

## **II. Tubulointerstitial diseases**

- two major groups of processes
  - (1) ischemic or toxic tubular injury, leading to *acute kidney injury (AKI)* and acute renal failure, and
  - (2) inflammatory reactions of the tubules and interstitium (*tubulointerstitial nephritis*).

# Acute Kidney Injury (AKI) (Acute Tubular Necrosis, ATN)

- AKI, a term increasingly favored over acute tubular necrosis (ATN)
- Is a clinicopathologic entity signifies rapid reduction of renal function and urine flow, falling within 24 hours to less than 400 mL per day.

**Note: Is the most common cause of acute renal failure, accounts for some 50% of cases of acute renal failure in hospitalized patients**

- In addition to its frequency, the potential reversibility of AKI adds to its clinical importance.
- Proper management means the difference between full recovery and death.

- The two major forms are:

I. **Ischemic AKI:**

- Caused by *interrupted blood flow, examples of which include diffuse involvement of the intrarenal blood vessels such as*

*a. In microscopic polyangiitis,*

*b. Malignant hypertension,*

*c. Microangiopathies*

*d. Severe hypoperfusio*

## **II. Nephrotoxic AKI caused by:**

- a. Drugs: such as gentamicin and other antibiotics;
- b. Radiographic contrast agents;
- c. poisons, including heavy metals (., mercury);
- d. and organic solvents (, carbon tetrachloride).

# Other toxins

## 1. Myoglobin In Rhabdomyolysis

- It causes myoglobinuria and the myoglobin
- Rhabdomyolysis is the most common cause of can be caused by traumatic or nontraumatic injuries
- (most cases of rhabdomyolysis are nontraumatic, such as related to drug-induced muscle toxicity such as statins

2. hemoglobinuria, AKI is a rare complication of hemolysis and hemoglobinuria, and most often, it is associated with transfusion reactions (in contrast to myoglobin,
- Hemoglobin has no apparent direct tubular toxicity, and AKI to hypotension and decreased renal perfusion)



# Pathogenesis.

- , The critical events in both types are due to:

## (1) Tubular injury

- *Tubular epithelial cells are particularly sensitive to ischemia and are also vulnerable to toxins.*
- A. *Several factors predispose the tubules to toxic injury, including*
  - Tubular reabsorption,*
  - Active transport systems for ions and organic acids*

## *B. Ischemia causes numerous*

- i. Structural Alterations in epithelial cells which include those of reversible injury such as cellular swelling, loss of brush border and polarity, and those associated with lethal injury (necrosis and apoptosis).*
- ii. Functional (Biochemically) which include depletion of ATP; and Accumulation of intracellular calcium; with activation of proteases such as calpain*

*along with activation of phospholipases, which damage membranes;*

## **Mechanism of ischemic AKI**

- 1- One early reversible result of ischemia is loss of cell polarity due to redistribution of membrane of Na-K ATPpase from basolateral to luminal side of the tubular cells resulting in
  - a. an abnormal ion transport across the cells and

b. increase delivery of sodium to distal tubular cells which causes vasoconstriction through **tubuloglomerular feedback**

2. Ischemic tubular cells express cytokines such as monocyte chemoattractant protein 1 recruiting leukocytes that participate in subsequent injury

- 3- In time injured cells detach from tubular basement membranes causing obstruction of lumen, increase intratubular pressure and thus decreased GFR
4. Ischemic renal injury results in hemodynamic disturbances that cause decreases GFR
  - a. intrarenal vasoconstriction that will result in decrease Glomerular blood flow and decrease oxygen delivery to the to the

straight segment of the proximal tubules and thick ascending limb of loop of Henle

- Several vasoconstrictor pathways include

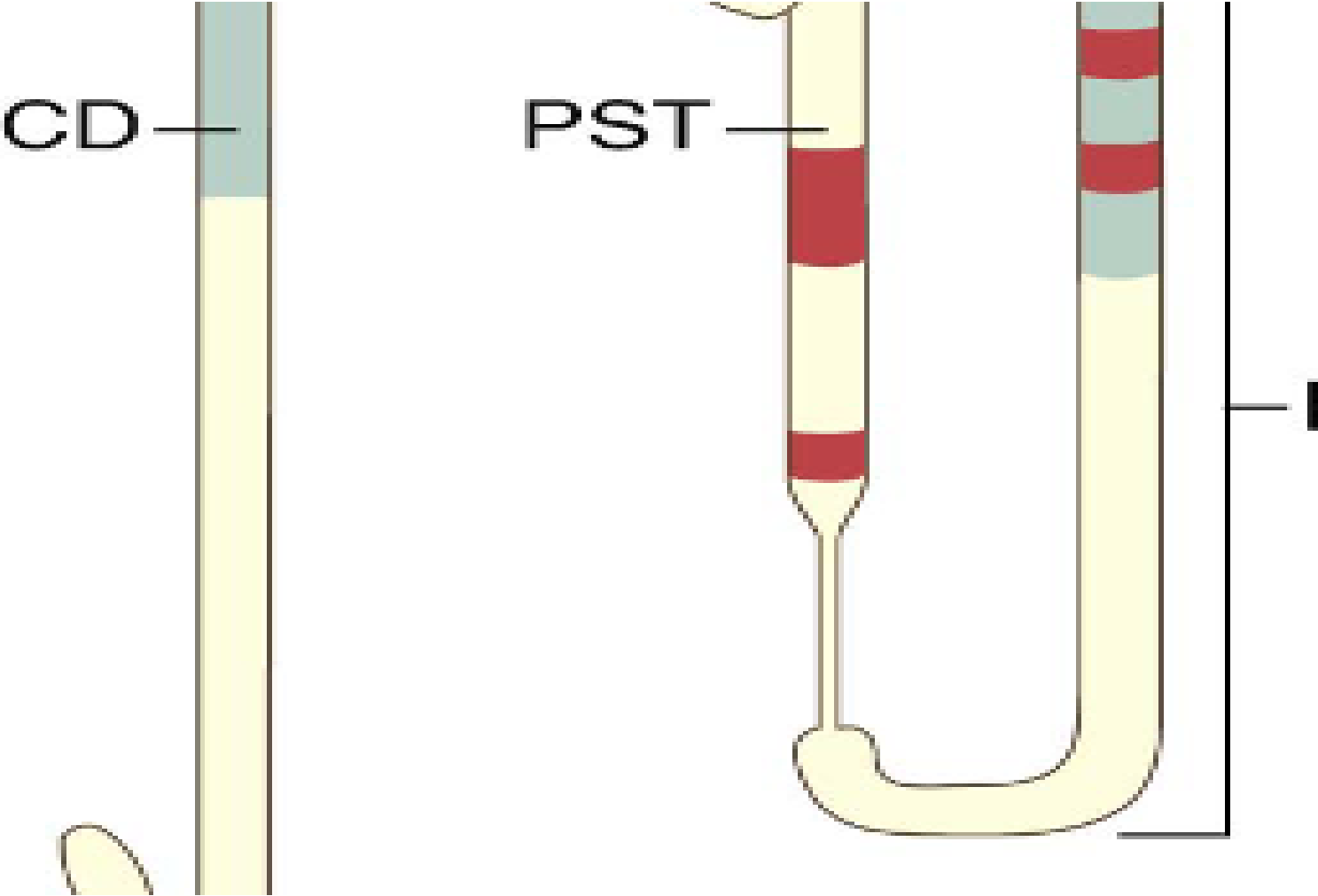
1. The renin angiotensin system stimulated by increased distal sodium delivery, (via tubuloglomerular feedback)

2. And endothelial injury leading to increase release of endothelin and decrease vasodilator NO and prostacyclin

# Morphology

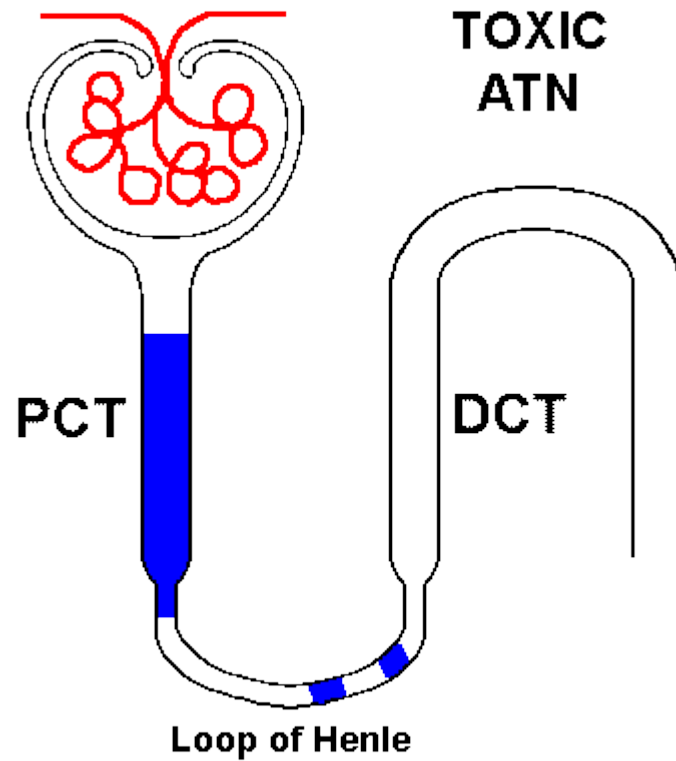
- Ischemic AKI is characterized by:
  - a. Focal tubular epithelial necrosis at multiple foci with large skip areas in between
  - b. accompanied by rupture of basement membranes called tubulorrhexis and occlusion of tubular lumina by casts
- The straight portion of the proximal tubules and the thick ascending portion of loop of Henle are especially vulnerable

# Ischemic injury

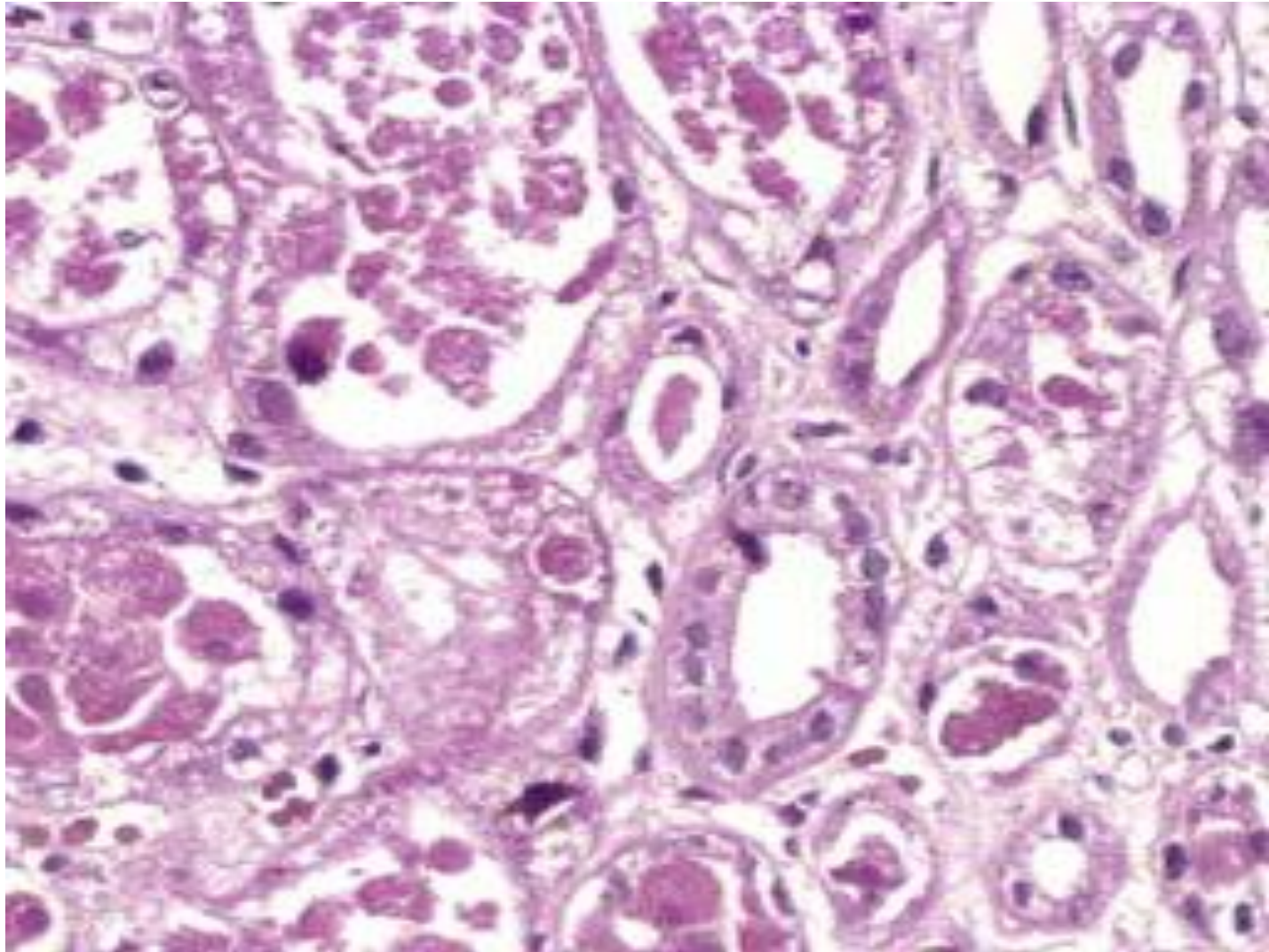


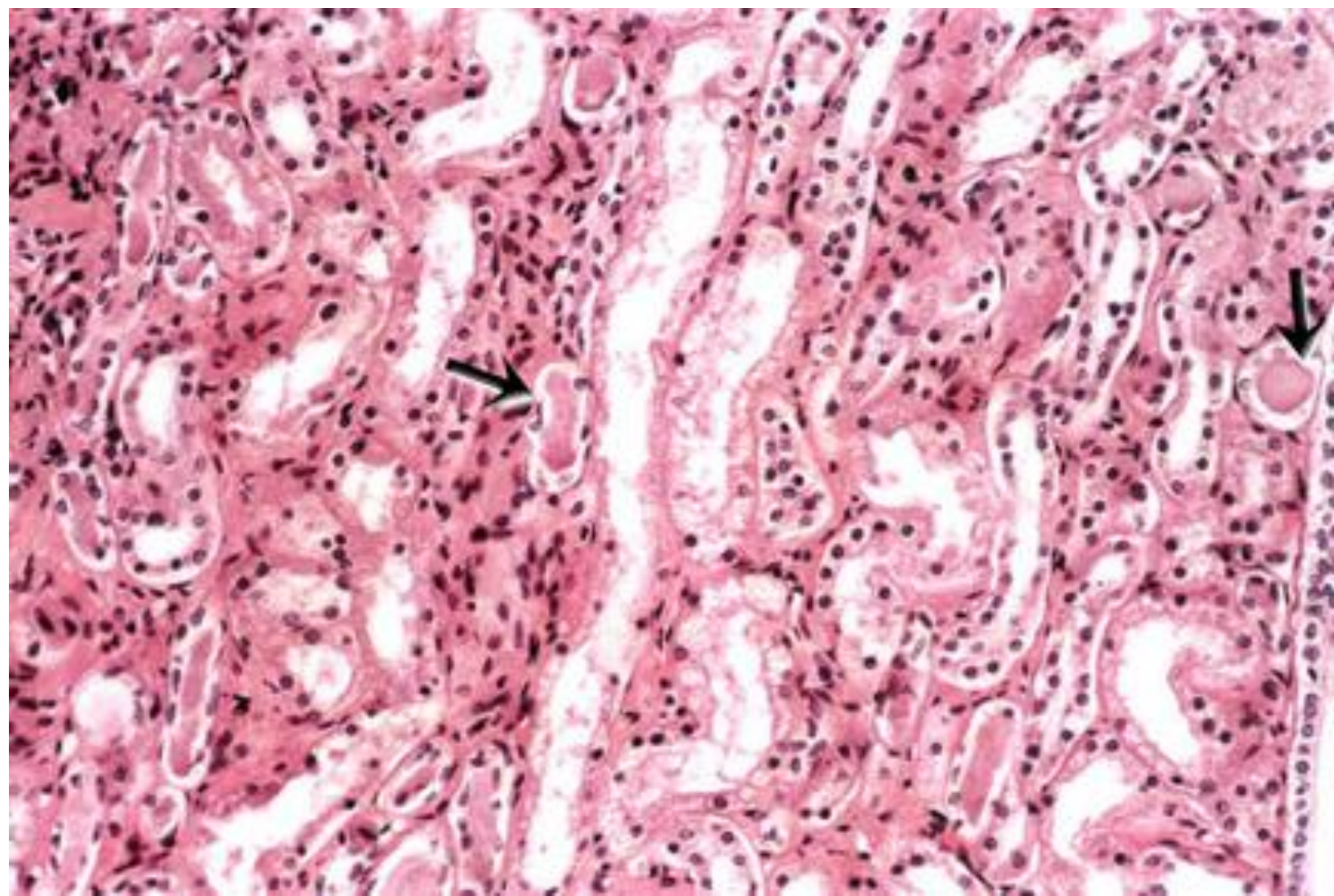


# Toxic AKI

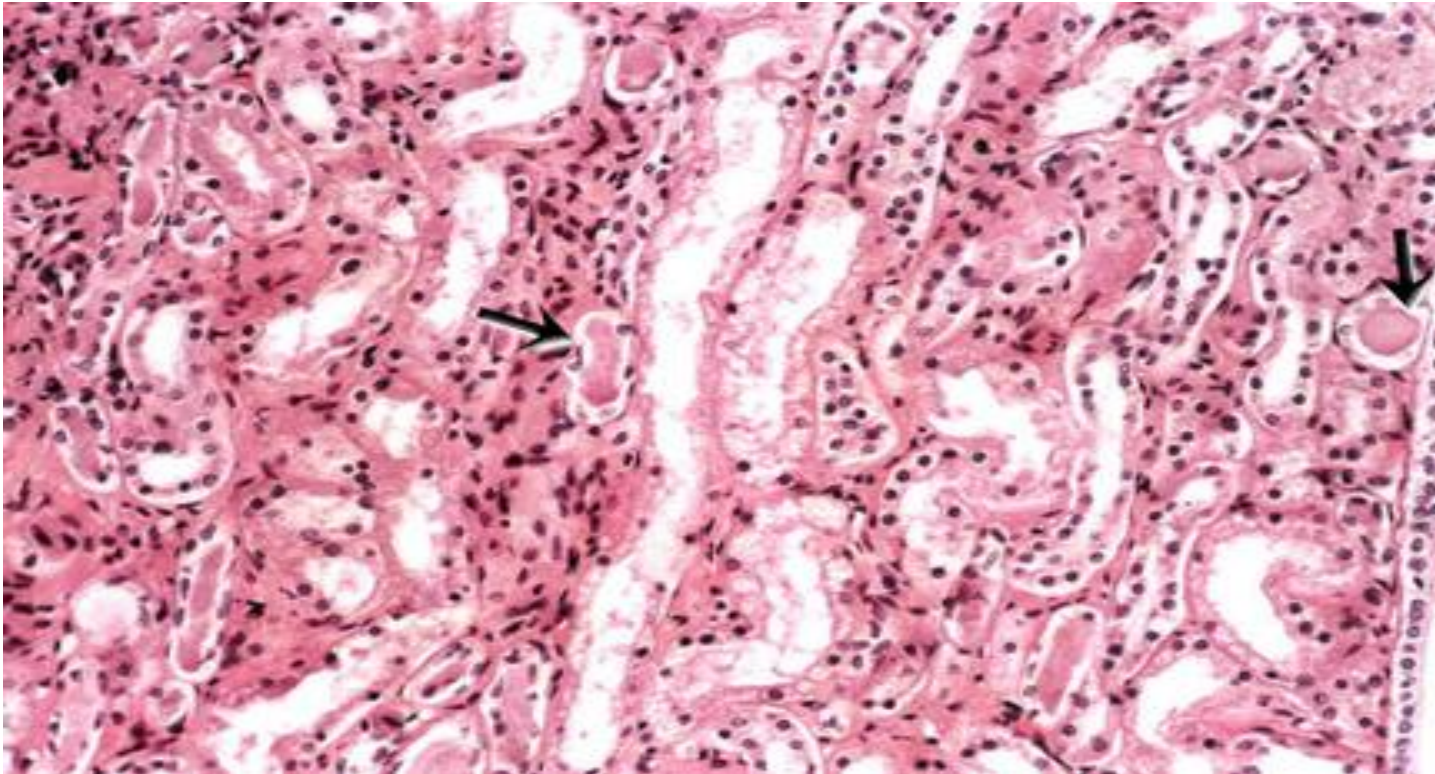


# AKI, necrotic epithelial cells





# Casts in AKI



## Note:

- The patchiness of necrosis of tubular epithelial cells and maintenance of the integrity of the basement membranes along many segment allow repair of the necrotic foci and recovery of the function if the precipitating factor is removed

- II. Toxic acute kidney injury is characterized by :
  - a. acute tubular injury in the distal tubules and the histologic appearance is not specific except in certain situation
    - 1. In mercuric chloride poisoning may see large acidophilic inclusions
    - 2. Carbon tetrachloride poisoning is characterized by accumulation of neutral lipids

## **Note:**

- The severity of morphologic finding does not correlate well with the clinical manifestations
- Eosinophilic hyaline casts and granular pigmented casts are common to be seen in distal tubules and collecting ducts

- These casts are composed of Tamm-Horsfall protein which is a urinary glycoprotein secreted by the thick loop of Henle and distal tubules
- There is evidence of tubular reepithelialization in the form of flattened epithelial cells with increased mitotic figures



# The clinical course

- The classic case is divided into three phase

## 1. Initiation phase

- Last for 36 hours and dominated by the inciting medical surgical or obstetric condition
- The only indication of injury is decrease in urinary output and rise in BUN

## 2. The maintenance phase

- Is characterized by

- a. sustained decrease in urine output to 40-400 ml/day (oliguria),
  - b. sodium overload and rise BUN,
  - c. hyperkalemia
  - d. and metabolic acidosis
- 3.

## The recovery phase

- Is characterized by increase in urine output to 3L/day
- The tubules are still damaged so large amounts of water, sodium and K are lost in urine
- Hypokalemia rather than hyperkalemia becomes a problem

- Eventually renal tubular concentrating ability is restored and BUN and creatinin decrease to normal
- Recovery with nephrotoxic AKI is expected if the toxin has not caused injury to other organs
- With supportive therapy, 95% of patients who don't succumb to the precipitating cause recove
- **In septic shock, burns and or other causes of multiorgan failure, the mortality rate reach 50%**

## II. Tubulointerstitial Nephritis

- Characterized by histologic and functional alterations that involve predominantly the tubules and interstitium.
- These disorders have diverse causes and different pathogenetic mechanisms
- **Causes**
  1. **Toxins**
    - a. Drugs such as analgesics
    - b. Acute hypersensitivity interstitial nephritis

## **II. Metabolic diseases**

- a. Uric acid nephropathy
- b. Nephrocalcinosis

## **III. Infections**

- a. Acute bacterial puyelonephritis
- b. RefluX nephropathy

**I. The acute tubulointerstitial nephritis** has a rapid clinical onset and characterized histologically by:

- a. Interstitial edema,
  - b. Interstitial and tubular Leukocytic infiltration
2. I tubular necrosis

**II. Chronic interstitial nephritis characterized by**

- a. Infiltration with mononuclear leukocytes,
- b. Prominent interstitial fibrosis, and tubular atrophy.

- The latter may be subtle and include
  - a. impaired ability to concentrate urine, evidenced clinically by polyuria or nocturia; salt wasting;
  - b. diminished ability to excrete acids (metabolic acidosis);



# 1. Acute Drug-Induced Interstitial Nephritis

- Most frequently occurs with
  - a. Synthetic penicillins (methicillin, ampicillin),
  - b. rifampin),
  - c. diuretics (Thiazides),
  - d. NSAIDs,

**Note: The disease begins about 15 days after exposure to the drug and is characterized by**

- a. *Fever*,
- b. *Eosinophilia* (which may be transient),
- c. *Skin rash* in about 25% of patients,
- d. and *renal abnormalities*.which takes the form of hematuria, mild proteinuria, and leukocyturia (often including eosinophils).

**Note: A rising serum creatinine level or acute renal failure with oliguria develops in about 50% of cases,**

# Pathogenesis.

- Many features of the disease suggest an immune mechanism and the immune response is not dose-related.
- Clinical evidence of hypersensitivity includes
  - A. The latent period,
  - B. The eosinophilia and rash,
  - c. The recurrence of hypersensitivity after re-exposure to the same or a cross-reactive drug.

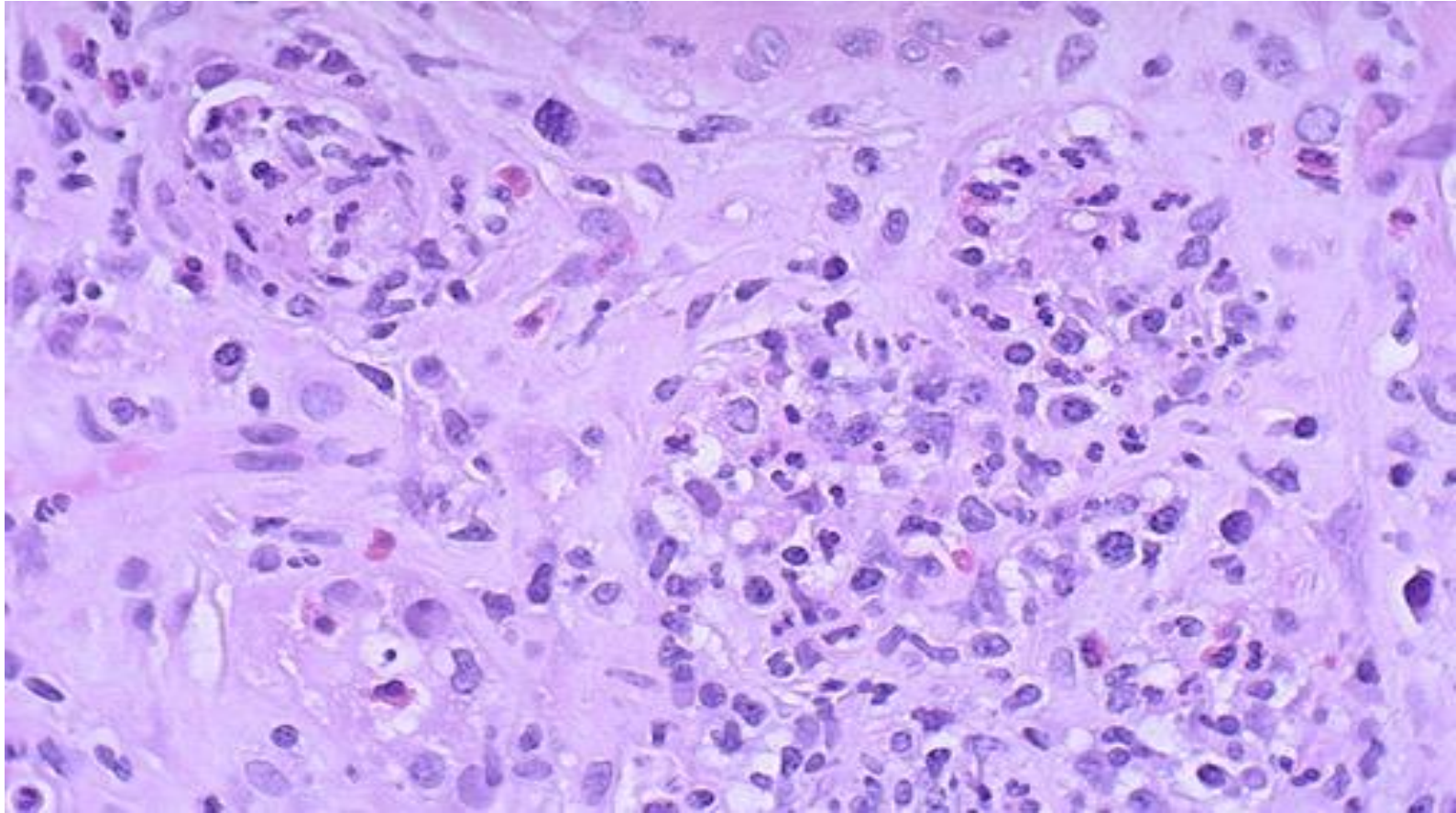
## Note:

- In some patients, serum IgE levels are increased, and IgE-containing plasma cells and basophils are present in the lesions, suggesting that the *late-phase reaction of an IgE-mediated (type I) hypersensitivity* may be involved in the pathogenesis
- In other cases, mononuclear or granulomatous infiltrate, together a T cell–mediated delayed-hypersensitivity reaction (type IV).

# Morphology.

- The abnormalities are in the interstitium, which shows
  1. Edema and infiltration by mononuclear cells, principally lymphocytes and macrophages.
  2. Eosinophils and neutrophils may be present and plasma cells and basophils are sometimes found in small numbers.
  3. With some drugs (e.g., methicillin, thiazides), interstitial granulomas containing giant cells may be seen.
  4. The glomeruli are normal except in some cases caused by NSAIDs,

# Drug induced interstitial nephritis



# Clinical Features

- It is important to recognize drug-induced renal failure because :
  - a. Withdrawal of the offending drug is followed by recovery, although it may take several months,
  - b. and irreversible damage occurs occasionally in older subjects

## 2. Analgesic Nephropathy

- *This is a form of chronic renal disease caused by excessive intake of analgesic mixtures*
- The renal damage is caused by intake of analgesic mixtures that contain aspirin, caffeine, acetaminophen , and codeine
- Who develop the disease usually ingest large quantities of mixture of at least two antipyretics



# Pathogenesis.

- Papillary necrosis occurs first, and cortical tubulointerstitial nephritis follows as a consequence of impeded urine outflow.
- 1. The phenacetin, the metabolite acetaminophen, deplete cells of glutathione, then injures these cells by subsequent generation of oxidative metabolites.

2. Aspirin induces its potentiating effect by inhibiting the vasodilatory effects of prostaglandins, predisposing the papillae to ischemia.

**Note:**

- Thus, the papillary damage may be due to a combination of direct toxic effects of phenacetin metabolites and ischemic injury to both tubular cells and vessels.

# Morphology.

## Gross appearance

- The papillae show various stages of necrosis, calcification, fragmentation, and sloughing. contrasts with the papillary necrosis seen in diabetic patients, in which all papillae are at the same stage of injury

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# Papillary necrosis



- **On microscopic examination** .
  - In early cases there is patchy necrosis of the papillae but in the advanced form the entire papilla is necrotic and remain as a structureless mass containing “ghosts” of tubules and foci of dystrophic calcification).
  - Segments of entire portions of the papilla may then be sloughed and excreted in the urine

# Clinical Features.

- Early renal findings include
  - a. Inability to concentrate the urine
  - b. Acquired distal renal tubular acidosis contributes to the development of renal stones
  - c. On occasion, entire tips of necrotic papillae are excreted, and these may cause gross hematuria or renal colic

## Note

- Progressive impairment of renal function may lead to chronic renal failure, but *with drug withdrawal, renal function may either stabilize or actually improve.*
- Unfortunately, a small percentage of patients with analgesic nephropathy develop *transitional papillary carcinoma of the renal pelvis.*

- **Papillary necrosis is not specific for analgesic nephropathy.**
- **It is also seen in**
  - a. diabetes mellitus,
  - b. sickle cell disease or trait
  - c. and focally in renal tuberculosis.



# 3.Nephropathy Associated with NSAIDs

- Are uncommon, complications
- Their adverse renal effects are related to their ability to inhibit cyclooxygenase-dependent prostaglandin synthesis.
- NSAID-associated renal syndromes include:
  1. Acute renal failure,: Due to the decreased synthesis of vasodilatory prostacyclin

2. Acute hypersensitivity interstitial nephritis,
  - Resulting in acute renal failure
3. Membranous nephropathy, with the nephrotic syndrome,.