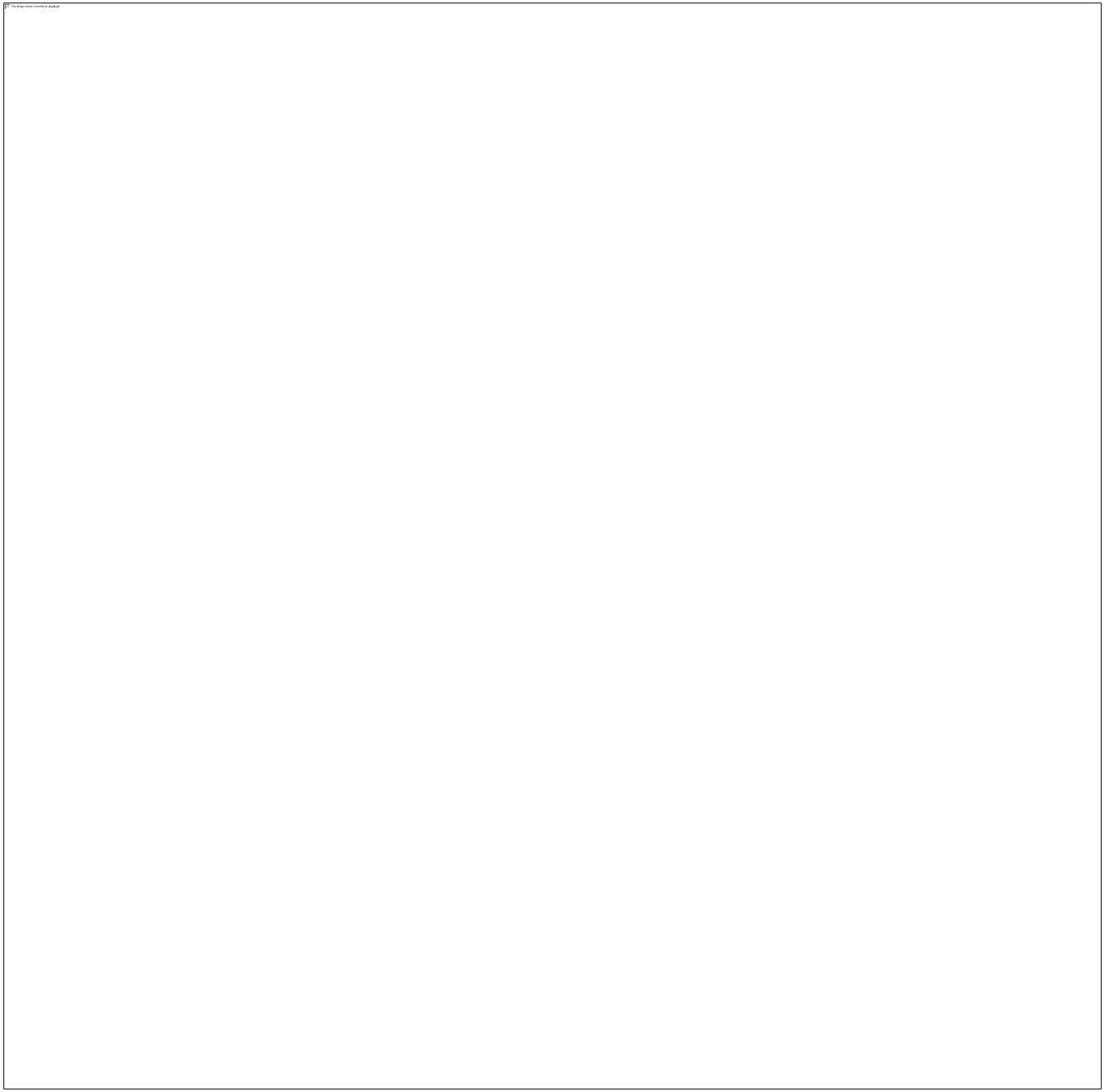
Inset: Several Michaelis–Gutmann bodies are seen in the cytoplasm.



Cysts of the kidneys

- Heterogeneous
  - hereditary
  - developmental
  - acquired

- **AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE**
    - hereditary
    - multiple expanding cysts of both kidneys
    - result in renal failure (4th-5th decade)
    - Mutations in PKD1 and PKD2 genes
    - polycystin-1, polycystic 2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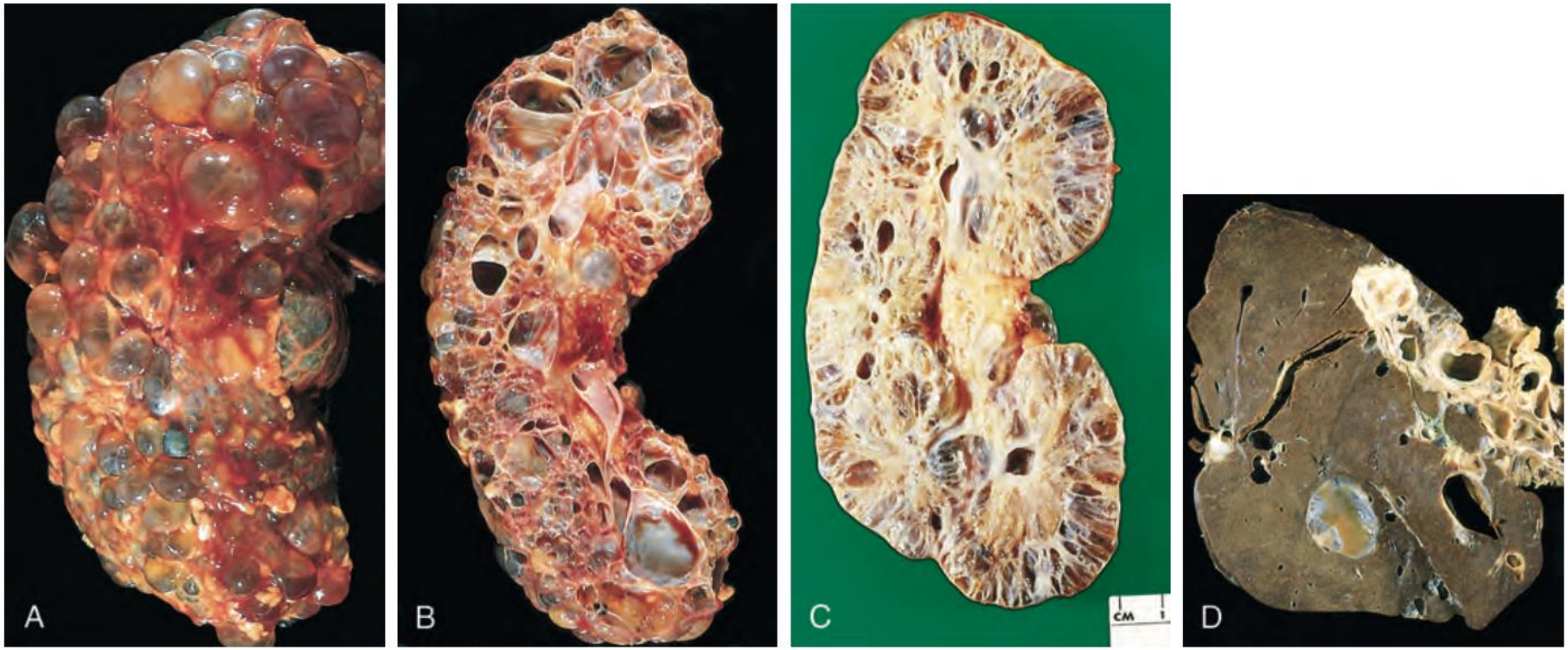
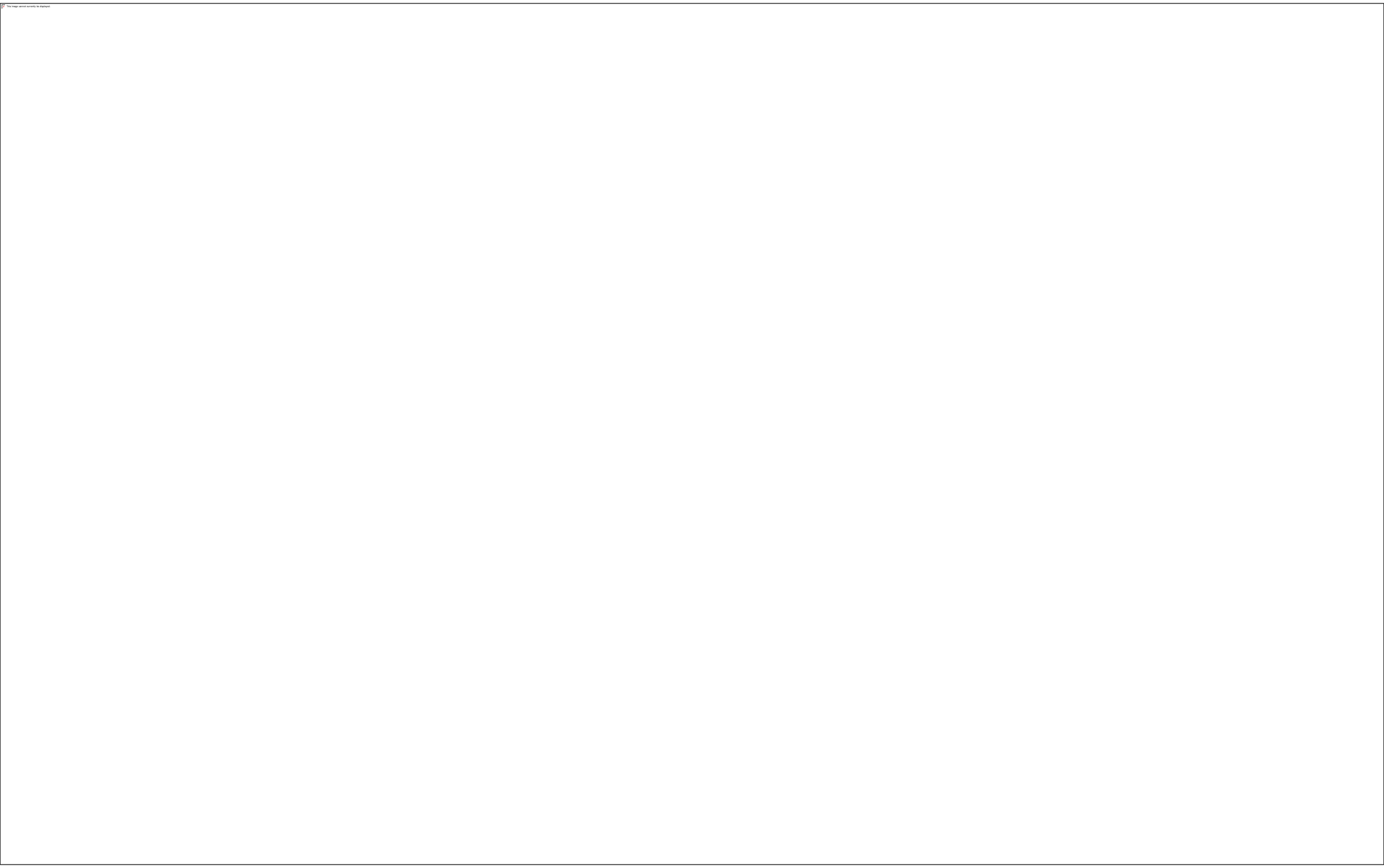


Figure 20-44 **A** and **B,** Autosomal dominant adult polycystic kidney disease (ADPKD) viewed from the external surface and bisected. The kidney is markedly enlarged and contains numerous dilated cysts. **C,** Autosomal recessive childhood PKD, showing smaller cysts and dilated channels at right angles to the corti

- **AUTOSOMAL RECESSIVE (CHILDHOOD) POLYCYSTIC KIDNEY DISEASE**
  - prenata, neonatal, infantile and juvenile
  - serious manifestations at birth
  - young infant=> rapid renal failure
  - mutations of the PKHD1 gene
    - expressed in kidney, liver and pancreas
  - PKHD1 gene=> fibrocystin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URINARY TRACT OBSTRUCTION

- increases susceptibility to;
    - infection
    - stone formation

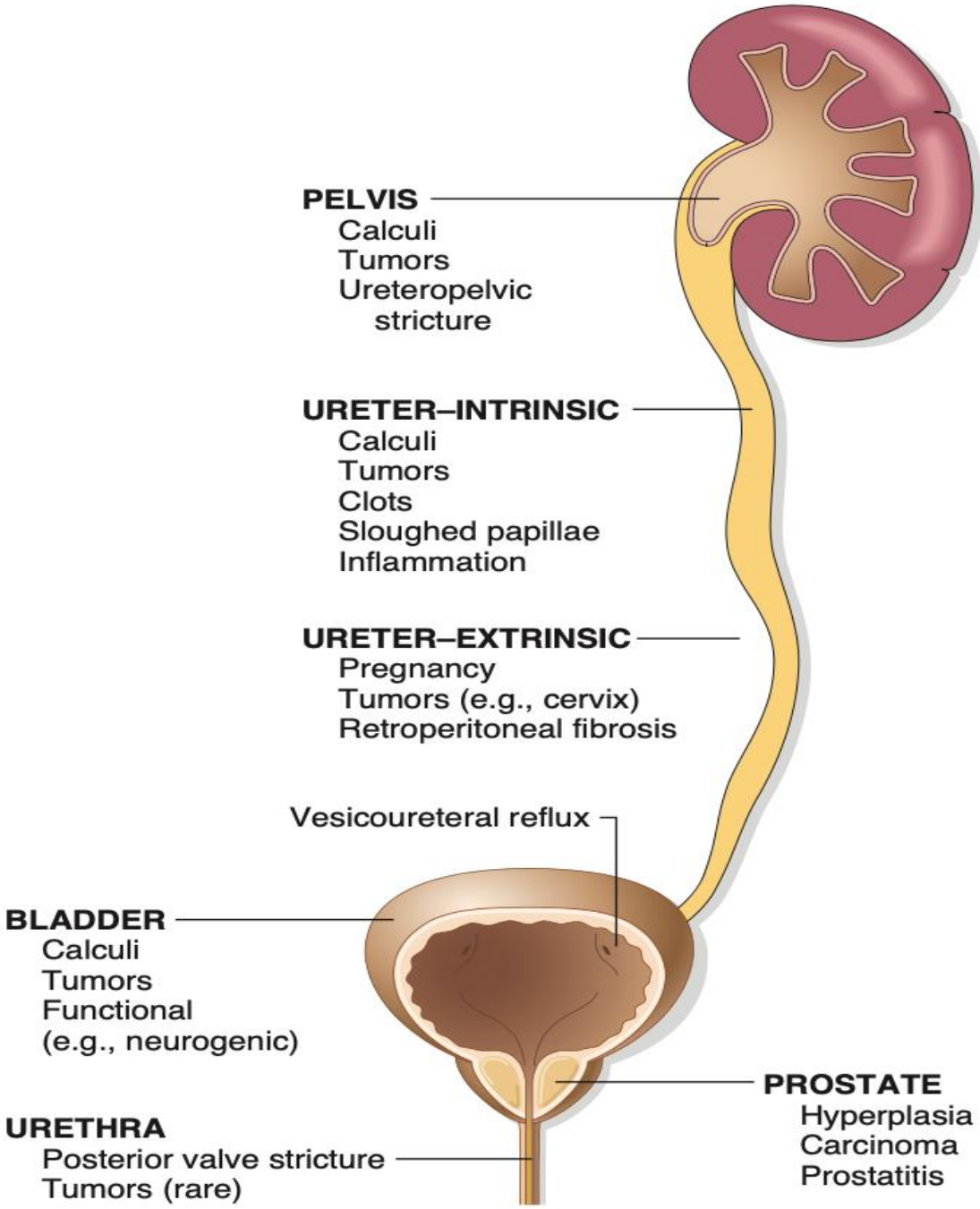
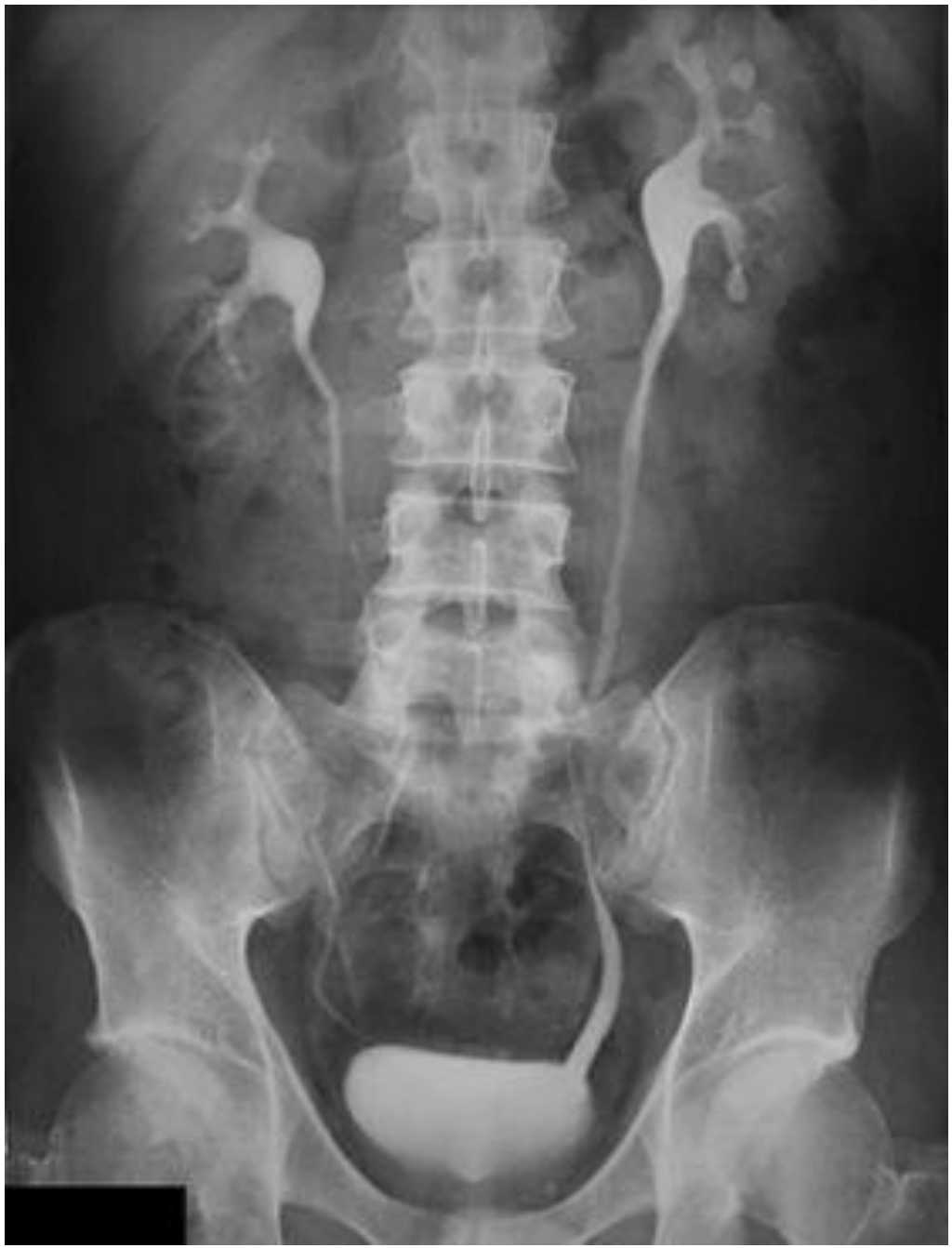
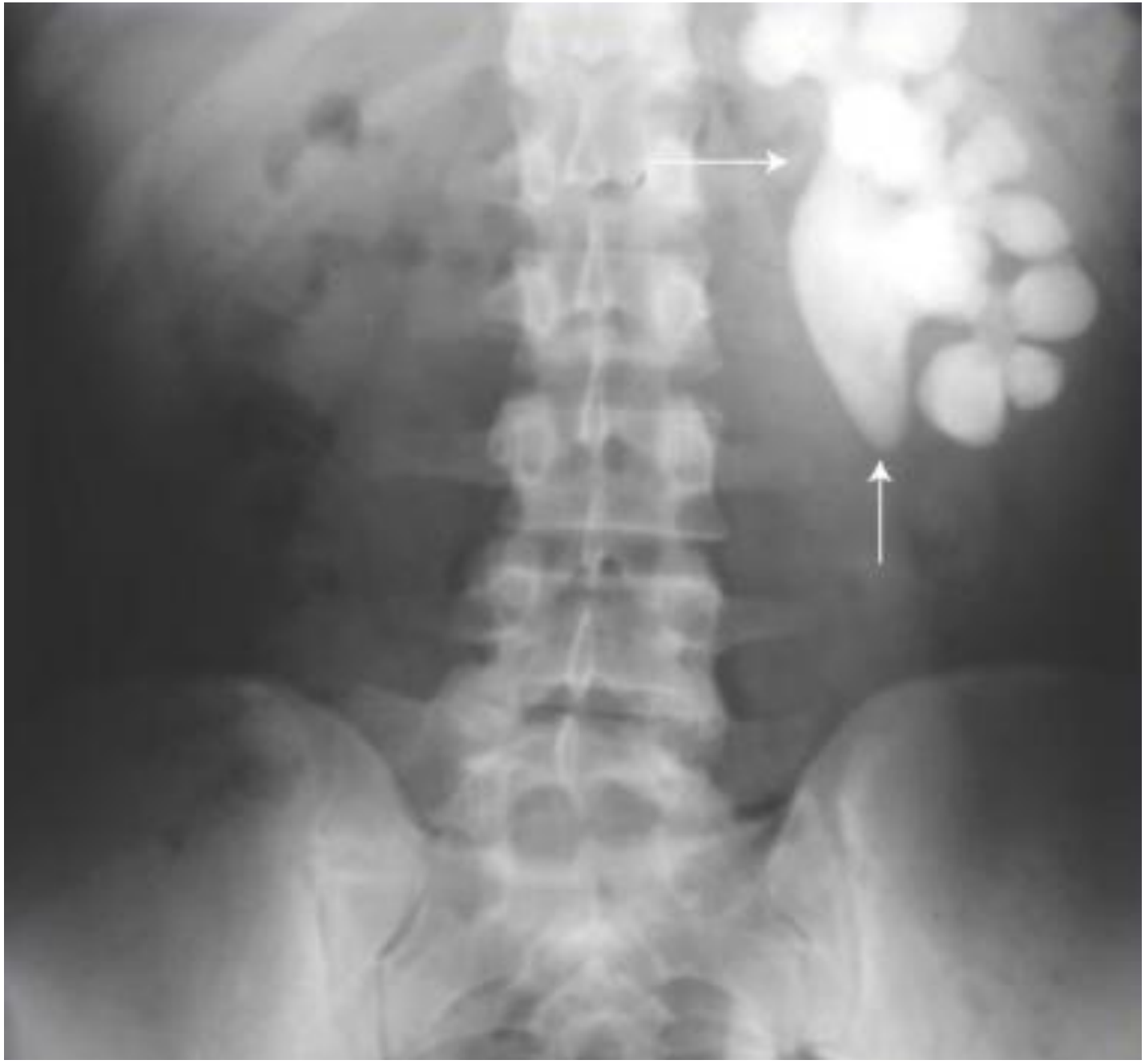


Figure 20-47 Obstructive lesions of the urinary tract.

intravenous pyelogram



- **Hydronephrosis**
    - dilatation of the renal pelvis and calyces associated with progressive atrophy of the kidney due to obstruction to urine outflow



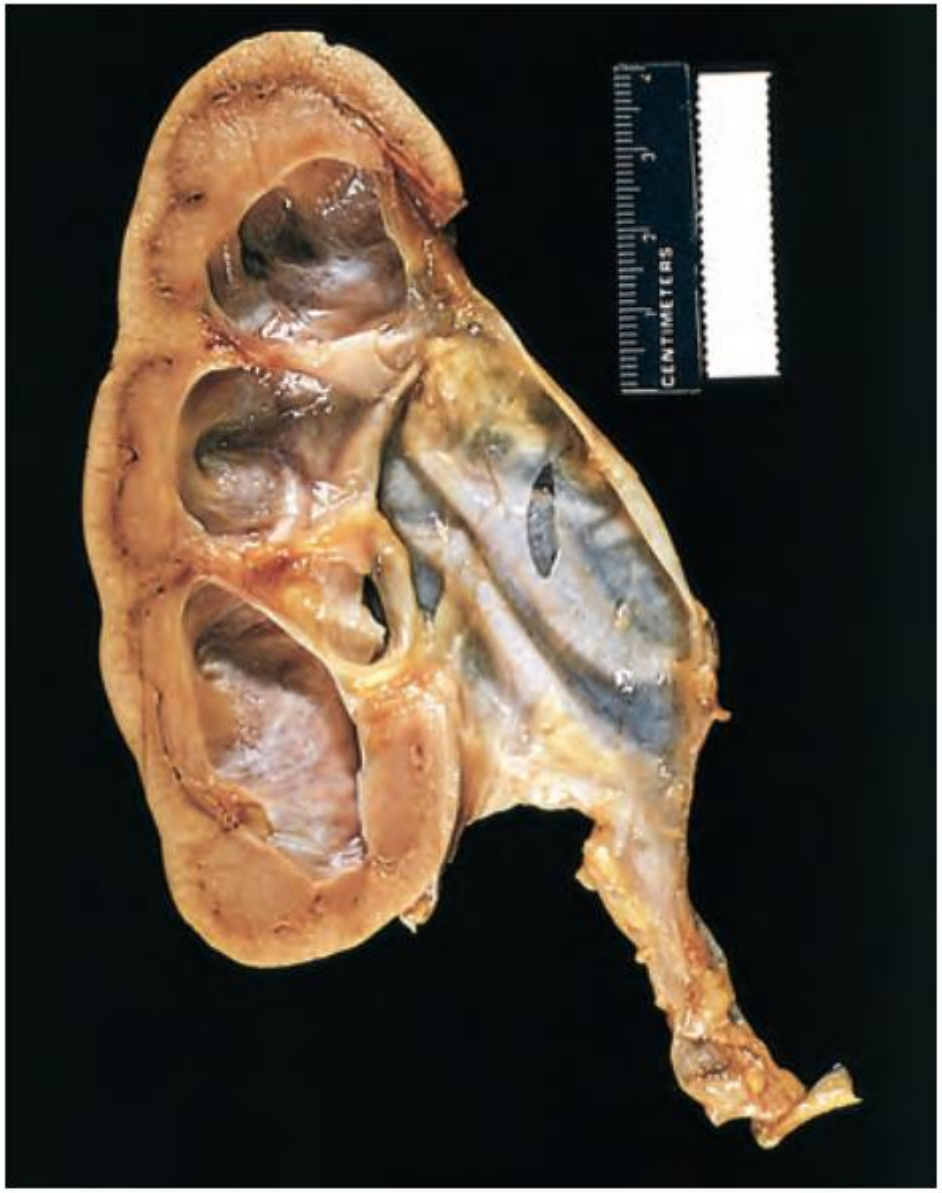


Figure 20-48 Hydronephrosis of the kidney, with marked dilation of the pelvis and calyces and thinning of the renal parenchyma.

- **UROLITHIASIS (RENAL CALCULI, STONES)**
    - most arise in the kidney
    - 4 main types
        - calcium stone (70%)
        - triple stones or struvite stones (Magnesium Ammonium Phosphate hexahydrate Mg-NH4-PO4)-(15%)
        - Uric acid stone stone (5-10%)
        - Cystine (1-2%)

Table 20-12 Prevalence of Various Types of Renal Stones

Stone Type	Percentage of All Stones
Calcium Oxalate and Phosphate	70
Idiopathic hypercalciuria (50%)	
Hypercalciuria and hypercalcemia (10%)	
Hyperoxaluria (5%)	
Enteric (4.5%)	
Primary (0.5%)	
Hyperuricosuria (20%)	
Hypocitraturia	
No known metabolic abnormality (15% to 20%)	
Magnesium Ammonium Phosphate (Struvite)	5-10
Uric Acid	5-10
Associated with hyperuricemia	
Associated with hyperuricosuria	
Idiopathic (50% of uric stones)	
Cystine	1-2
Others or Unknown	±5

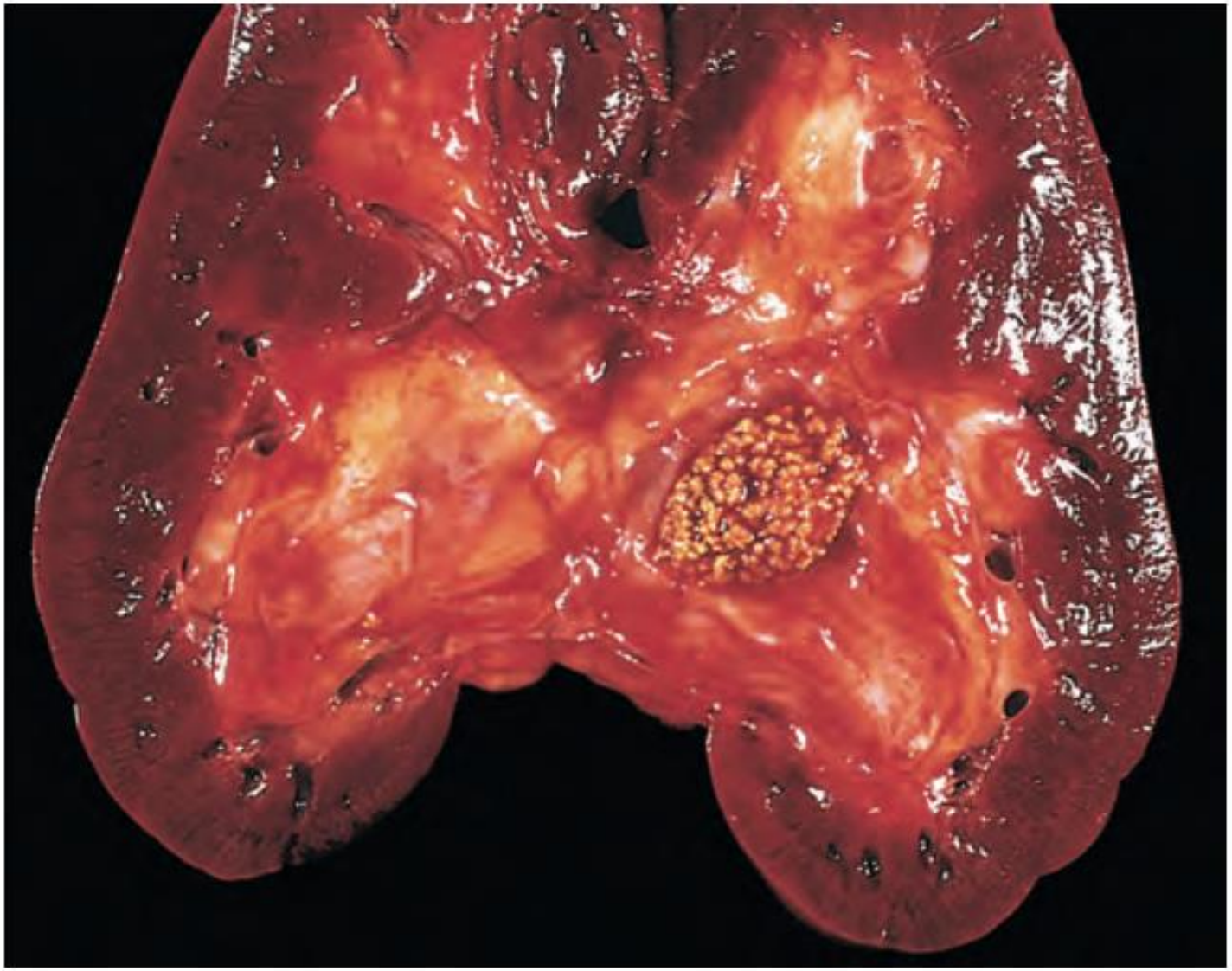


Figure 20-49 Nephrolithiasis. A large stone impacted in the renal pelvis. (Courtesy Dr. E. Mosher, Brigham and Women's Hospital, Boston, Mass.)

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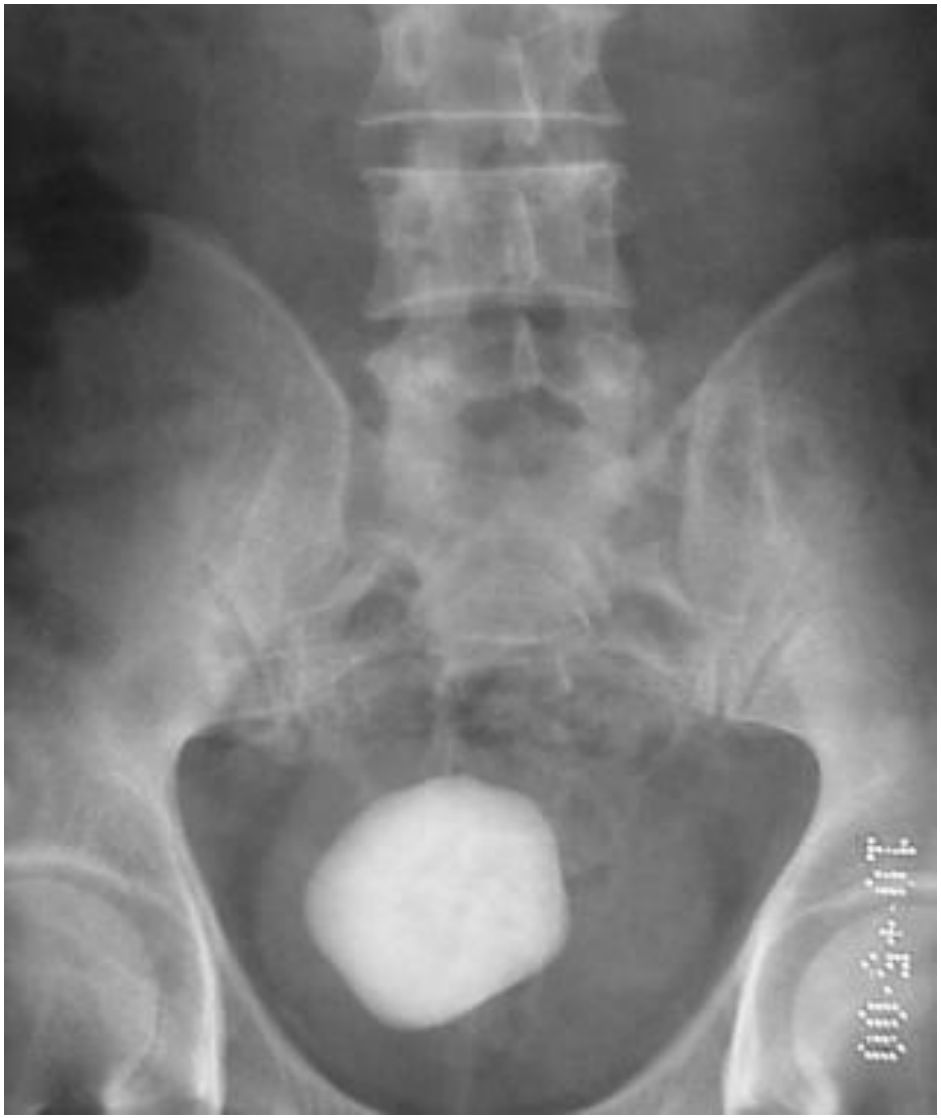
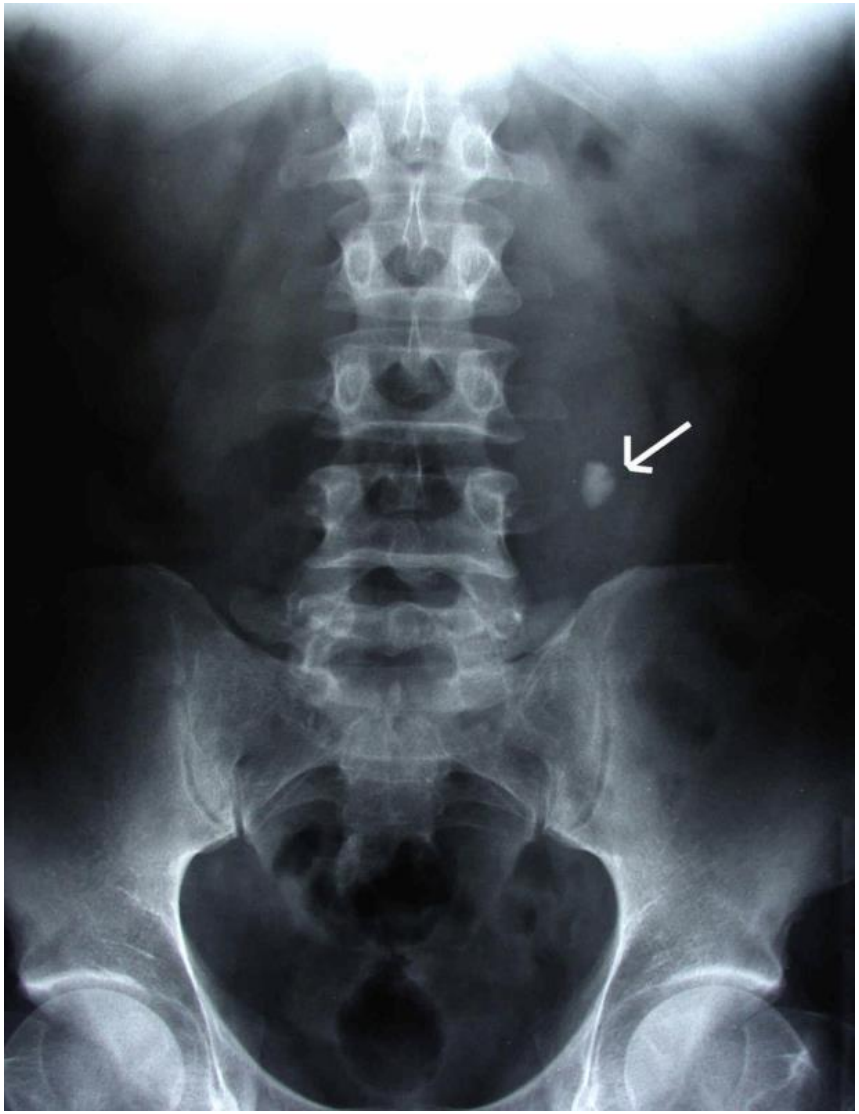


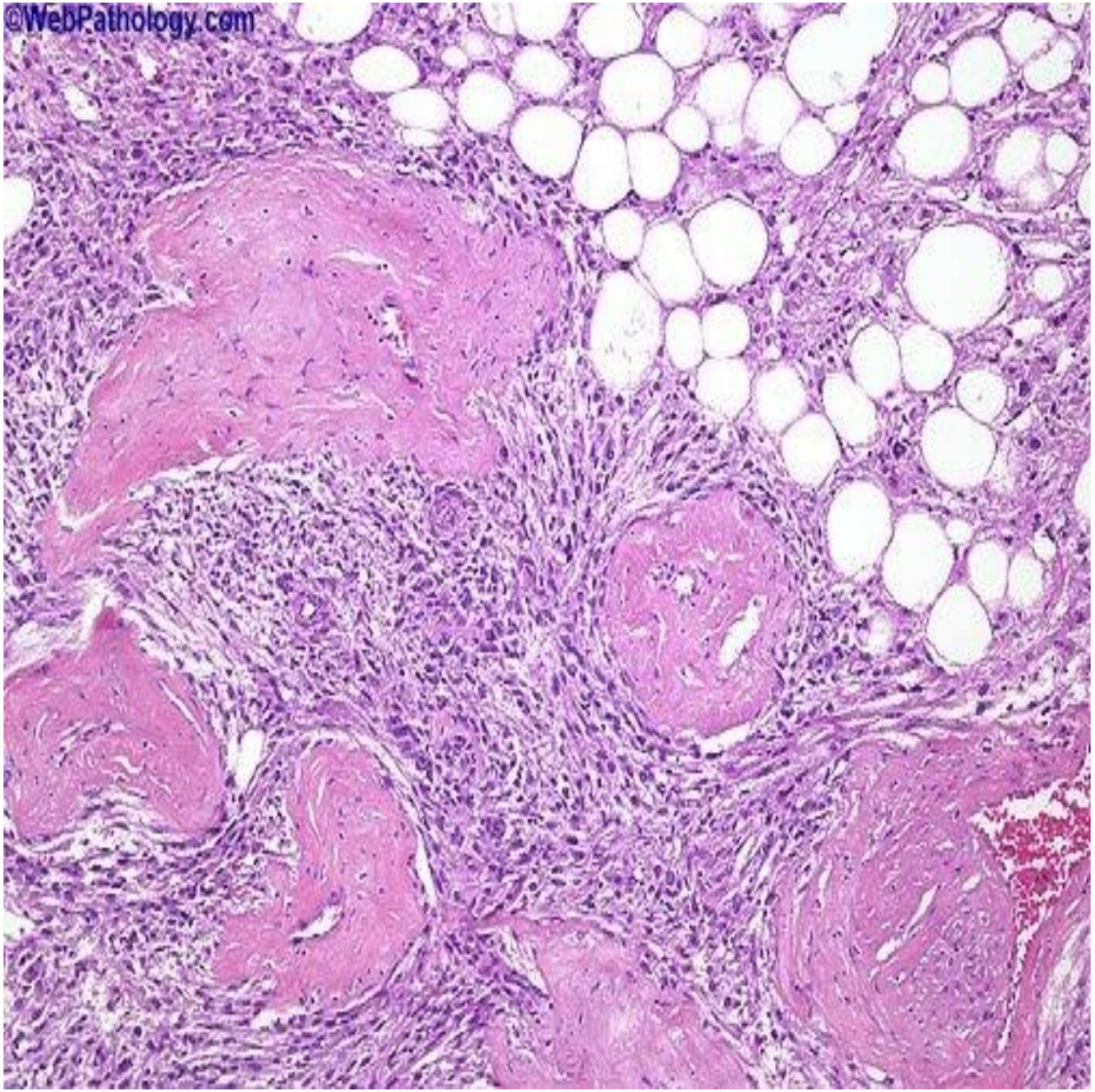


Tumours of the kidney

BENIGN TUMOURS

- **1. Renal cell adenoma**
    - arise from renal tubular epithelium
    - frequently papillary
    - usu. small, cortical

- **2. Angiomyolipoma**
  - comprising vessels, smooth muscle and fat/adipose tissue
  - originates from perivascular epithelioid cells
  - Tuberous sclerosis
    - »mutations in TSC 1 or 2 tumour suppressor gene
    - »50% will have angiomyolipoma
    - »also have
      - CNS
        - cerebral cortical tubers => epilepsy/mental retardation
        - SEGA
      - Skin- hypomelanotic macules, facial angiofibromas
      - LUNG- lymphangioleiomyomatosis
      - cardiac- rhabdomyomas
      - OTHER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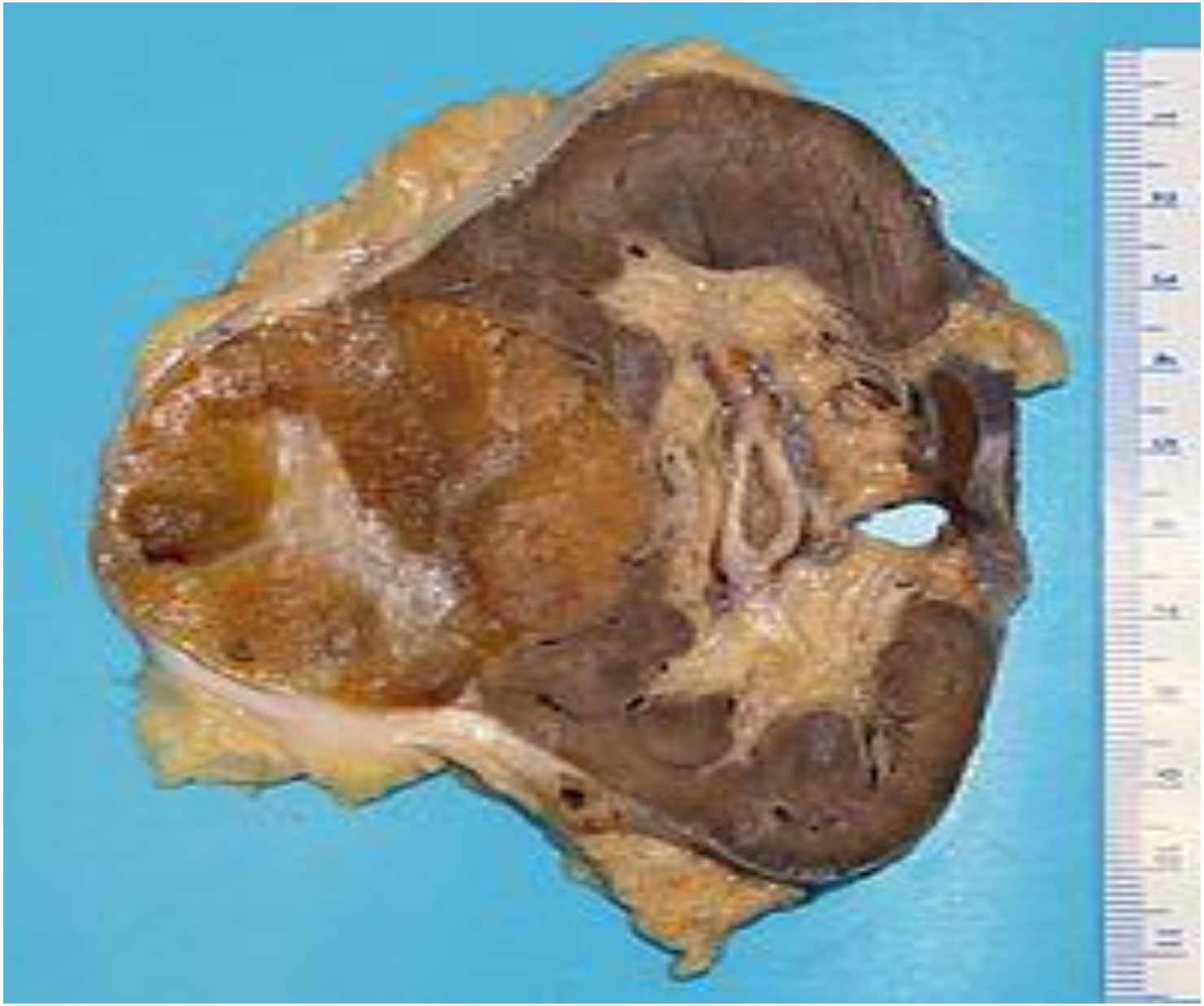
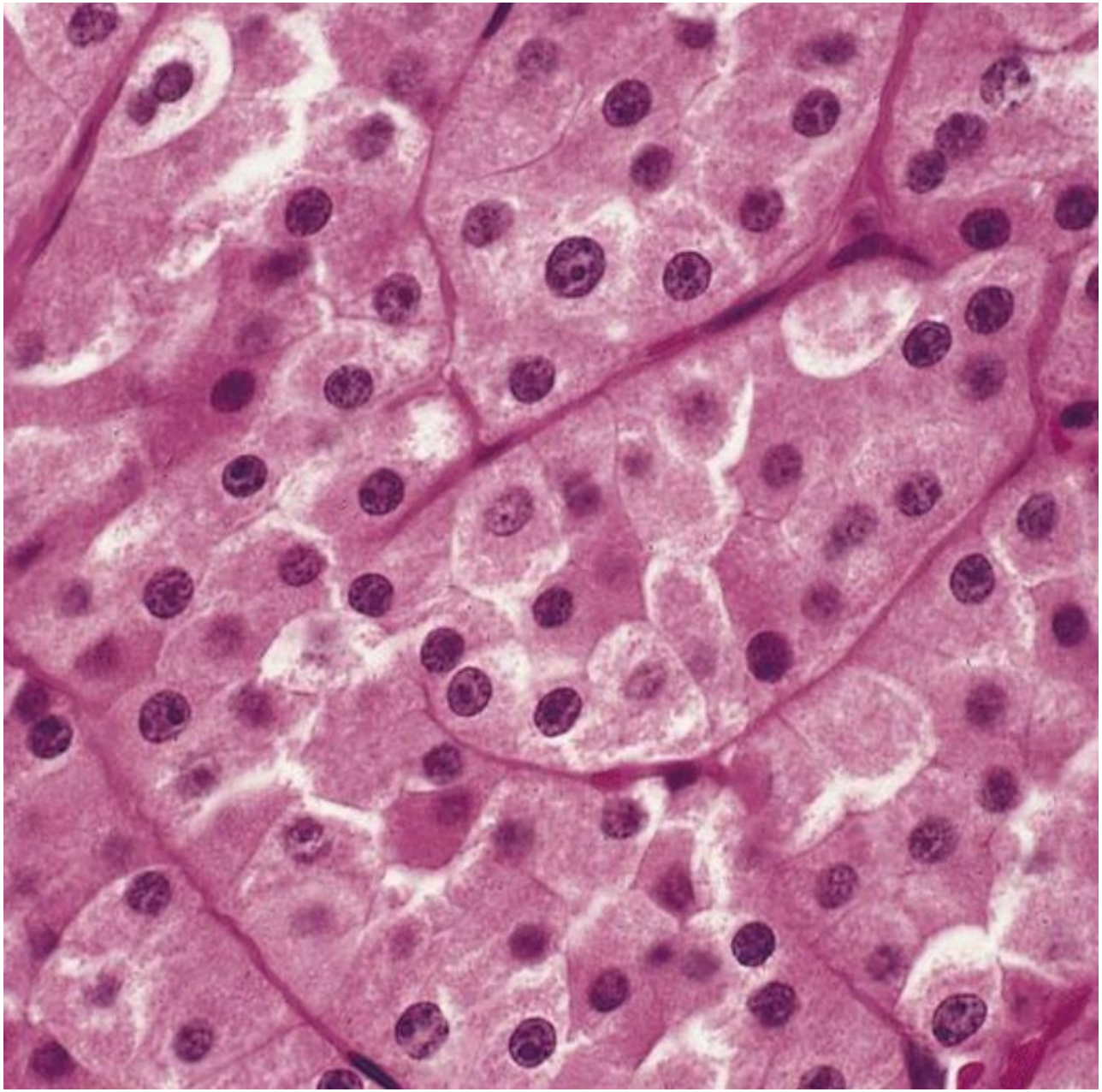
- **3. Oncocytoma**
    - ? arises from intercalated cells of collecting ducts
    - eosinophilic cells with numerous mitochondria





MALIGNANT TUMOURS

- **RENAL CELL CARCINOMA**
  - **usu adults**
  - **risk factors**
    - **cigerette smoking (x2)**
    - **obesity esp women**
    - **HTN**
    - **unoppesed estrogen**
    - **asbestos/petroleum products and heavy metal exposure**

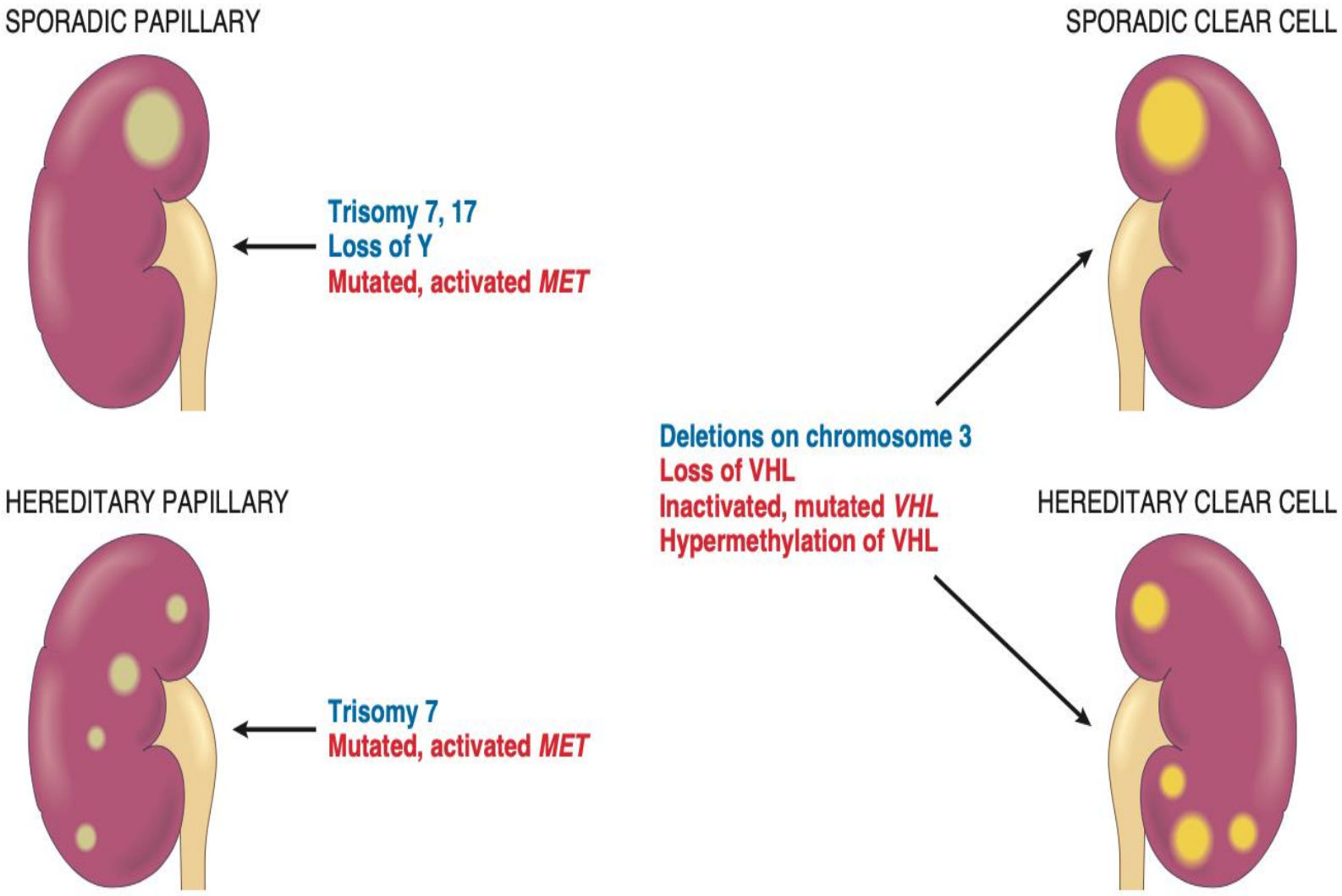


Figure 20-50 Cytogenetics (blue) and genetics (red) of clear cell versus papillary renal cell carcinoma. (Courtesy Dr. Keith Ligon, Brigham and Women's Hospital, Boston, Mass.)

- Familial variants
    - Von Hipple Lindau (VHL) syndrome
    - hereditary leiomymatosis and renal cell Ca syndrome
    - hereditary papillary carcinoma
    - Birt Hogg Dube syndrome

- Classification
    - Clear cell carcinoma 70-80% of renal cell cancers
    - Papillary carcinoma 10-15%
    - Chromophobe carcinoma 5%, excellent prognosis
    - Xp11 translocation carcinoma, young pt, TFE3 gene translocation
        - » clear cytoplasm + papillary architecture
    - Collecting duct (Bellini duct) carcinoma 1%

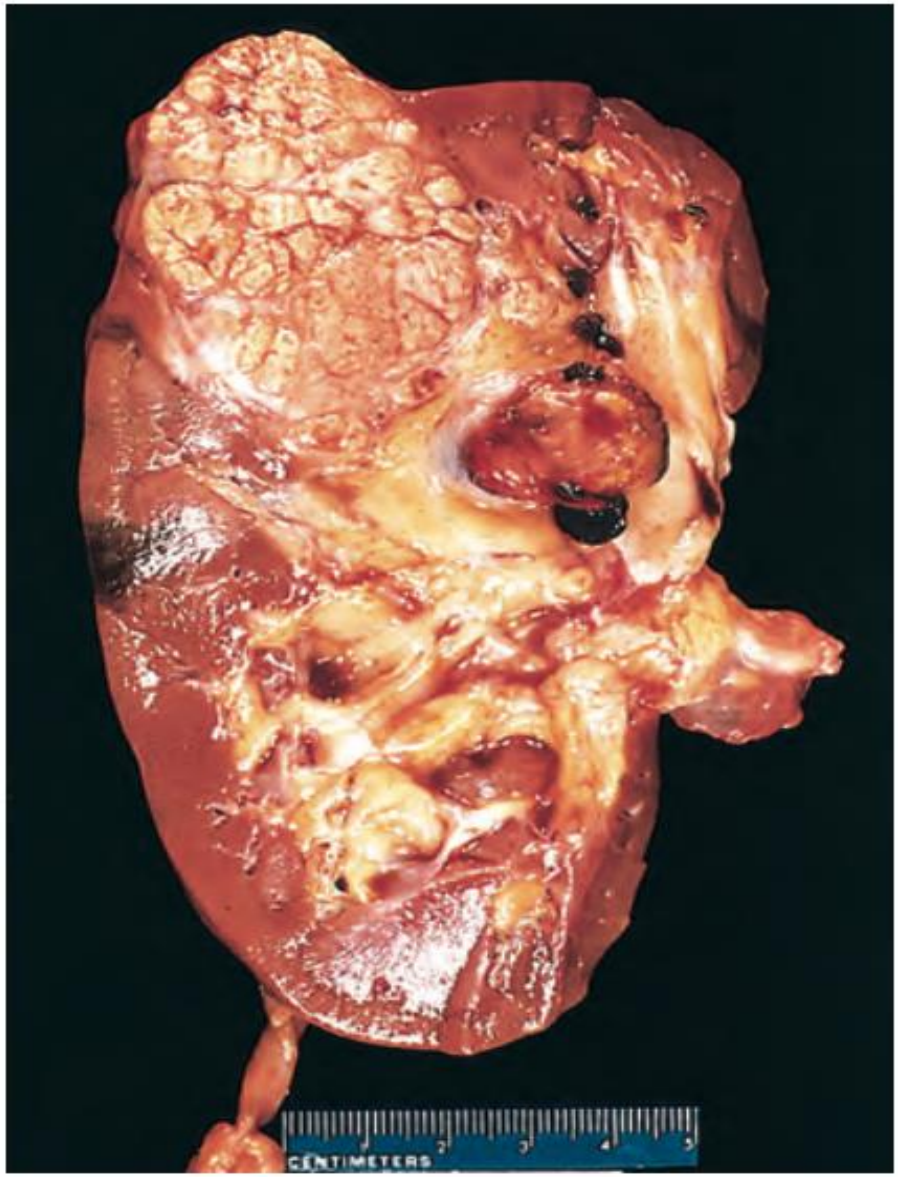
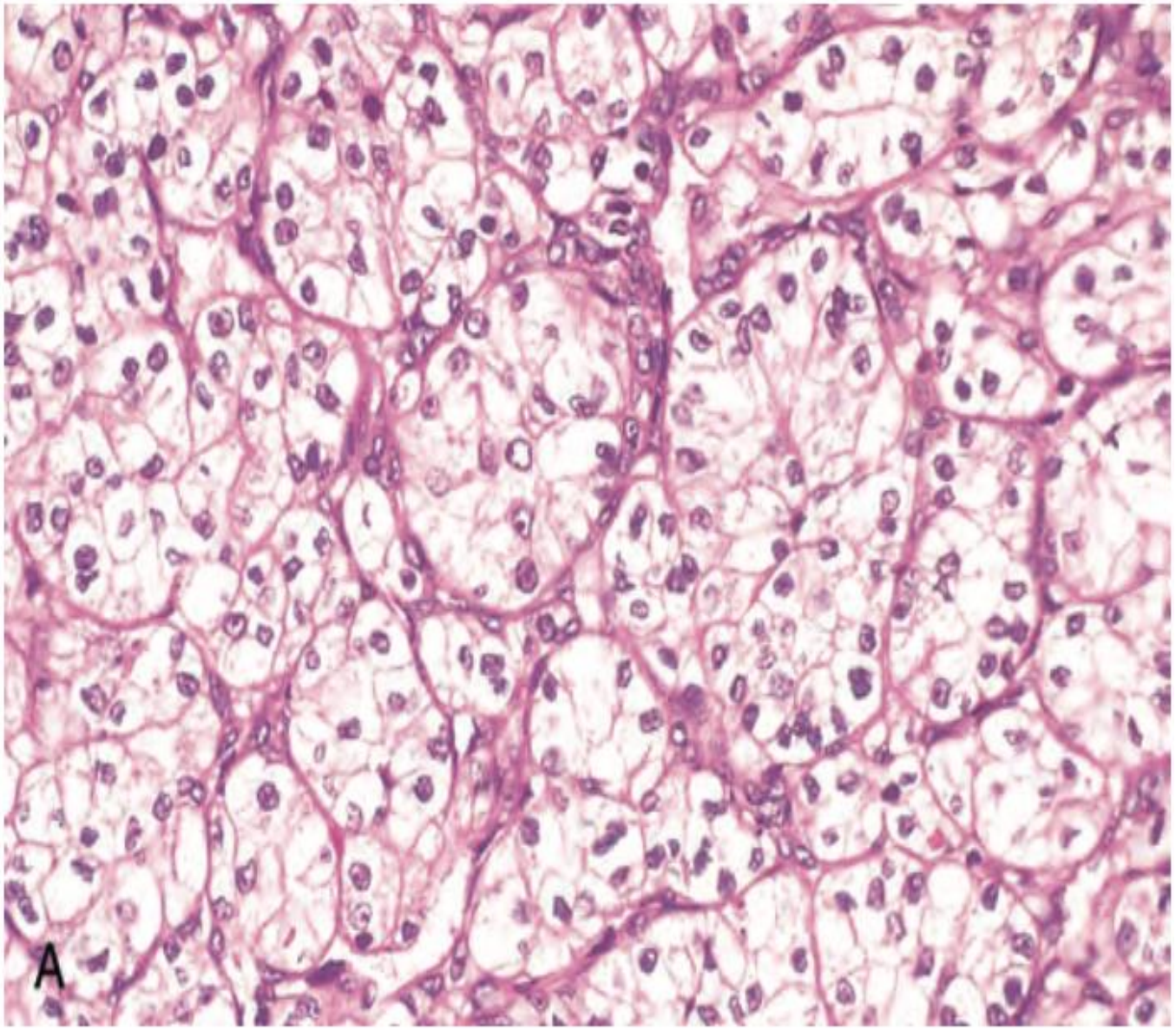


Figure 20-51 Renal cell carcinoma. Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated thrombosed renal vein.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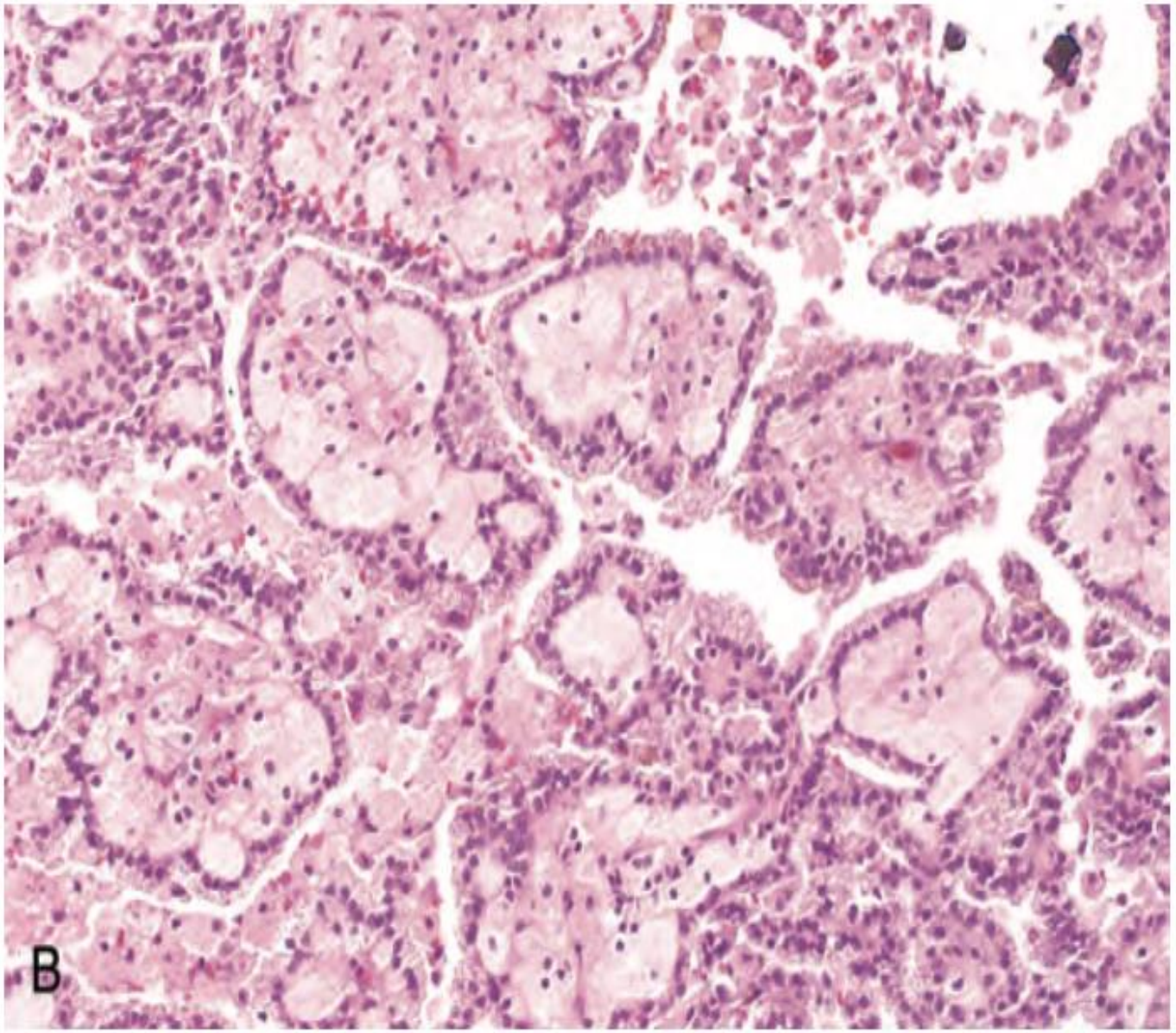
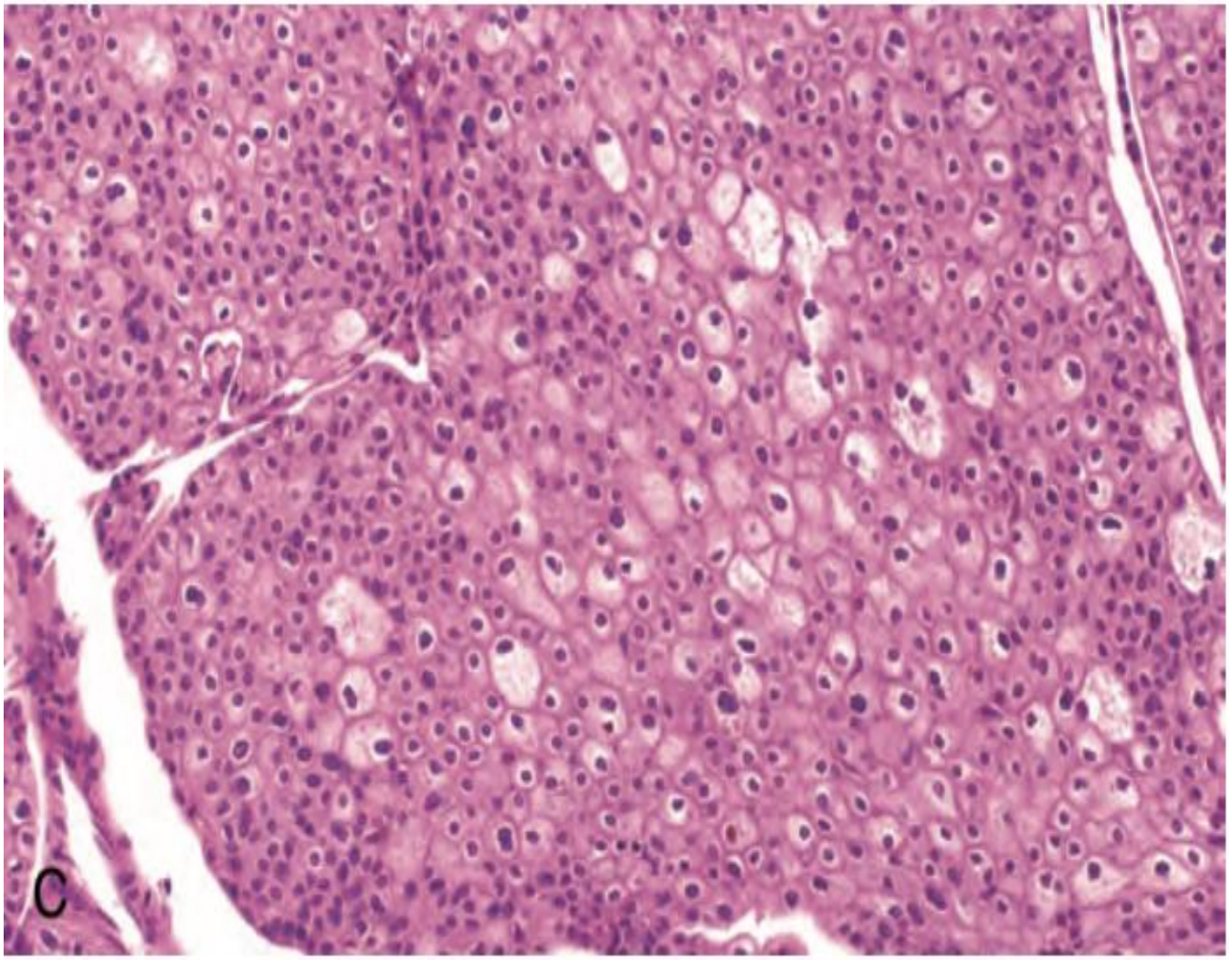

B


C

- C/F
  - cost-vertebral pain
  - palpable mass
  - hematuria
  - Polycythemia
  - hypercalcemia
  - hypertension
  - others?

- RX
    - Radical nephrectomy

- OTHER TUMOURS
  - originating from urothelium of the pelvis
    - » benign papillomas
    - » invasive urothelial (transitional cell) carcinoma

- similar to those found in the urinary bladder

End