Tubulointerstitial Diseases

Tubulointerstitial Diseases

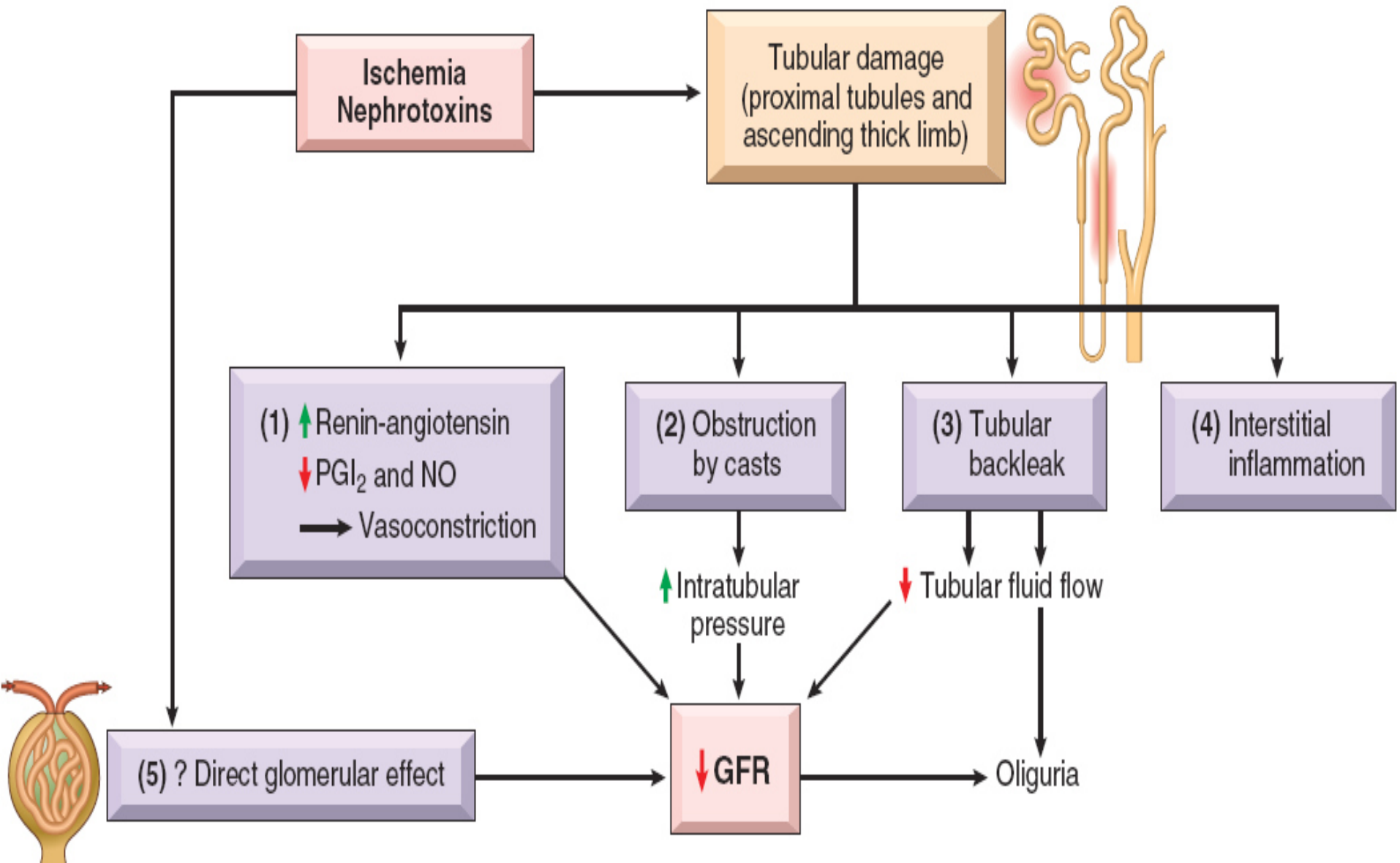
- Acute tubular injury (or necrosis).
- Tubulointerstial nephritis.

1. Acute tubular injury (ATI)

- "A clinicopathologic entity characterized *morphologically* by damaged tubular epithelial cells and *clinically* by acute suppression of renal function, ARF"
- ATI is the **commonest cause of acute renal failure.**
- Usually *reversible*.
- **Types:** Ischemic & nephrotoxic ATN.

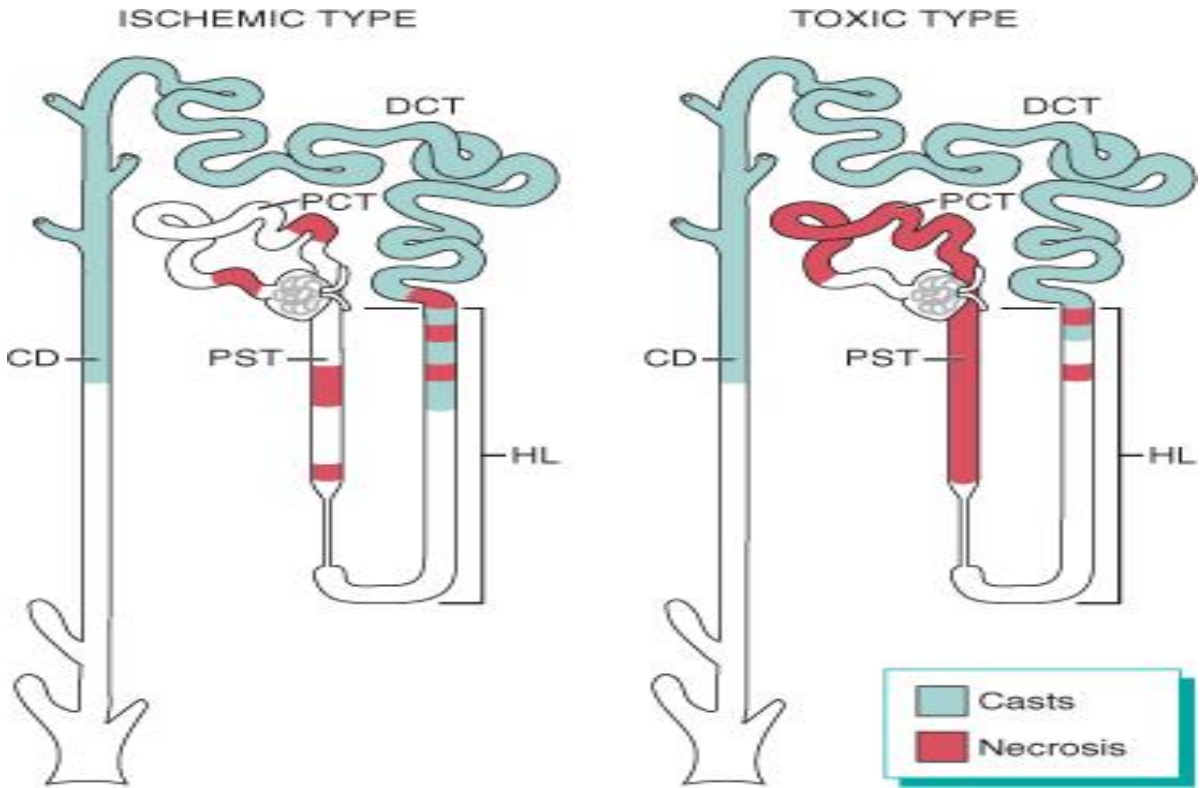
Ischemic	Nephrotoxic
Severe hypotension & shock ▪Severe hemorrhage ▪Loss of fluid (vomiting, diarrhea, burns) ▪Severe MI ▪Acute pancreatitis ▪Septicemia ▪Multiple injuries ▪Obstetric complications (Ante-partum hemorrhage, pre-eclamptic toxemia …)	**A variety of poisons:** •Heavy metals (e.g., mercury, arsenic) •Organic solvents (e.g., CCL4) •Drugs (e.g gentamicin) •Radiographic contrast agents
	Endogenous substances ▪*Hemoglobinuria* (mismatched blood transfusion) ▪*Myoglobinuria**

Pathophysiology of ATI



Morphology of ATI

- Lesions in *ischemic* ATI tend to be **focal and patchy** at multiple points along the nephron.
- Lesions of *nephrotoxic* ATI predominantly involve the **proximal convoluted tubule**.

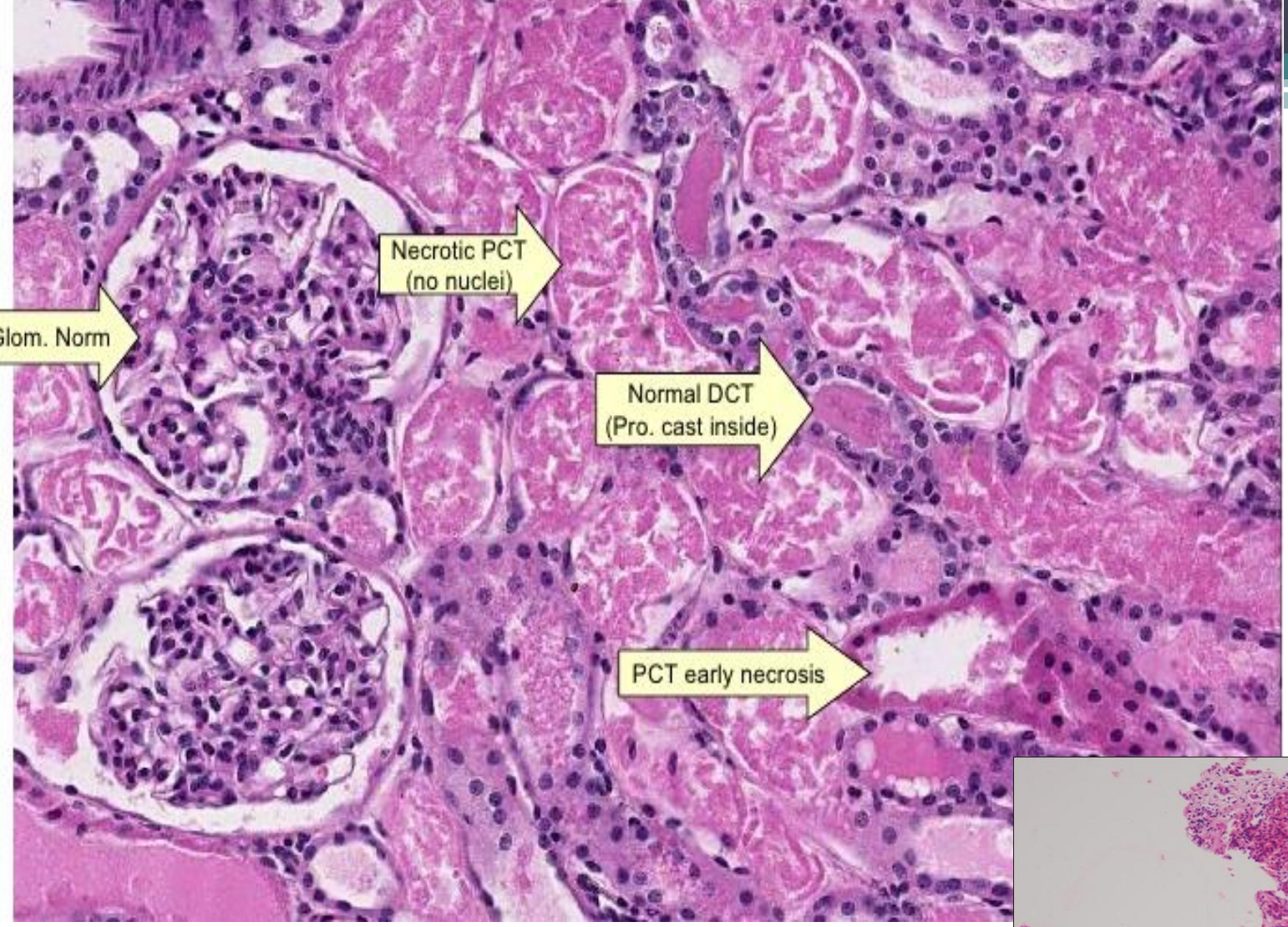


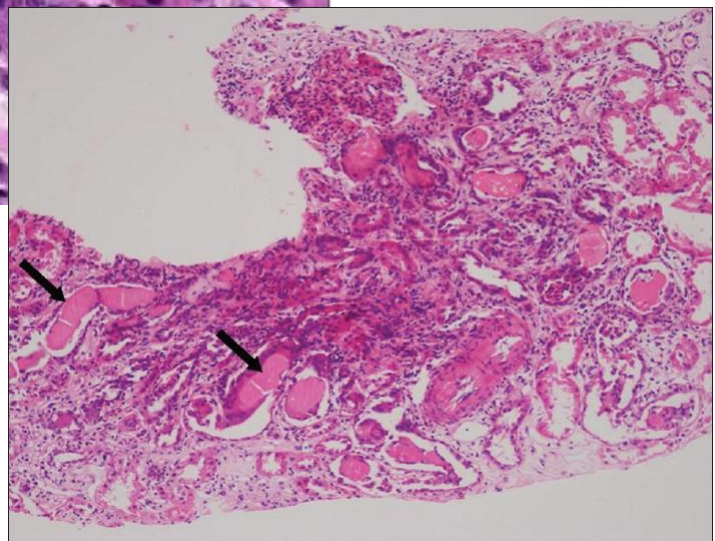
Microscopic morphology

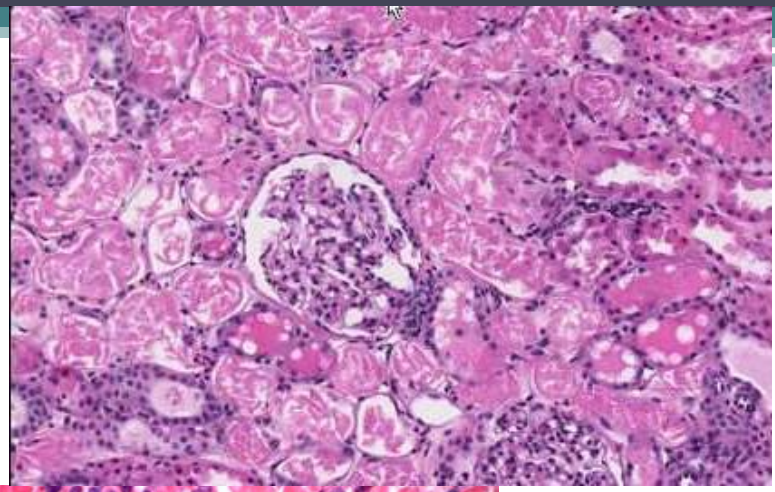
- Attenuation, blebbing of brush borders, and vacuolization of *PCT* cells (**early**) → necrosis & apoptosis of tubular epithelial cells (**late**) → detachment of tubular cells from BM with sloughing of cells into the urine → occlusion of distal & collecting tubules by hyaline & cellular casts.

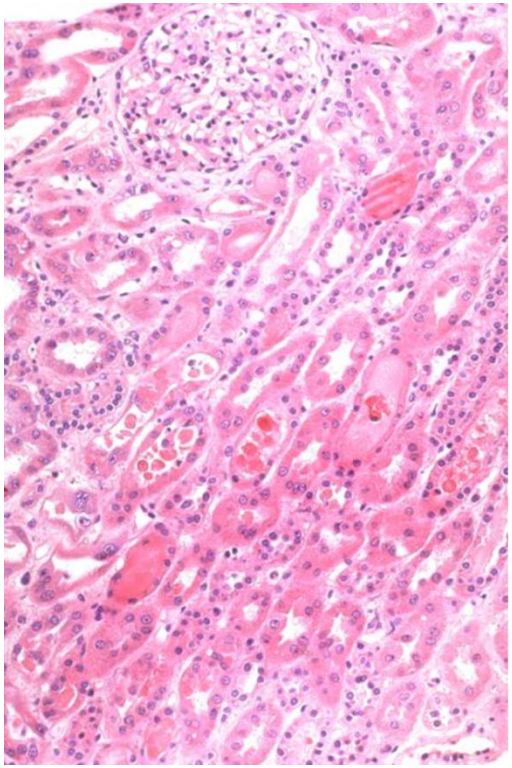
- Interstitial inflammation & edema (very minimal).

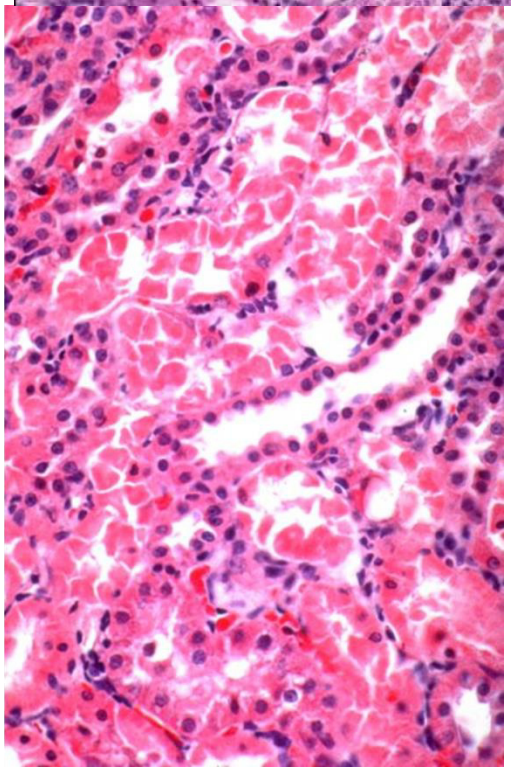
- Epithelial regeneration (after 1 wk).


Glom. Norm
Necrotic PCT
(no nuclei)
Normal DCT
(Pro. cast inside)
PCT early necrosis



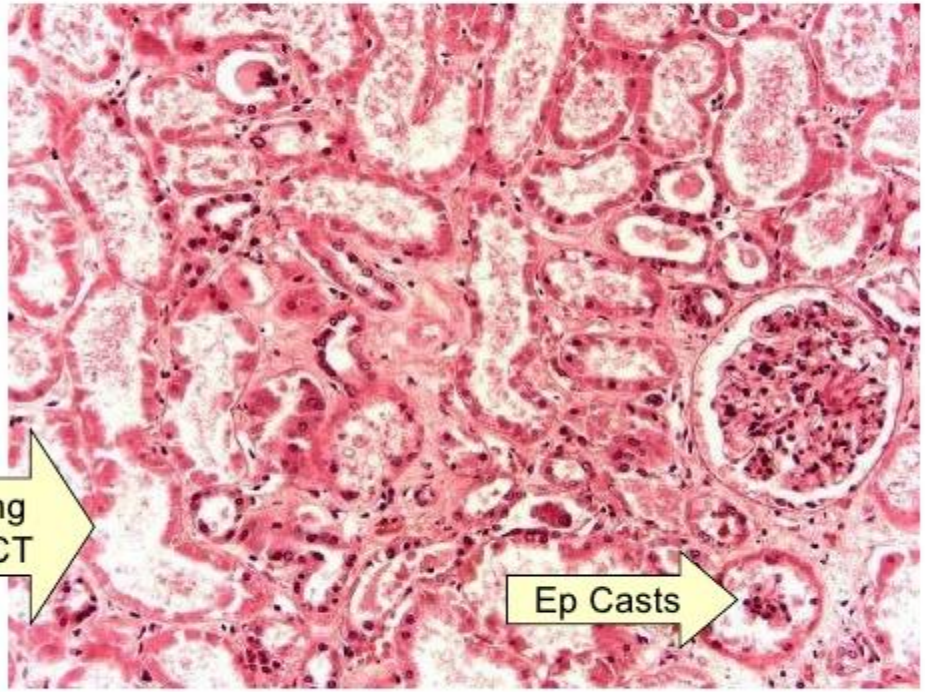






Acute Tubular Necrosis:

- Most common cause of ARF.
- Drugs (aminoglycosides)
- Toxins – Mercury, CCL4, Radiocontrast.



Clinical course of ATI (stages)

- **Three phases:**
  - Initiation
  - Maintenance
  - Recovery

A. The initiation phase

- During the *first 36 hours.*
- Dominated by the initiating event.
- Slight decline in urine output.
- Slight rise in serum creatinine.

B. The maintenance phase

- Begins anytime from the 2nd to 6th day.
  - **Oliguria**; complete anuria is rare.
    - Oliguria may last only a few days or persist as long as 3 weeks.
  - **Uremia & fluid overload:**
    - ↑ BUN, hyperkalemia & metabolic acidosis

- **Rx:** careful supportive treatment or dialysis

C. The recovery phase

- **Polyuria:** steady ↑ in urine output to ~ 3L/d.
- Tubular function is ***still deranged*** (hypokalemia & hyponatremia may occur) → return gradually.
- Increased vulnerability to infection.
- Gradual improvement of renal function.
- With modern methods of care, **95%** of patients that survive the precipitating cause can recover.

2.Tubulointerstitial nephritis (TIN)

- A group of inflammatory diseases of the kidneys that primarily involve the interstitium and tubules.
- TIN produces features of *tubular dysfunction* rather than features of glomerular injury:
  - Impaired concentration → Polyuria & nocturia.
  - Impaired reabsorption → Salt wasting.
  - Impaired secretion → Metabolic acidosis.
  - RF in advanced cases.

    →*Absence of nephritic or nephrotic syndromes.*
- **Causative factors:**
  - *Primary* (Infections & drugs mainly)
  - *Secondary* (to GN, vascular dis. ….).

Causes of tubulointerstial nephritis

INFECTIONS
- **Acute bacterial pyelonephritis**
- **Chronic pyelonephritis (including reflux nephropathy)**
- Other infections (e.g., viruses, parasites)

PHYSICAL FACTORS
- Chronic urinary tract obstruction
- Radiation nephropathy

NEOPLASMS
- Multiple myeloma (cast nephropathy)

TOXINS
- *Drugs*
  - **Acute-hypersensitivity interstitial nephritis**
  - **Analgesics nephropathy**
- *Heavy metals*

IMMUNOLOGIC REACTIONS
- Transplant rejection
- Sjögren syndrome
- Sarcoidosis

METABOLIC DISEASES
- Urate nephropathy
- Nephrocalcinosis (hypercalcemic nephropathy)
- Acute phosphate nephropathy
- Hypokalemic nephropathy
- Oxalate nephropathy

VASCULAR DISEASES

MISCELLANEOUS
- Balkan nephropathy
- Nephronophthisis-medullary cystic disease complex
- Idiopathic interstitial nephritis

Clinically & morphologically classified into

Acute TIN	Chronic TIN
-Rapid clinical course	-Slowly progressive
-Leucocytic infiltration of the interstitium & tubules (mainly neutrophils ± eosinophils) -Interstitial *edema* -Focal tubular *necrosis*	-Leucocytic infiltration with predominant mononuclear leucocytes -Interstitial *fibrosis* -Tubular *atrophy*

Urinary tract infection (UTI) & pyelonephritis

I. Urinary tract infection (UTI) & pyelonephritis

- Extremely **common**.

- **UTI:** Presence of bacteria in the urine.
  - Asymptomatic bacteriuria.
  - Lower UTI (cystitis, prostatitis, urethritis)
    - Produces dysurea, frequency, urgency & suprapubic pain.
    - May stay localized or spread to kidneys.
  - Upper UTI (Pyelonephritis [PN]).

Predisposing factors

- **Patient's sex and age:**
  - 1st year: More in *males* (more risk of cong. anomalies).
  - After 1st year- age 40: more in *females*.
    - Due to short urethra, urethral trauma, absent antibacterial properties or hormonal changes
  - With increasing age, the incidence in males rises due to BPH & instrumentation.

- **Pregnancy:**
  - 4% to 6% of develop bacteriuria.
  - 20% to 40% of these develop symptomatic UTI.

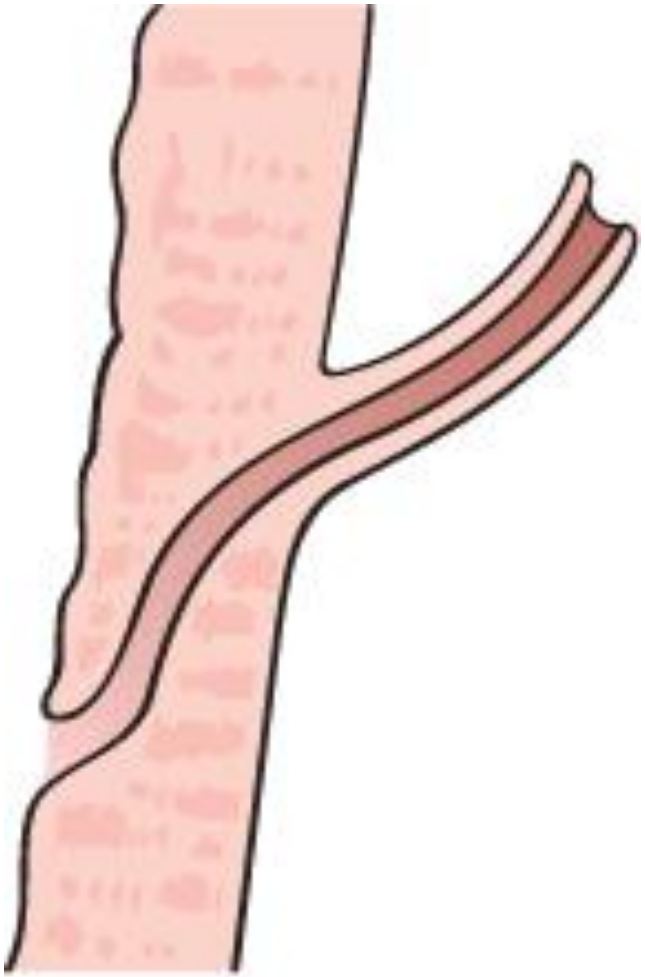
Predisposing factors

- **Urinary obstruction:**
  - Congenital.
  - Acquired (BPH and uterine prolapse).
- **Instrumentation:** esp. catheterization
- **Vesicoureteral reflux.**
- **Diabetes mellitus:**
  - Increased susceptibility to infection
  - Neurogenic bladder dysfunction
- **Immunosuppression and immunodeficiency.**

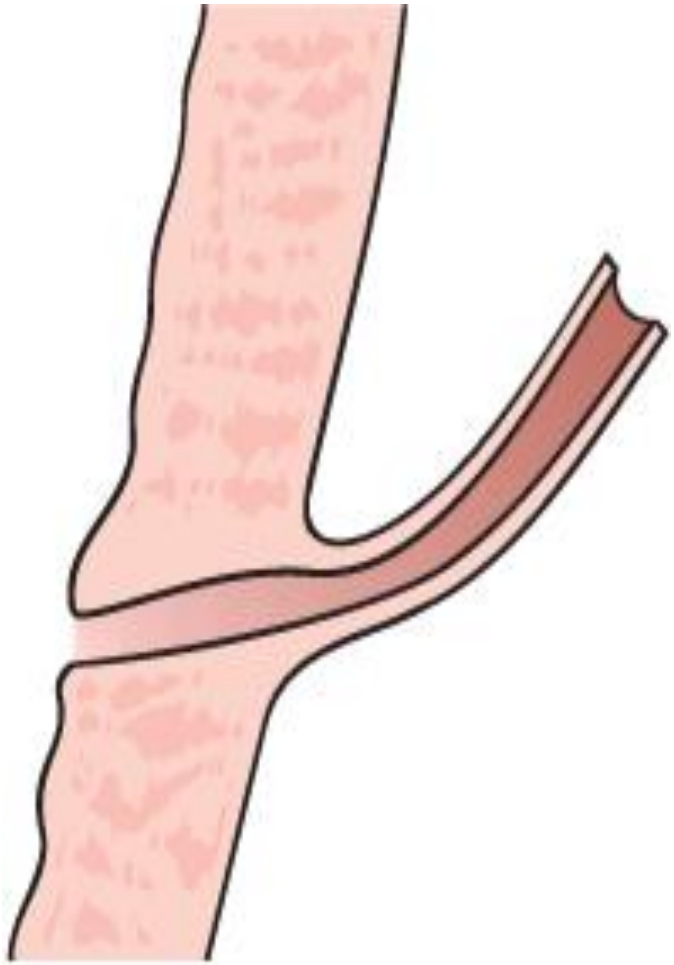
Vesicoureteric reflux

- An incompetent vesicoureteral orifice allows the reflux of bladder urine into the ureters → recurrent acute pyelonephritis → chronic pyelonephritis.
- Seen in **20% - 40%** of young children with UTI.
- **Causes:**
  - Congenital (usually):
    - Absence or shortening of the intravesical portion of the ureter.
  - Acquired:
    - Flaccid bladder due to spinal cord injury.
    - Neurogenic bladder dysfunction due to DM.
- **Effect:**
  - Residual urine in urinary bladder after voiding favors bacterial growth.
  - VUR leads to intrarenal reflux:
    - Infected bladder urine can reach the renal pelvis and the renal parenchyma (pyelonepritis).
    - Mainly in the *upper and lower poles.*

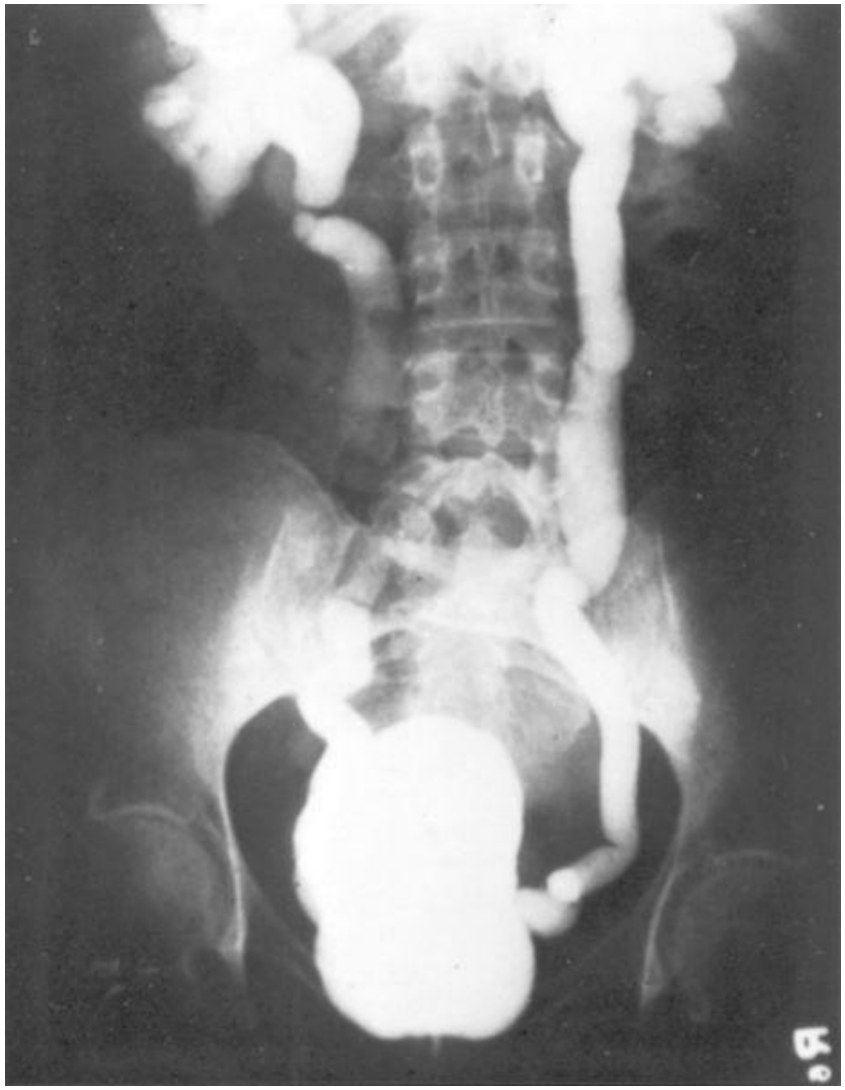
Vesicoureteric reflux



A NORMAL



B REFLUX



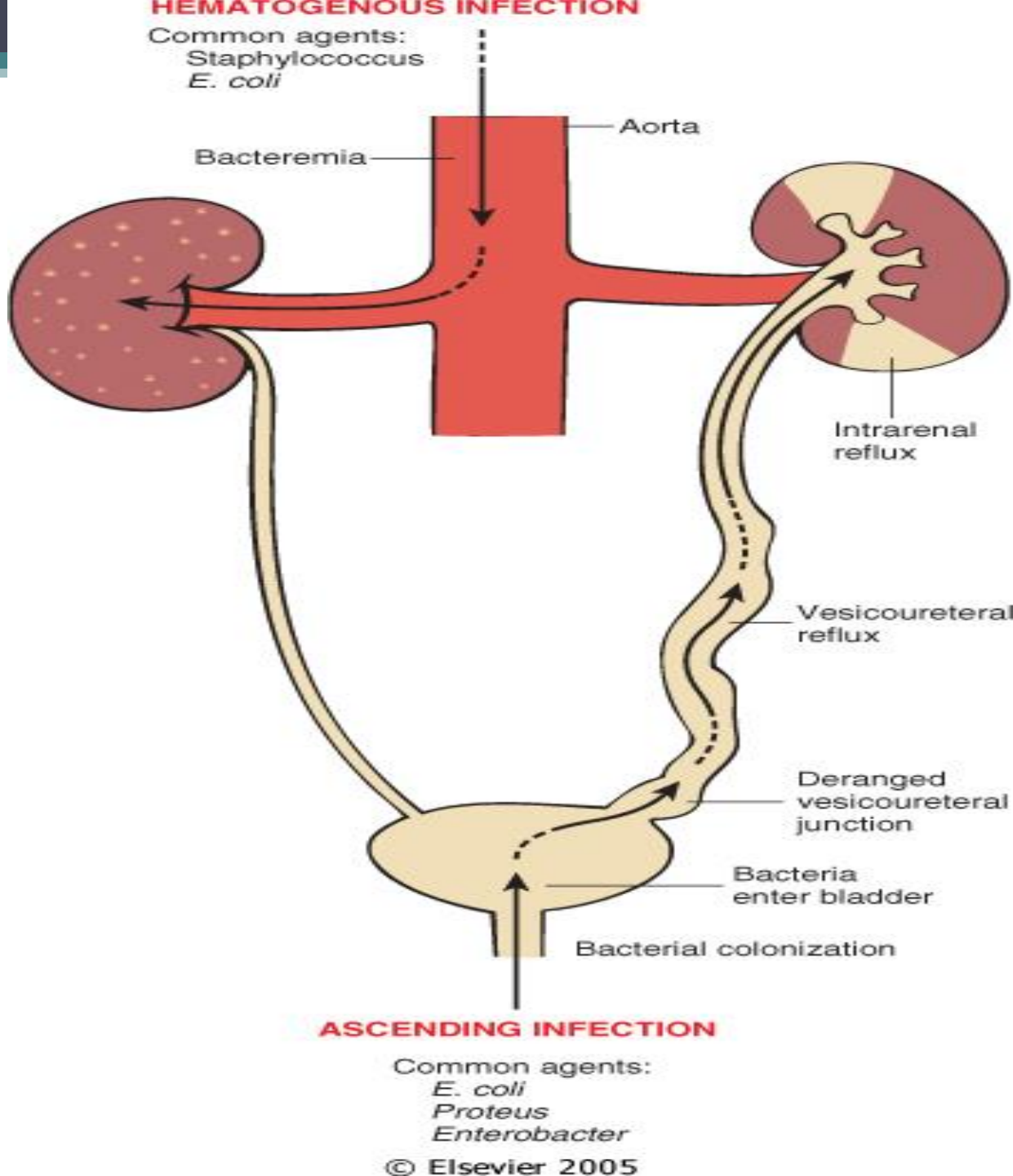
VUR demonstrated by a voiding cystourethrogram. Dye injected into the bladder refluxes into both dilated ureters, filling the pelvis and calyces.

A. Acute pyelonephritis:

- Suppurative inflammation of the kidney and the renal pelvis caused by *bacterial infection*
- Most of cases are associated with the lower UTI.
- **Causative organisms:** usually *enteric gram-negative rods*.
  - *Escherichia coli* **(most common).**
  - Species of *Klebsiella, Enterobacter, Proteus, Pseudomonas*. Ass. with:
    - Recurrent infections, urinary tract manipulations & anomalies
  - *Staphylococci* & *Streptococcus faecalis* (uncommon).

Route of spread:

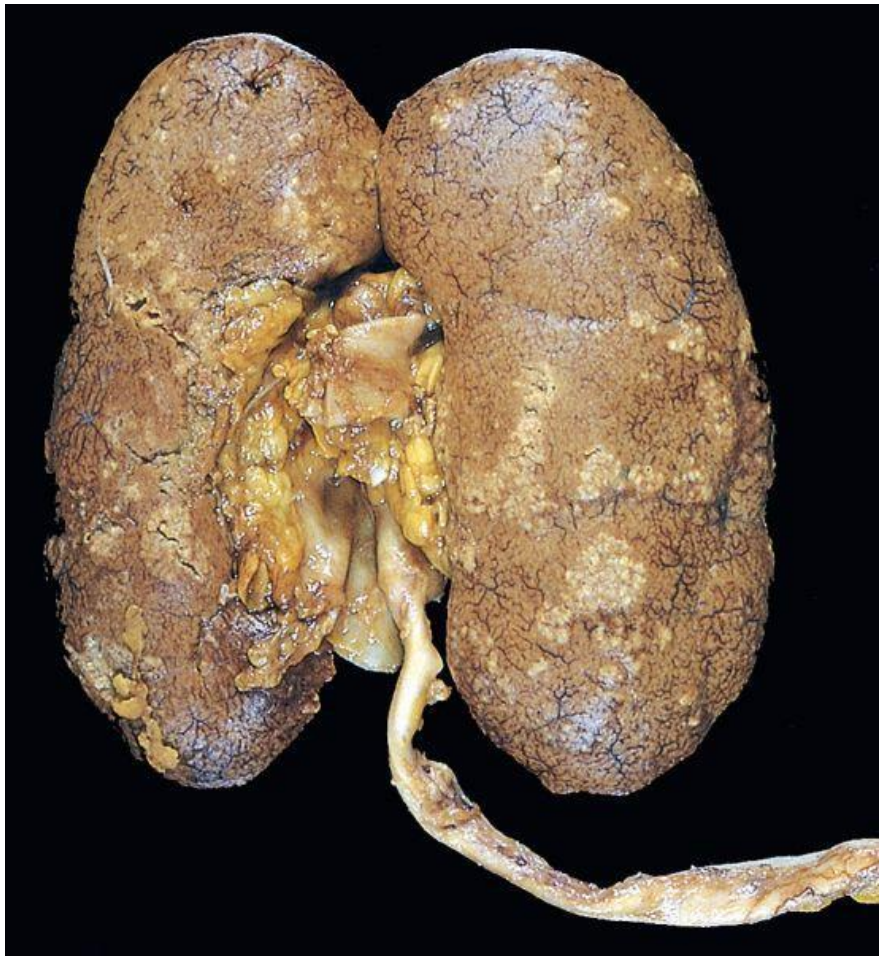
- Ascending infection (<u>commoner</u>)
- Hematogenous



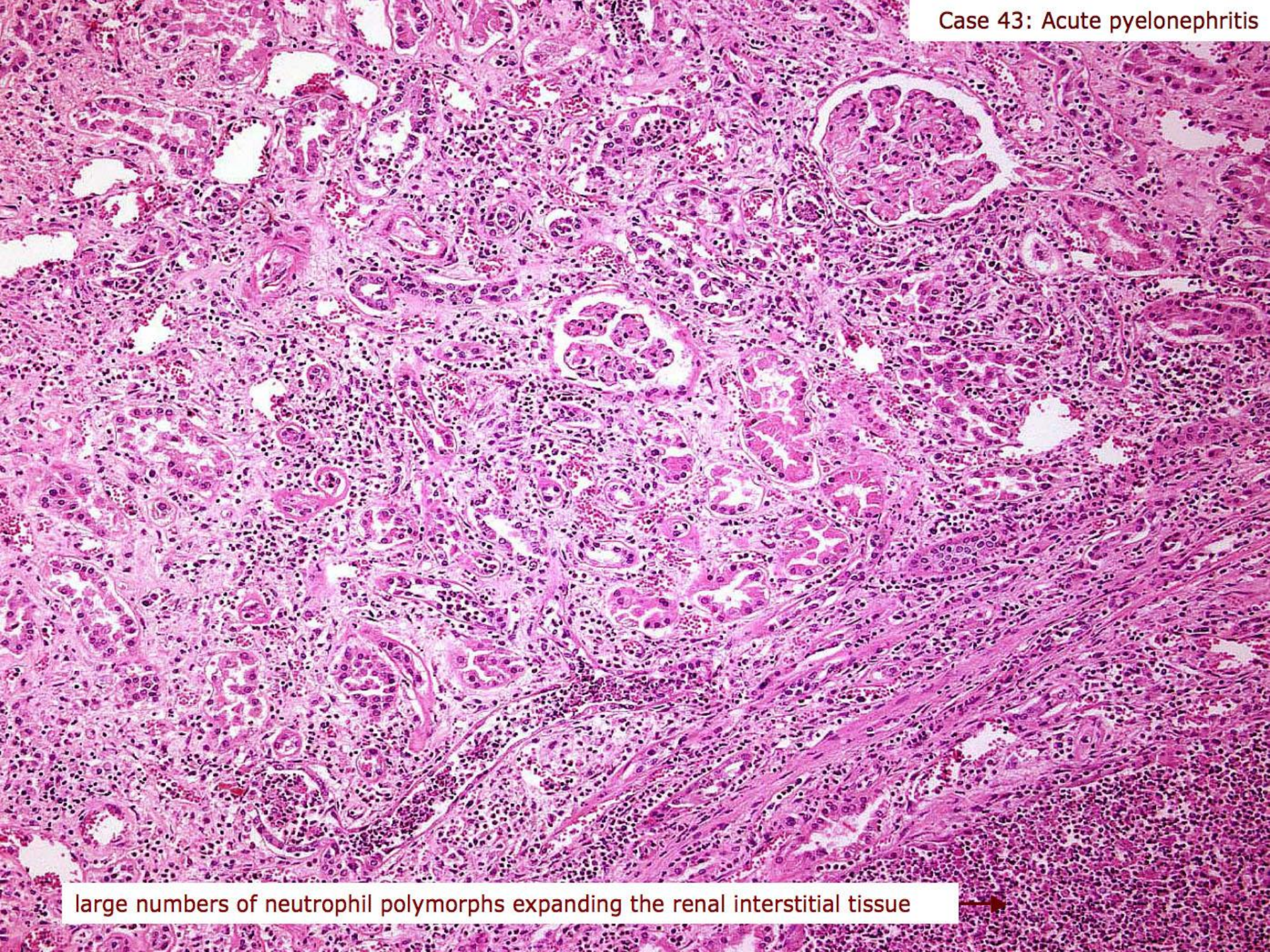
Morphology of acute pyelonephritis

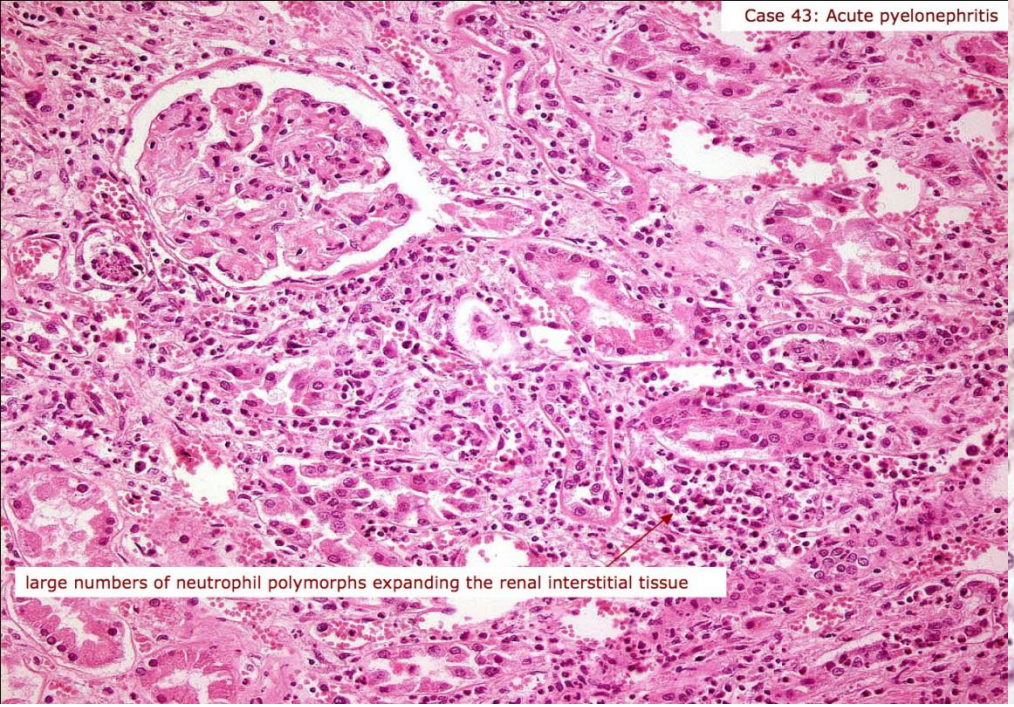
- **Gross:**
  - Usually *unilateral*. Normal in size or enlarged.
  - Widely scattered or limited to one region.
  - Discrete, yellowish, raised abscesses on the renal surface.
- **Microscopic:**
  - Patchy interstitial suppurative inflammation (± abscess) and tubular necrosis.
  - Starts in the interstitial tissue then rupture into tubules leading to *pyuria & WBCs casts.*
  - The glomeruli are not affected.

Acute pyelonephritis



Cortical surface shows grayish white areas of inflammation and abscess formation.


Case 43: Acute pyelonephritis
large numbers of neutrophil polymorphs expanding the renal interstitial tissue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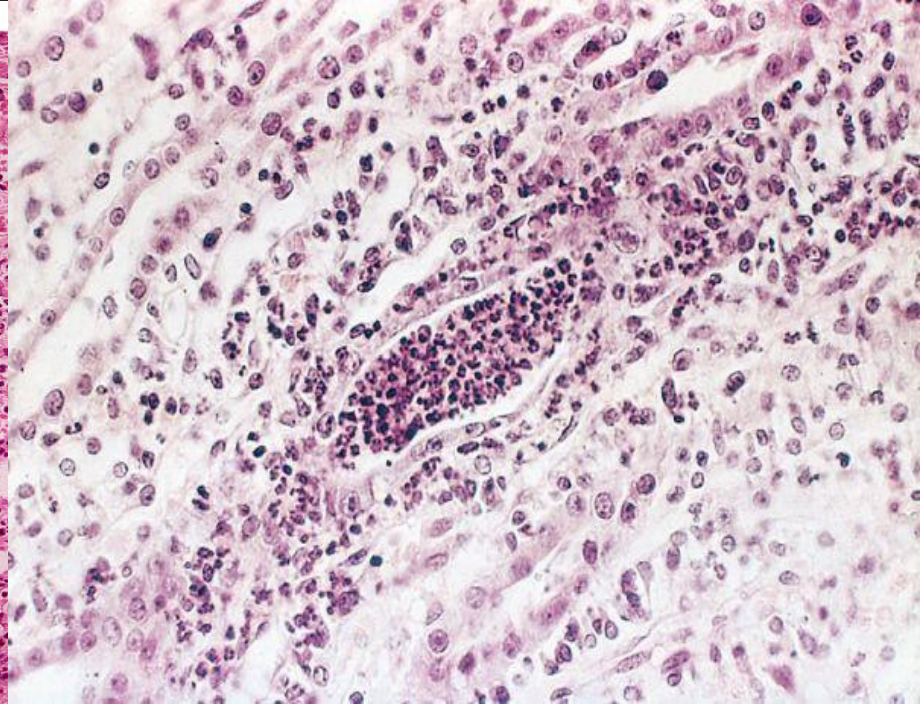
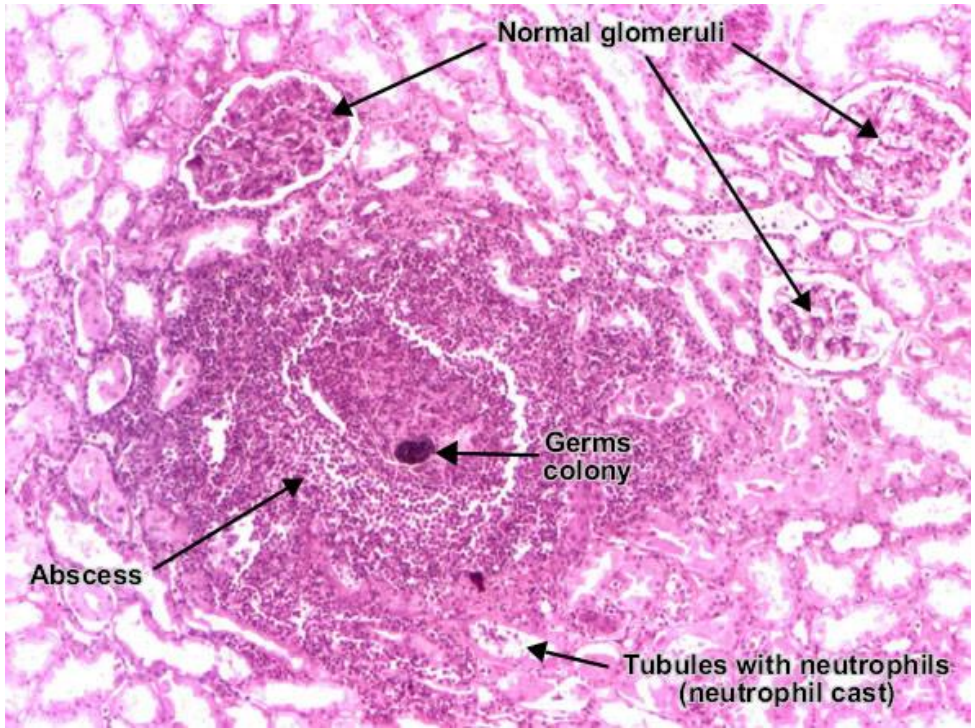


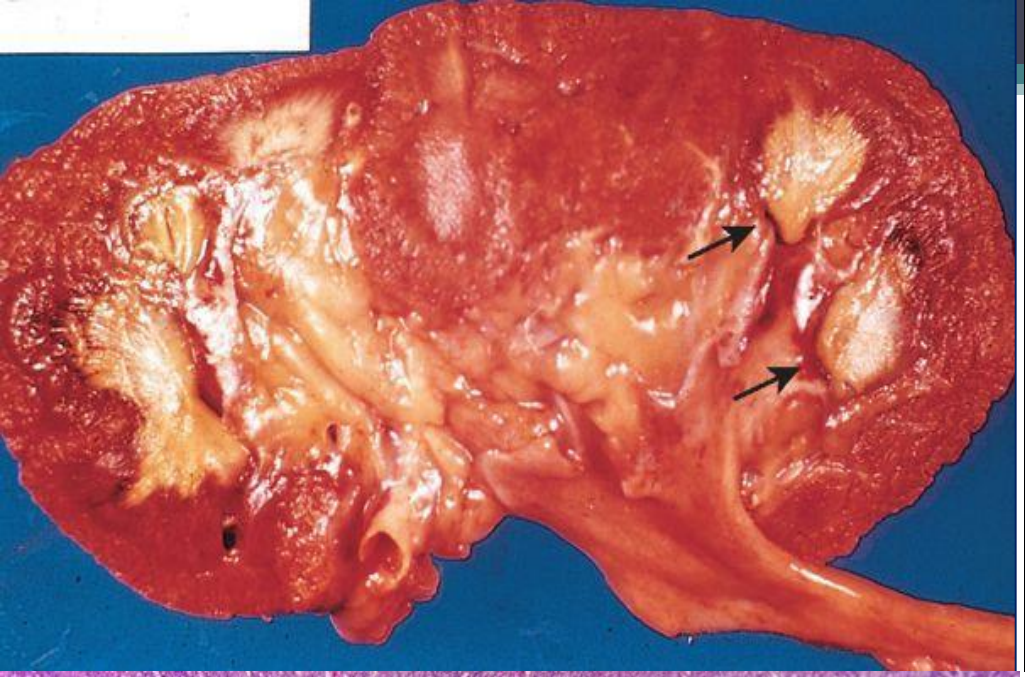

Normal glomeruli
Germs colony
Abscess
Tubules with neutrophils (neutrophil cast)

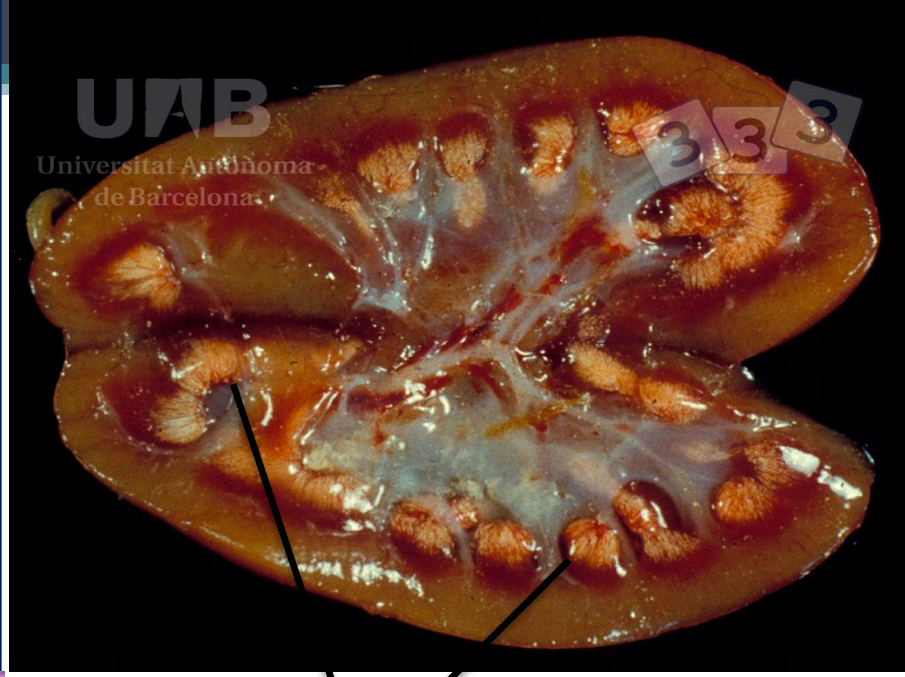
Clinical findings

- Fever, rigors & chills, loin pain (+ costovertebral tenderness), and symptoms of LUTI.
- **Urinalysis:** Bacteruria, pyuria, WBC casts.
- **Prognosis:**
  - Usually self-limited if treated well (Antibiotics).
  - Predisposing factors lead to recurrent or chronic pyelonephritis

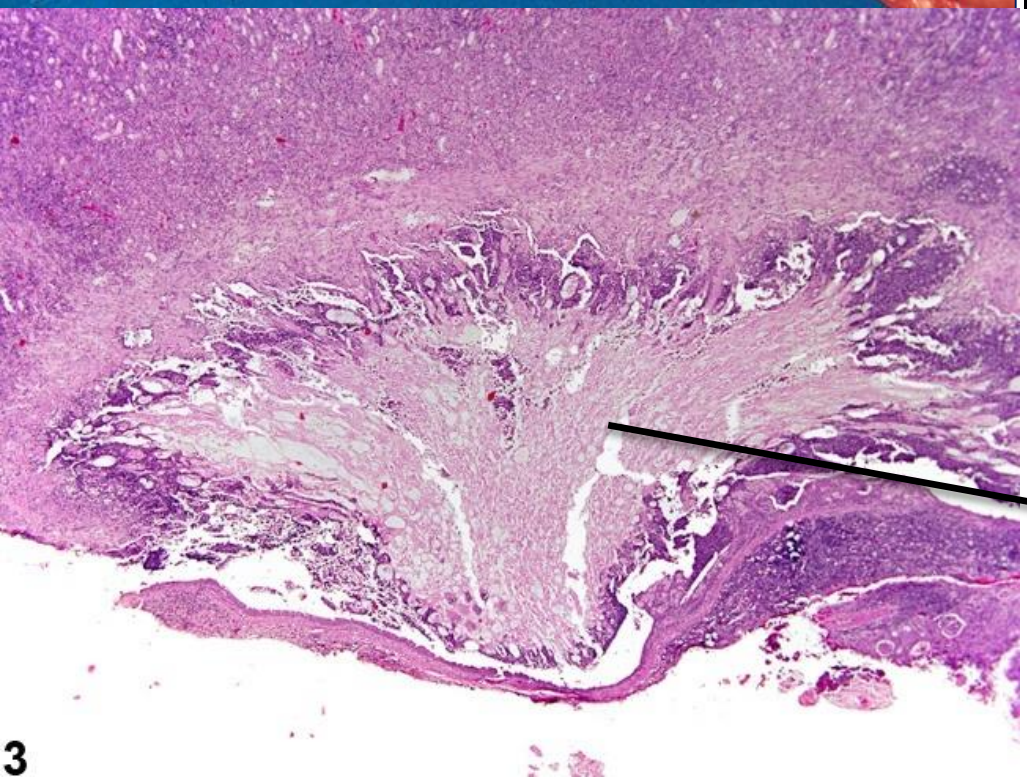
Papillary necrosis

- Uncommon, may complicate acute pyelonephritis esp. in **DM** and significant obstruction.
- A combination of ischemic and suppurative necrosis of renal papillae.
- Carries *poor* prognosis.





Sharply defined areas of necrosis involving several papillae.



Coagulative necrosis, with surrounding neutrophilic infiltrate

B. Chronic pyelonephritis

- A morphologic entity in which interstitial inflammation and scarring of the renal parenchyma is associated with *grossly visible scarring* and deformity of the pelvicalyceal system
- Important cause of **CRF** → **10-20%** of cases.
- **Two forms:**

I. Chronic Reflux-Associated PN (Reflux nephropathy):

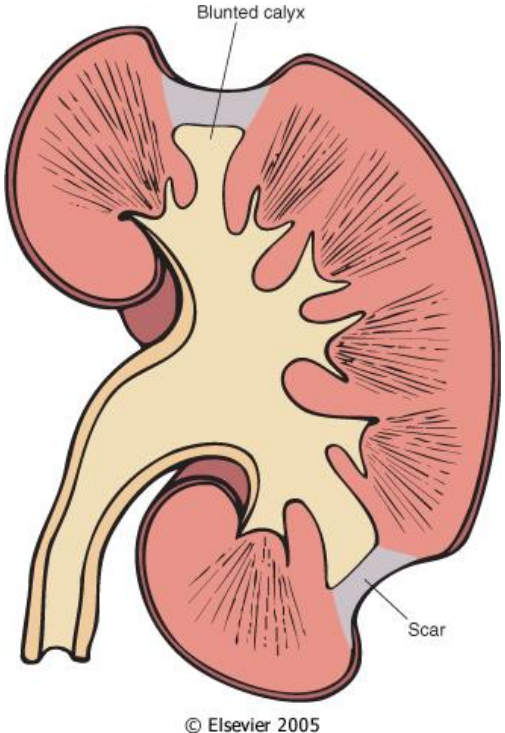
  - Commonest form of PN.
  - Can be **unilateral** or **bilateral** (leads to CRF).

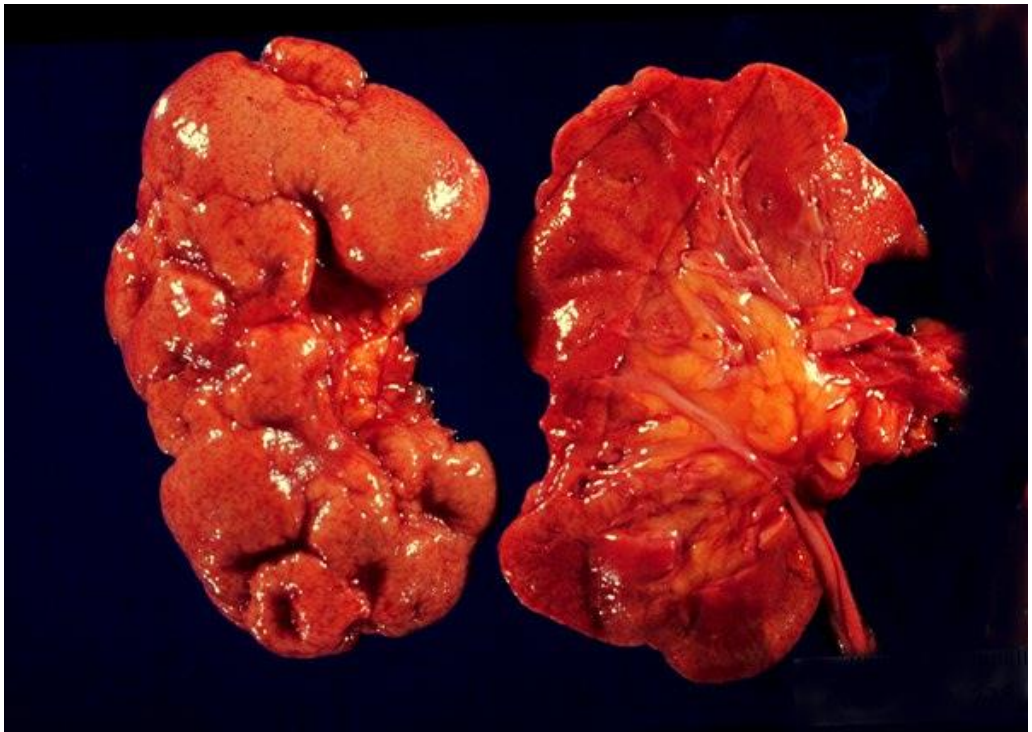
II. Chronic obstructive PN:

- Obstruction of UT lead to recurrent bouts of renal inflammation and scarring. Can be:
  - **Unilateral** (commoner): As in case of unilateral uretric calculus.
  - **Bilateral**: As anomalies of urethra (posterior urethral valves) → leads to CRF.

Morphology of chronic PN

- **Gross:**
  - Unilateral or bilateral. Diffuse or patchy involvement.
  - ***Asymmetrical**** contracted kidney with blunted or deformed calyces.

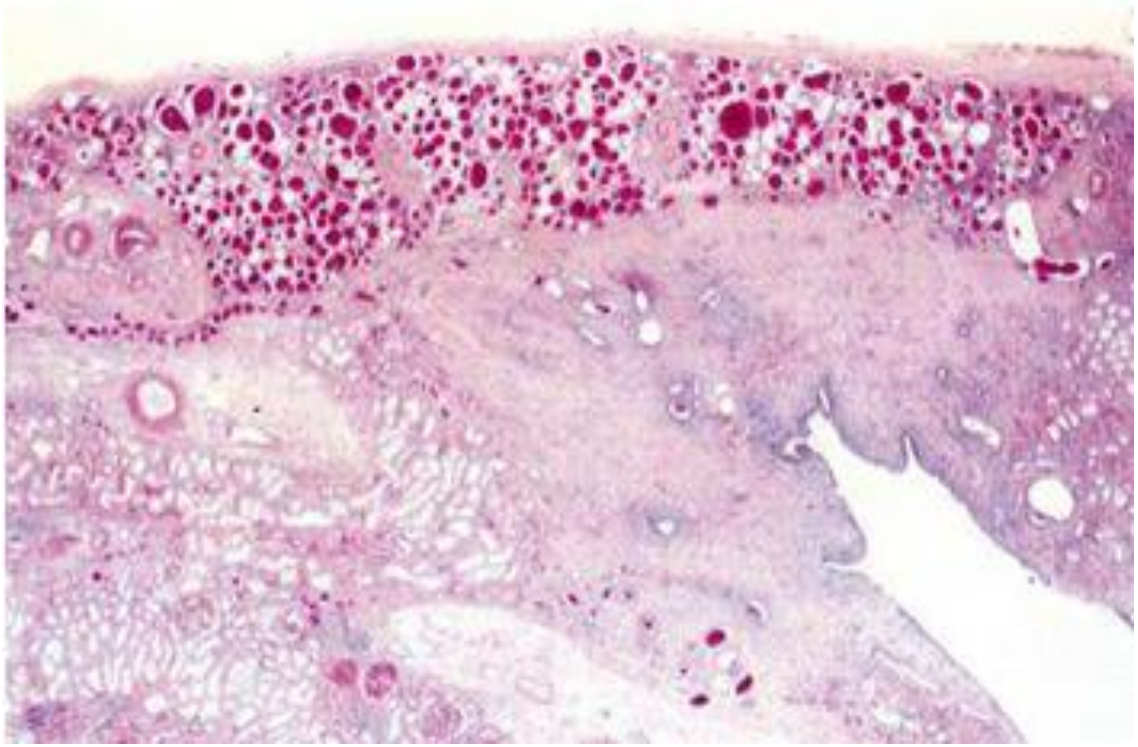


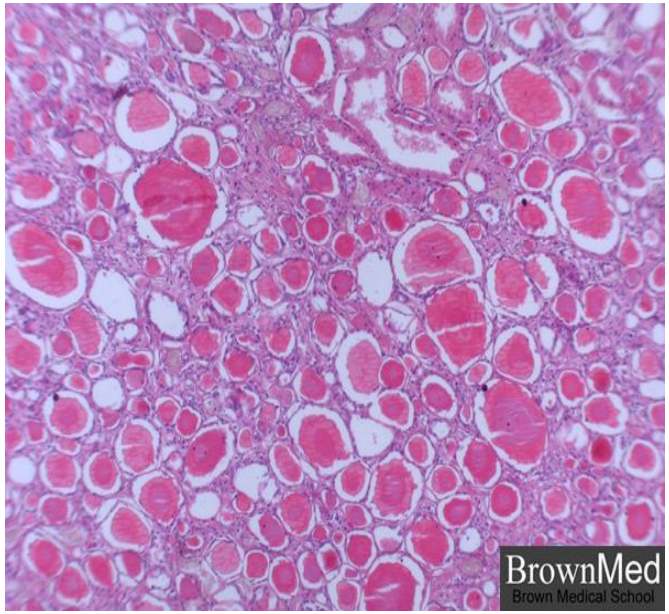


Morphology of chronic PN

- **Microscopically:**
  - Chronic inflammation & fibrosis of interstitium & calyceal mucosa.
  - *Thyroidization of tubules*: tubules* with atrophied epithelium containing PAS+ casts**.
  - Benign arteriosclerosis due to HTN.
  - Glomeruli may gradually undergo sclerosis (FSGS → complete sclerosis).

Chronic PN





A corticomedullary renal scar with an underlying dilated deformed calyx. Note the thyroidization of tubules in the cortex.