Lecture 3&4
Renal pathology

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❖ IgA Nephropathy

- one of the most common causes of recurrent microscopic or gross hematuria
- children and young adults.
- hematuria 1 or 2 days after nonspecific upper respiratory tract infection.
- hematuria lasts several days and then subsides and recur every few months.

IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria &is the most common G disease revealed by renal biopsies worldwide.

The pathogenic hallmark is the deposition of IgA in the mesangium.

★**Clinically,** IgA nephropathy usually & most often affects children & young adults.

★More than **50%**of patients present with **gross hematuria** (that occurs within 1 or 2 days of a nonspecific upper RTI, or, less commonly, GIT or UT infection); the hematuria typically lasts for several days & then subsides, only to return every few months & is often associated with **loin pain**.

★**40%**have only **microscopic hematuria,**with or without proteinuria;

★up to **10%**develop acute nephritic syndrome.

Pathogenesis

- **abnormality in IgA production and clearance.**
- **LM: variable**
- **IF: mesangial deposition of IgA**with C3
- **EM:** deposits in the mesangium

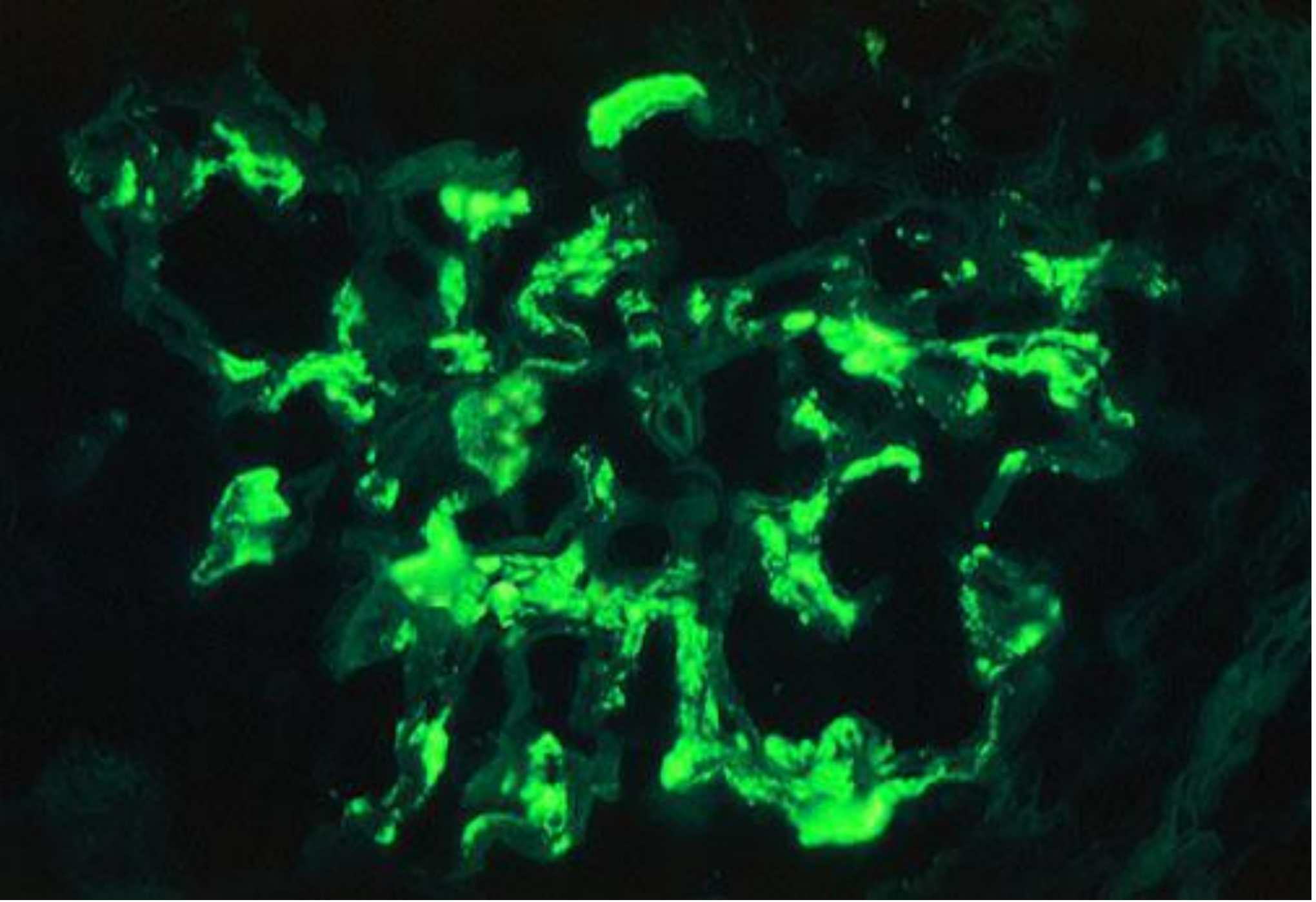
Pathogenesis of IgA nephropathy

- Normally, IgA, the main immunoglobulin in mucosal secretions, is at low levels in normal serum. IgA is ↑in 50% of patients with IgA nephropathy due to ↑production in the bone marrow. A **genetic influence** is suggested by it's occurrence in families & in HLA-identical siblings.

►Studies suggest that ↑**IgA synthesis** in response to respiratory or GIT exposure to environmental agents (e.g., viruses, bacteria, & food proteins) **may lead to deposition of IgA & IgA-containing immune complexes in the mesangium**, where they activate the alternative complement pathway & initiate **G** injury.

Morphology

◘H, the lesions in IgA nephropathy vary considerably. The **G** may be **normal**, or may show mesangial widening & segmental inflammation confined to some **G**(**focal proliferative GN**); diffuse mesangial proliferation (**mesangioproliferative**); or (rarely) overt **crescentic GN**



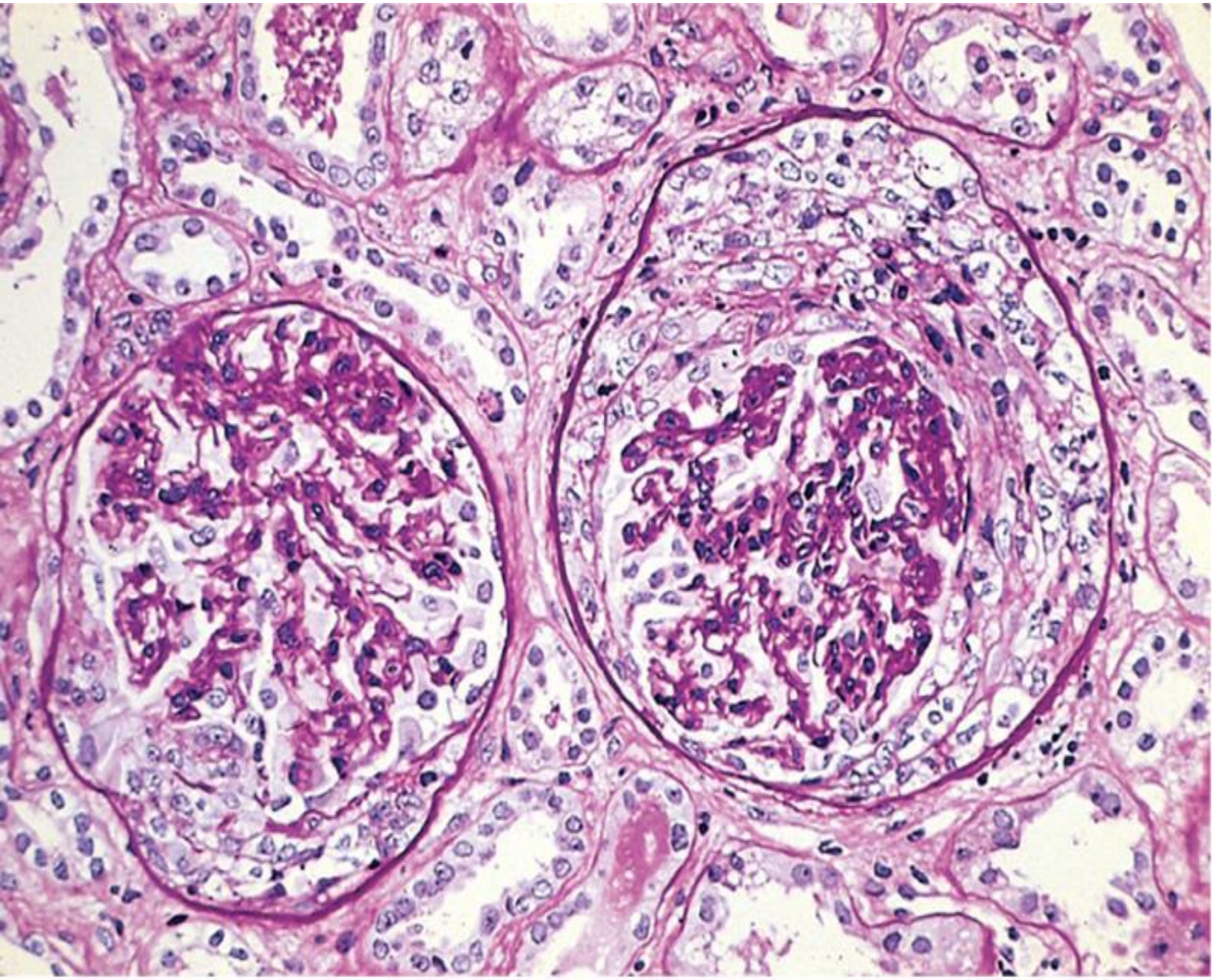
IF : IgA mesangial staining.

Rapidly Progressive (Crescentic) Glomerulonephritis

•characterized by the presence of **crescents**(crescentic GN).

•proliferation of the parietal epithelial cells of Bowman's capsule in response to injury and infiltration of monocytesand macrophages

•**nephritic syndrome rapidly progresses to oliguriaand azotemia.**



Crescentic GN (PAS stain). the collapsed glomerular tufts and the crescent-shapedmass of proliferating cells and leukocytes internal to Bowman's capsule.

Hereditary Nephritis

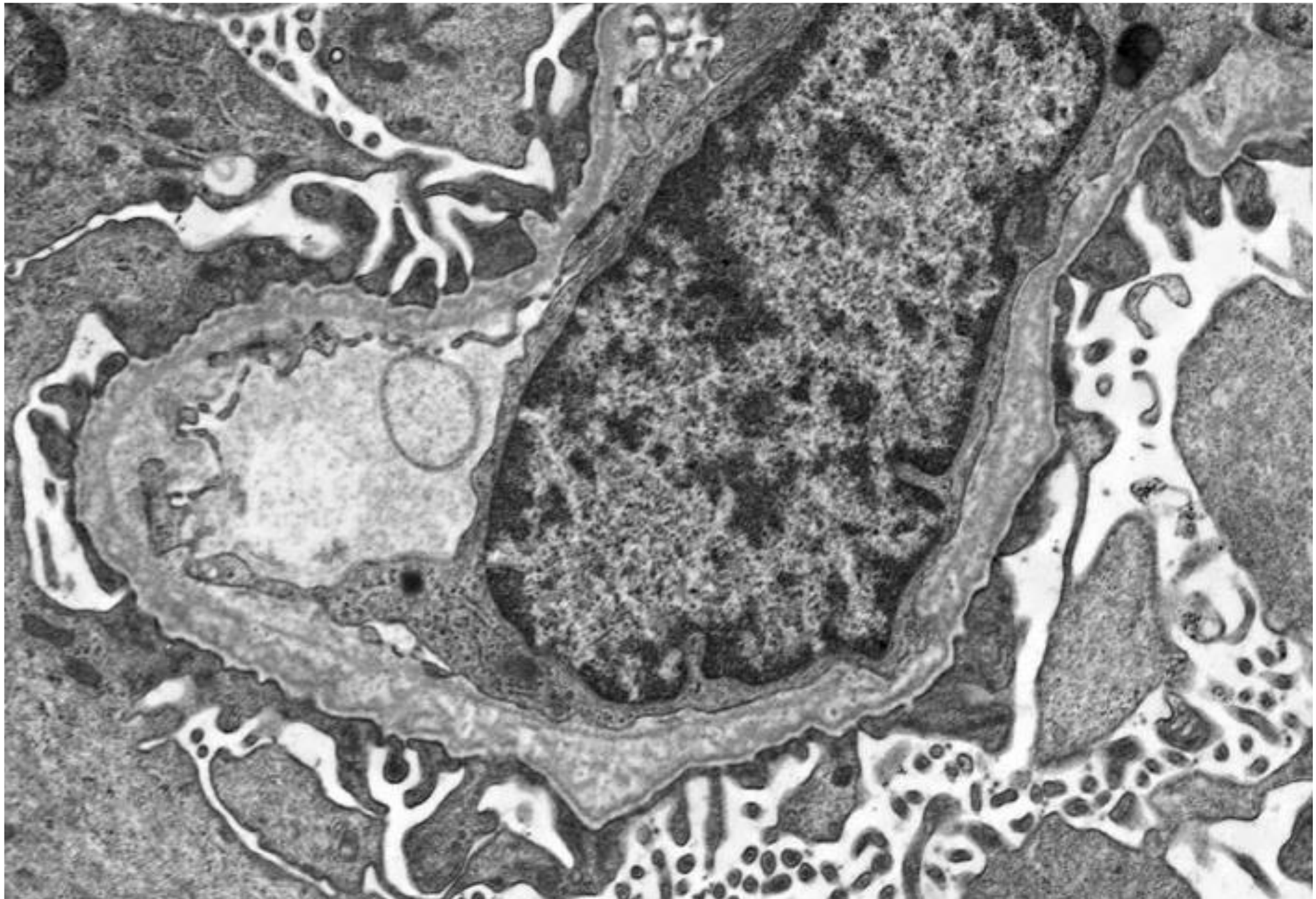
•**a group of hereditary glomerular diseases caused by mutations in GBM proteins (most common** X-linked**).**
•**Most important type: Alport syndrome**

- **Alport syndrome**

nephritis + nerve deafness + eye disorders (lens dislocation, posterior cataracts, corneal dystrophy).

- Pathogenesis:
- Mutation of any one of the **α chains of type IV collagen**
- renal failure occurs between 20-50 yrs of age

- **EM**
- **GBM thin and attenuated**
- **GBM later develops splitting and lamination "basket-weave" appearance**



Basket weave GBM in Alport syndrome

Chronic GN

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.,

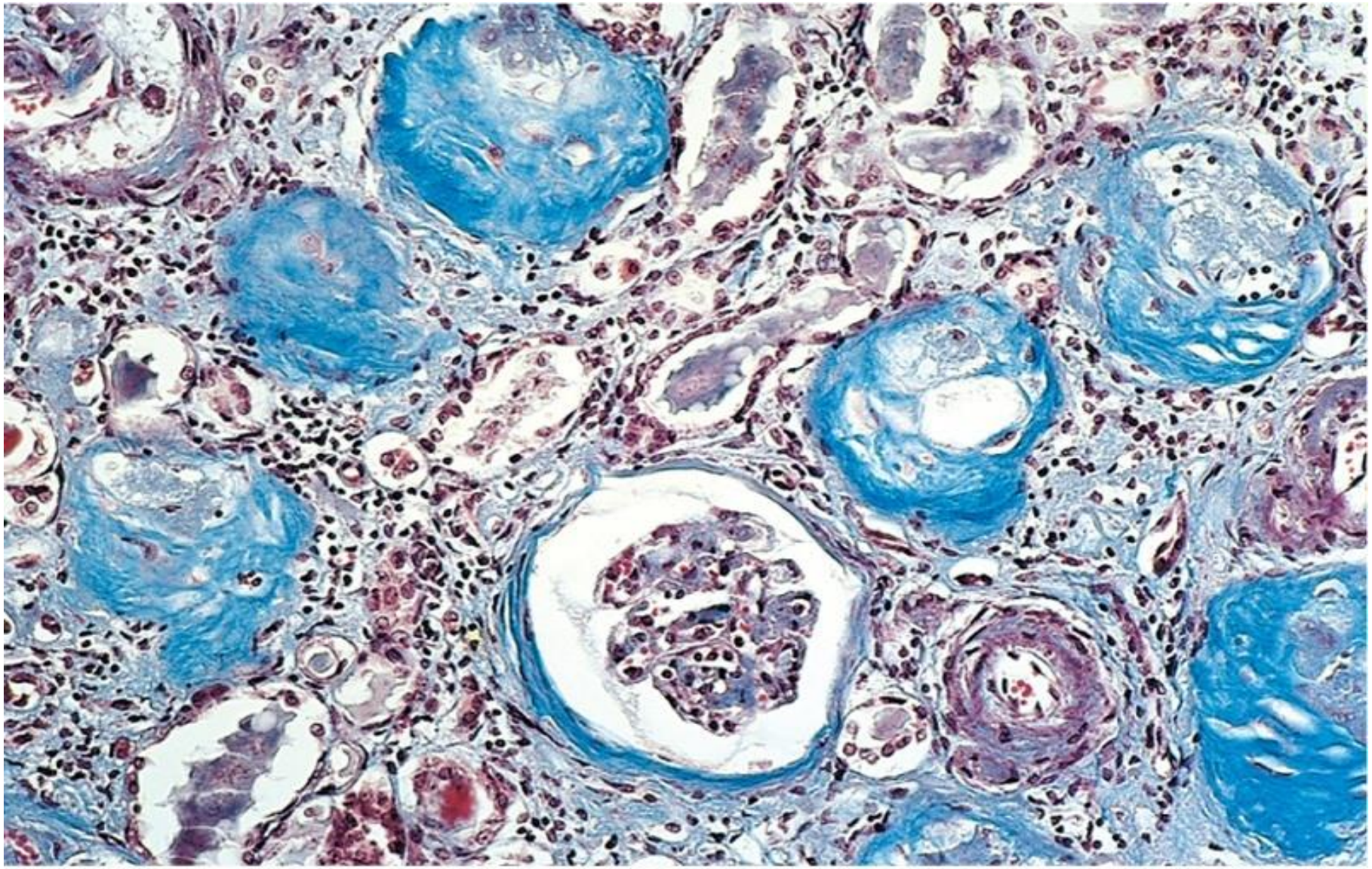
★Among 3700 Jordanian cases **whom require chronic hemodialysis** or renal transplantation in **2011**,**30%**are **chronic GN; 30%**are **diabetic; 30%**are **hypertensive;10%** are renal **adult polycystic** disease.

★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.**
Histopathological E : **Advanced scarring & obliteration of the G**, sometimes to the point of 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 GN. Masson trichrome stain, shows complete replacement of virtually all glomeruli by **blue-staning 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.

Tubulointerstitial Nephritis

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

TIN refers to a group of primary inflammatory diseases of the renal interstitium & T .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), viralinfections, & immune reactions.

can be divided into

1- acute

2- chronic categories on the basis of clinical features & the character of the inflammatory exudate, .

URINARY TRACT INFECTIONS

1-lower UTI (cystitis, prostatitis, urethritis).

2-upper UTI (pyelonephritis).

Infectious : Acute Pyelonephritis

- inflammation of kidney and renal pelvis, usually due to bacterial infection.
- Most commonly:

1-Escherichia coli

Others:

2-Proteus.

3-Klebsiella.

4-Enterobacter.

5-Pseudomonas.

6-Staphylococci and Streptococcus faecalis(uncommon).

❑ **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**), **UTIs are extremely common clinical problems**, which implies involvement of the lower UT (urethritis, cystitis & prostatitis,) or upper UT (pyelonephritis), or both. 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.

❖ Pathogenesis

- ❑ 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

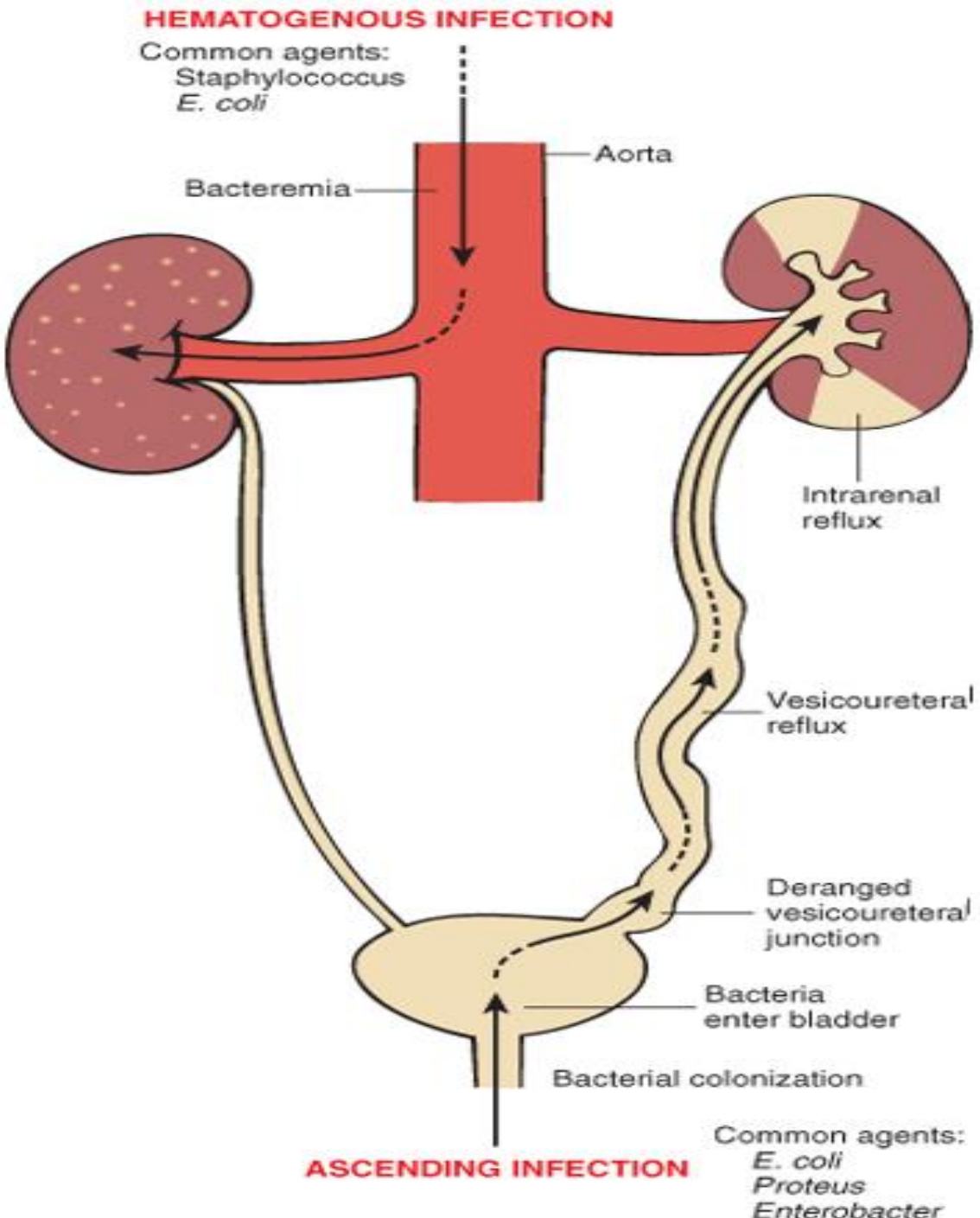
Bacteria can reach the **kidneys** by 2 routes:

1- **Rarest is hematogenous route,**through the bloodstream, results from seeding of the kidneys 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, in which…

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.



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.

- **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 entry into the bladder.

- **Normally**, bladder urine is sterile, as a result of the:

(a) Antimicrobial properties of the bladder mucosa
(b) flushing action associated with periodicvoiding of urine.

The bladder **outflow obstruction** or **bladder dysfunction** predispose to UTI.
1-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.
In the **3rdstep**, the bacteria from the contaminated bladder urine **ascend along the ureters** to infect the **renal pelvis**& **parenchyma**.

- 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.

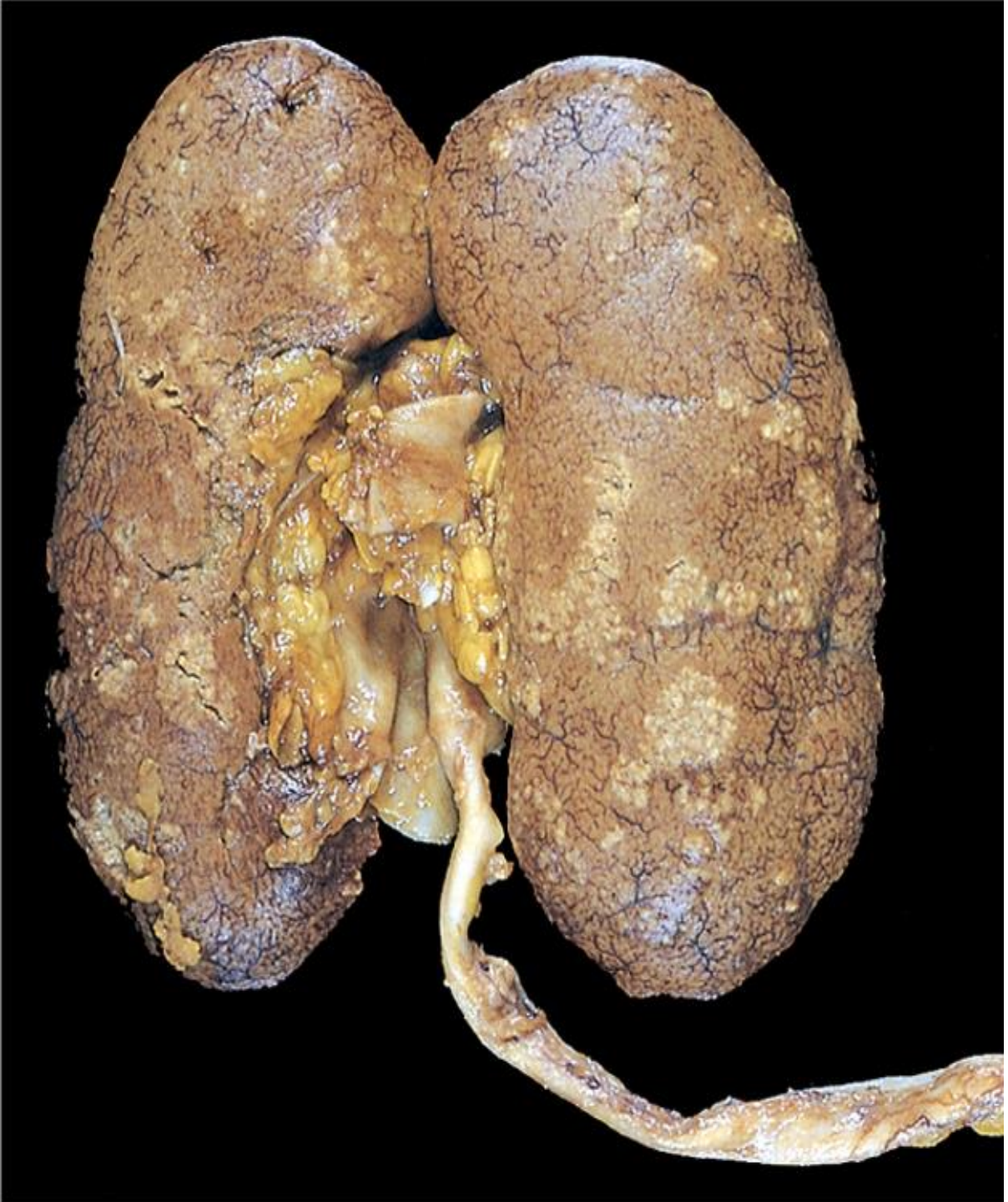
- Although **obstruction**is an important predisposing factor in the pathogenesis of ascending infection, it is the…. incompetence of the **vesicoureteral orifice** that allows bacteria to ascend the ureter into the pelvis.
- The **normal** ureteral insertion into the bladder is a competent **one-way 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 }.

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 ureterovesical valve,

2- VURcan also be **acquired** in individuals with a flaccid bladder resulting from **spinal cord injury**& with **neurogenic** bladder dysfunction secondary to DM.

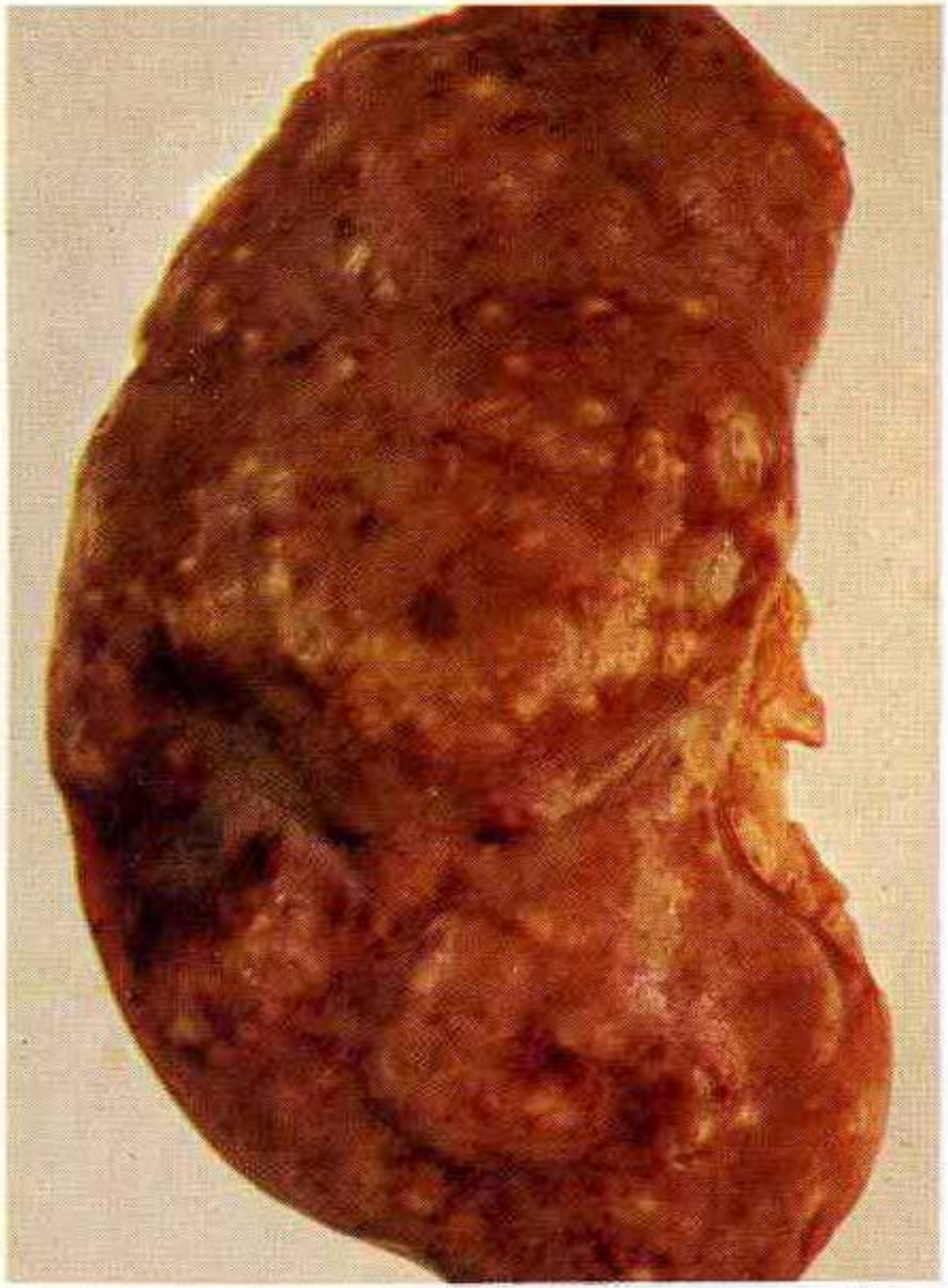
❑ Morphology

Grossly,in a**cute 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.**They may be limited to one region of the kidney, or widely scattered.



Acute pyelonephritis.

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



10.19 Acute suppurative pyelonephritis

Acute suppurative pyelonephritis

★Capsular surface of the kidney showing multiple, discrete, yellowish-white abscesses, with ★a broad shallow scar (center left), evidence of chronic pyelonephritis

- ❑ H, 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.
- ❑ When obstruction is prominent, the pus may be unable to drain & thus fills the renal pelvis, calyces, producing (pyonephrosis).

A second **infrequent** form of pyelonephritis is necrosis of the renal papillae, known as **papillary necrosis.**

(1) This is particularly common among **diabetics** who develop acute pyelonephritis

(2) may complicate acute pyelonephritis when there is significant **UT obstruction**. It is also seen with the

(3) chronic interstitial nephritis associated with **analgesic abuse**.

- Papillary necrosisis 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 yellownecrosis of the apical 2/3 of 1,2 or all the pyramids papillae (F10-21).
- H, 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

- 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.

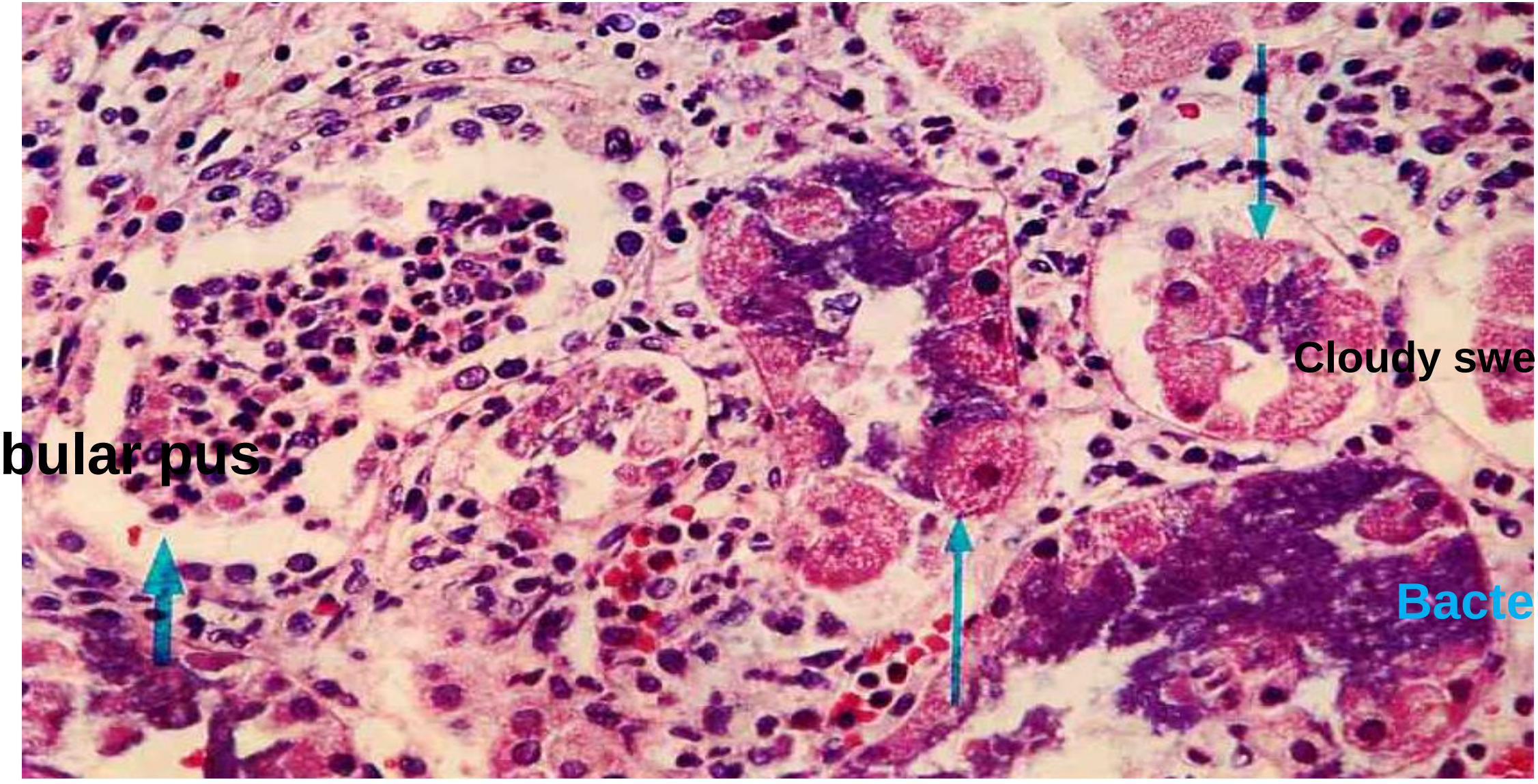
Often,a patient with renal papillary necrosis will have numerous conditions acting synergistically to bring about the disease.

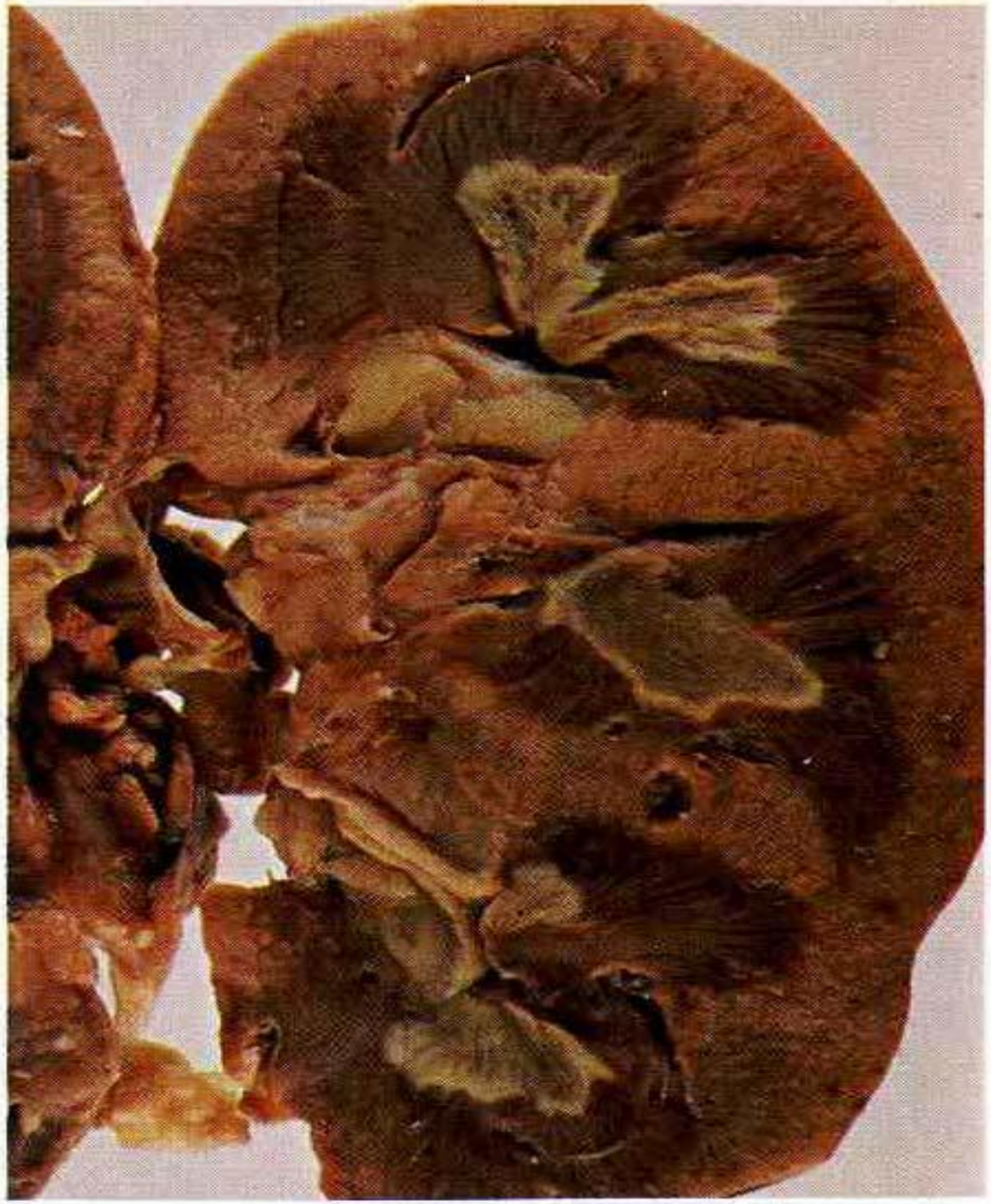
- Analgesic nephropathy is a common cause of renal papillary necrosis(NSAID).

Pathophysiology

This condition is due to ischemia of the renal papillae, the portion of the kidney that collects urine from the nephron. The papillae are vulnerable to ischemia as they are supplied by small caliber arteries which are liable to obstruction. All of the underlying causes of papillary necrosis cause diminished flow through these arteries, either through direct mechanical obstruction (sickle cell), obstruction secondary to inflammation (vasculitides), or vasoconstriction (NSAIDs). Papillary necrosis is more likely to develop when multiple of these underlying factors are present.Ultimately, necrosis of the papillae results in sloughing into the lumen, causing hematuria. If the degree of necrosis is substantial post-renal failure may occur, though this is uncommon.

Acute pyelonephritis: kidney X200. (1) Theinterstitial 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).





10.21 Acute pyelonephritis and papillary necrosis

Acute pyelonephritis and papillary necrosis.

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

Predisposing conditions for acute pyelonephritis are:

➔Obstruction of the UT, congenital or acquired,

➔Vesicoureteral reflux (VUR),

➔Instrumentation of the UT, most commonly catheterization,

➔Immunosuppression & immunodeficiency.

➔Pregnancy.4% to 6% of pregnant women develop bacteriuria sometime during pregnancy,

➔ Patient's sex & age. After the first year of life (when congenital anomalies in males commonly become evident) & as far as around the age of 40 years, infections are much more frequent in **females**.With age, the incidence in males rises as a result of **prostatic hyperplasia**& **frequent instrumentation**.

➔ DM,in which acute pyelonephritis is caused by susceptibility to infection & neurogenic
bladder dysfunction.

➔Preexisting renal lesions,causing intrarenal scarring & obstruction

- 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.

- Even without antibiotic treatment, the disease tends to be benign & self-limited. 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

Drug-Induced Interstitial Nephritis

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

Pathogenesis

- **immune mechanism.**
- **? type I hypersensitivity.**
- **? T cell-mediated (typeIV) hypersensitivity reaction.**

Pathogenesis: the drugs act as **haptens** that, during secretion 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

•interstitium: lymphocytes and macrophages, eosinophils and neutrophils

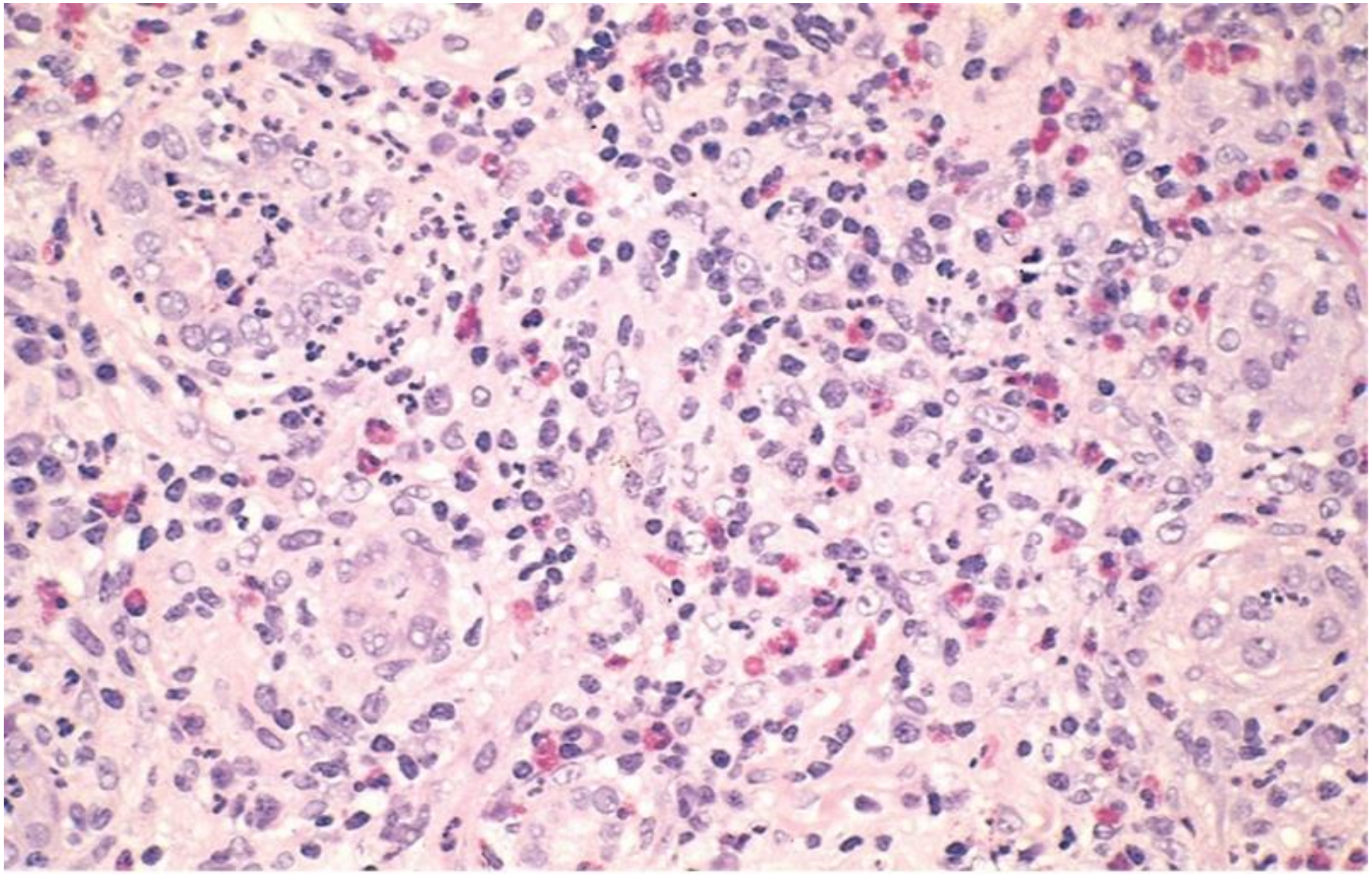
•glomeruli are normal

- Microscopically :

The interstitium shows pronounced (I) **edema & (II) infiltration** by large numbers of lymphocytes, macrophages **,**eosinophils & neutrophils, & **(III)**With some drugs (e.g., methicillin, thiazides, rifampin), interstitial non-necrotizing **granulomas** with giant cells may be seen. The **G** 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

- **Clinically**, the disease begins 2 to 40 days (average15 days) after exposure to the drug & is characterized by fever & rash & eosinophilia in about 25% 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. It is important to recognize drug-induced RF, because the withdrawal of the offending drug is followed by recovery, although it may take several months for renal function to return to normal .

Drug-induced interstitial nephritis, edema with prominent eosinophilic & mononuclear infiltrate



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.

- **covalent binding and oxidative damage**
- **inhibition of prostaglandin synthesis**

- Acetaminophen, a phenacetin metabolite, injures cells by both, covalent binding & oxidative damage.
- The ability of aspirin to inhibit prostaglandin synthesis suggests that aspirin may induce its potentiating effect by inhibiting the vasodilatory effects of prostaglandin & predisposing the papilla to ischemia.
- Thus, the papillary damage may be caused by a combination of **direct toxic** effects of phenacetin metabolites as well as **ischemic injury** to both tubular cells & vessels

Clinical Course

- **Progressive renal impairment, chronic renal failure, hypertension and anemia….**
- **A complication of analgesic abuse is: increased incidence of transitional-cell carcinoma of the renal pelvis**

Acute Tubular Necrosis (ATN)

- **characterized morphologically by damaged tubular epithelial cells and clinically by acute suppression of renal function** with oliguria(urine flow of <400 mL/day)..

- **It is the most common cause of acute renal failure (ARF).**

other causes of ARF are

(1) Severe G diseases, manifesting as RPGN, (2) Acute papillary necrosis associated with acute PN, (3) Acute drug-induced interstitial nephritis (Paracetamol)(4) Diffuse cortical necrosis.
(5) Diffuse renalvascular diseases, e.g., microscopic polyangiitis & thrombotic microangiopathies

- **ATN is a reversible condition if treated properly and quickly.**
- **Clinical manifestations: electrolyte abnormalities, acidosis, uremia, signs of fluid overload, often oliguria.**
- **Proximal tubular epithelial cells are particularly sensitive to hypoxemia and toxins**

- ATN is quite frequent disorder that can arise in many clinical settings, in one of 2 patterns:

(1st) Ischemic ATN cause by shock, in which a period of hypotension & shock is common in most of these settings (ranging from severe trauma to acute pancreatitis to septicemia). A similar picture can be produce by mismatched blood transfusions, hemolytic crises, & myoglobinuria.

(2nd)Nephrotoxic ATN,is caused by a variety of poisons**,**including heavy metals(e.g., **mercury**); organic solvents(e.g., **CCl4**); & **drugs** such as gentamicin& other antibiotics, & **radiographic** contrast agents e.g., those used for angiogram.

Pathogenesis

- Tubular epithelial cells are vulnerable to **toxins**& very sensitive to **anoxia**.
- Therefore, the 2 major factors in the pathogenesis of both ischemic & nephrotoxic ATN are:

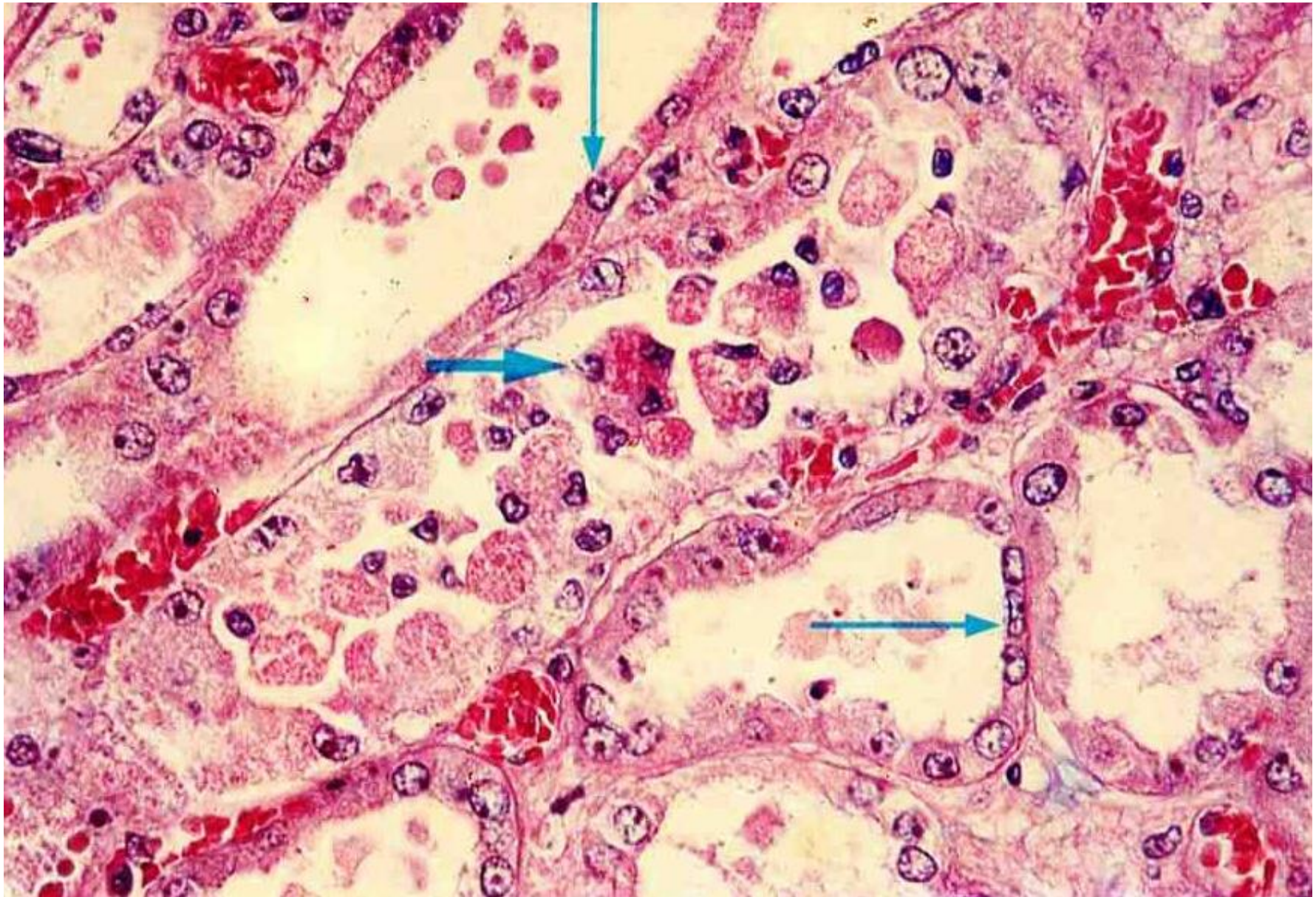
(1)tubular injury

(2) persistent & severe **ischemia** caused by **intrarenal** vasoconstriction, resulting in both:

(a) decrease **G** plasma flow, resulting in decrease **GFR**&

(b) decrease **O2**delivery to the functionally important tubules in the outer medulla **.**

Acute Tubular Necrosis: kidney. Patient died from RF, 7 days following pericardiectomyfor constrictive pericarditis
(1) Most of the collecting tubules epithelial cells are **died**& the necrotic cells are sloughed into the lumen (**thick**arrow).
(2) The **surviving** cells attempts at **repair**& already the tubules are lined by flat epithelium (**thin**arrow).



❑ Renal biopsy shows:

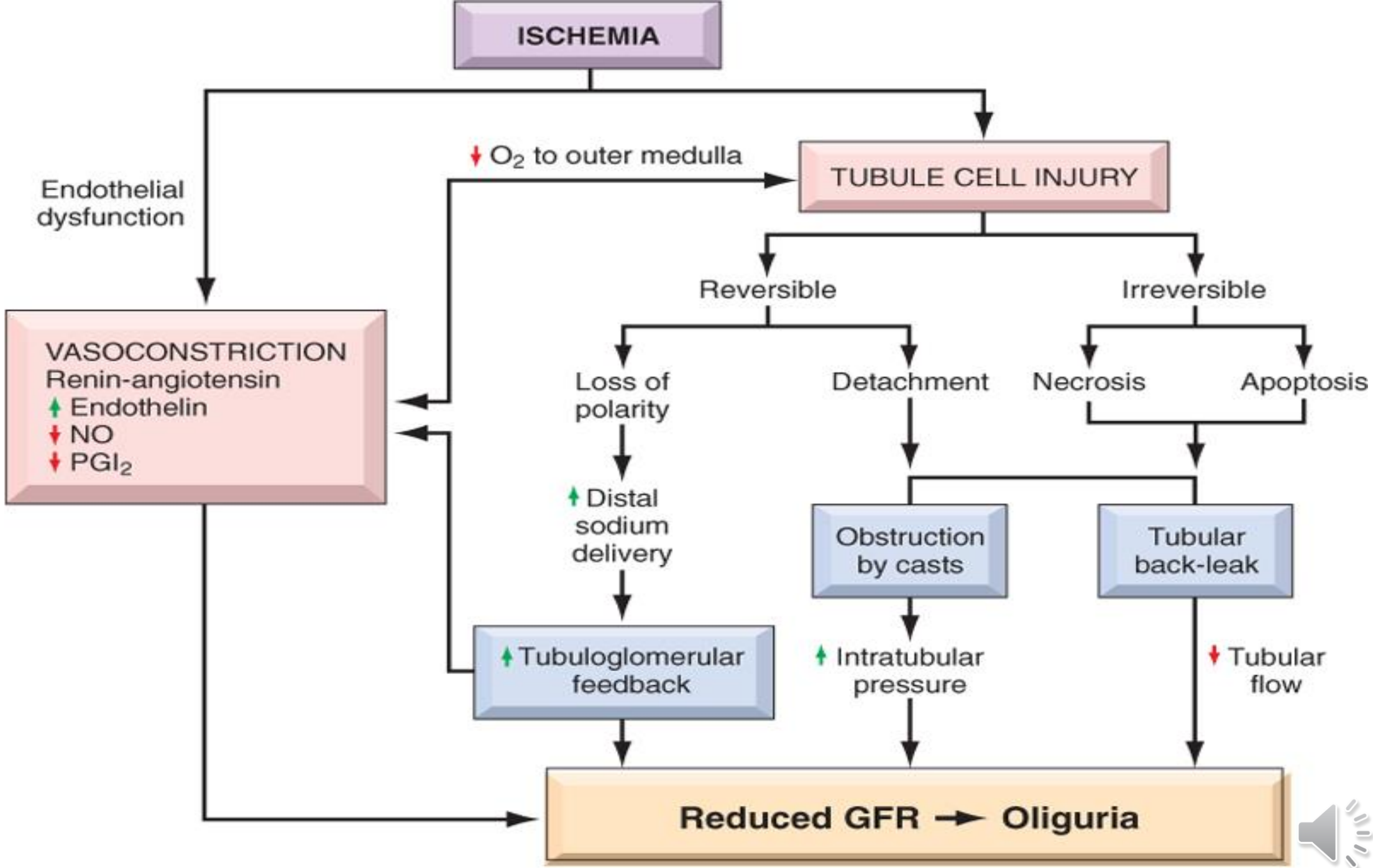
(1) blebbing; vacuolization; **necrosis**& **detachment** of tubular cells from their underlying BM & their **sloughing** in the lumen

(2)Proteinaceous casts in the distal tubules & collecting ducts is a **striking** additional finding.

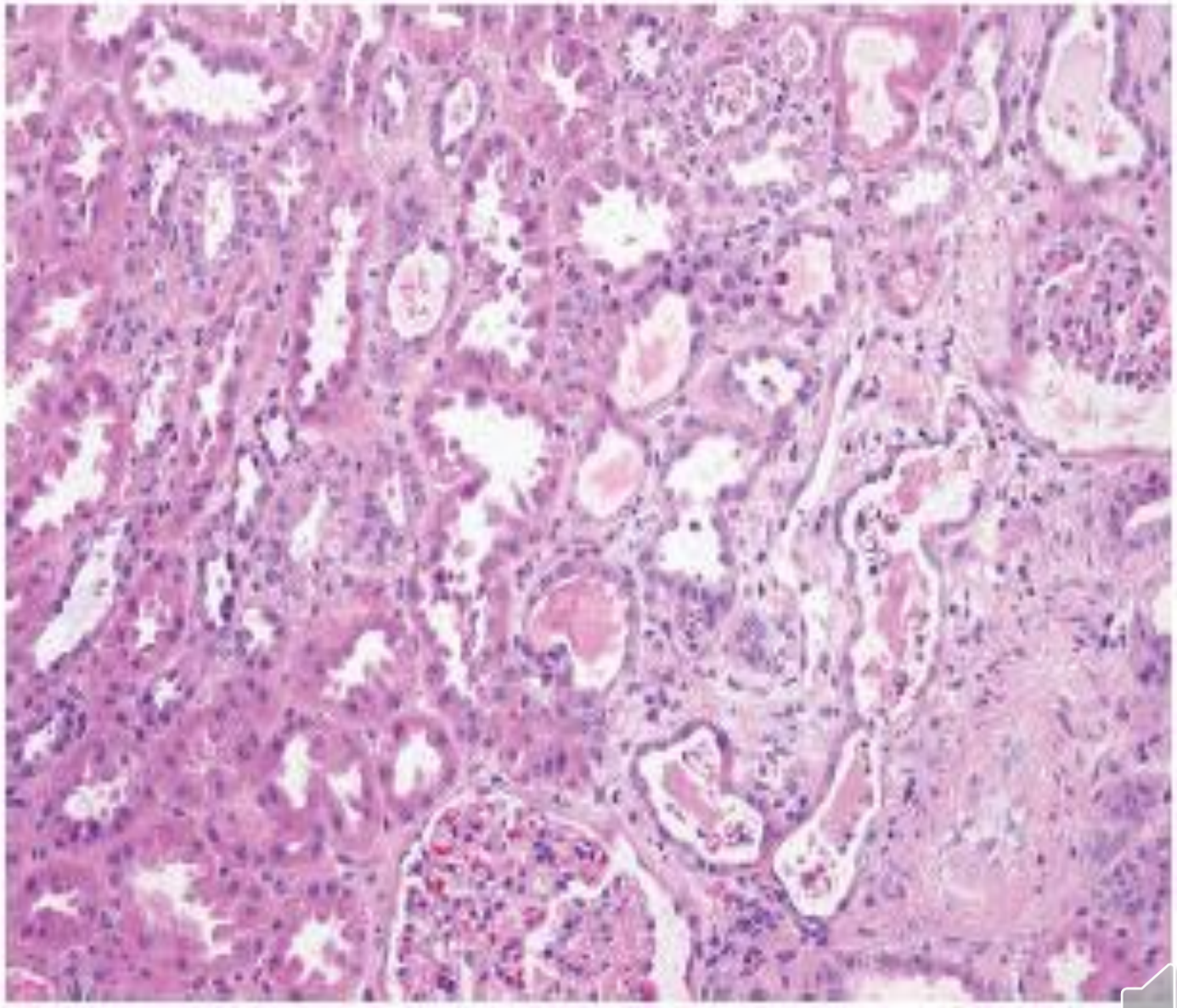
❑ They consist of **Tamm-Horsfall protein (secreted normally by tubular epithelium)** along with hemoglobin & other plasma proteins.

▼When **crush injuries** have produced ATN, the casts are composed of **myoglobin**

Postulated sequence in acute renal failure



- Acute tubular epithelial cell injury with blebbing at the luminal pole, detachment of tubular cells from their underlying basement membranes,and granular casts



ATI-management

- repair and tubular regeneration →gradual clinical improvement
- With supportive care, patients who survive have a good chance of recovering renal function
- those with preexisting chronic kidney disease, complete recovery is less frequent

DISEASES INVOLVING Blood Vessels

- All kidney diseases involve the renal BV **secondarily.**
- Systemic vascular diseases, e.g., **arteritis**, also involve renal BV, & often the effects on the kidney are clinically important.
- The kidney is intimately involved in the pathogenesis of both essential & secondary **hypertension**(**H**)

- Benign Nephrosclerosis (Hyaline arteriolosclerosis)

term used for the renal changes in benign H.

- Some degree of benign nephrosclerosis, albeit mild, is present at autopsy in many persons older than 60 years of age.
- But the frequency & severity of the lesions are increase at any agewhen Hor DM are present.

Pathogenesis

Many renal diseases cause H, which in turn is associated with benign nephrosclerosis.

- Thus, nephrosclerosis is often seen superimposed on other primary kidney diseases.
- Morphology
- Grossly,both kidneys are symmetrically atrophic,each weighing 110 to 130 gm (Normal 300 gm), with a diffusely fine granular surface that resembles grain leather

- Histologically : there is hyaline arteriolosclerosis, with subendothelial homogeneous, pink hyaline thickening causes narrowing of the BV lumen, resulting in marked decrease blood flow & ischemia through the affected BVs.All structures of the kidney show ischemic atrophy.

- In advanced cases: the G tufts may become globally sclerosed, with diffuse tubular atrophy & interstitial fibrosis.
- **Benign Nephrosclerosis,** alone, rarely causes severe renal damage. A mild proteinuria is a frequent present

MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

- Malignant **H** is **far less common** in the US **than benign H** & occurs in only about 5% of persons with elevated BP. It may arise **de novo**(i.e., from the start, without preexisting **H**), or it may appear suddenly in a person who had mild **H**.

Pathogenesis

Long-standing benign **H** eventually injure the arteriolar walls, resulting in

(a) **EC injury**, (b) increase **permeability** of the small BVs to fibrinogen & other plasma proteins, (c) **platelet deposition.**These 3 changes constitute the… **Fibrinoid necrosis**of arterioles & small arteries & intravascular thrombosis.

- Mitogenic factors from platelets (e.g., PDGF) & plasma cause intimal SMCs hyperplasia of BVs, resulting in the…

➔**Hyperplastic arteriolosclerosis(onion-skin lesion),** with further narrowing of the luminae,**typical of malignant H** & of morphologically similar thrombotic microangiopathies.

- The kidneys become markedly ischemic& the severe ischemia of the renal afferent arterioles… stimulates the renin-angiotensin system (persons with malignant H have markedly elevated levels of plasma renin).
- This then sets up a vicious cycle O, in which, angiotensin II causes intrarenal vasoconstriction & the resulting renal ischemia increase renin secretion.
- Aldosterone levels are also elevated& salt retention undoubtedly contributes to the elevation of BP.

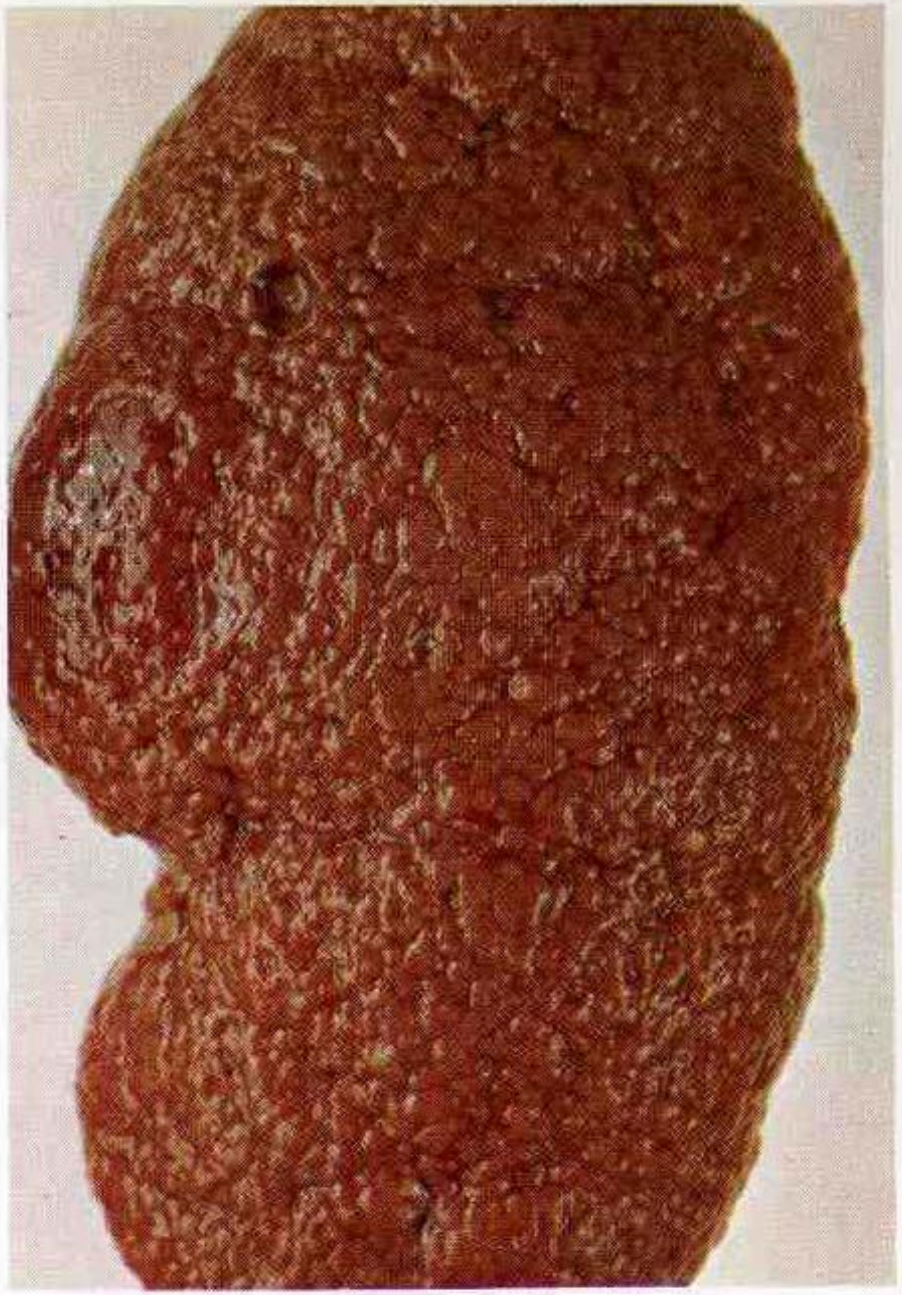
- The consequences of the markedly elevated BP on the BVs throughout the body are known as malignant arteriolosclerosis,& the renal disorder is referred to as malignant nephrosclerosis.
- **Grossly,**the kidneys in malignant H may be normal in size or slightly shrunken. Multiple small, pinpoint petechial hemorrhages appear on the cortical surface, from rupture of arterioles or G capillaries, giving the kidney flea-bitten appearance.

- H, there are
- (I) **fibrinoid necrosis**of the arterioles

(II) **Hyperplastic arteriolosclerosis** in the interlobular arteries & larger arterioles, in which **concentric** proliferation of intimal SMCs producing an **onion-skin appearance**

- Similar lesions are seen in persons with acute thrombotic microangiopathies.
- Clinically, malignant **H** characterize by ⇧diastolic BP (>120 mm Hg), papilledema, encephalopathy, RF & cardiovascular abnormalities, Most often, the early symptoms are related to ↑intracranial pressure& include headache, nausea, vomiting, & visual impairment

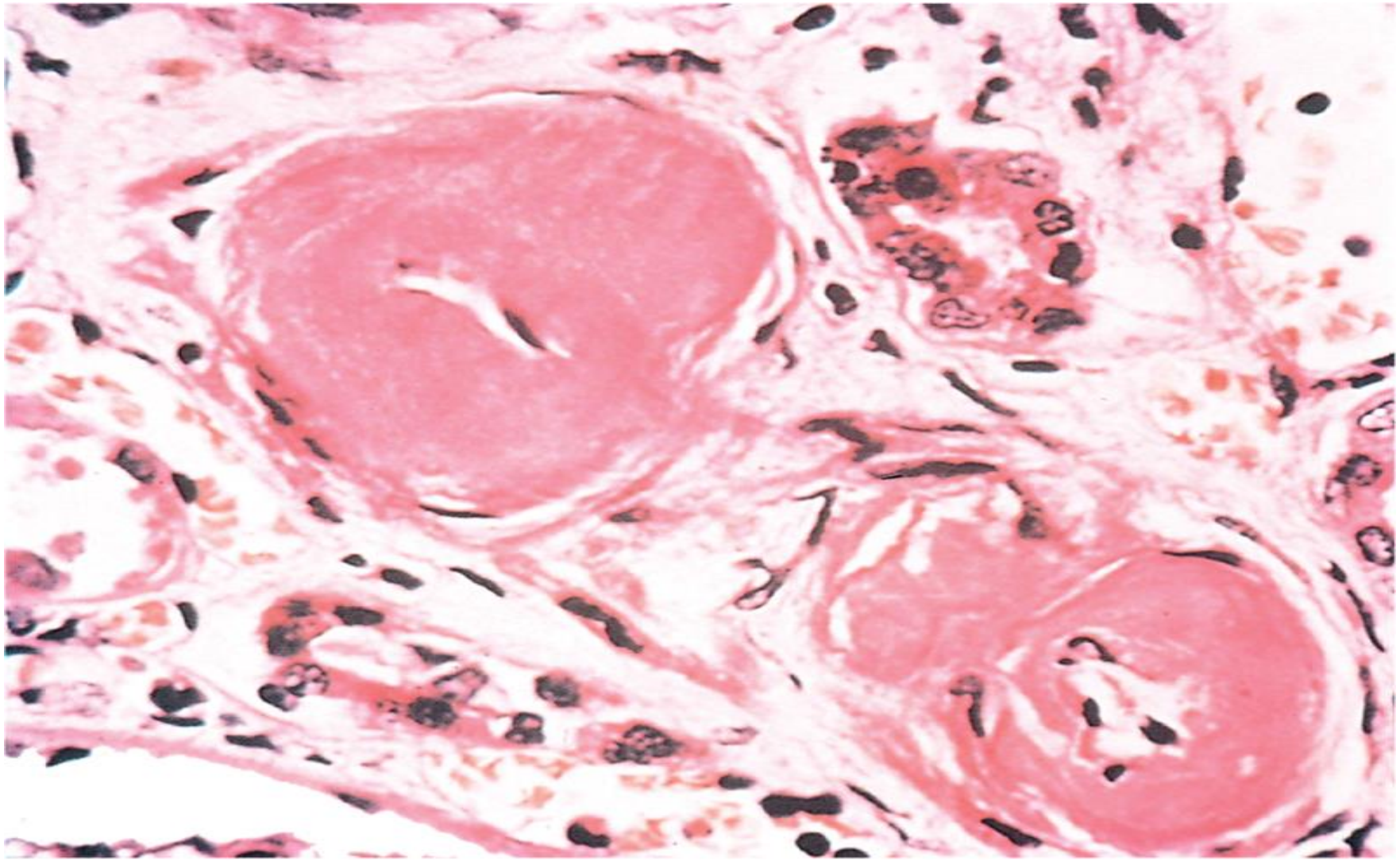
- Without treatment, malignant H is **fatal**, with 90% of deaths caused by **uremia** & 10% by **cerebral hemorrhage** or **cardiac failure.**



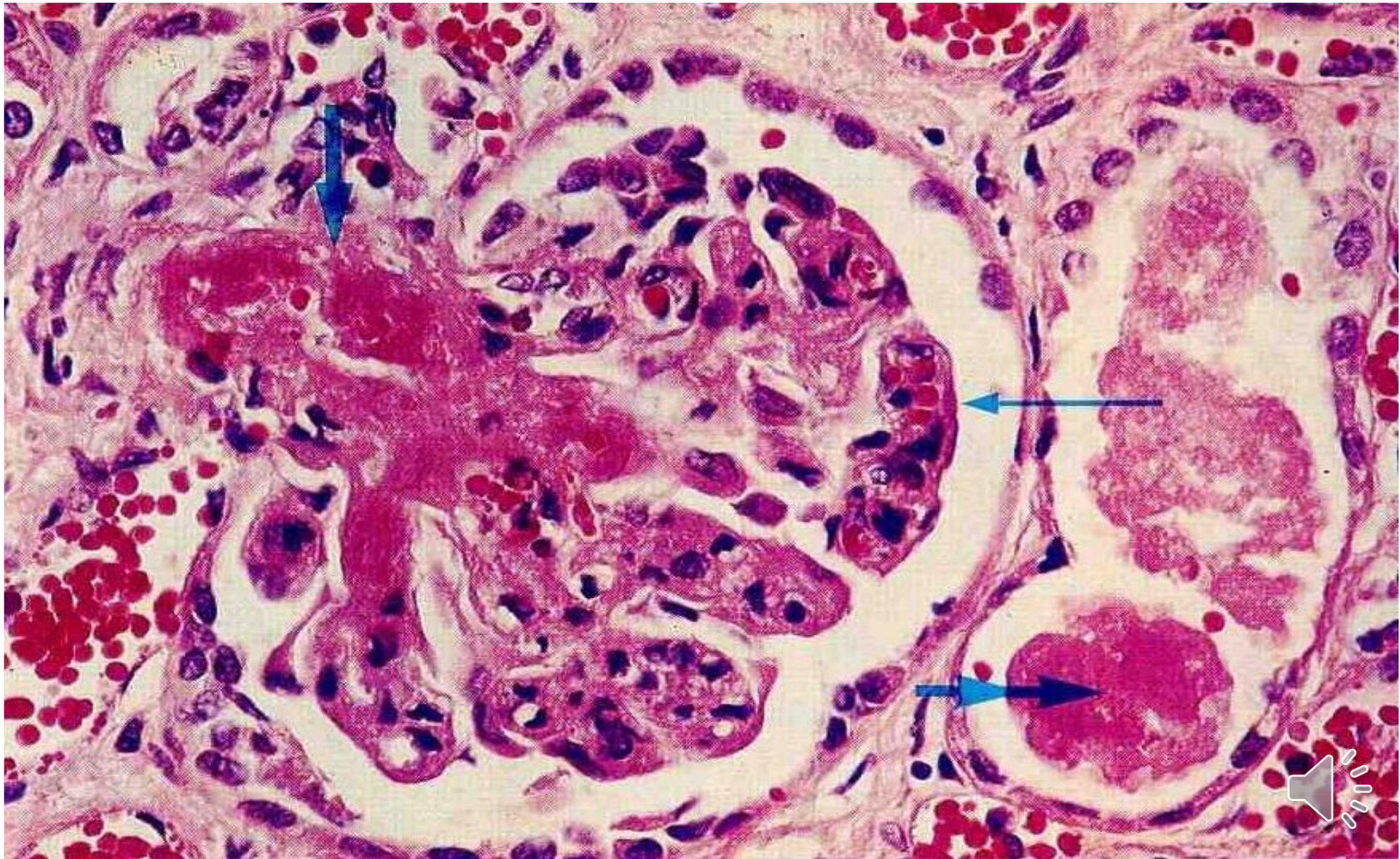
10.39 Hypertensive nephrosclerosis

Benign Nephrosclerosis (Hyaline arteriolosclerosis). ★Diffusely fine granular Kidney surface that resembles **grain leather.** ★**Both kidneys** were equally affected & ★together weighed 200 grams.

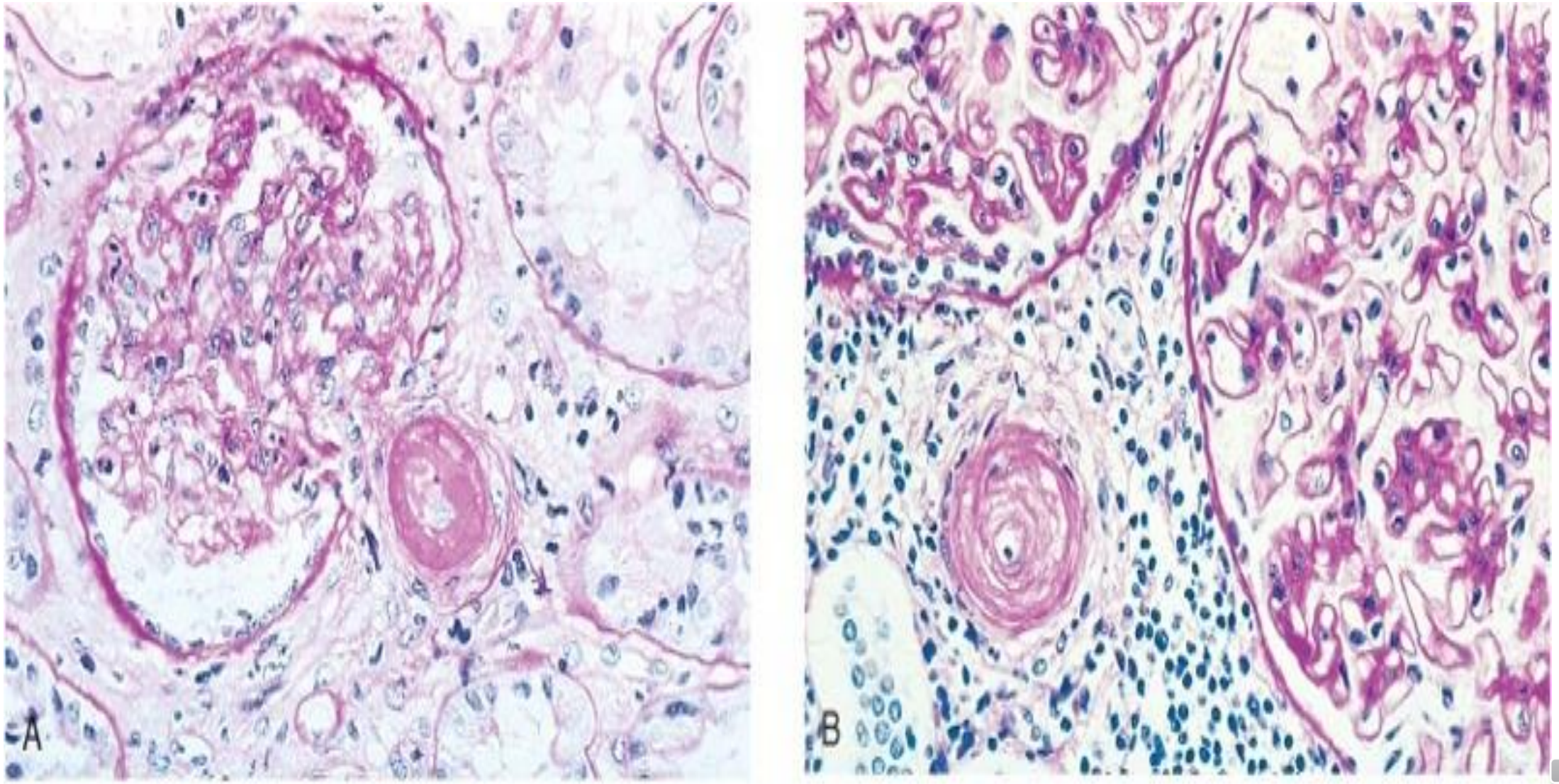
Benign nephrosclerosis. HP view of two arterioles with hyaline deposition, resulting in marked thickening of the walls, & narrowing of the lumen



Malignant hypertension: Kidney. ★The afferent arteriole (**thick**arrow) & the adjacent part of the glomerular tuft show **fibrinoidnecrosis**, with deposition of homogeneous, granular eosinophilic fibrin. ★Dense protein cast is seen in the tubule (**double**arrow).



Malignant hypertension.A, Fibrinoid necrosis of afferent arteriole (PAS stain). **B,**Hyperplastic arteriolosclerosis (onion-skin lesion).



THROMBOTIC MICROANGIOPATHIES

This term describes lesions seen in various clinical syndromes, characterized:

(a) morphologically by widespread thrombosis in the microcirculation(DIVC) &
(b) clinically by microangiopathic hemolytic anemia, thrombocytopenia,&, in certain instances RF.

Common diseases that cause these lesions include:

(1) Childhood Hemolytic Uremic Syndrome (HUS),
(2) various forms of adult HUS,
(3) Thrombotic Thrombocytopenic Purpura (TTP).

Pathogenesis

Although clinically overlapping, HUS & TTP are pathogenetically distinct. Central to the pathogenesis of HUS is endothelial cell (EC) injury & activation,with resultant intravascular thrombosis; while the…

TTPis now known to be caused by an acquired defect in proteolytic cleavage of von Willebrand factor (vWF) multimers

CHILDHOOD HUS

- 75% of childhood HUS cases follow intestinal infection with Shiga toxin-producing E. coli, such as occurs in epidemics caused by ingestion of infected ground meat (e.g., hamburgers) & infections with Shigella dysenteriae type I.
- **Pathogenesis**: Shiga toxin is carried by neutrophils in the circulation, targeting the renal G EC , because they express the membrane receptor for the toxin.
- The toxin has multiple effects on the EC, including **(I) Cytotoxic, the toxin gains entry to the cells & directly causes cell death, (II) (in the presence of cytokines, such as TNF) EC damage, (III) adhesion of WBCs, endothelin production, & loss of EC nitric oxide (both favoring vasoconstriction) .**

- **The resultant EC damage leads to thrombosis,most prominent in interlobular arteries, afferent arterioles, Gcapillaries, as well as microangiopathy**. 10% of the cases of HUS in children are notpreceded by diarrhea caused by Shiga toxin-producing bacteria

Morphology:In childhood HUS, there is fibrinoid necrosis,similar to lesions of classic thrombotic microangiopathy, with fibrin thrombi predominantly involving G & extending into arterioles & larger arteries in severe cases. Cortical necrosis may be present.

Clinically,

1-typical childhood HUS characterized by the sudden onset,
2-usually after GIT infection or flulike prodromal episode,
3- severe oliguria,
4-bleeding manifestations (hematuria) &
5- microangiopathic hemolytic anemia (DIVC) .
6-This disease is one of the main causes of acute RF in children.
However,if managed properly with dialysis, most patients with childhood HUS recover in a matter of weeks

Thank You ☺