بسم الله الرحمن الرحيم

Nephritic syndrome

MID | Lecture 4

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﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾

Pathology Lecture
Nephritic syndrome

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Nephritic Syndrome: Presentation

- **PHAROH**
- ***P**roteinuria*
  - *<3.5g/1.73m2/day*
- ***H**ematuria*
  - *Abrupt onset*
- ***A**zotemia*
  - *Increased creatinine and urea*
- ***R**BC Casts*
- ***O**liguria*
- ***H**TN*

Peripheral Edema/Puffy Eyes

Two urine samples showing gross and microscopic hematuria: in Nephritic Syndrome

See next slide

- **P**roteinuria in nephritic syndrome is not as heavy as the proteinuria in nephrotic syndrome. It's usually non-nephrotic range proteinuria meaning that it's less than 3.5g/day.

- **H**ematuria means the presence of RBCs in urine.

- **A**zotemia means increased levels of creatinine and urea in the blood indicating impairment of the renal function.

- **R**ed blood cell casts are an indication of a glomerular origin of the hematuria.

- **O**liguria means decreased urine output also as a manifestation of the renal impairment.

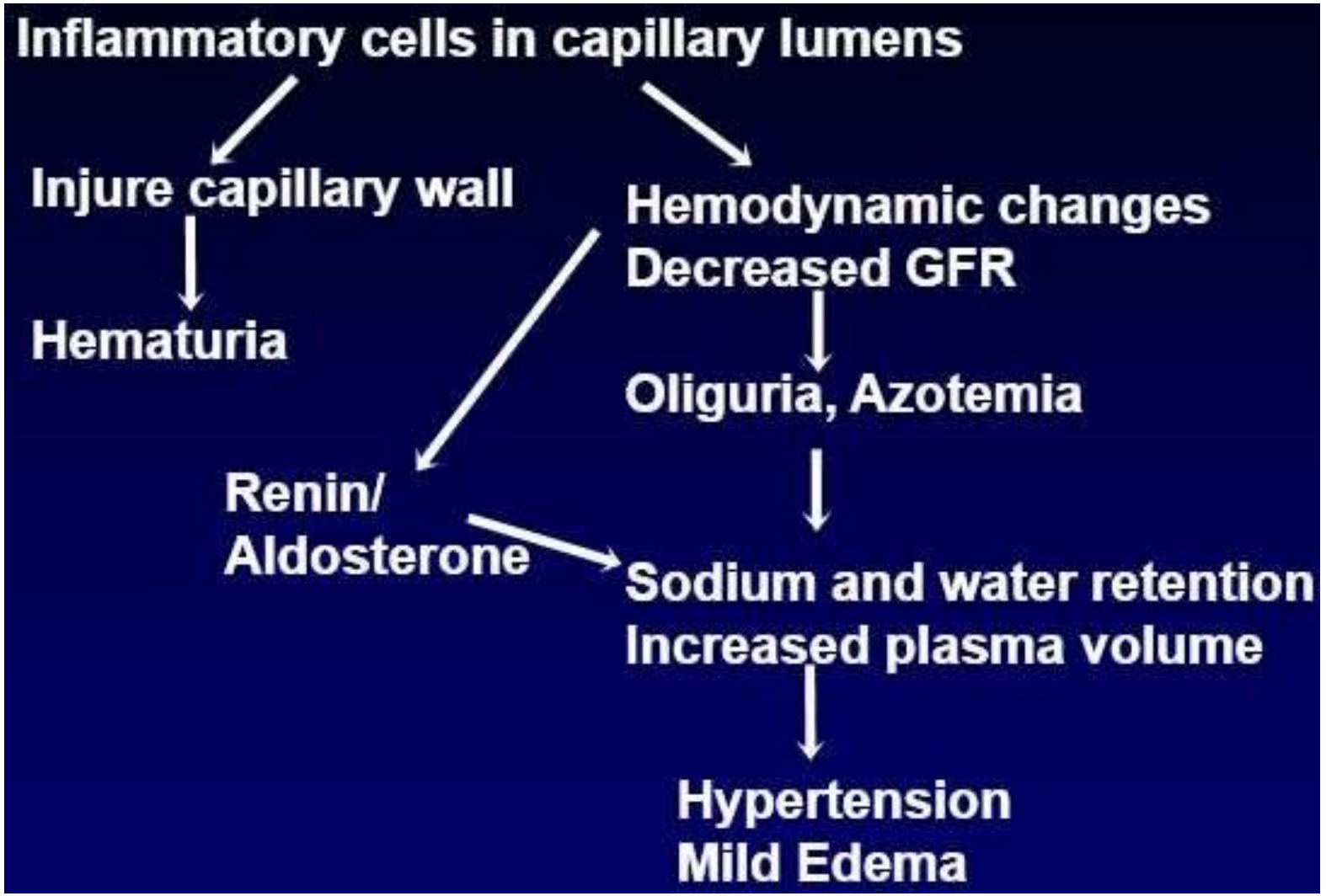
- **H**ypertension is related to the fluid retention and the azotemia.

The Nephritic Syndrome

- Pathogenesis: inflammation (glomerular inflammation)

- **leukocytes infiltration** that will produce different kinds of chemicals that will stimulate the **proliferation of cells in glomeruli.**
- **Injury of capillary walls → escape of RBCs into urine (hematuria & RBC casts).**
- **↓ GFR** (glomerular filtration rate) → **oliguria, fluid retention (edema), and azotemia** (impairment of the renal clearance of toxic substances).
- **Hypertension (result of both fluid retention and ↑renin release from kidneys).**
- **May have some proteinuria.** Not heavy proteinuria as in nephrotic patients

Pathogenesis



Recap regarding the pathogenesis of nephritic syndrome:

- It begins with inflammation within the glomerular capillary lumina. This inflammation, along with the presence of inflammatory cells, leads to injury of the capillary walls, resulting in the escape of red blood cells into the urine, causing hematuria and red blood cell casts.

- At the same time, these changes cause hemodynamic alterations that lead to a decreased GFR. This results in oliguria and azotemia.

- Together with renin and aldosterone axis augmented work, this will lead to sodium and water retention, increased plasma volume and the production of hypertension and edema.

Glomerular diseases mostly presenting with Nephritic syndrome

1- Membranoproliferative Glomerulonephritis (MPGN)

- **Abnormal proliferation of glomerular cells** as well as inflammation
- **Usually nephritic syndrome; some have a combined nephrotic-nephritic picture.**
- **<u>Types of MPGN:</u>**

1 type I (80% of cases)→ immune complex disease (The inciting antigen is not known)

2 type II → ***excessive complement activation***

Type I MPGN

- **circulating immune complexes**
- **Many associations :hepatitis B and C; SLE; infected A-V shunts.**

- Certain circulating **immune complexes** travel through the circulation, reach the kidney, and get deposited inside the glomeruli. When they are deposited there, they elicit an inflammatory reaction.
- This inflammation begins a cascade of changes that leads to the pathogenesis of nephritic syndrome.

Type II MPGN (*dense-deposit disease*)

- ***Cause*: *excessive complement activation***
- **autoantibody against C3 convertase called *C3 nephritic factor* (it stabilizes the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway).**

- **Result: Hypocomplementemia** and consumption of C3.

The activated C3 particles will travel in the circulation, they will reach the glomeruli and get deposited there.

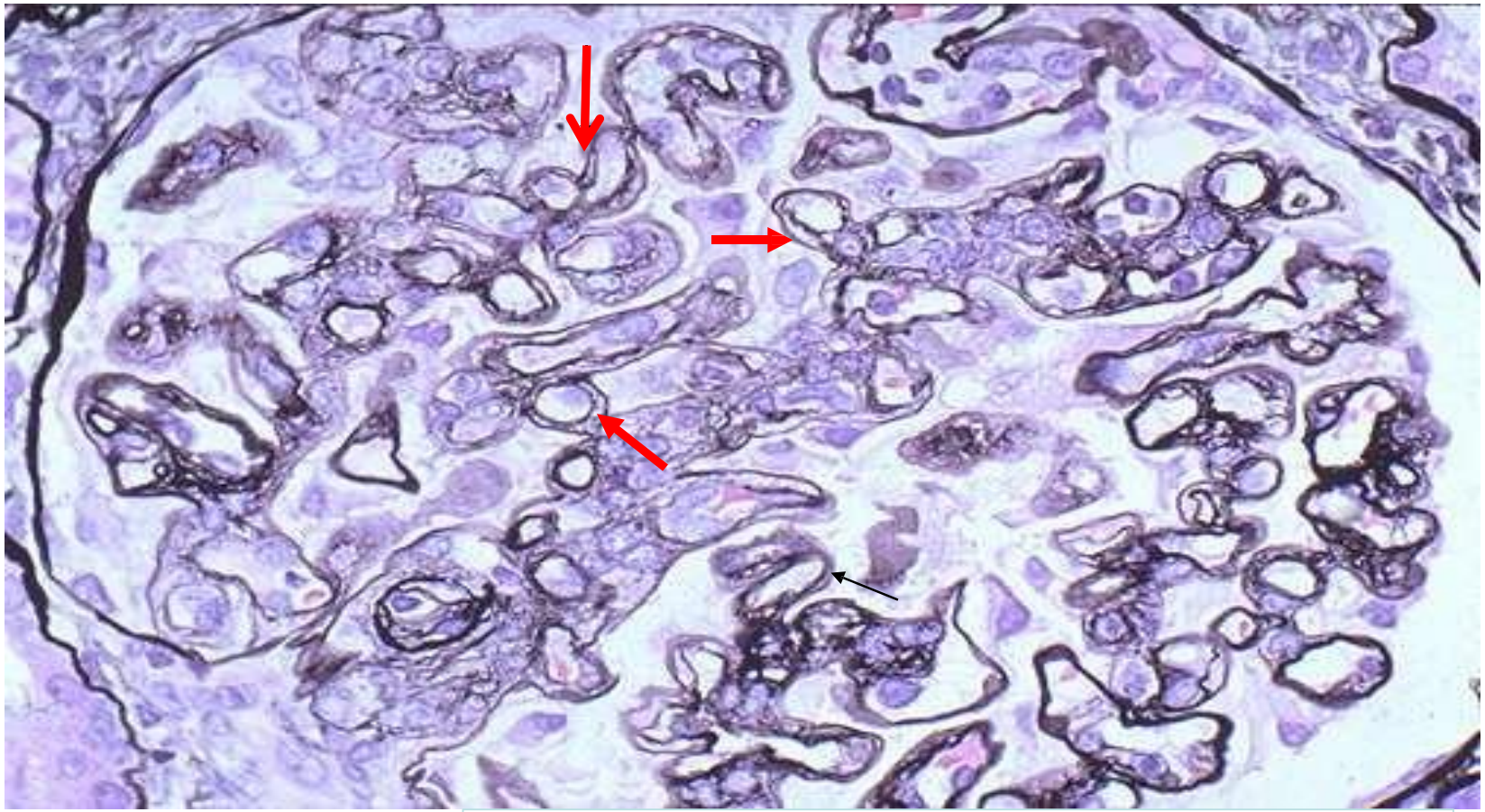
- **Morphology**
- **LM**
- both types of MPGN are similar by LM.
- glomeruli are large with accentuated **lobular appearance** and show **proliferation of mesangial and endothelial cells** as well as infiltrating leukocytes
- **GBM is thickened** because of the inflammation as well as the injury that happens inside the glomerular basement membrane and deposition of immune complexes (**double contour** or **"tram track"**)
- The **tram track** appearance is caused by **"splitting" of the GBM**

GBM= Glomerular basement membrane
LM = light microscope

“tram-track“ appearance

2 parallel lines in the basement membrane instead of one

Double contour of the basement membranes("tram-track") that is characteristic of (MPGN)(arrows).



silver stain: stains basement membranes black

- The black color represents the glomerular basement membrane (GBM), silver stain is used to show us the elastic fibers inside the basement membrane.
- The red arrows show us a double lines of basement membrane instead of a normal single line and this is the double contour or the tram-tracking appearance.

- ✓ Regarding the immunofluorescence test in MPGN, there is a difference between type 1 and type 2.
- ✓ It differs from the light microscopy findings because the pathogenesis is different.

- **IF**

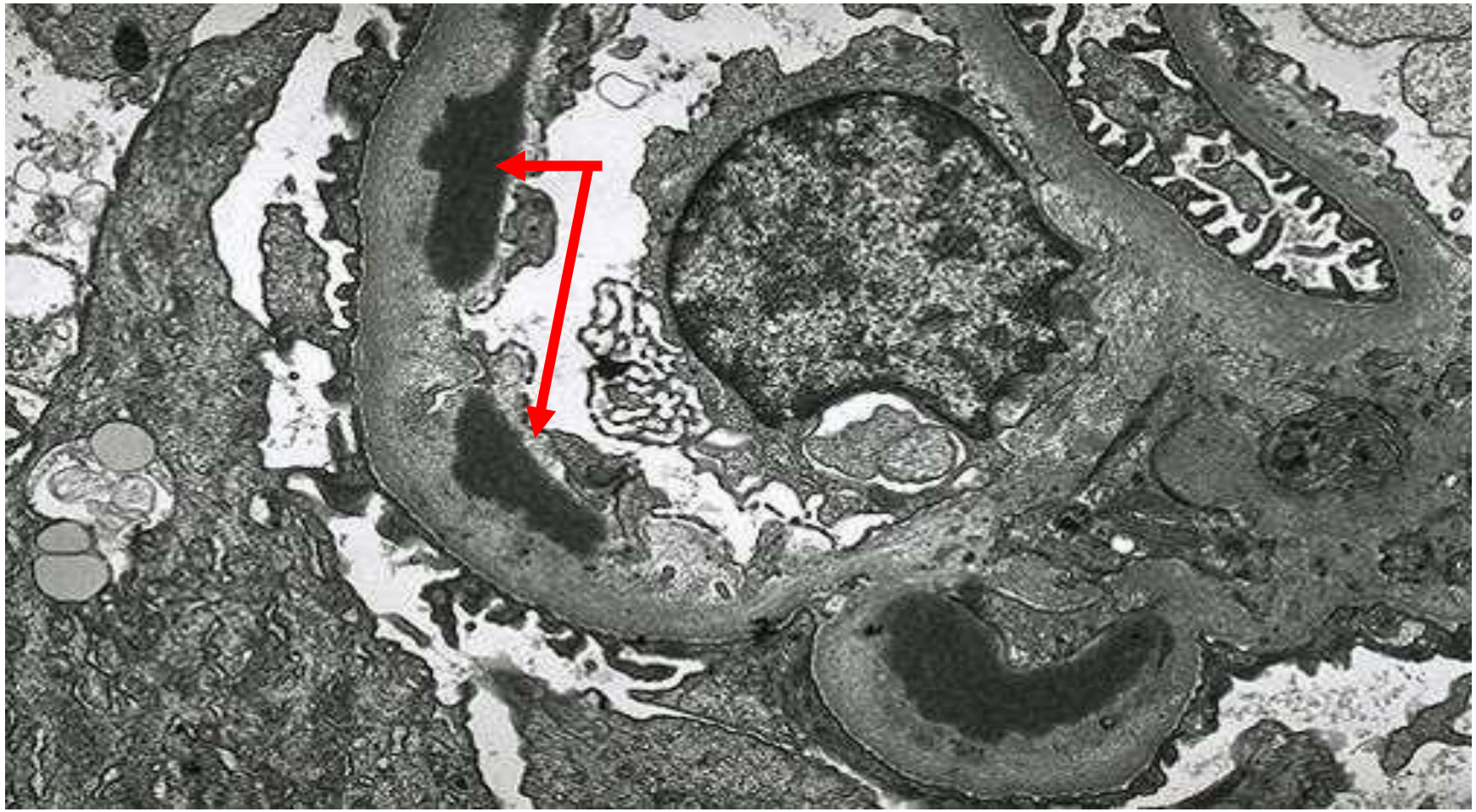
- **Type I MPGN →subendothelial electron- dense deposits (IgG** and **complement C1q and C4)**

  Type 1 MPGN involves the presence of immune complexes in the glomeruli. Therefore, the immunofluorescence test shows a positive reaction for immunoglobulins and complement. There will be subendothelial electron-dense deposits, mainly immunoglobulin G, along with other immunoglobulins and complements such as C1q and C4.

- **Type II MPGN→ C3 alone in GBM**

  In type 2 MPGN, the pathogenesis is related to excessive and abnormal C3 complement activation. Therefore, immunofluorescence shows C3 alone deposited along the glomerular basement membrane.

EM- dense deposits in the basement membrane of MPGN type II in a ribbon-like mass (arrows)



- The red arrows here shows us some dense immune deposits within the basement membrane in this case of type 2 MPGN and there is some ribbon-like mass formation.
- Because the color of these deposits is very dark and dense it was called dense deposit disease.
- These deposits are composed of C3 without immunoglobulins.

- ***Clinical Course***
- prognosis poor.
- No remission.
- 40% progress to end-stage renal failure.
- 30% had variable degrees of renal insufficiency.
- **Dense-deposit disease (type II) has a worse prognosis.**
- **It tends to recur in renal transplant recipients**
  - ➢ It tends to recur because the problem is within the immune system of the patient not inside the glomeruli themselves.

2- Acute Postinfectious (Poststreptococcal) Glomerulonephritis (PSGN)

- deposition of **immune complexes** and inflammation + proliferation of glomerular cells and leukocytes (neutrophils)
  - The main inflammatory cells in this condition are the **neutrophils**.

- Not **direct** infection of the kidney

- Cause: an immune-mediated reaction to a previous infection of pharynx or skin
- most commonly, **Post-streptococcal** infection
- Infections by other organisms also possible as pneumococci and staphylococci

Poststreptococcal GN (PSGN)

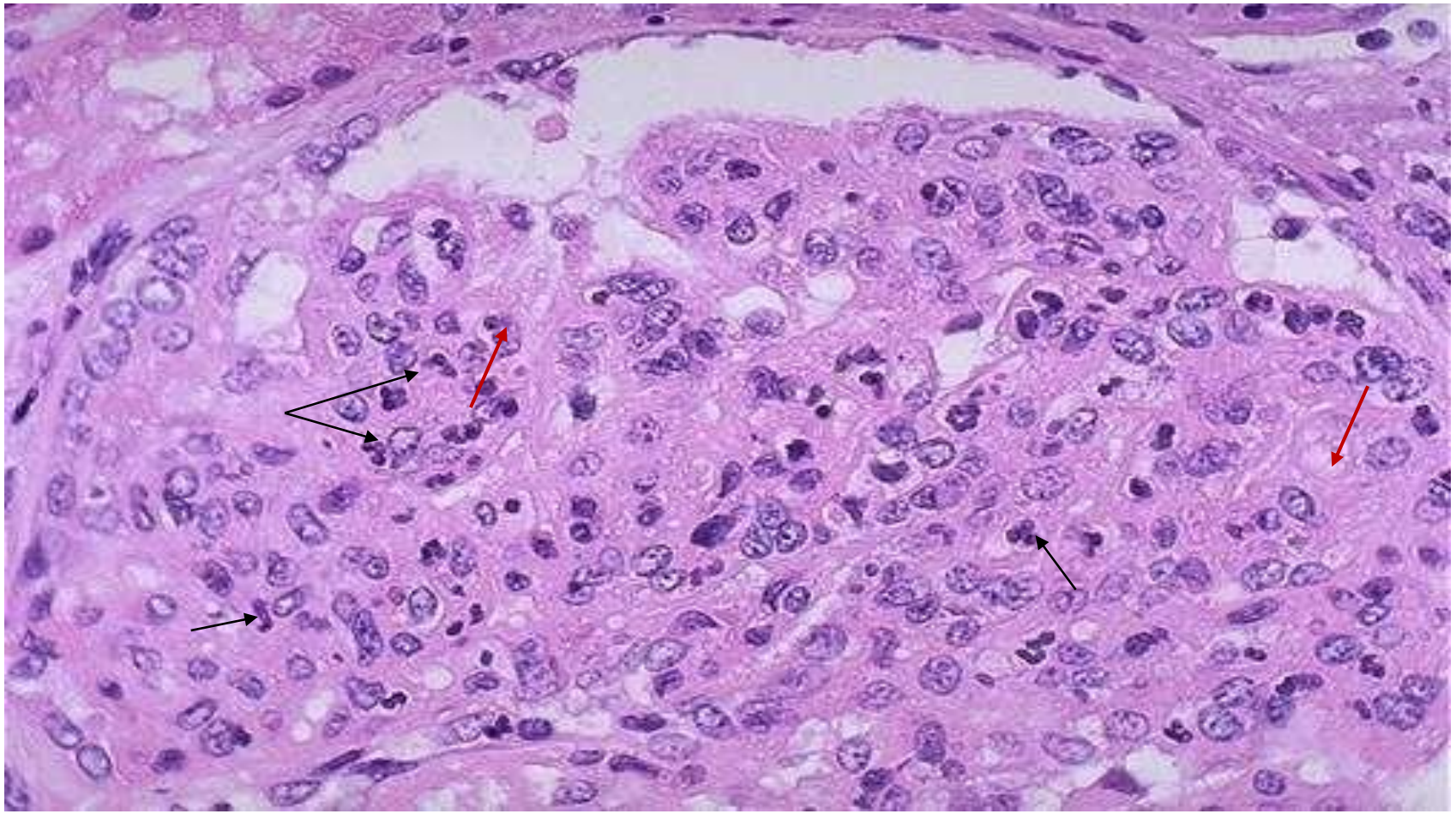
- 1-4 wks after recovery from a group A streptococcal infection (pharynx or skin), the Patient starts to develop clinical manifestations related to the glomerular inflammation)
- A few strains (3%)of β-hemolytic streptococci are capable of this (Not all streptococcal strains can produce this condition.)
- **Mechanism: binding of immune complexes to GBM proteins (**Immune complexes formed against streptococcal antigens get deposited in the **glomerular basement membrane)**

- **or antibodies to bacterial antigens "planted" in the GBM**

Regardless of the mechanism :
→ This will lead to activation of inflammatory cascades within the glomeruli
→ Resulting in a nephritic picture.

PSGN: increased epithelial, endothelial, and mesangial cells as well as neutrophils in and around the capillary loops (arrows)

(The presence of all these cells inside the glomerulus causes crowding within the glomerular tuft and occlusion of the capillary lumen.)

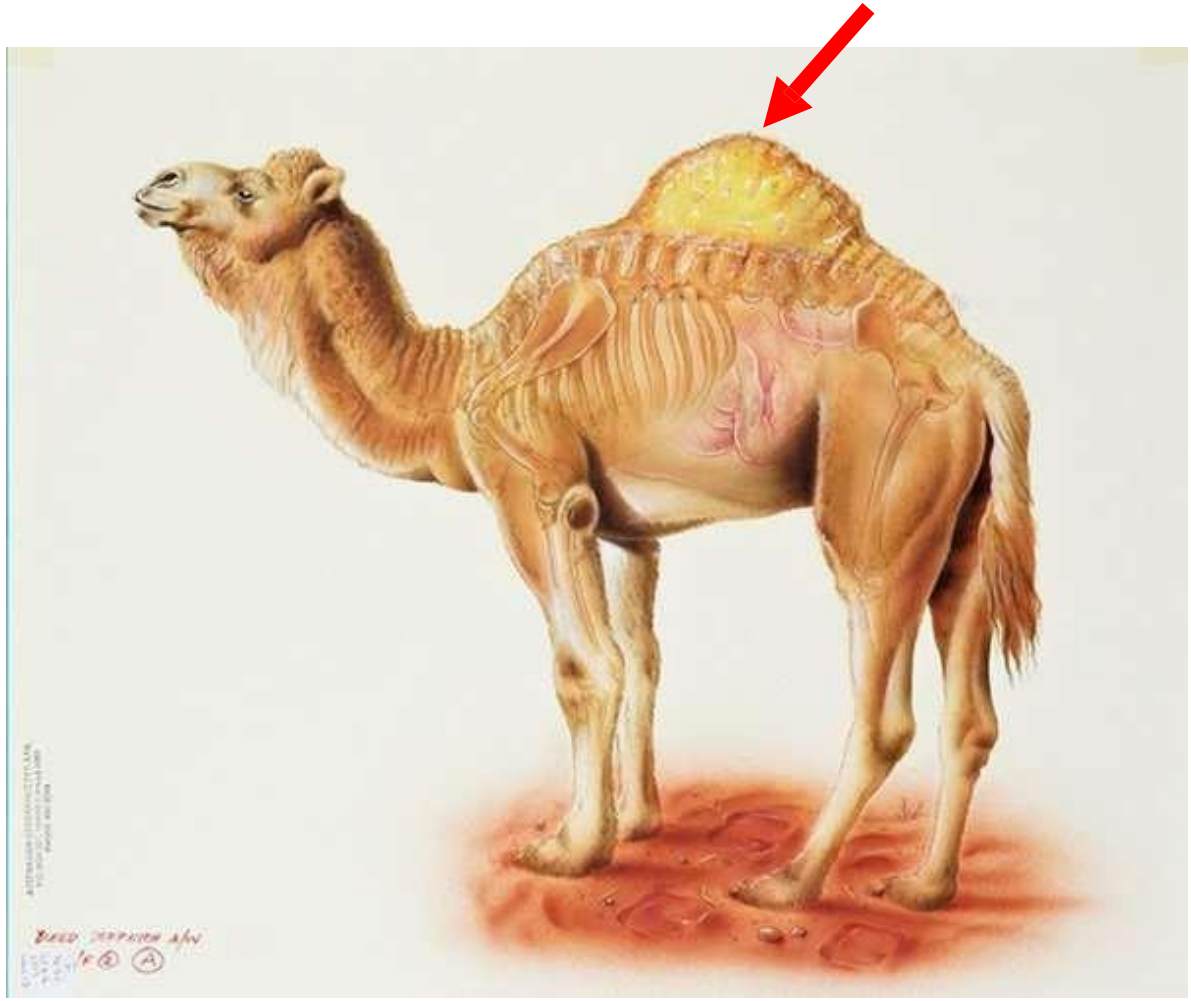


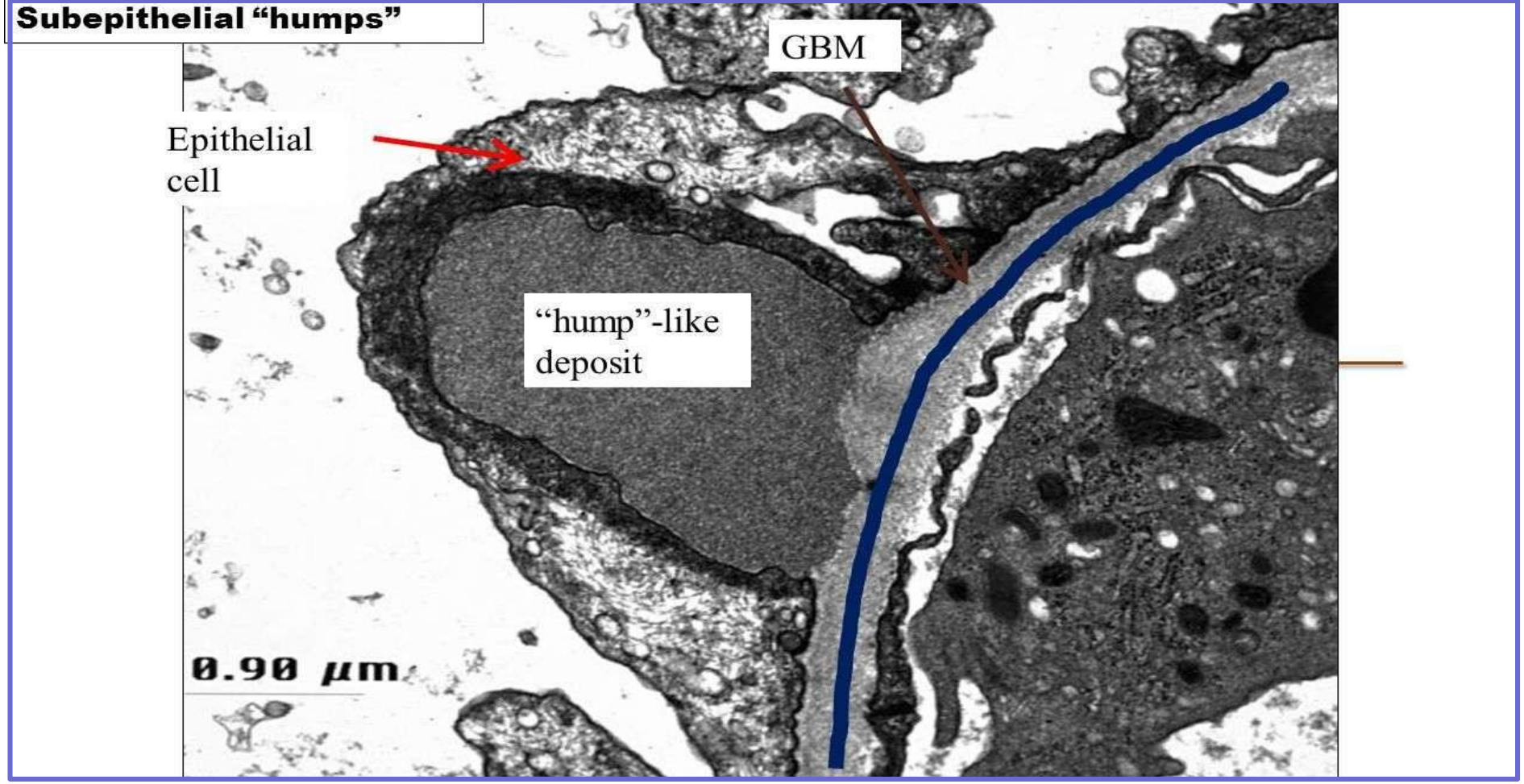
- This is light microscopic picture from glomerulus That is Affected by PSGN
- The black arrows indicate increase in the inflammatory cells which are neutrophils

The red arrows indicates the presence of glomerular cells

- **LM**
- proliferation of endothelial and mesangial cells and neutrophilic infiltrate.
- **IF (immunofloruscense test)**
- **deposits of IgG and complement** within the **capillary walls** (Because the pathogenesis involves inflammation with immune complex formation and deposition in the glomeruli, IgG and complement are detected along the capillary walls, IF test is positive .)
- **EM**
- immune complexes inside sub epithelial zones forming "**subepithelial "humps"** in GBM.

Hump





An electron microscopic image from a case of PSGN shows subepithelial humps, (that look like the humps of The camel) . They are located just beneath the podocytes on the GBM(as indicated by the brown arrow), so they are sub epithelial in the location . These findings are characteristic of post-infectious glomerulonephritis.

These deposits show IgG and C3 positivity on immunofluorscence

Look at the humps of the camel in the previous slide.

PSGN- Clinical Course

- **acute onset .**
- **Many of patients are children**
- **fever, nausea, and nephritic syndrome.**
- **gross hematuria.**
- **Mild proteinuria.**

Serum complement levels are low during the active phase of the disease.

Serum hypocomplemetnemia: Serum complement levels are decreased(mainly c3) , indicating activation of the complement system, mainly via the alternative pathway.

- **↑serum anti-streptolysin O antibody titers.**

(Higher serum levels of anti-streptolysin O or other streptococcal antibody titers indicate prior streptococcal infection, and confirms the diagnosis of PSGN.)

- **Recovery occurs in most children.**

The pathogenesis is due to an abnormal immune response with antibody production, which are later cleared from circulation, leading to recovery in most cases.

3- 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 then recur every few months.

***The Clinical* scenario :**

A child or young adult who usually presents with hematuria. The hematuria may be microscopic or gross, and it typically appears within **1–2 days** following a nonspecific upper respiratory tract infection.

Pathogenesis

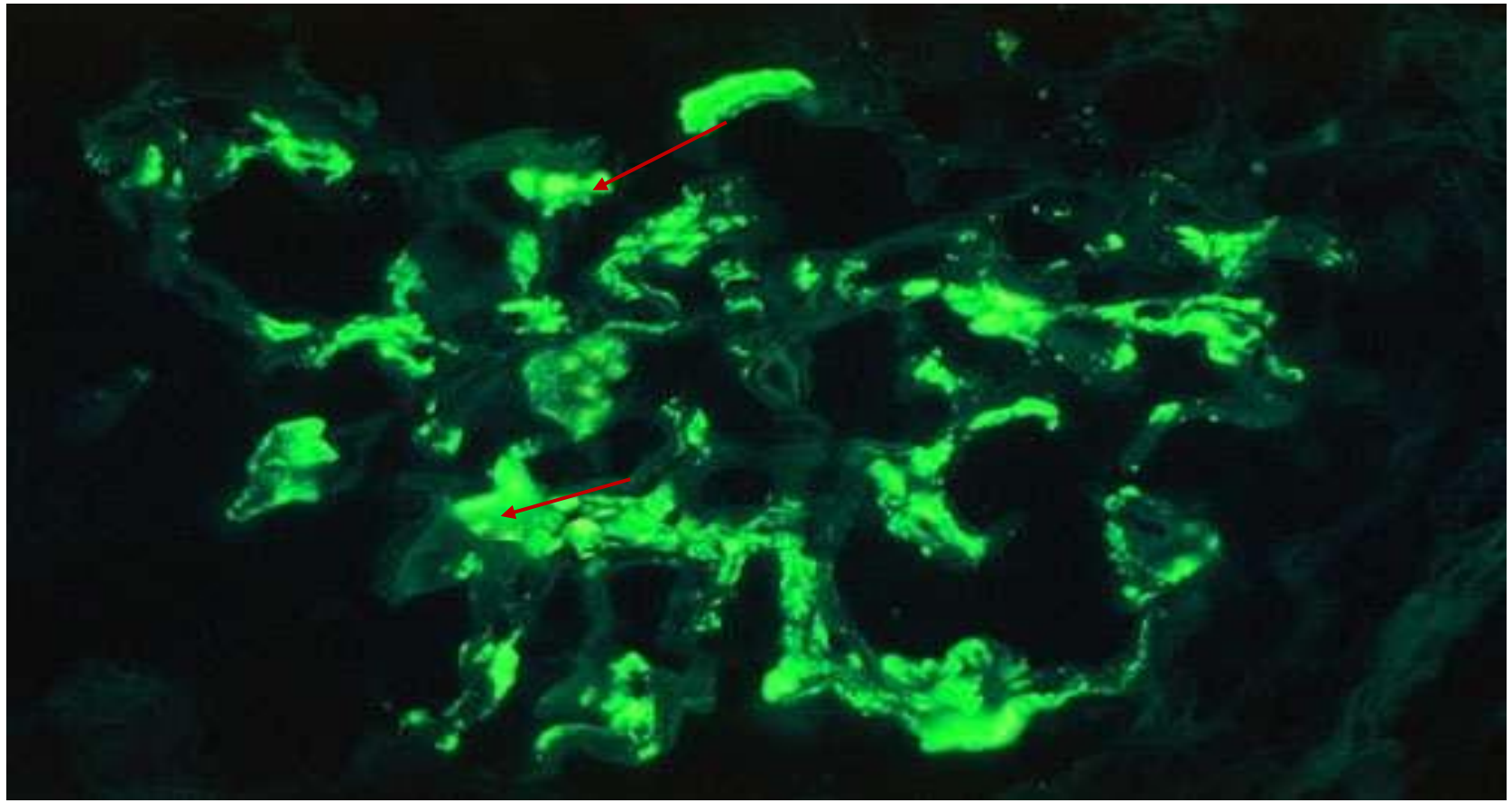
- **abnormality in IgA production and clearance.**

- **LM: variable**
- **IF: mesangial deposition of IgA** with C3 (The immunofluorscence is Very characteristic and we need to memorize it)
- **EM:** deposits in the mesangium

LM : light microscope
IF :immunofluorscence
EM : electron microscope

IF : IgA mesangial staining.

An immunofluorescence image representing a case of IgA nephropathy. The green fluorescent areas (indicated by the arrows) represent the mesangium within the glomeruli. These areas show positive fluorescence due to IgA deposition,which becomes visible when antibodies against IgA are used



- After studying nephrotic and nephritic syndromes ,the most effective way to review these conditions is by using a table like this.

Disease	Usual Presentation	Age	LM	IF	EM	Prognosis
MCD	nephrotic	Children	none	negative	Effaced foot processes	good
FSGS	nephrotic	adults	Segmental sclerosis	negative	Effaced foot processes	Progressive
MNP	nephrotic	adults	Thickened GBM	IgG+ C3+	Sub-epithelial spikes and domes	Progressive
MPGN-type1	Nephritic/ nephrotic	adults	Tram track	Ig s	Subendothelial deposits	poor
MPGN-type2	Nephritic/ nephrotic	adults	Tram track	C3+	Dense deposits	poor
IgA nephropthy	nephritic	Children, young adults	variable	IgA+	Mesangial deposits	variable
PSGN	nephritic	children	hypercellularity	IgG+ C3+	Subepithelial deposits (humps)	good

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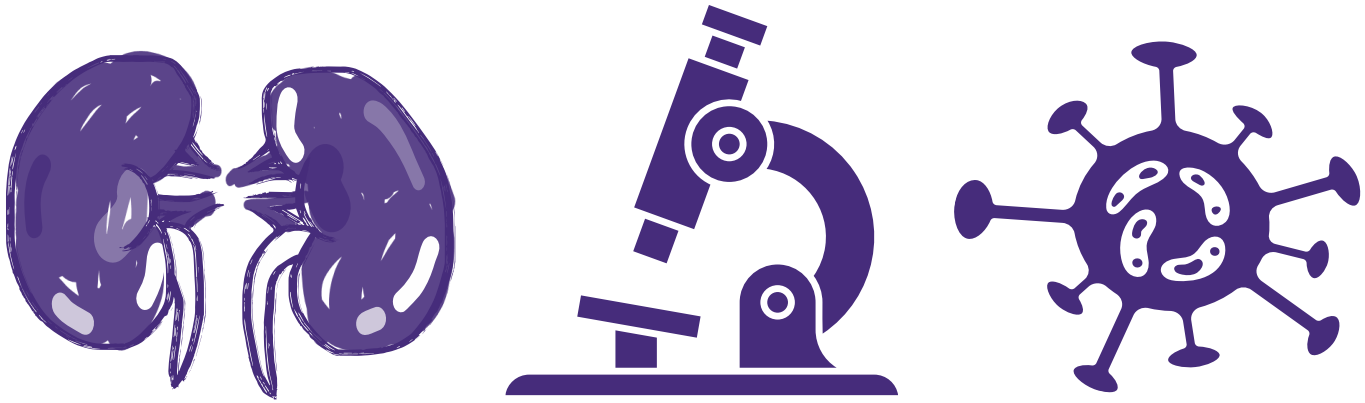

PATHOLOGY QUIZ

LECTURE 4

External Resources

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