Renal Pathology
Acute kidney injury

April 2020

Reference: Robbins & Cotran Pathology and Rubin's Pathology

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Acute kidney injury

Objectives:

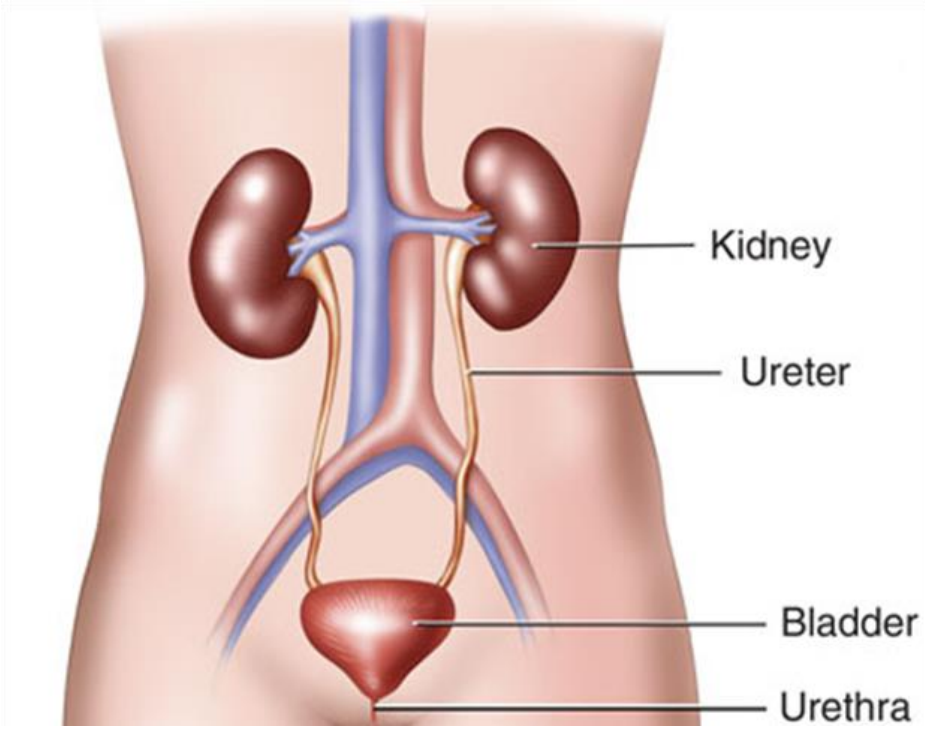
Upon completion of this lecture the students will be able to:

- Describe the guidelines of the renal biopsy.
- Recognize the types of acute kidney injury.
- Recognize the clinical manifestations of acute kidney injury.
- Describe the pathological findings in acute kidney injury.

Key Outlines:

- Brief review of the normal anatomy and histology of the kidney and urinary tract.
- Terminology.
- Etiology.
- Pathophysiology.
- Clinical manifestations with diagnostic approach.
- Pathological evaluation: The four elements possibly implicated: Gross and histological findings.
- Conclusion.

GROSS ANATOMY AND HISTOLOGY



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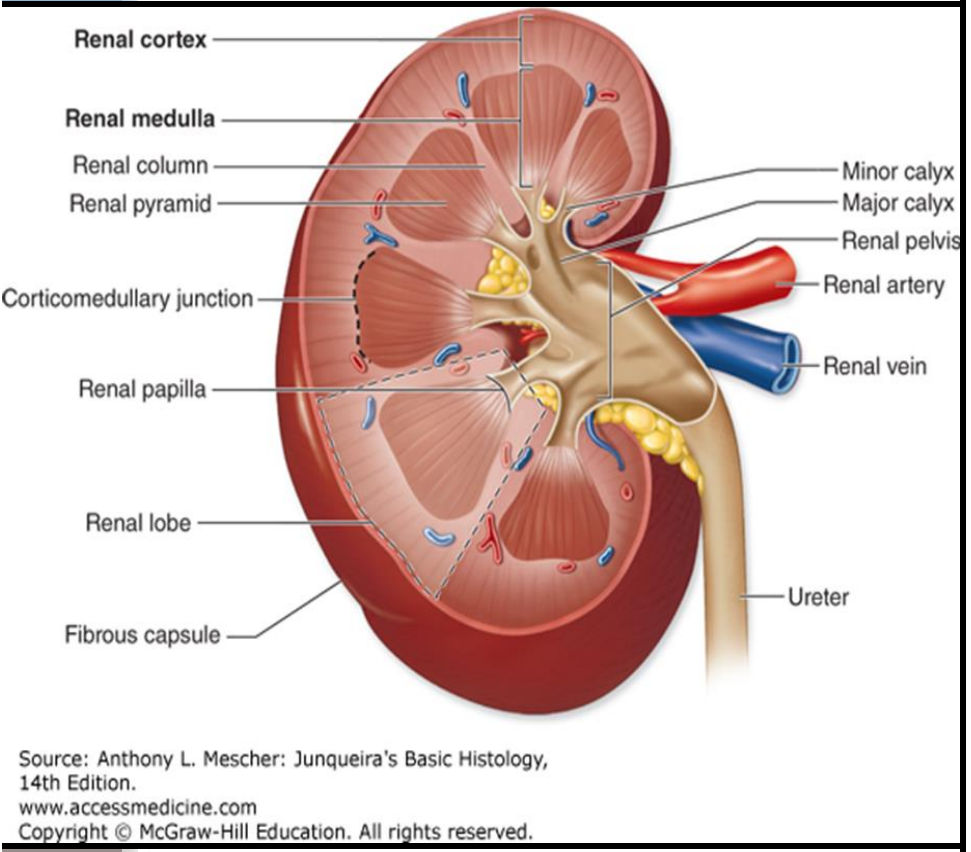
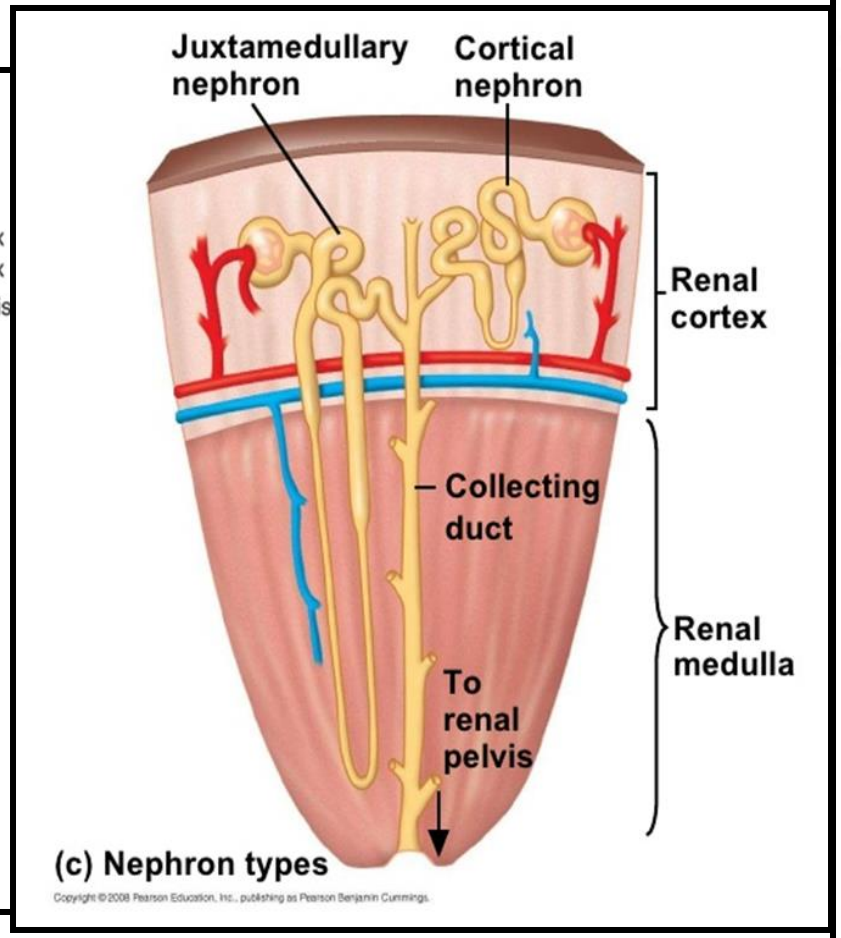
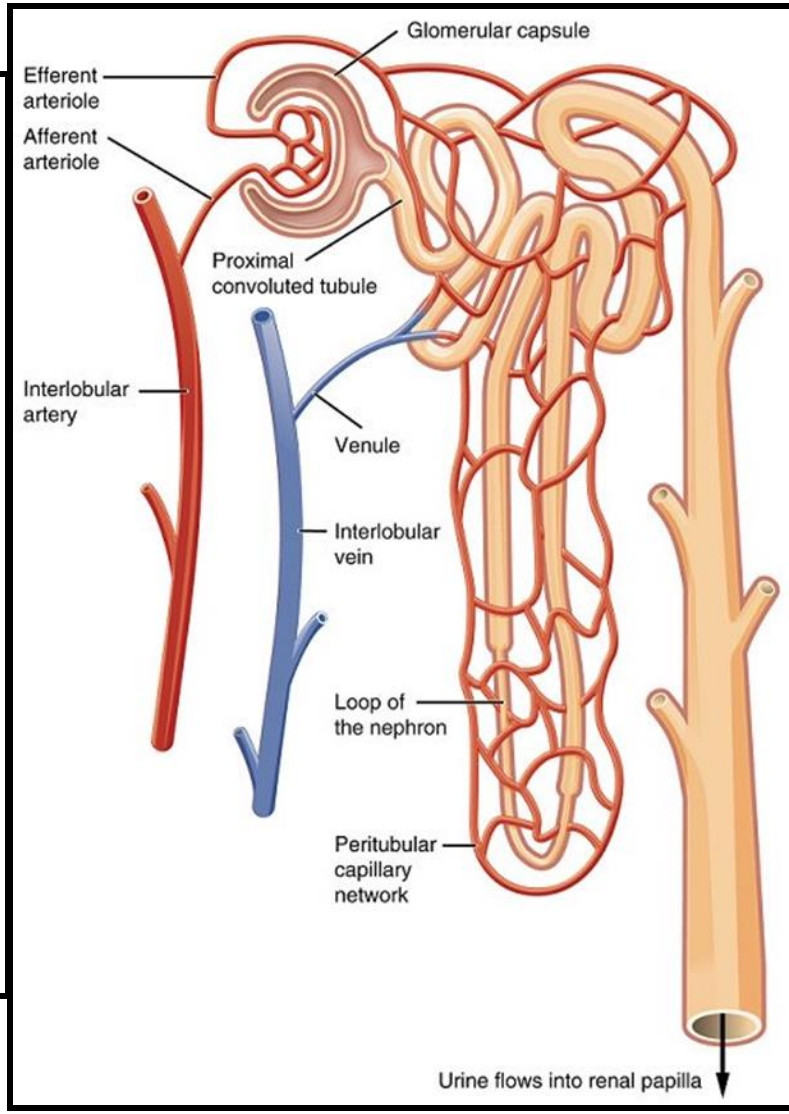
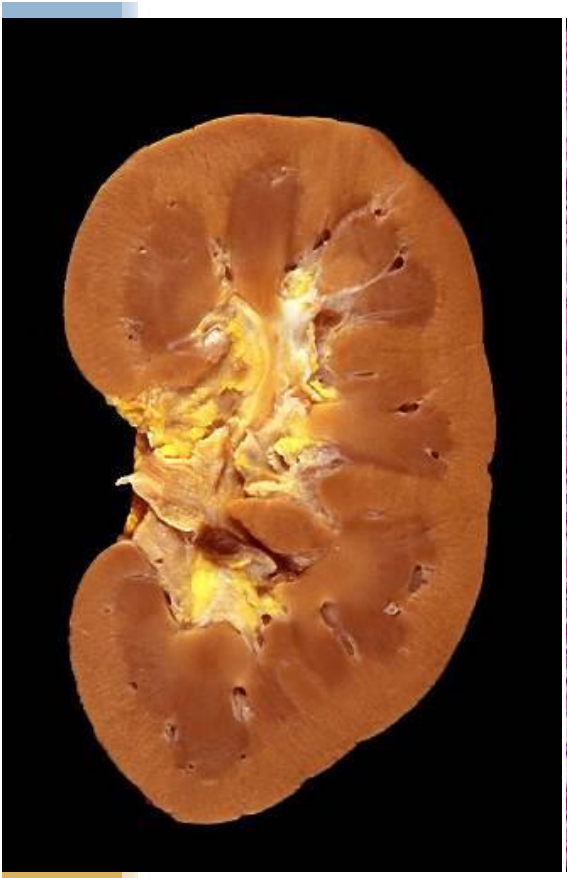


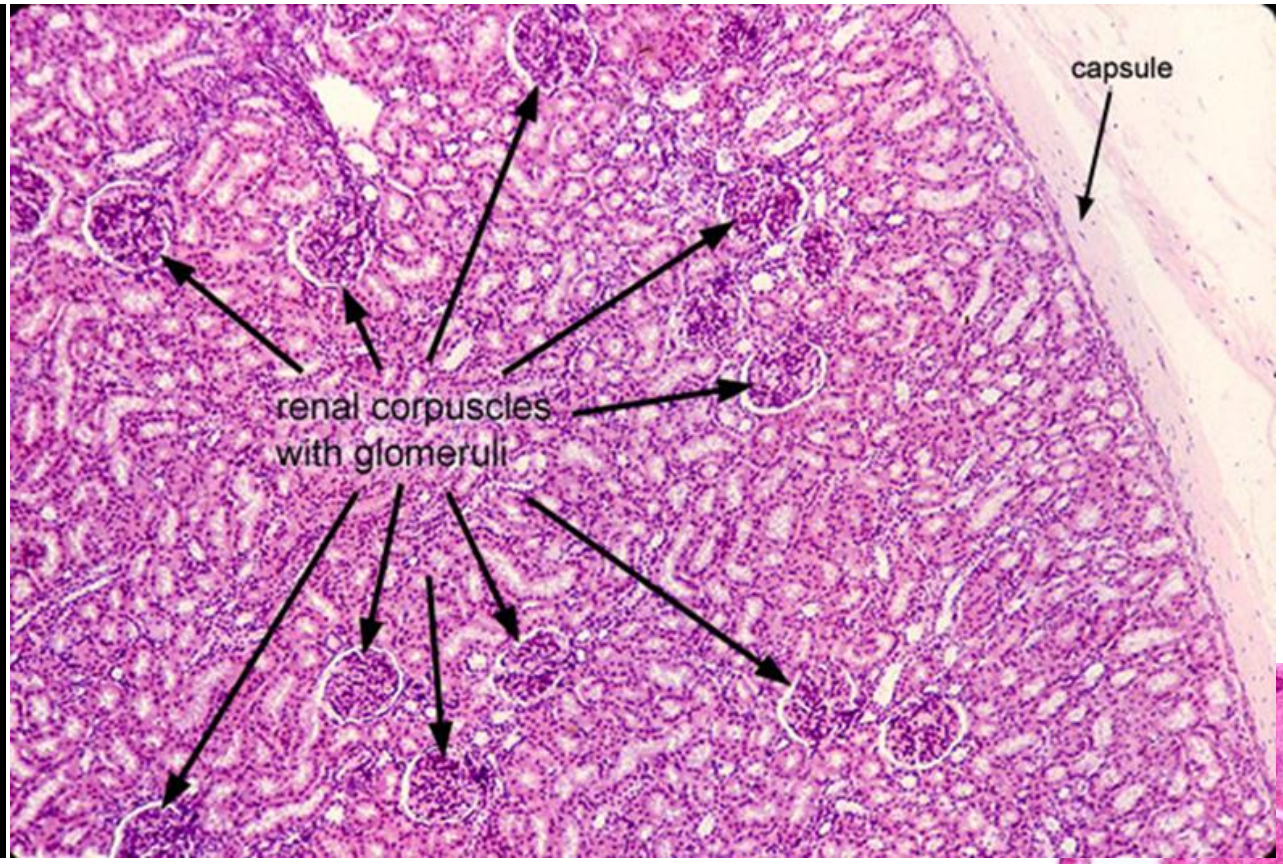
Source: Anthony L. Mescher: Junqueira's Basic Histology, 14th Edition.
www.accessmedicine.com

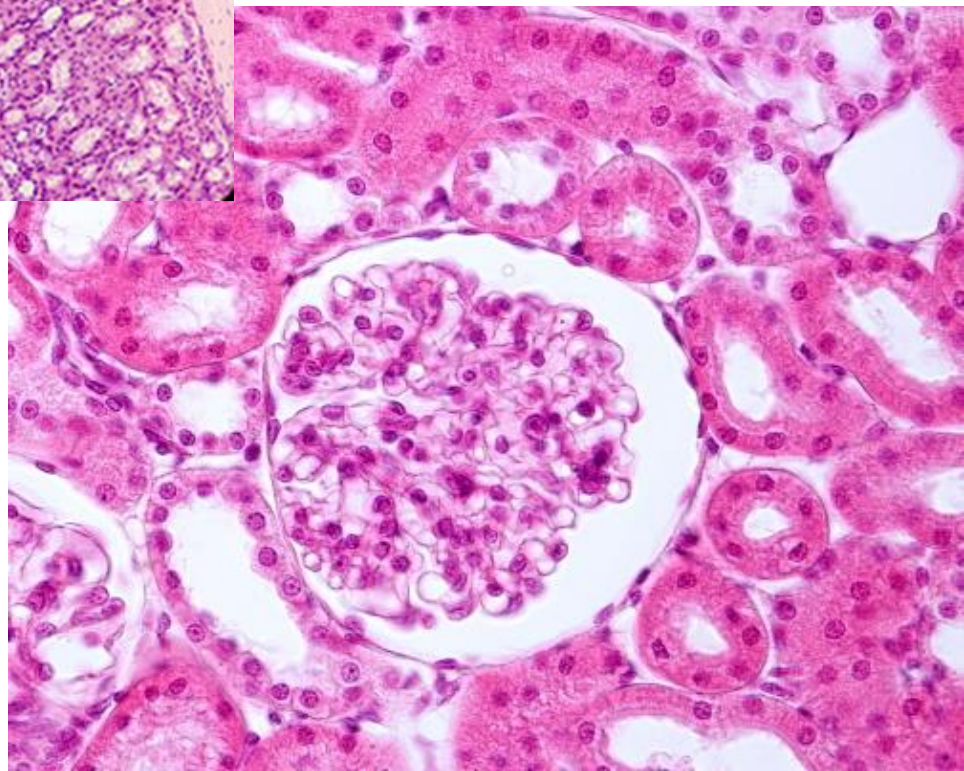




By OpenStax College - Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013., CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=30148538







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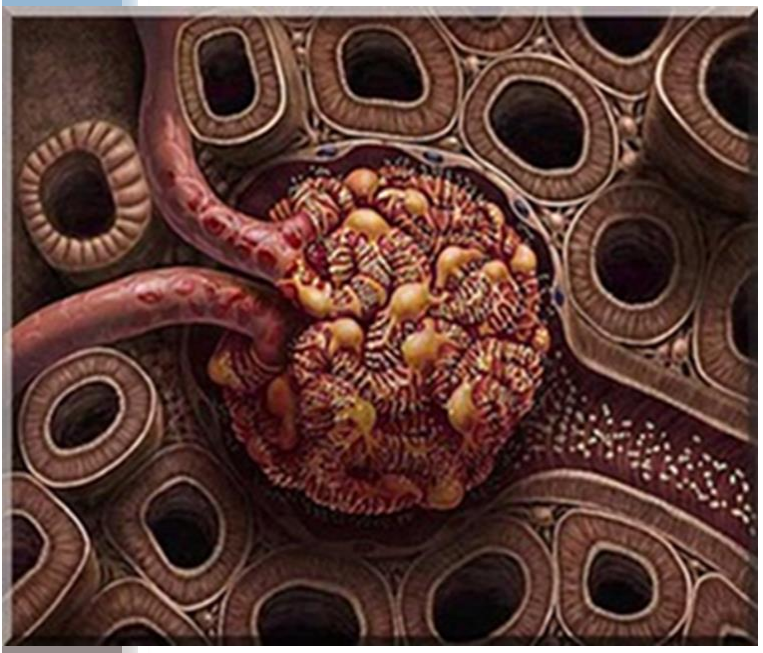

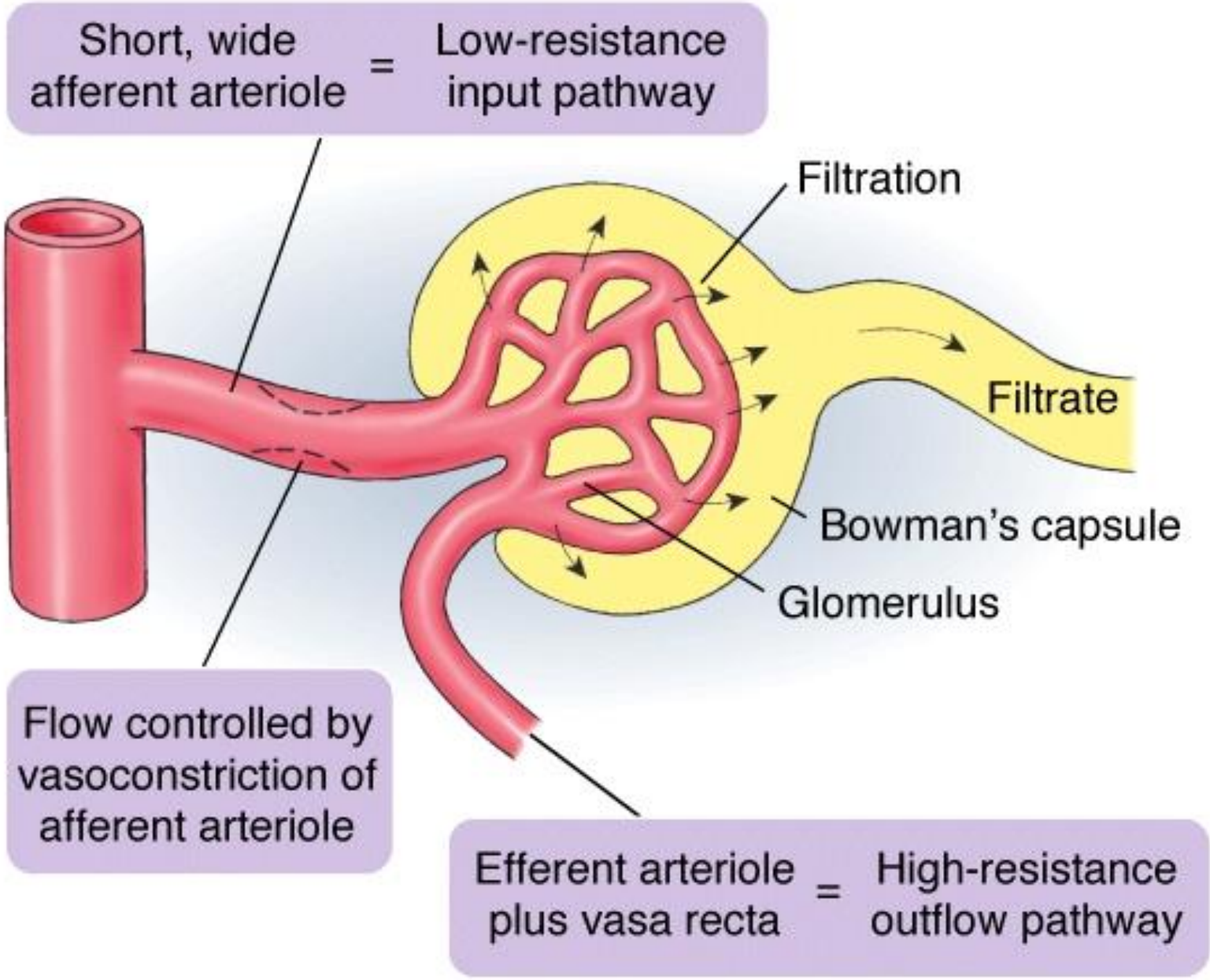

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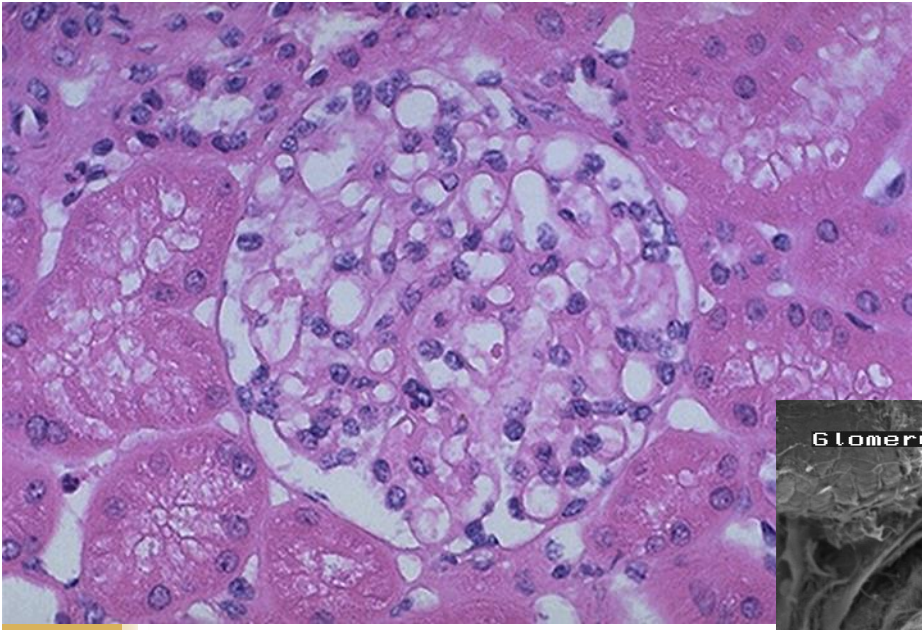
Glomerulus on Scanning EM



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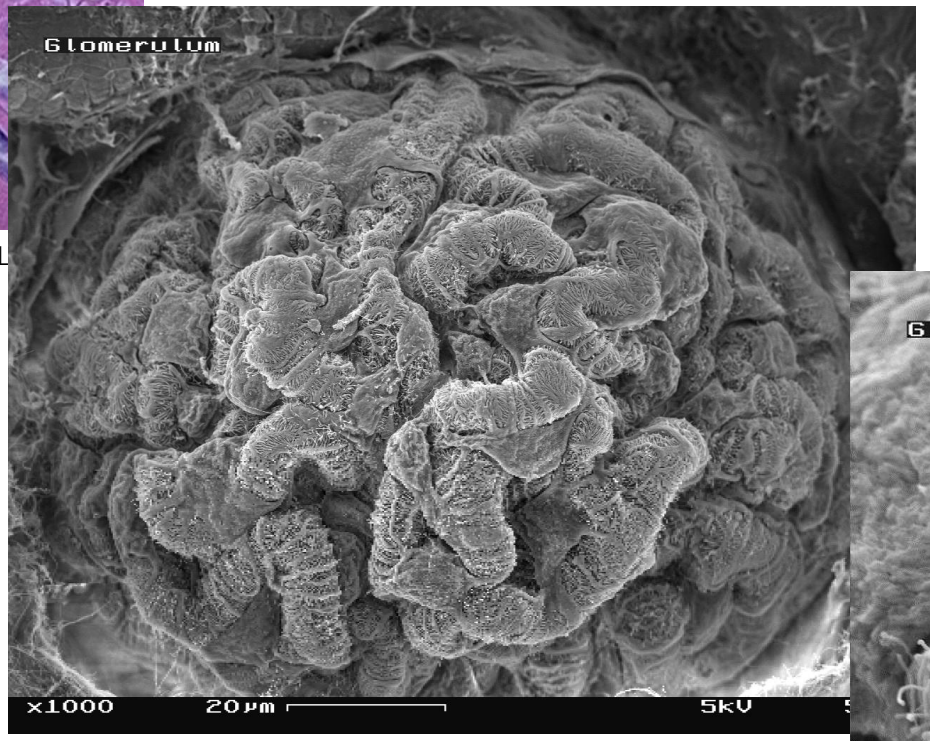

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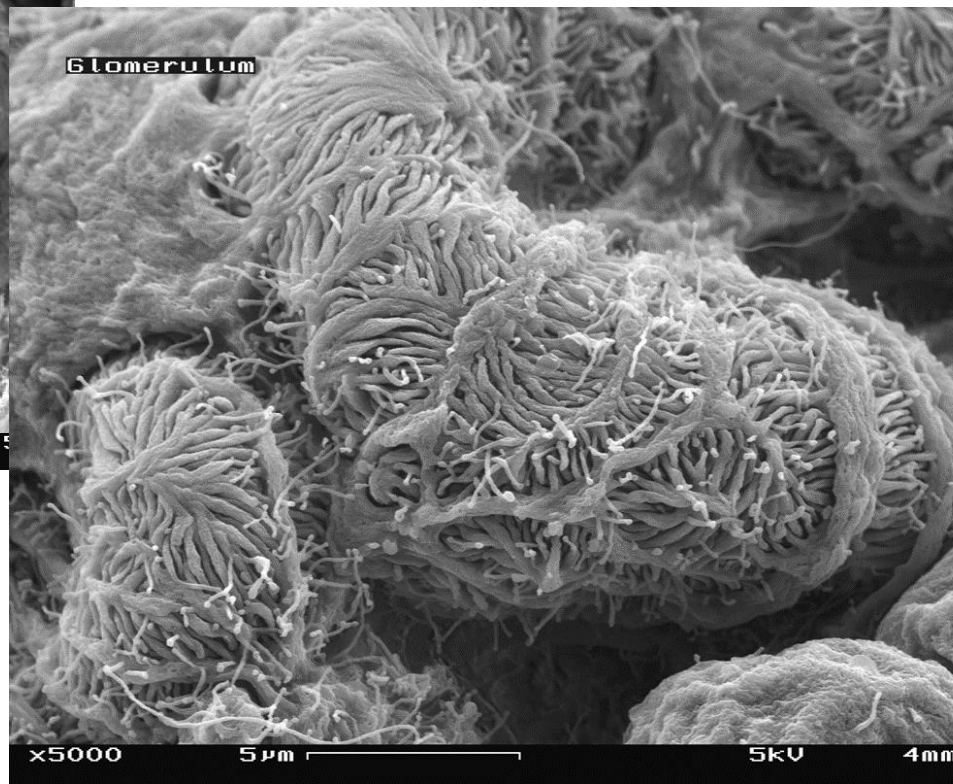
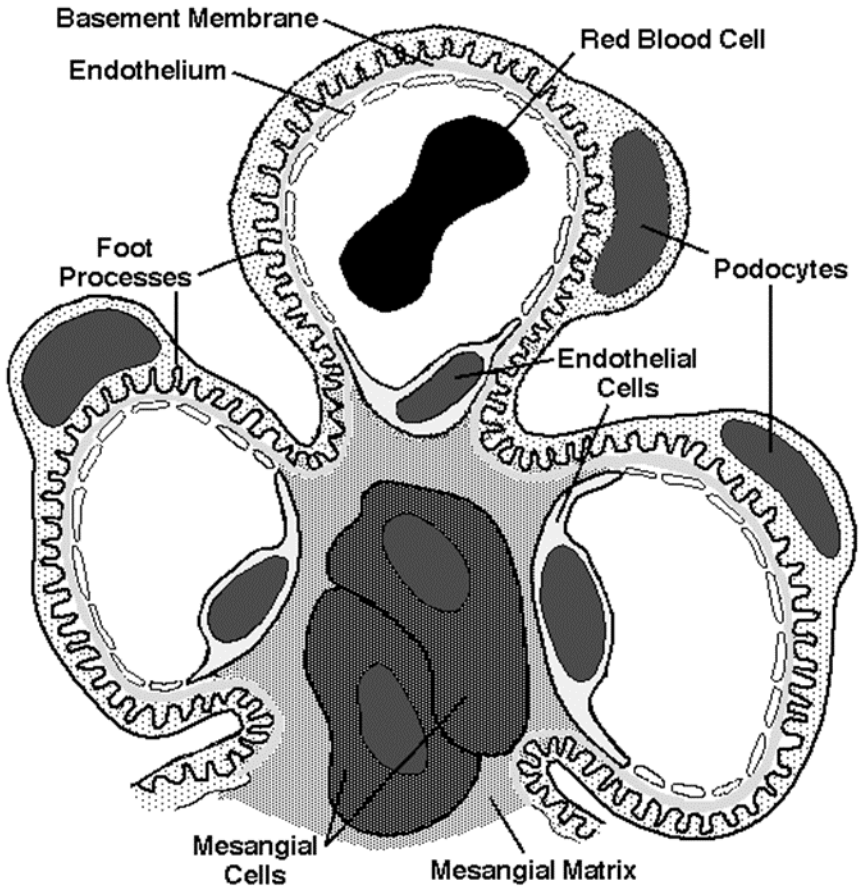
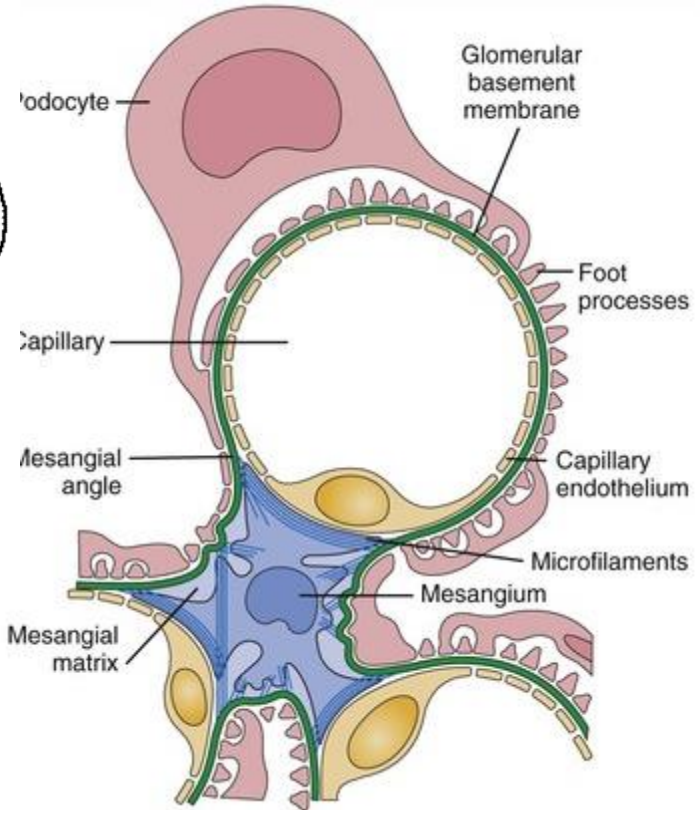


Glomerulus n Transmission EM





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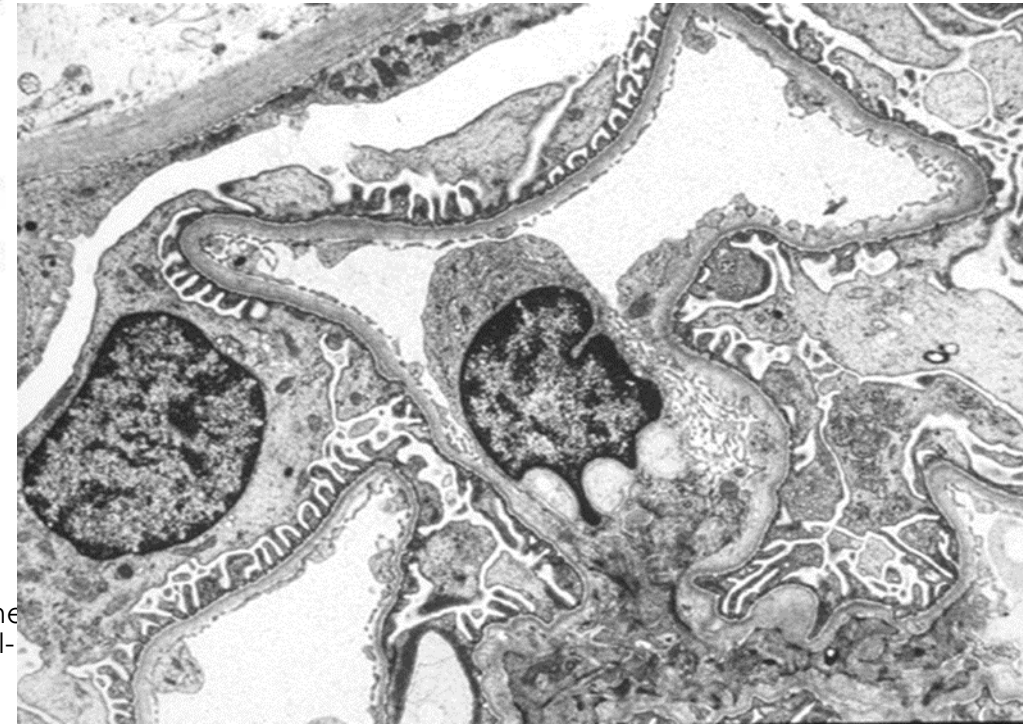


Normal Kidney Function

- **Excretory function:**
  - to detoxify blood, removal of toxins, nitrogenous wastes (urea and creatinine), drugs etc.
- **Homeostatic function:**
  - maintain and regulate water balance and osmolality
  - maintain and regulate electrolyte balance (Na^+, K^+, Ca^{2+}, Cl^-, Mg^{2+} ions etc.)
  - maintain and regulate acid-base balance (pH, H^+ and $HCO3^-$ ions).
- **Endocrine function:**
  - secretes renin from the JGA cells → to regulate BP and electrolyte balance
  - secretes erythropoietin from the endothelial cells lining the cortical peritubular capillaries → to stimulate the bone marrow to produce rbcs
  - Kidney converts inactive Vit D3 to active 1,25- dihydroxycholecalciferol by alpha one hydroxylase enzyme under the influence of PTH → increases calcium absorption

What a Kidney Does

WATER. Ensures that there's not too much or too little water in the body.

BLOOD PRESSURE. Makes sure that pressure isn't too high or too low.

WASTES. Gets rid of urea, uric acid, toxins, and other wastes via urine.

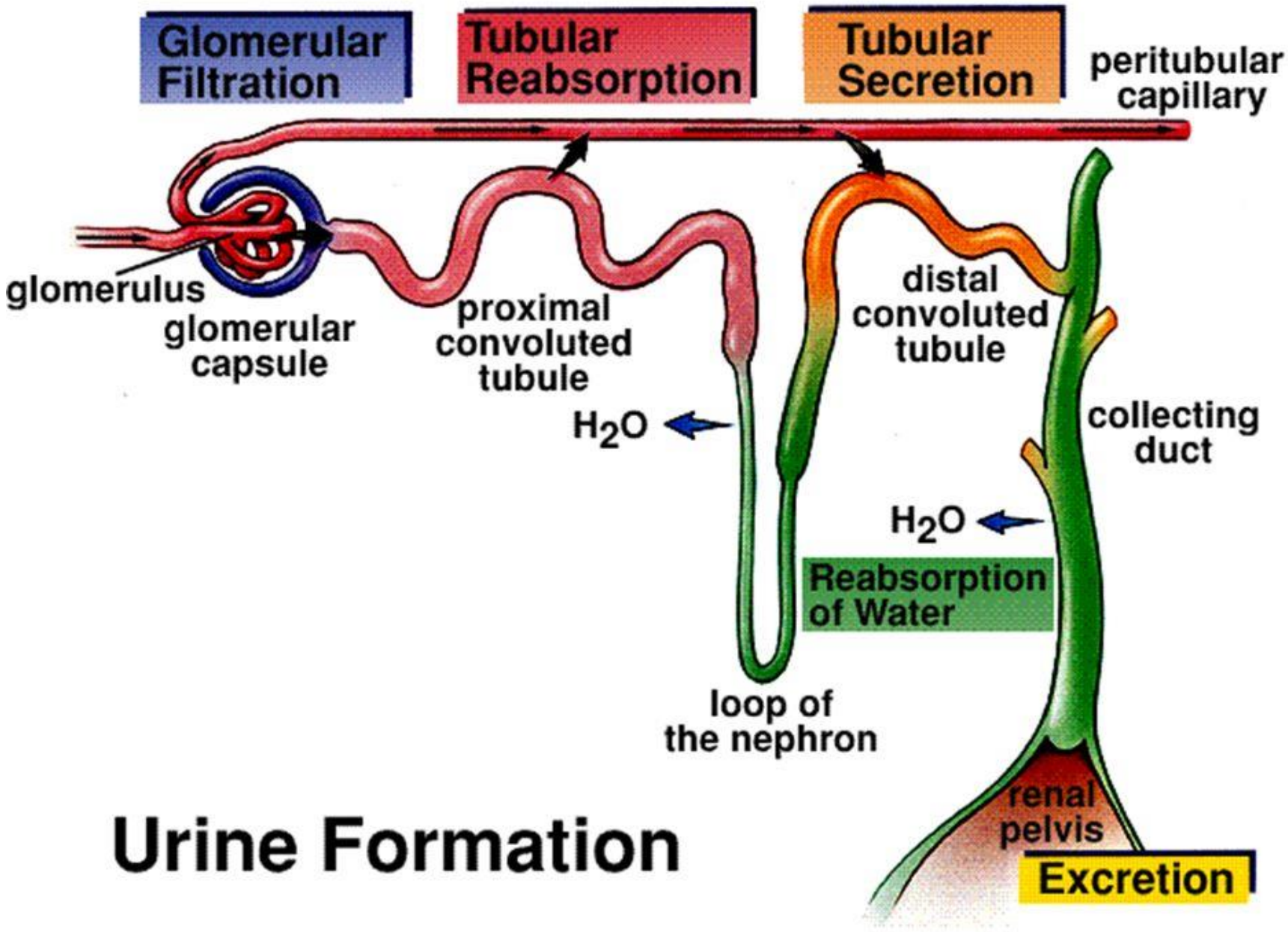
BONES. Activates vitamin D, which helps the body absorb calcium.

ACID-BASE BALANCE. Makes sure that the body isn't too acidic or too alkaline.

HEART. Maintains a balance of electrolytes (like potassium, sodium, and calcium), which is critical for heart rhythm.

BLOOD. Releases erythropoietin, which tells bone marrow to make red blood cells.

https://www.weyburnreview.com/news/kidney-function-can-be-seen-using-new-tool-1.2216753



Urine Formation

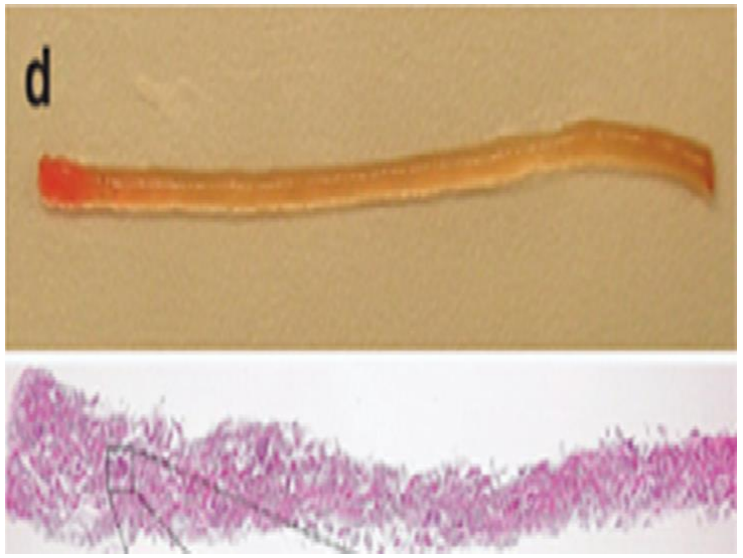
Terminology

- **Uremia:** is a clinical syndrome associated with fluid, electrolyte, and hormone imbalances and metabolic abnormalities, which develops with deterioration of renal function. It is due to the accumulation of organic waste products that are normally cleared by the kidneys. The word uremia means urine in the blood. Uremia can be seen in both chronic kidney disease and acute kidney injury.
- **Azotemia:** is abnormally high levels of nitrogen-containing compounds (such as urea, creatinine etc) in the blood. It can lead to uremia if not controlled. It is an elevation of blood urea nitrogen (BUN) and serum creatinine levels.
- **Oliguria:** urine output less than 400 ml/24 hours
- **Anuria:** urine output less than 200 ml/24 hours

RENAL PATHOLOGY

KIDNEY BIOPSY

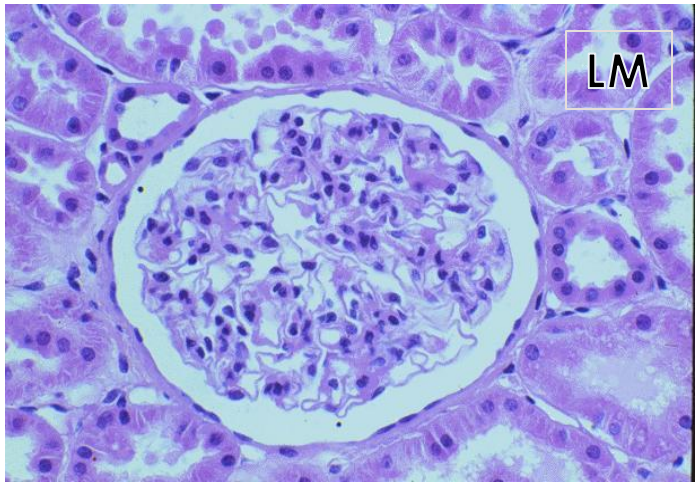
Kidney biopsy

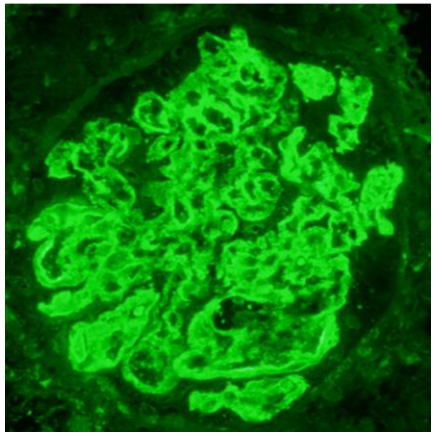


Kidney biopsy

The tissue obtained is used to make slides for

1. **Light microscopy (LM)** to study the histology in renal cortex & medulla.
2. **Immunofluorescence (IF)** study is to detect
   - the presence of immunoglobulins (IgA, IgG, IgM) and complements (C3 and C1q) in the glomerular mesangium or in the wall of the glomerular capillary loops.
3. **Electron microscopy (EM) (ultrastructural)** study is to detect the presence or absence of
   - effacement of the epithelial cell (podocytes)foot processes.
   - electron dense immune complex deposits
   - If deposits are present then to identify the location of the deposits in the glomeruli (mesangial/paramesangial, subepithelial, subendothelial).





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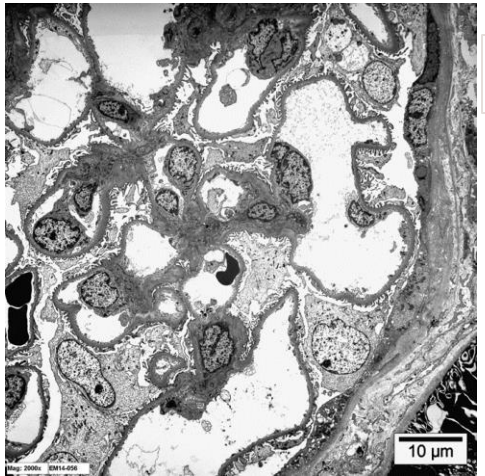


EM

Renal (kidney) failure

- **Renal failure** (**renal insufficiency**): is when the kidneys fail to adequately filter toxins and waste products from the blood.
- In renal failure there is decrease in glomerular filtration rate and an elevated serum creatinine level.

Note: Creatinine clearance or filtration is dependent on the glomerular filtration rate (GFR).

Renal failure can be classified in 3 ways:

1. **It can be acute or chronic**

   Acute is sudden onset, rapid reduction in urine output and usually reversible **(acute kidney injury).**

   It can be acute or chronic Chronic is gradually progressive with nephron loss and usually not reversible **(chronic kidney disease).**

2. **It can be pre-renal, renal or post-renal**
3. **It can be oliguric, non-oliguric or anuric**

   Oliguric: urine output less than 400cc/24hr.

   Non-oliguric: urine output greater than 400cc/24hr.

   Anuric: urine output less than 100cc/24hr.

Note: sometimes more than 70% of renal function can be lost before it is clinically noticeable

ACUTE KIDNEY INJURY

Acute kidney injury (AKI)

(previously called acute renal failure [ARF])

AKI is a syndrome defined by a sudden loss of renal function over several hours to days resulting in the accumulation of nitrogenous compounds such as urea and creatinine. It is characterized by

- Sudden decrease in GFR (hours to days)
- Accumulation of nitrogenous waste products.
- **Rapid rise in serum creatinine**
- **Oliguria: the urine output is markedly decreased** (usually it is less than 400 ml/day)
- Fluid imbalance; electrolyte imbalance; acid-base disturbance; and mineral disorders.

Note: in AKI → there is reduction in renal blood flow/ renal perfusion → decrease in glomerular filtration rate (this is the common pathologic pathway for AKI regardless of the cause). The decreased GFR → activation of renin-angiotensin-aldosterone system. These physiologic changes result in increased sodium reabsorption, increased water retention, increased urinary creatinine concentration, increased urine specific gravity and increased urine osmolality. Acids are retained and HCO_3 is excreted.

Acute kidney injury (AKI)

Definition [based on Kidney Disease Improving Global Outcomes (KDIGO)]**:** AKI is defined by the presence of any one of the following:

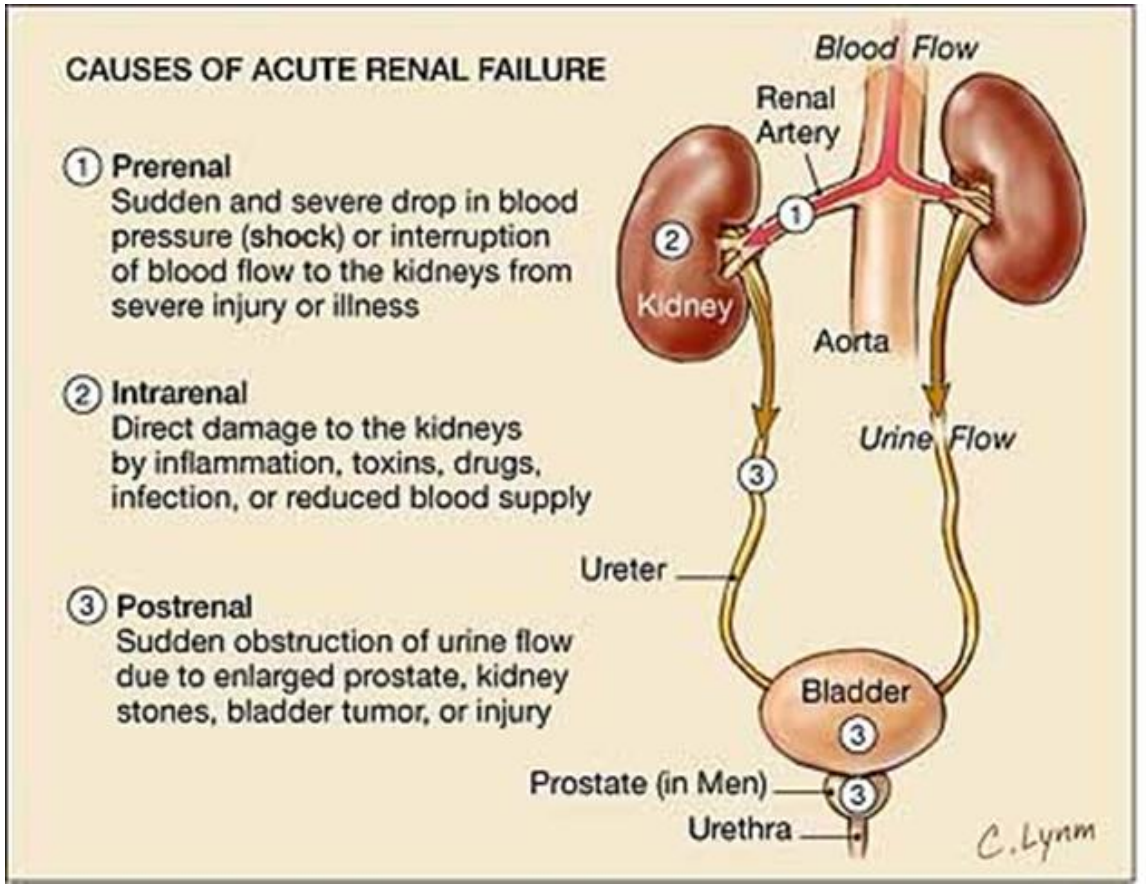
AKI is *defined* as any of the following:	
1	Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
2	Increase in sCr ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
3	Urine volume <0.5 mL/kg/h for 6 hours.

Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012;2 :1-138.

Causes of AKI (etiologic classification)

AKI can be divided into pre-renal, renal or post-renal etiology.

- **Pre-renal (55-60%)**: the renal tubular and glomeruli are normal. Here the GFR is decreased due to reduced renal perfusion.
- **Renal/ intrarenal/ intrinsic (35-40%)**: is due to diseases of the kidney itself (which is associated with release of renal afferent vasoconstrictors)
- **Post-renal (5-10%)**:



Pre-renal causes of ARF (pre-renal azotemia)

- Pre-renal pathology is the most common cause of ARF
- It results from **decreased renal perfusion/ hypoperfusion** (i.e. decreased effective blood flow to the kidney).
- Initially the body tries to compensate but in severe hypoperfusion → GRF is markedly decreased → AKI.
- The treatment of the cause restores the renal function.

Pre-renal causes of ARF are:

- Anything that leads to renal hypoperfusion:
  - Hypovolemia: e.g. hemorrhage, volume depletion (dehydration or GIT fluid loss in vomiting, diarrhea), hypoalbuminemia, diuretics, third space losses (burns, peritonitis, muscle trauma) etc.
  - Impaired cardiac function (cardiac failure, myocardial infarction, massive pulmonary embolism)
  - Sepsis, septic shock.
  - Cirrhosis (it can cause renal vasoconstriction → kidney injury called “hepatorenal syndrome”)
  - Anaphylaxis
  - Other causes: surgery, NSAIDS and other nephrotoxic drugs etc.

Renal causes of AKI
(intrinsic causes)

- Diseases of the kidney → can lead to AKI.
- The diseases of the kidney can be
    - glomerular
    - tubular
    - vascular
    - or interstitial
- The disease may involve one or more of the above mentioned renal compartments.
- Common causes include acute tubular injury/necrosis, acute interstitial nephritis and severe forms of active glomerulonephritis.

Note: the contrast medium/dye used in various radiological tests can occasionally induce AKI.

RENAL causes of AKI

Glomerular diseases

There is glomerular injury in severe forms of active glomerulonephritis (GN) → leads to reduction in total filtration area → reduction in GFR. Examples include:

- Post infectious GN
- Rapid progressive crescentic GN
- Active autoimmune GN
- Etc.

Tubular diseases

Acute Tubular Injury/ Necrosis

It can be ischemic cause or nephrotoxic cause

Ischemic: prolonged ischemia to nephrons leads to tubular injury and necrosis

Toxic: toxicity to nephrons leads to tubular injury & necrosis

I) Endogenous toxins

Pigments and casts:

- Myoglobinuria (in Rhabdomyolysis)
- Hemeglobinuria
- Myeloma casts etc.

II) Exogenous toxins

Nephrotoxic drugs:

- Aminoglycosides (antibiotic).
- Amphotericin B
- Calcineurin inhibitors (e.g., tacrolimus) etc.

Radiograph contrast medium (dyes induced toxicity)

Vascular diseases

Various forms of vasculitis and emboli lead to reduced renal blood flow due to vascular obstruction or destruction, thus lowering the GFR

e.g.

- Vasculitis
- Thromboembolic disease (renal artery/ renal vein thrombosis)
- Thrombotic microangiopathies (HUS/ TTP)
- Malignant hypertension

Interstitial diseases

Acute Tubulo-interstitial Nephritis (TIN)

e.g.

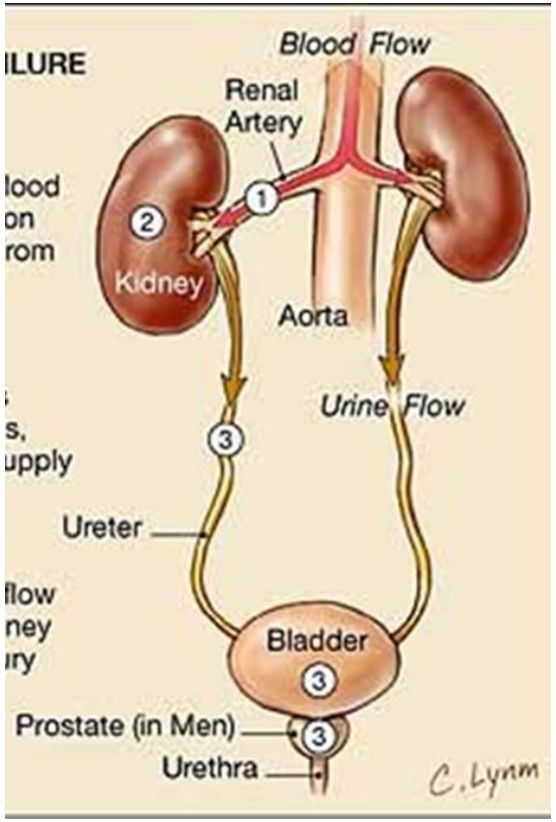
- Drug induced TIN
- Autoimmune TIN
- Infections TIN

Rarely malignant infiltration in interstitium can cause AKI

Post renal causes of AKI/ ARF

Any obstruction to the outflow of urine:

- Congenital or structural abnormality
- Benign prostatic hyperplasia (older men)
- Stones in the urinary tract
- A tumor in the urinary tract (e.g. ureter, bladder, prostate, urethra).
- External compression from the outside of the urinary tract (e.g. retroperitoneal fibrosis or tumors like carcinoma of cervix).



Summary of causes of AKI

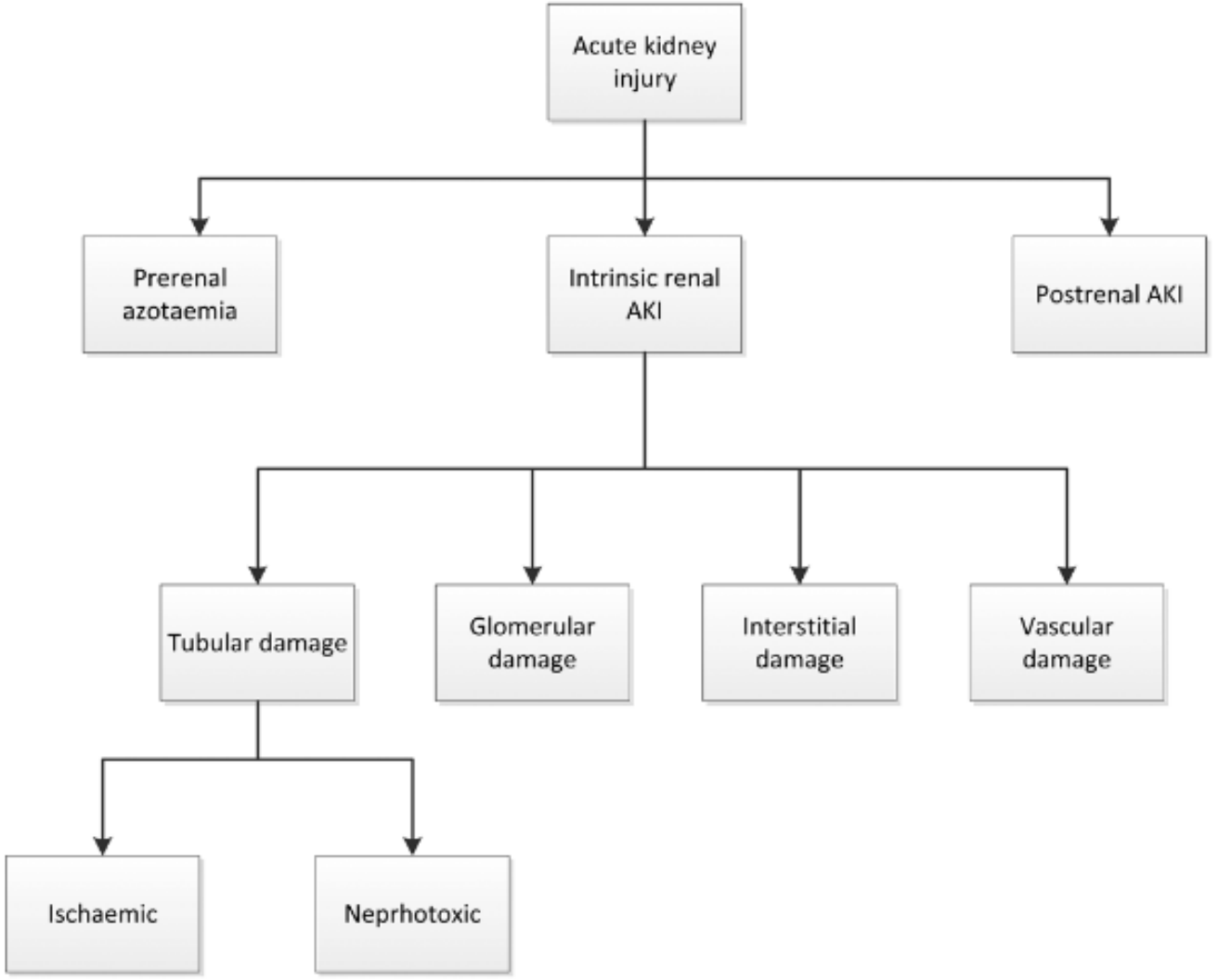
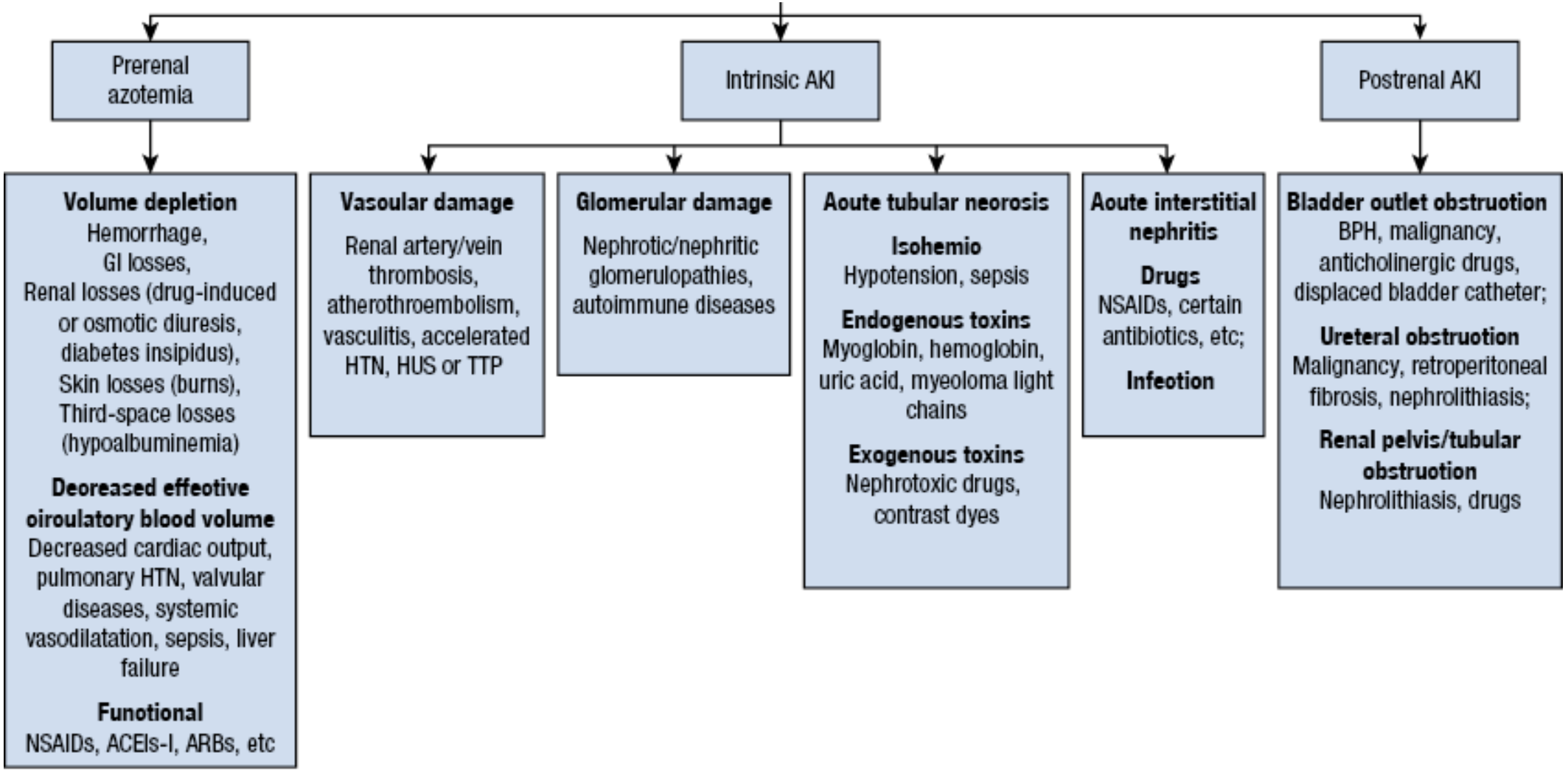


Figure 1. Aetiologies of acute kidney injury

Clin Biochem Rev 37 (2) 2016

Summary of causes of AKI



Source: Wells BG, DiPiro JT, Schwinghammer TL, DiPiro CV: *Pharmacotherapy Handbook,* Eighth Edition

Note: Common causes of AKI

The kidney biopsy of a patient with AKI can show any of the previously mentioned causes. The common causes are:

- Tubular cause: acute tubular injury/ acute tubular necrosis
- Interstitial cause: acute tubulointerstitial nephritis (later lectures)
- Glomerular cause:
    - Post infectious glomerulonephritis (later lectures)
    - Rapid progressive crescentic glomerulonephritis (later lectures)

Acute tubular injury/ necrosis

(tubular cause of AKI)

Acute tubular injury and Acute tubular necrosis

In acute tubular injury/ necrosis there is damage to the epithelial cells of the renal tubule and it leads to rapid decline of renal function (i.e. AKI) and presence of granular casts and tubular cells in urine. The damage can be induced by:

1. **Ischemia leading to renal ischemic injury**:

   renal ischemia → reduction in GFR → acute tubular injury/ necrosis. The proximal tubule is most vulnerable to ischemia. [renal ischemia can be caused by any condition that causes prolonged persistent hypovolemia or circulatory shock e.g. extensive trauma, burns, hemorrhage, pancreatitis, incompatible blood transfusions, dehydration, septic shock, etc.]

2. **Substances toxic to the kidney leading to nephrotoxic injury:**

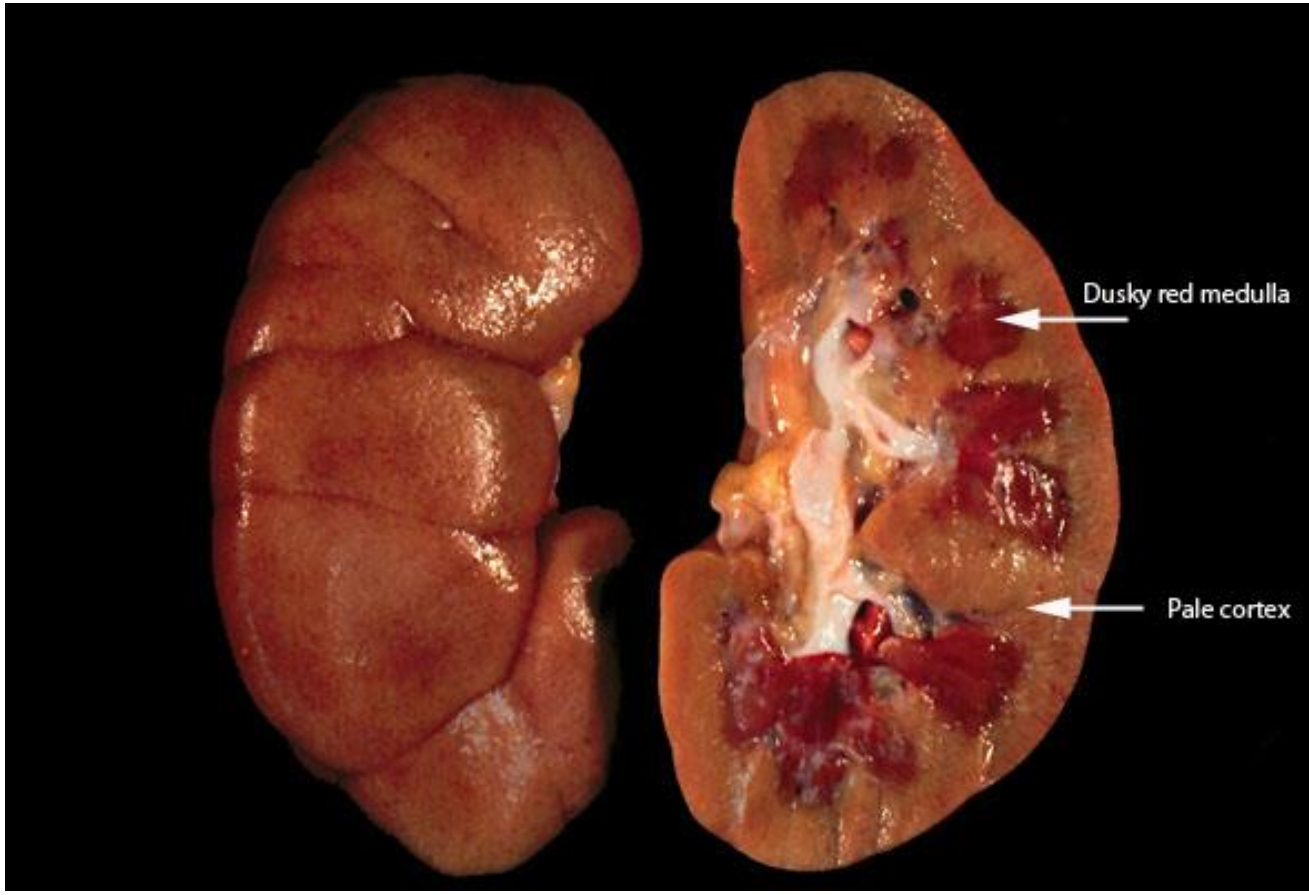
   here the AKI is caused by direct injury of the tubules by toxins. Causes include:

   - Antibiotics: Aminoglycosides, Tetracyclines, Amphotericin, Cephalosporins etc.
   - Heavy metals: Mercury, Lead, Arsenic, Gold salts, Barium etc.
   - Others: Cisplatin, Doxorubicin, Carbon tetrachloride, Radiographic contrast agents, etc.

Acute tubular injury/ necrosis

Gross morphology

- bilaterally enlarged & swollen kidneys (due to edema)
- Cut surface shows a pale cortex and a dark & congested medulla

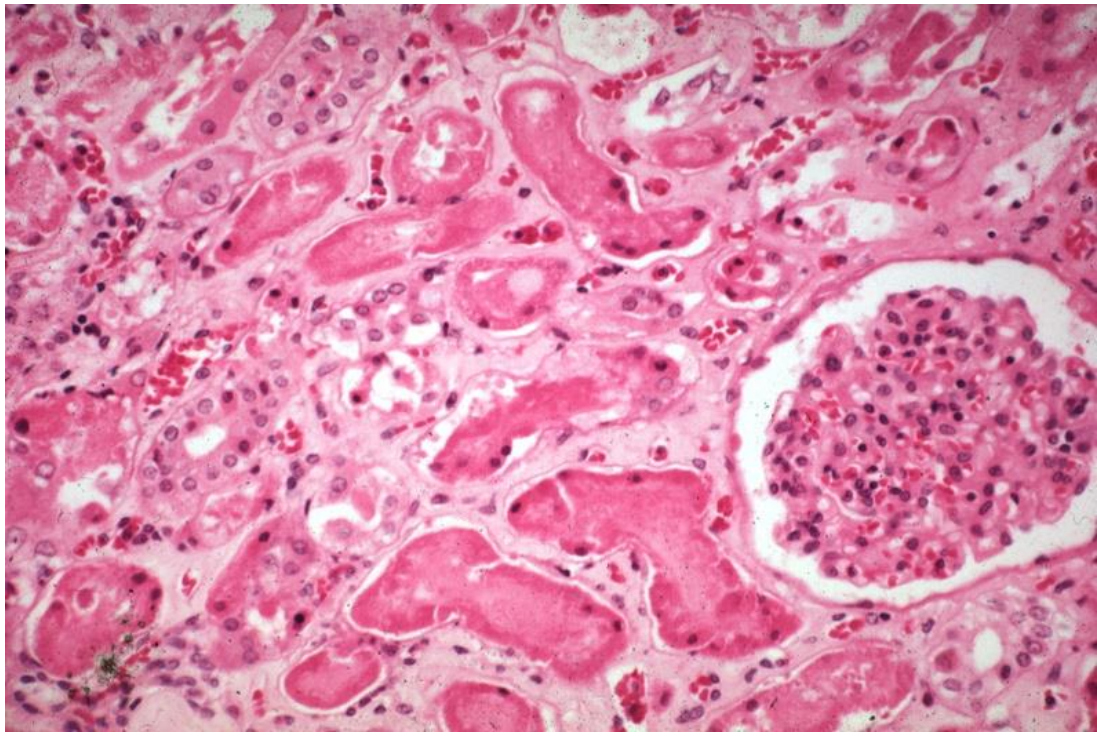


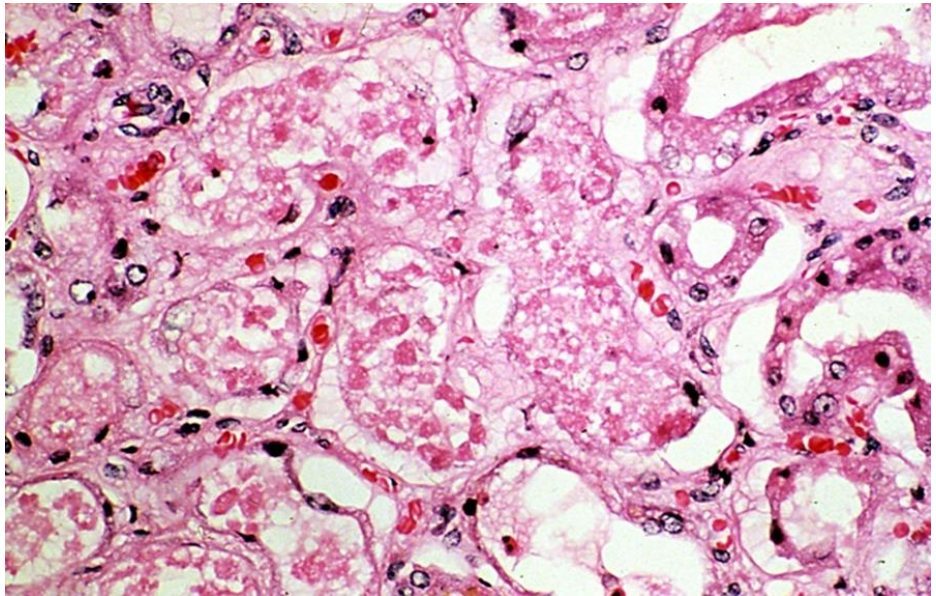
http://pathology.jcu.edu.au/Virtual%20Museum/Images/E.%20Urinary/ER-11.htm

Acute tubular injury/necrosis

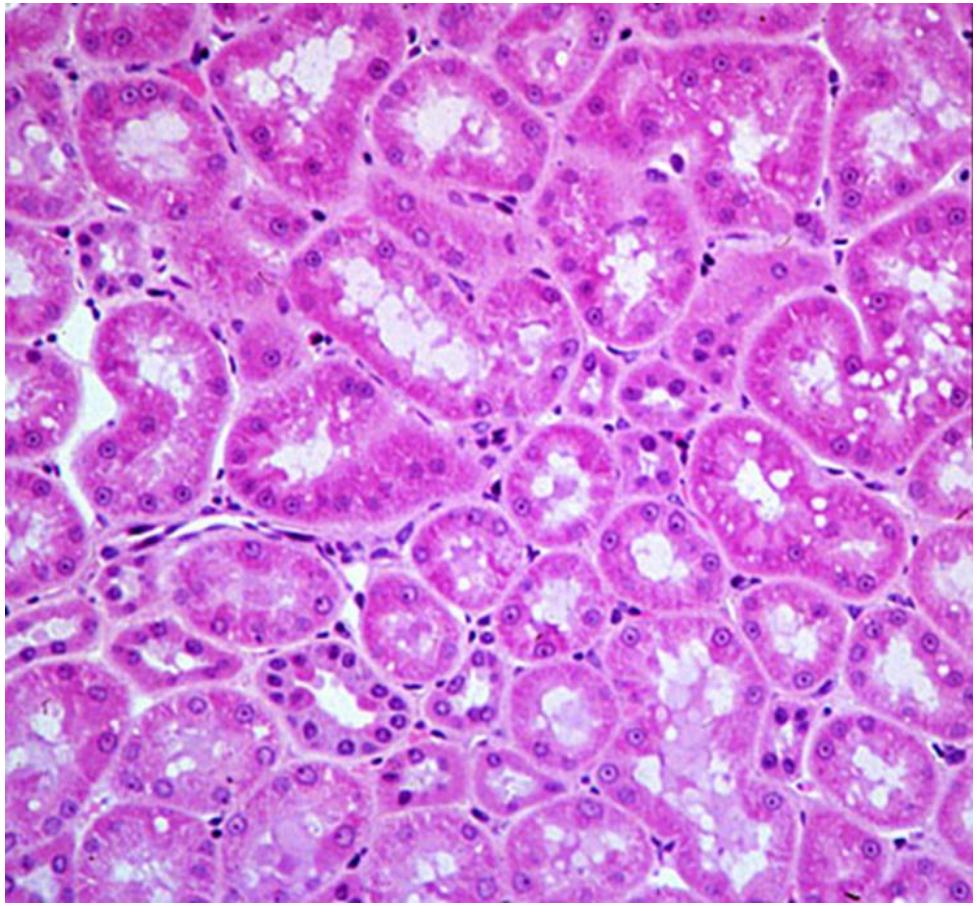
Histology:

- Ranges from tubular epithelial cell swelling (mild injury) to tubular epithelial cell necrosis (severe injury).
- The proximal tubules are dilated with thin of tubular wall.The tubular epithelial cells are flattened and show loss of brush border.
- In necrosis there is loss of nucleus of tubular epithelial cells and sloughing of necrotic cells in the lumen of the tubule.
- Casts may be present in the lumen of the distal tubules.
- Interstitium → mild edema.
- Later as healing begins there is regeneration of the tubular epithelial cells





Normal tubule



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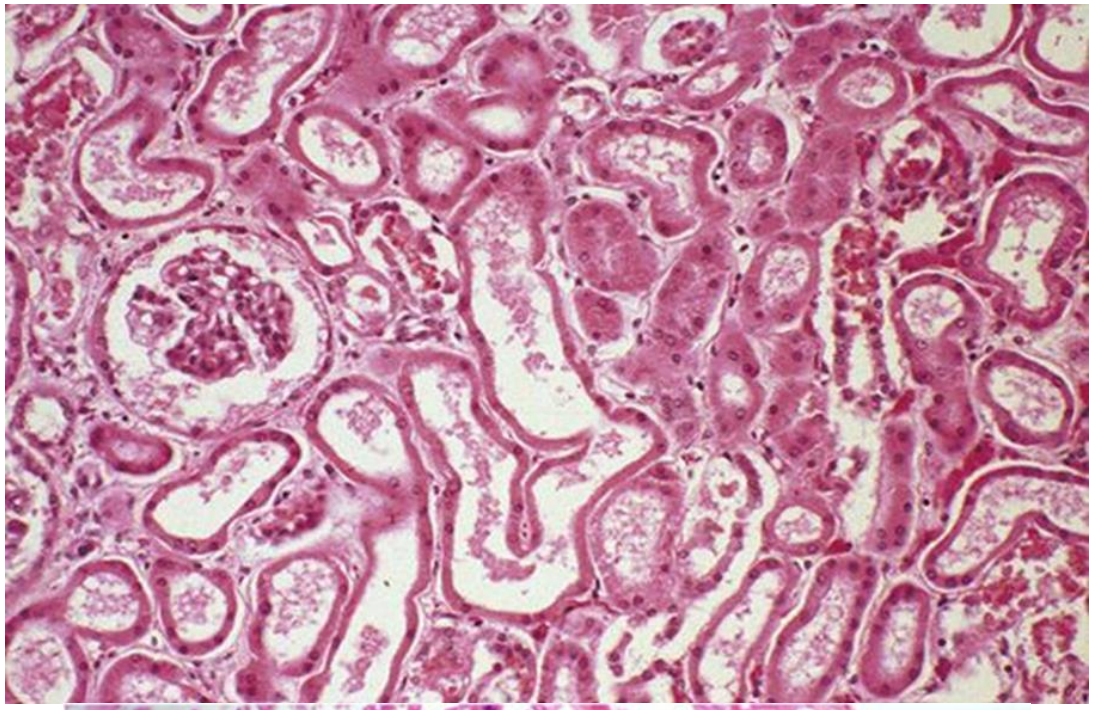
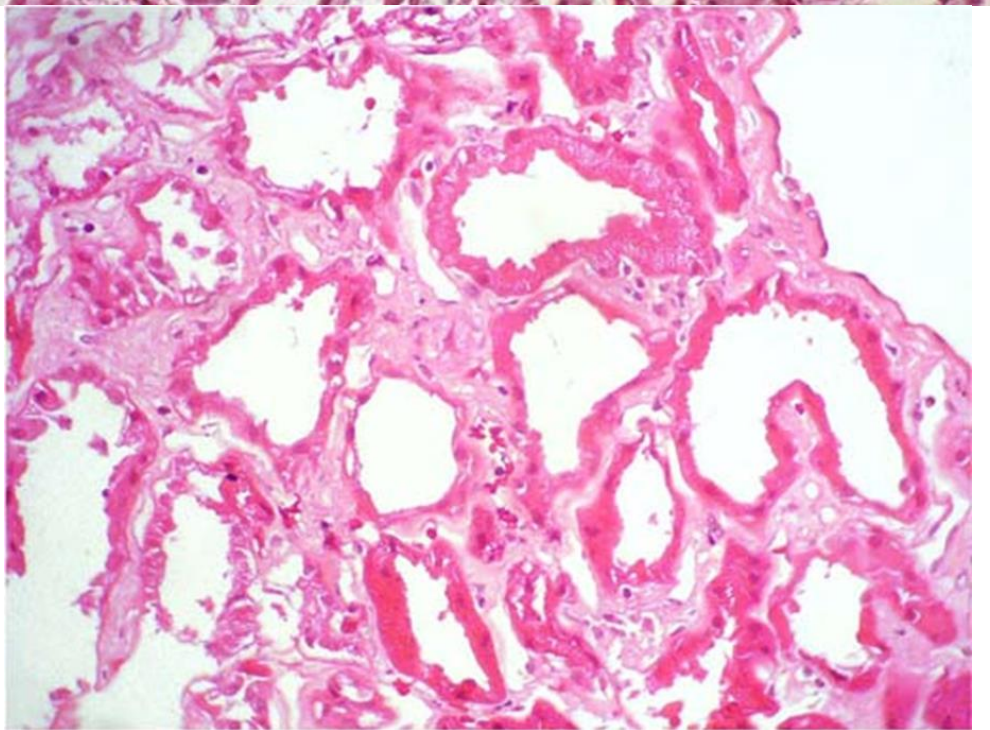


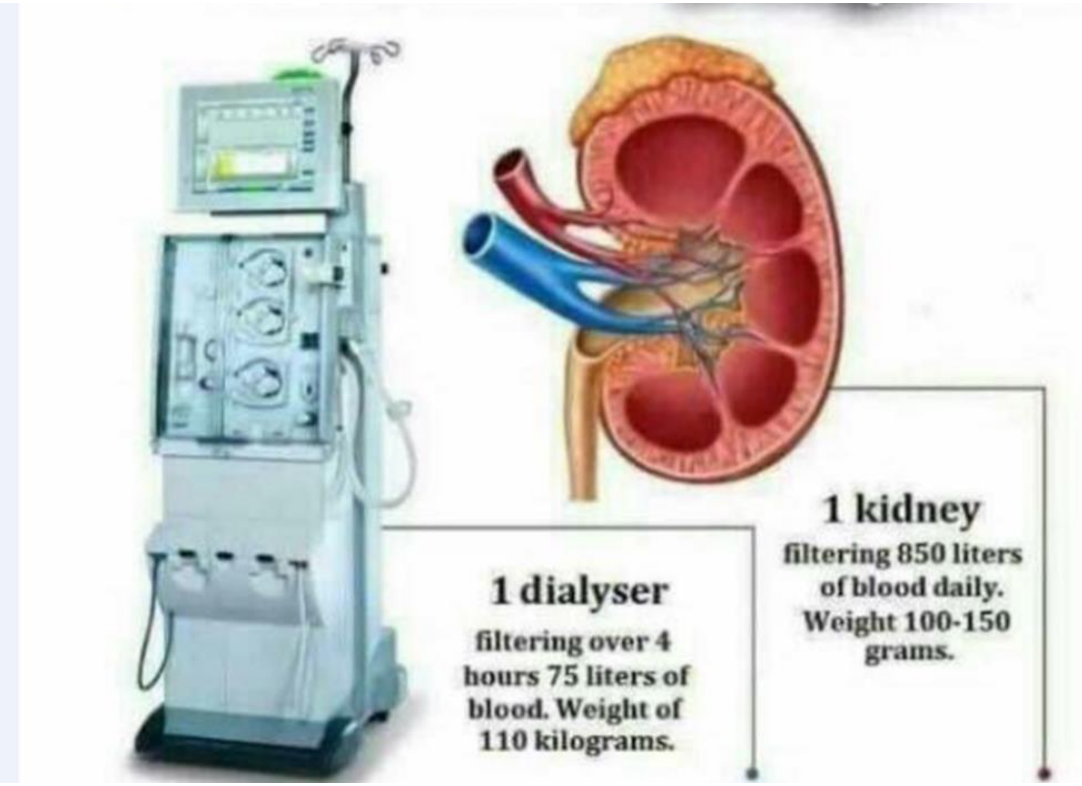


Clinical features of AKI:

- **Oliguria**: Decreased urine output (occasionally urine output remains normal). Typically the urinary output is < 400 ml/day.
- Defective elimination of metabolic waste, water, electrolytes, and acids from the body. Waste material is accumulated in the body which causes azotemia (→ **nausea & vomiting**), acid-base imbalance (→ **acidosis**) and electrolyte imbalance like **hypernatremia and hyperkaliemia** (→ **abnormal heart rhythms, risk of heart failure, weakness and muscle paralysis**).
- Salt and water retention → generalized **edema** starting with swelling in your legs, ankles or feet.
- **Pulmonary edema** (shortness of breath due to extra fluid on the lungs).
- Other features: hypotension, nephritic syndrome, flank pain, fatigue, uremic encephalopathy, confusion, seizures or coma in severe cases
- Sometimes acute kidney failure causes no signs or symptoms and is detected through lab tests done for another reason.

Treatment

- Treat the underlying etiology.
- Dialysis
- Correction of fluid imbalance.
- Correction of acidosis and electrolyte imbalance e.g. hyperkalemia:



Thank you