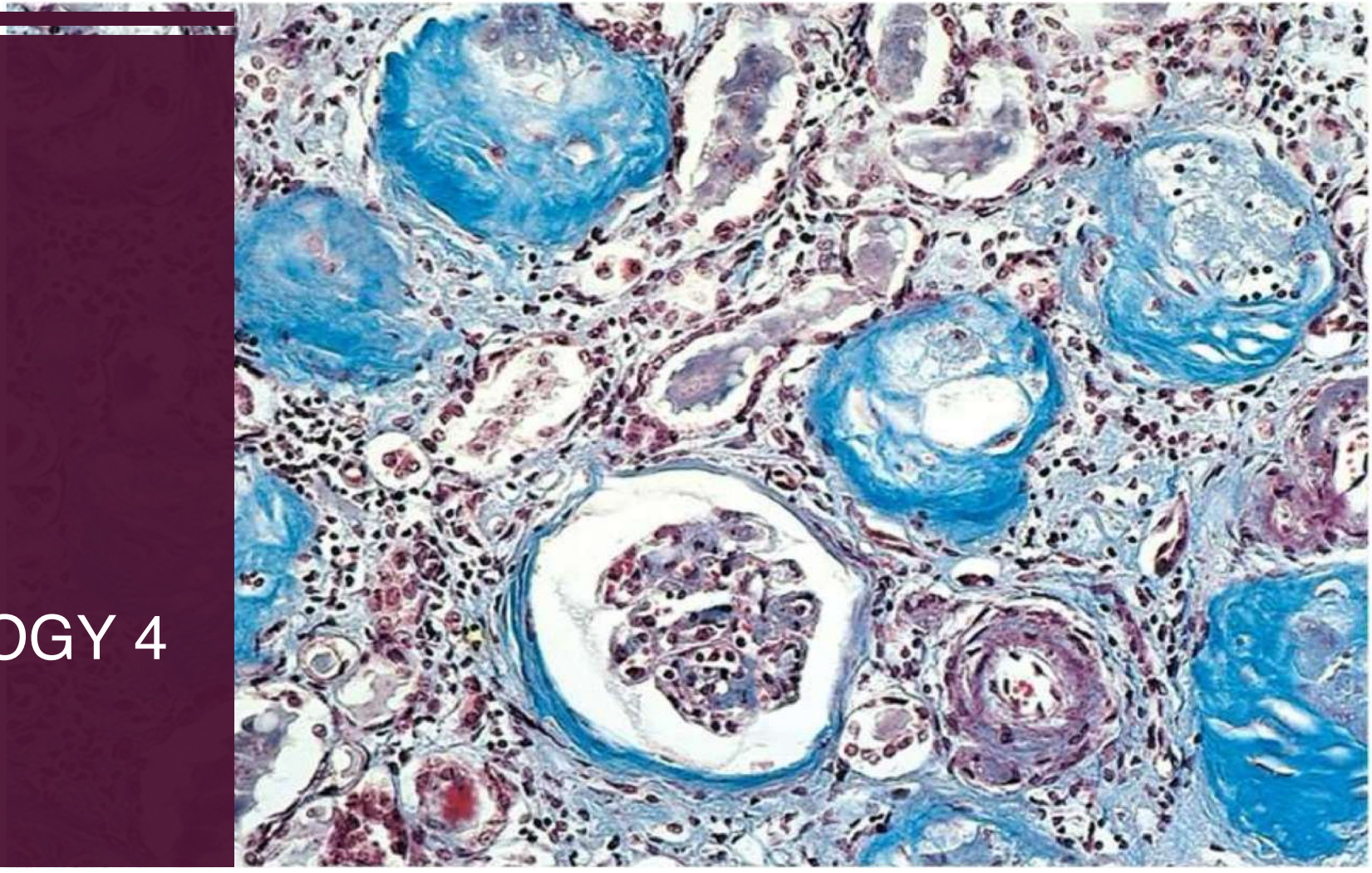
RENAL PATHOLOGY 4



CHRONIC GLOMERULONEPHRITIS

- **Chronic GN** is the **final outcome of various forms of G disease**, irrespective of whether there has been preceding **G** inflammatory injury.
- When it is discovered, the **G** changes are so **far advanced** that it is difficult to ascertain the original lesion.
- **It represents the end stage of a variety of entities, including Cr GN, FSGS, MN, MPGN & IgA nephropathy.**
- Although it may develop at any age, it is usually first noted in young & middle-aged adults.
- It is a common & important cause of CRF, e.g.,

CHRONIC GLOMERULONEPHRITIS

- It has been estimated that **20% of chronic GN cases arise with no history** of symptomatic renal disease!
- Grossly, **both kidneys are symmetrically contracted**& their surfaces are red-brown & **diffusely granular.**
- **Histopathology** : showing
- Advanced scarring & obliteration of the G, sometimes to the pointof complete sclerosis.
- Atrophy of the tubules in the cortex
- Interstitial fibrosis, with marked lymphocytic cell infiltrates.
- the small & medium-sized arteries are frequently thick walled& narrowed, due to hypertension secondary to the chronic GN
- Such markedly damaged kidneys are designated " **end-stage kidneys“!**

Chronic Glomerulonephritis

- Causes include repeated episodes of acute glomerular nephritis, hypertensive nephrosclerosis, hyperlipidemia, and other causes of glomerular damage.
- Symptoms vary; may be asymptomatic for years, as glomerular damage increases, before signs and symptoms develop of renal insufficiency/failure.
- Abnormal laboratory tests include urine with fixed specific gravity, casts, and proteinuria; and electrolyte imbalances and hypoalbuminemia.
- Medical management is determined by symptoms.

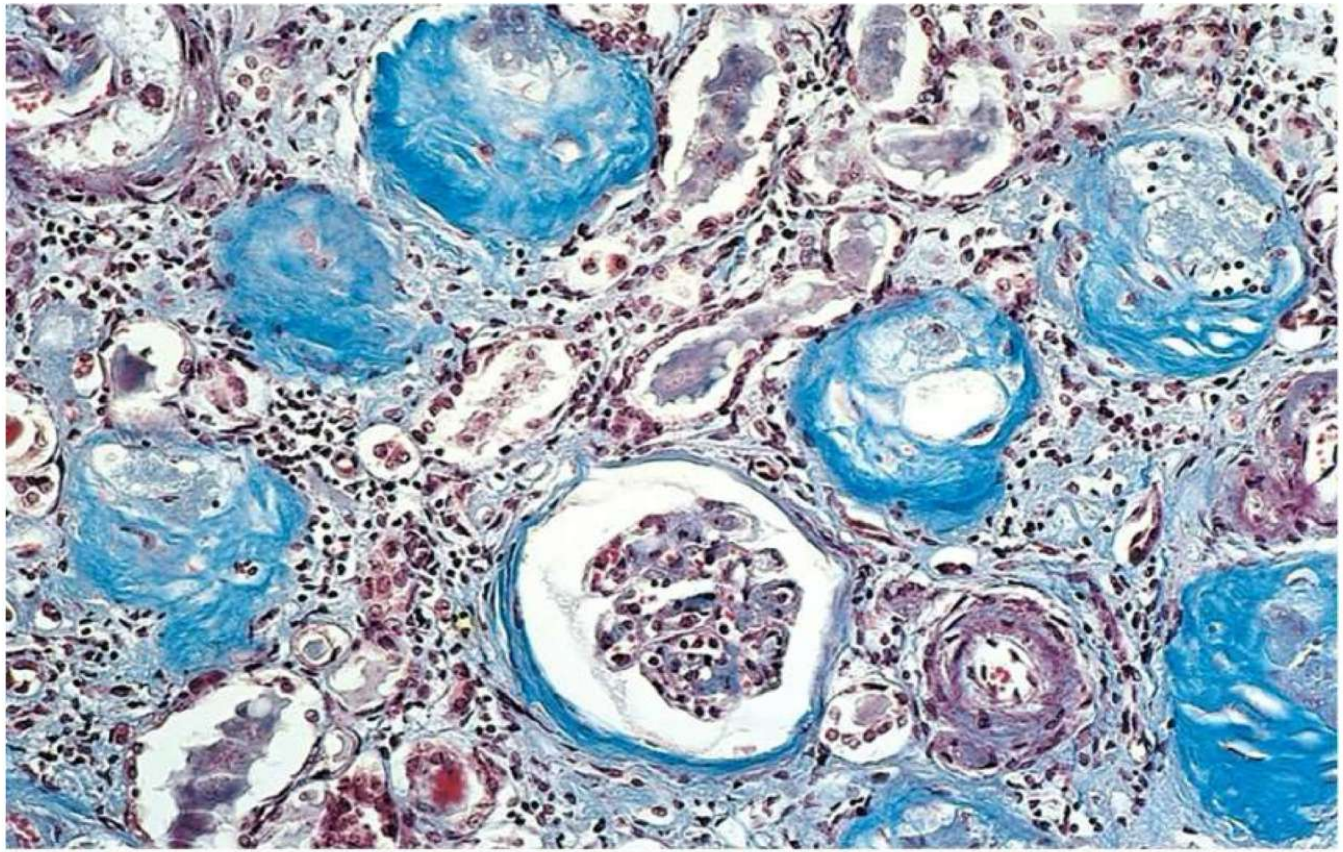
ASSESSMENT & DIAGNOSTIC FINDINGS

Urinalysis reveals a specific gravity of 1.010, proteinuria, and urinary casts.
BUN Elevation

As renal failure progresses the GFR falls below 50ml/min and the following changes occur:
Hyperkalemia
Metabolic Acidosis
Anemia
Hypoalbuminemia
Increased Serum Phosphorus
Decreased Serum Calcium
Mental Status Changes

C-xray reveal cardiac enlargement & pulmonary edema
ECG- normal or indicate Left ventricular hypertrophy
CT/MRI reveal reduced size of renal cortex

virtually all glomeruli by **blue-staining collagen**.



DISEASES AFFECTING TUBULES (T) & INTERSTITIUM

- Most forms of T injury also involve the interstitium, The disease characterized either :
- (1) inflammatory involvement of the T& interstitium (interstitial nephritis)
- (2) ischemic/ toxic T injury, leading to acute tubular necrosis& acute RF.

I.TUBULOINTERSTITIAL NEPHRITIS

- TIN refers to a group of primary inflammatory diseases of the renal interstitium & Tubule .
- The G may be spared altogether or affected only late in the course.
- The **term pyelonephritis** is used for cases of TIN caused by bacterial infection, with prominent involvement of the renal pelvis.
- The term **interstitial nephritis** is reserved for cases of TIN that are nonbacterial in origin, including T injury resulting from **drugs, metabolic disorders (e.g., hypokalemia), physical injury (e.g., irradiation), viral infections, & immune reactions.**
- It can be divided into
- 1- acute
- 2- chronic categories on the basis of clinical features & the character of the inflammatory exudate,

CAUSES OF TUBULOINTERSTITIAL NEPHRITIS

- **Causes :**
- **1-bacterial infection.**
- **2-drugs.**
- **3-metabolic disorders**
- **4-physical injury (irradiation).**
- **5-immune reactions.**

TUBULOINTERSTITIAL NEPHRITIS

- Urinary tract infections
- UTIs are extremely common clinical problems, which implies involvement of the lower UT (urethritis, cystitis & prostatitis,) or upper UT (pyelonephritis), or both.
- 1-lower UTI (cystitis, prostatitis, urethritis).
- 2-upper UTI (pyelonephritis).

A. INFECTIOUS : ACUTE PYELONEPHRITIS

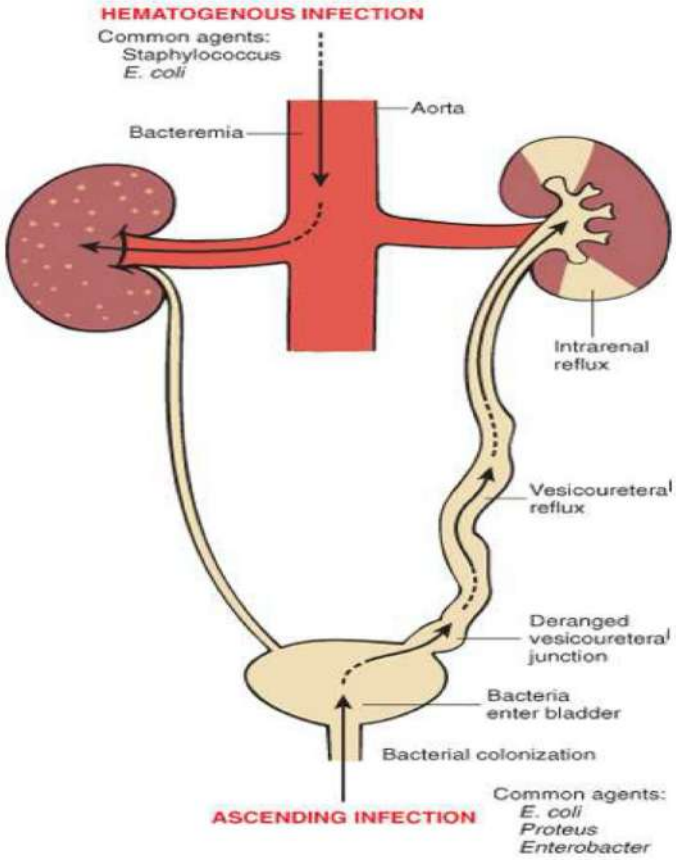
- Acute Pyelonephritis is a common suppurative inflammation of the kidney & the renal pelvis caused by bacterial infection.
- It is an important manifestation of urinary tract infection (UTI),
- The great majority of cases of upper UTI are associated with lower UTI.
- However, lower UTI may remain localized, without extending to involve the kidney.

ACUTE PYELONEPHRITIS

- **UTI most commonly affects females,** as colonization by enteric bacteria is favored, due to the
- **(I) close proximity of the urethra to the rectum,**
- **(II) the short urethra, &**
- **(III) trauma to the urethra during sexual intercourse facilitate the bacterial entryinto the bladder.**
- **Normally**, bladder urine is sterile, as a result of the:
- (a) Antimicrobial properties of the bladder mucosa
- (b) flushing action associated with periodic voiding of urine.
- The bladder **outflow obstruction or bladder dysfunction predispose** to UTI.
- Bladder obstruction results in **incomplete emptying** & increase residual volume of urine.
- In the presence of **stasis** ,bacteria introduced into the bladder can multiply undisturbed, without being flushed out or destroyed by the bladder wall.

PATHOGENESIS OF ACUTE PYELONEPHRITIS

- The principal causative organisms are the enteric gram-negative rods. the most common is **Escherichia coli(E coli).**
- Other organisms are species of **Proteus, Klebsiella, Enterobacter,& Pseudomonas; these are usually associated with recurrent infections,**
- especially in persons who undergo UT manipulations **(e.g. catheterization & cystoscopy)or have congenital or acquired anomalies of the lower UT.**
- **Routes of acute pyelonephritis infection**
- **Bacteria can reach the kidneys by 2 routes:**
- **1- Rarest is hematogenous** route, through the bloodstream, results from seeding of thekidneys by bacteria in the course of septicemia or infective endocarditis.
- **2- Commonest& most important is ascending route** by which the bacteria reach the kidney is through ascending from the lower UT....



- **Pathways of renal infection**
- **Hematogenous** infection results from bacteremic spread. ➔Commonest **ascending infection,**which results from a combination of urinary bladder infection, vesicoureteral reflux, & intrarenal reflux.

PATHOGENESIS OF ACUTE PYELONEPHRITIS

- **The 1st step** in the pathogenesis of ascending UTI is **adhesion of bacteria to mucosal surfaces, followed by colonization of the distal urethra (& the introitus in females)**
- **In the 2nd step,** the organisms must gain access to the bladder, by expansive growth of the colonies & by **moving against the flow of urine**. This may occur during urethral instrumentation, e.g., catheterization & cystoscopy, which are important predisposing factors in the pathogenesis of UTIs.
- **In the 3rd step**, the bacteria from the contaminated bladder urine **ascend along the ureters** to infect the **renal pelvis& parenchyma.**

PATHOGENESIS OF ACUTE PYELONEPHRITIS

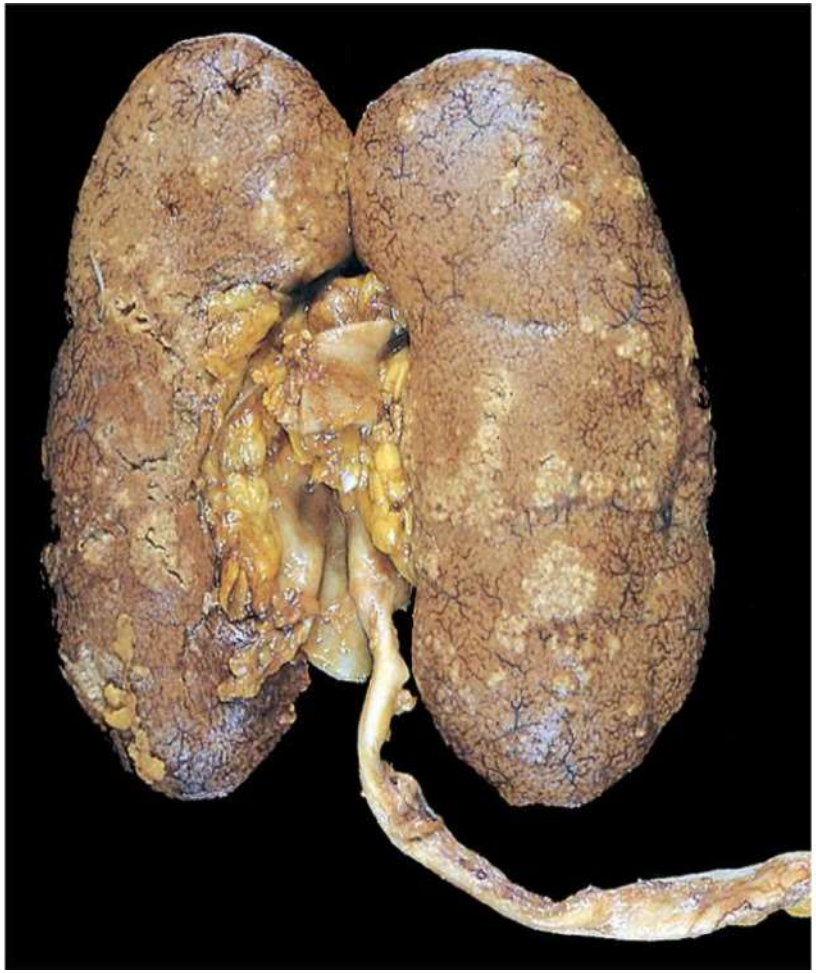
- Accordingly, UTI is common among individuals with UT obstruction, as may occur with **benign prostatic hyperplasia & uterine prolapse,& stones.**
- UTI is also in **DM** because of the susceptibility to infection & **Neurogenic** bladder dysfunction, which in turn predisposes to stasis.
- Although **obstruction** is an important predisposing factor in the pathogenesis of ascending infection, it is the.... incompetence of the **vesicoureteral orifice** that allows bacteria to ascend the ureter into the pelvis.
- The **normal** ureteral insertion into the bladder is a competent **one-way valve that prevents retrograde flow of urine**, especially during micturition, when the intravesical pressure increase.
- An incompetent vesicoureteral orifice allows the reflux of bladder urine into the ureters, {vesicoureteral reflux = VUR }.

PATHOGENESIS OF ACUTE PYELONEPHRITIS

- 1- **VUR** is present in **20% to 40% of young children with UTI,** in which VUR is a **congenital defect** that results in incompetence of the ureter vesical valve.
- 2- **VUR** can also be **acquired** in individuals with a flaccid bladder resulting from **spinal cord injury**& with **neurogenic** bladderdysfunction secondary to DM.

MORPHOLOGY OF ACUTE PYELONEPHRITIS

- **Grossly**
- **, in acute PN,**one or both kidneys may be involved. The affected kidney may be normal in size or enlarged.
- **Characteristically, multiple abscesses, raised,** discrete, & yellowish, are grossly apparent on the **renal surface.**



Acute pyelonephritis.

The cortical surface is studded with multiple, focal, pale abscesses, Between the abscesses there is dark congestion of the renal surface

MORPHOLOGY OF ACUTE PYELONEPHRITIS

- **Microscopically**
- the characteristic histologic feature of acute PN is renal abscess formation, within the renal parenchyma.
- Early, the suppuration is limited to the interstitial tissue, but later the abscesses rupture into tubules, & the masses of intratubular neutrophils extend into the collecting ducts, giving rise to the characteristic WBC (granular) casts found in the urine .
- Typically, the G are not affected.

PYELONEPHRITIS (PAPILLARY NECROSIS)

- **A second infrequent form of pyelonephritis is necrosis of the renal papillae, known as Papillary Necrosis**.
- I. This is particularly common among **diabetics** who develop acute pyelonephritis.
- II. May complicate acute pyelonephritis when there is significant **UT obstruction**.
- III. It is also seen with the chronic interstitial nephritis associated with **analgesic abuse.**

PAPILLARY NECROSIS

- Papillary necrosis is a combination **of (I) ischemic + (II) suppurative necrosis of the tips of the renal pyramids (renal papillae).**
- The Pathognomonic gross feature of papillary necrosis is **sharply defined, gray-white to yellow necrosis of the apical 2/3 of 1,2 or all the pyramids papillae.**
- Microscopically , the papillary tips show ischemic coagulative necrosis, with surrounding neutrophilic infiltrate
- Symptoms (and signs) consistent with renal papillary necrosis are:
- Back pain
- Cloudy urine
- Tissue pieces (in urine)
- Fever
- Painful/frequent urination
- Urinary incontinence

CAUSES OF PAPILLARY NECROSIS

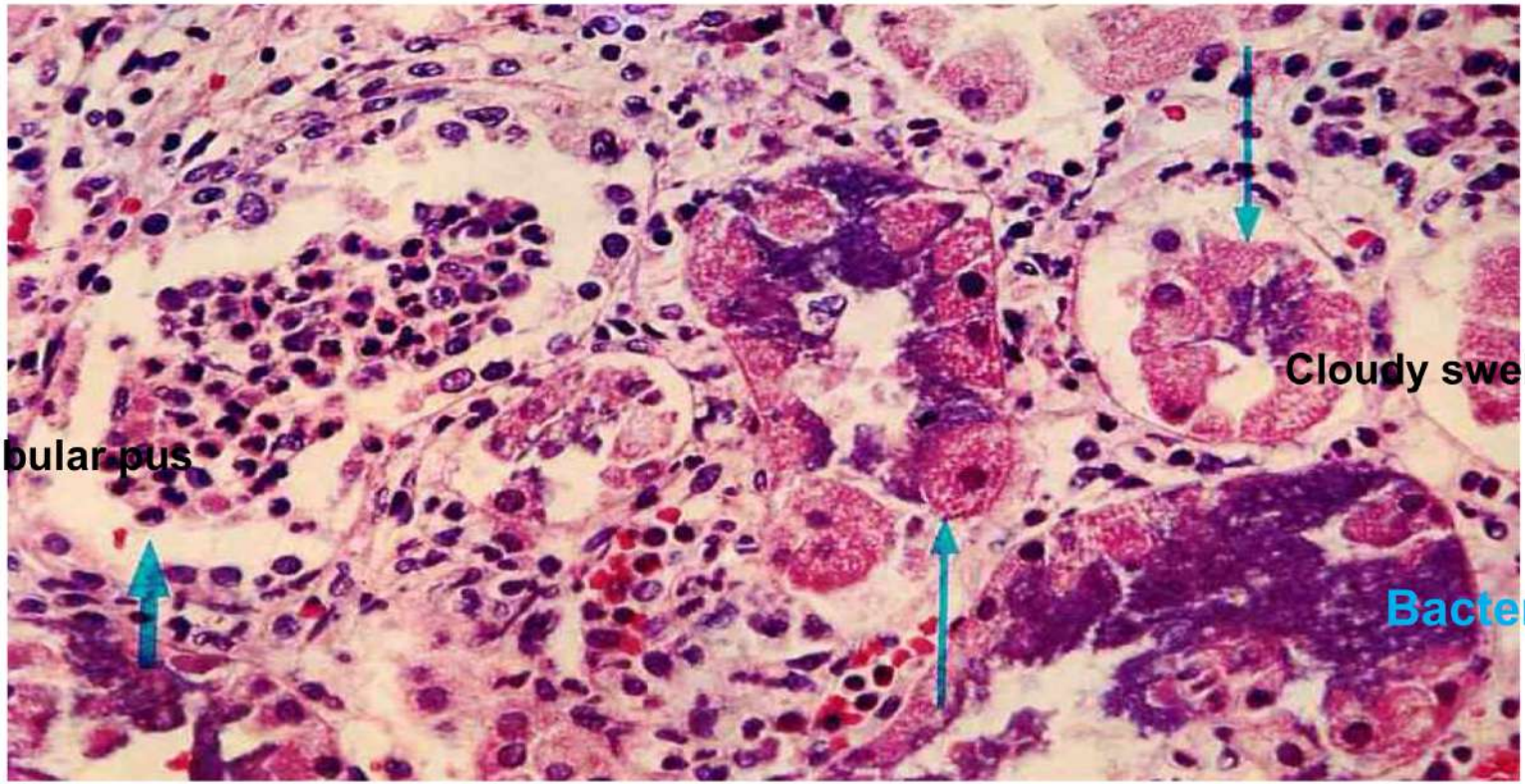
- **In terms of cause, almost any condition that involves ischemia can lead to renal papillary necrosis.**
- Pyelonephritis, obstruction of the urogenital tract, sickle cell disease, tuberculosis, cirrhosis of the liver, analgesia/alcohol abuse, renal vein thrombosis, diabetes mellitus, and systemic vasculitis. Often, a patient with renal papillary necrosis will have numerous conditions acting synergistically to bring about the disease.
- Analgesic nephropathy is a common cause of renal papillary necrosis(NSAID).

PATHOPHYSIOLOGY OF PAPILLARY NECROSIS

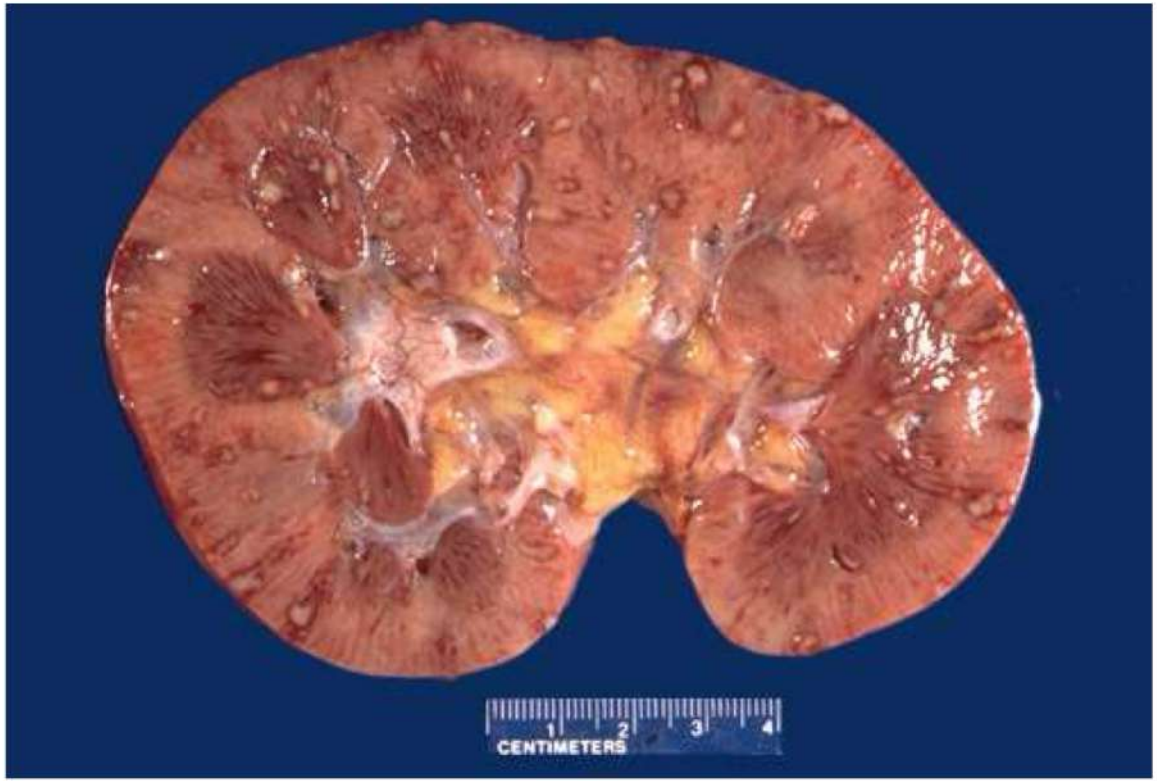
- This condition is due to ischemia of the renal papillae, the portion of the kidney thatcollects urine from the nephron.
- The papillae are vulnerable to ischemia as they are supplied by small caliber arterieswhich are liable to obstruction, necrosis of the papillae results in sloughing into thelumen, causing hematuria.
- If the degree of necrosis is substantial post-renal failure may occur, though this is uncommon.

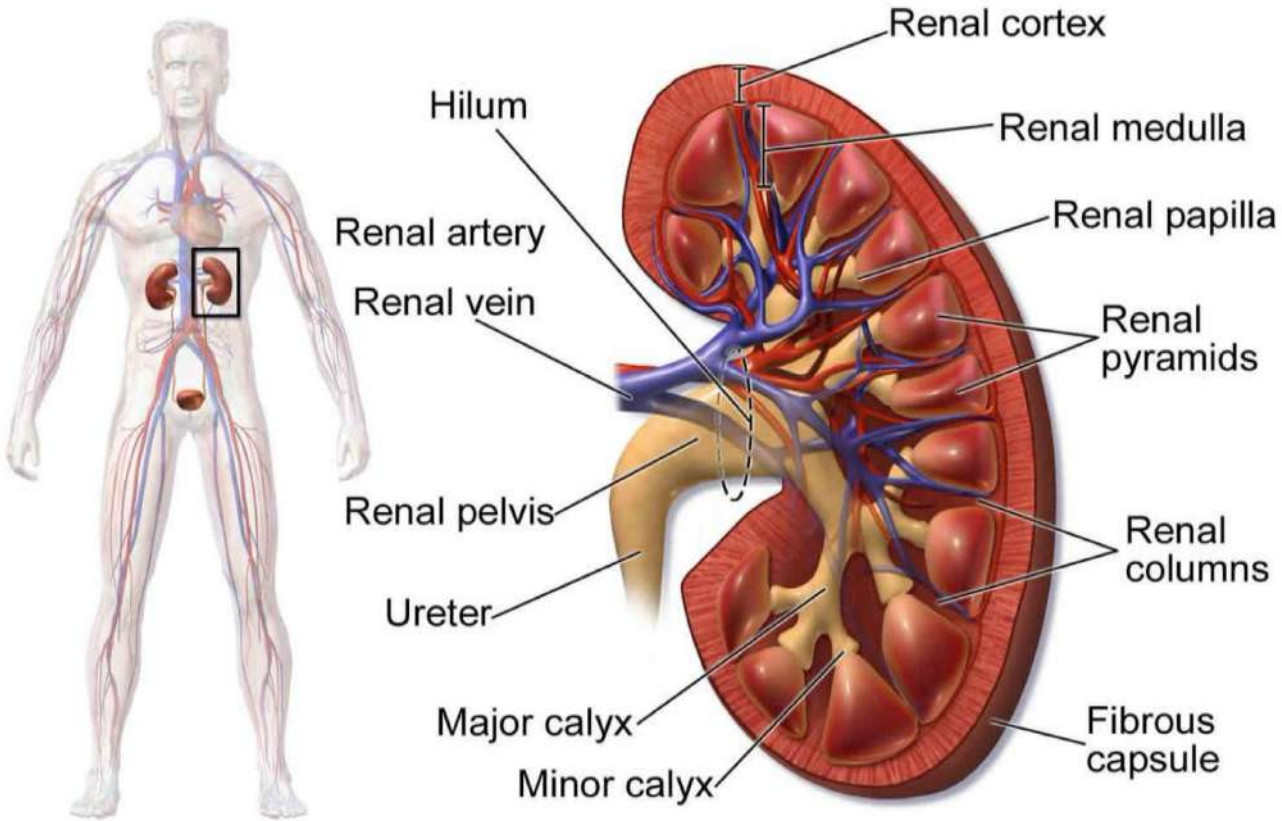
Acute pyelonephritis: kidney X200.

(1) The interstitial tissue are infiltrated with polymorphs, lymphocytes & plasma cells, (2) some tubules show severe cloudy swelling (thin arrow), in others, tubular cells are necrotic & contain large number of bacteria (stained deep blue), &
(3) some tubules are full of pus & lost most of its epithelial lining (thick arrow).



- The cut surface of the kidney reveals many small yellowish microabscesses in both cortex and medulla.
- This type of pyelonephritis is most typical for hematogenous dissemination of infection to the kidney, rather than the more typical ascending urinary tract infection.

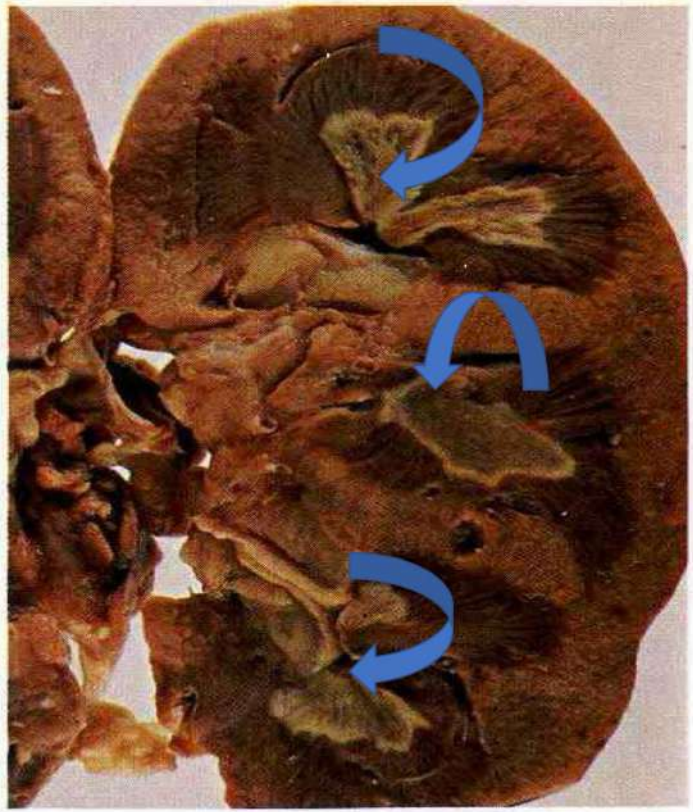




Kidney Anatomy

CLINICALLY

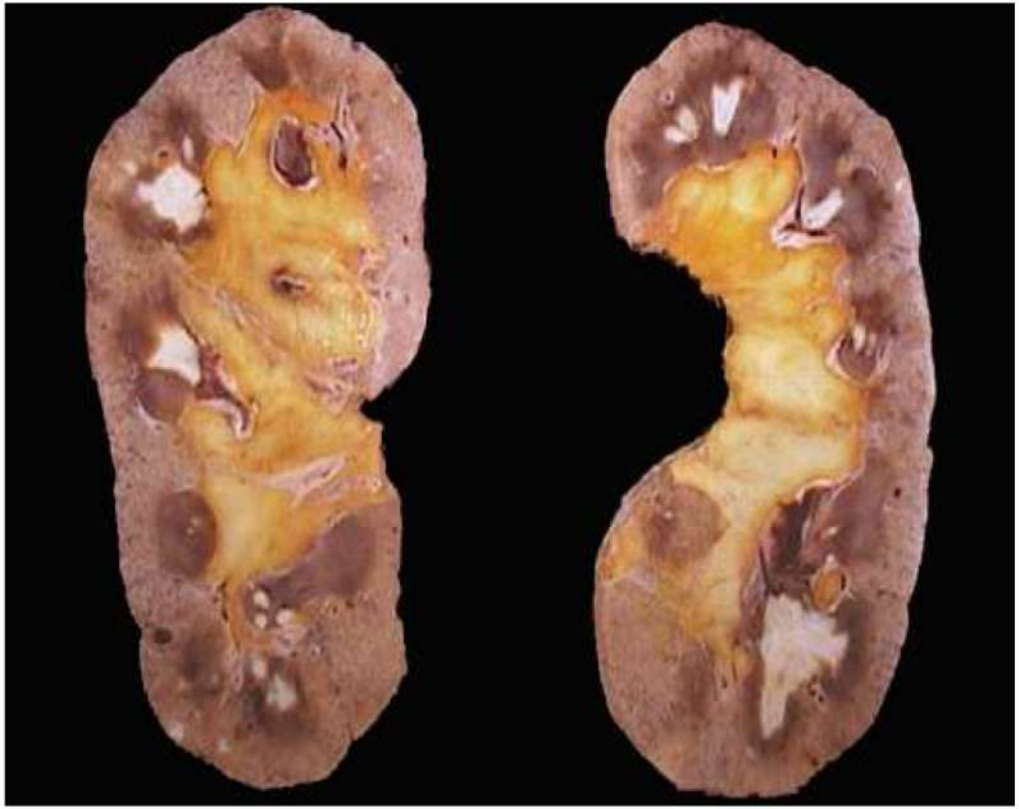
- The onset of uncomplicated acute pyelonephritis is usually **sudden**, with **pain** at the costovertebral angle & systemic evidence of infection (**chills, fever, & malaise**), & indications of bladder & urethral irritation **(dysuria, frequency, & urgency).**
- **Diagnosis** of acute pyelonephritis is **established** by finding **"pyuria& bacteriuria** by urinalysis & urine culture
- The disease is usually unilateral, & individuals thus do not develop RF because they still have one unaffected kidney. In cases with predisposing influences, the disease may become recurrent or chronic, particularly when it is bilateral.
- The development of papillary necrosis is associated with very poor prognosis.



10.21 Acute pyelonephritis and papillary necrosis

Acute pyelonephritis and papillary necrosis.

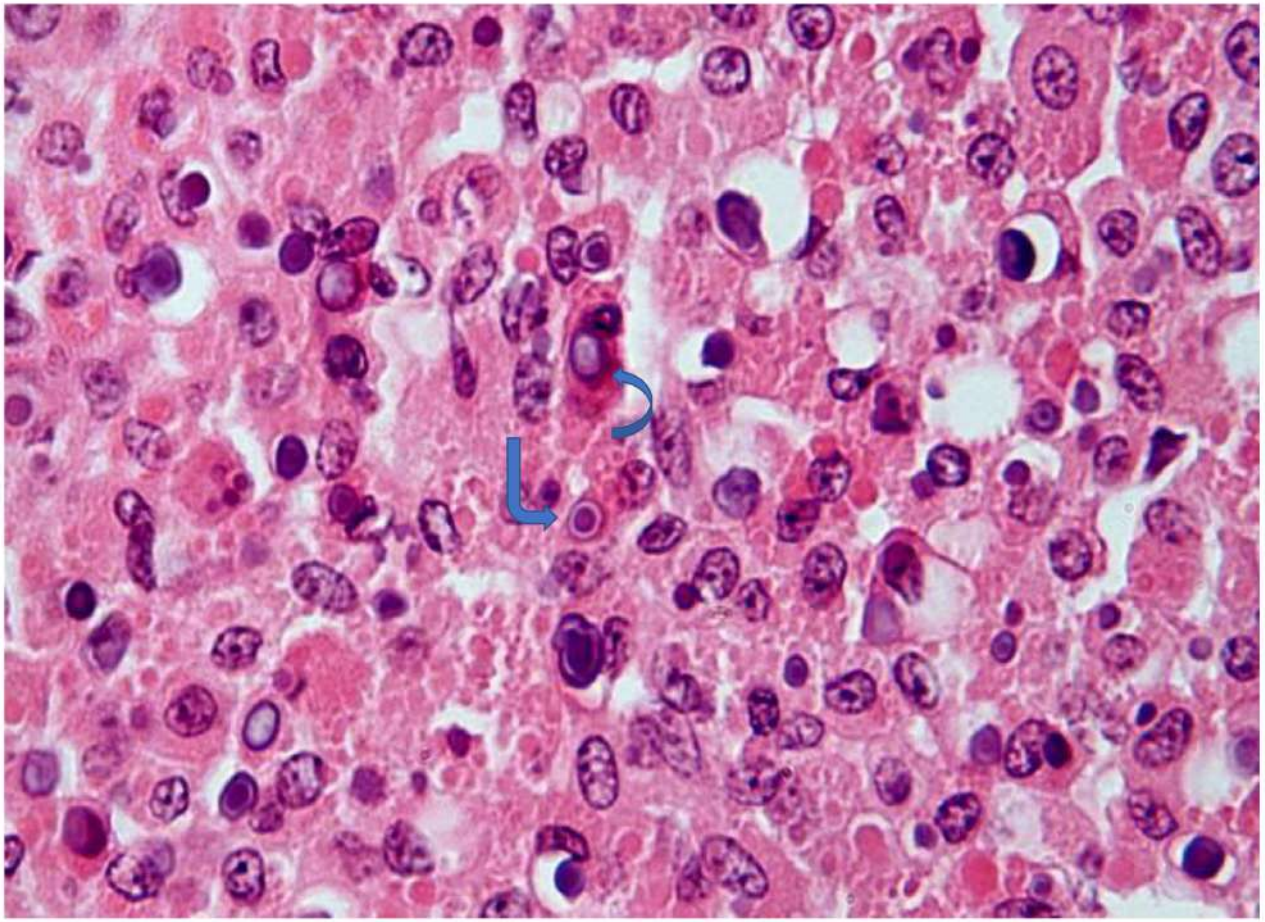
★The distal part of each of three papillae (Arrows) is necrotic, greyish-white & with a congested border.



- The pale white areas involving some or all of many renal papillae are areas of papillary necrosis.
- This is an uncommon but severe complication of acute pyelonephritis, particularly in persons with diabetes mellitus. Papillary necrosis may also accompany analgesic nephropathy.

MALAKOPLAKIA

- **Malakoplakia** is an uncommon chronic granulomatous inflammatory condition, It usually involves gram-negative bacteria.
- It makes its presence known as a papule, plaque or ulceration that usually affects the genitourinary tract.
- It may also be associated with other bodily organs.
- Malakoplakia is thought to result from the **insufficient killing of bacteria by macrophages.** Therefore, the partially digested bacteria accumulate in macrophages and leads to a deposition of iron and calcium.
- **Foamy macrophages with PAS+ granular cytoplasm** due to phagosomes stuffed with bacterial debris and **Michaelis-Gutmann bodies** (laminated mineralized concretions) Calcium and iron



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- It usually involves gram-negative bacteria
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DRUG-INDUCED INTERSTITIAL NEPHRITIS

- **Two forms:**
- **1-Acute Drug-Induced Interstitial Nephritis**
- **2-chronic (Analgesic) Nephropathy**
- **AcuteTIN**
- **Most common: synthetic penicillins(methicillin, ampicillin)**
- **Others: synthetic antibiotics; diuretics;NSAIDs; other drugs**

PATHOGENESIS OF DRUG-INDUCED INTERSTITIAL NEPHRITIS

- **immune mechanism.**
- **type I hypersensitivity.**
- **T cell-mediated (typeIV) hypersensitivity reaction.**
- **Pathogenesis**
- the drugs act as **haptens (small molecule that stimulates the production of antibody molecules only when conjugated to a larger molecule) So** during secretion of the drug by tubules, covalently bind to some cytoplasmic or extracellular component of tubular cells & become immunogenic.
- The resultant tubulointerstitial injury is then caused by immunological, either IgE-(**Type I)** or cell-mediated immune (**Type IV)** reactions to tubular cells or their BMs.

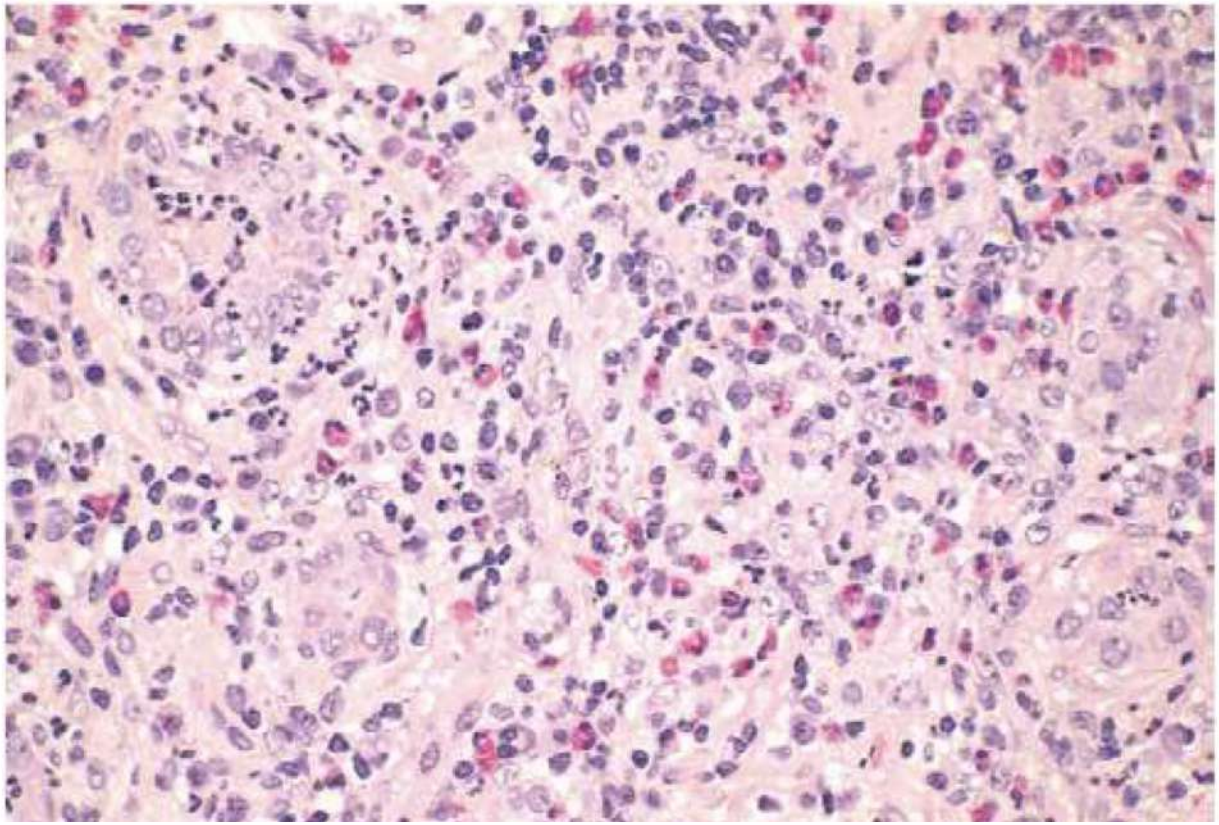
MORPHOLOGY OF DRUG-INDUCED INTERSTITIAL NEPHRITIS

- The interstitium shows pronounced (I) **edema** & (II) **infiltration** by large numbers of lymphocytes, macrophages ,eosinophils & neutrophils.
- **glomeruli are normal.** except in some cases caused by **NSAID**, when the hypersensitivity reaction also leads to podocyte foot process effacement & the development of **nephrotic** syndrome.
- With some drugs (e.g., methicillin, thiazides, rifampin), interstitial non-necrotizing **granulomas** with giant cells may be seen

CLINICALLY

- the disease begins 2 to 40 days (average15 days) after exposure to the drug.
- is characterized by fever & rash & eosinophilia in about25% of persons, & renal abnormalities including hematuria, mild proteinuria, & leukocyturia.
- A rising serum creatinine or, acute RF with oliguria,develops in about 50% of cases, particularly in older patients.
- withdrawal of the offending drug is followed by recovery.

Drug-induced interstitial nephritis



ANALGESIC NEPHROPATHY : CHRONIC DRUG-INDUCED

- Consumption of large quantities of analgesics over long periods may cause **chronic interstitial nephritis** often with **renal papillary necrosis.**
- **Aspirin and acetaminophen are common.**
- While they can cause renal disease in apparently healthy individuals, preexisting renal disease seems to be a necessary precursor to analgesic-induced RF.
- **Pathogenesis not entirely clear.**
- Papillary necrosis is the initial event, followed by the interstitial nephritis in the overlying renal parenchyma.