MEDICINE
KING SAUD UNIVERSITY

Revised by
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Renal Block

Lecture One

Immune Complex Nephritis

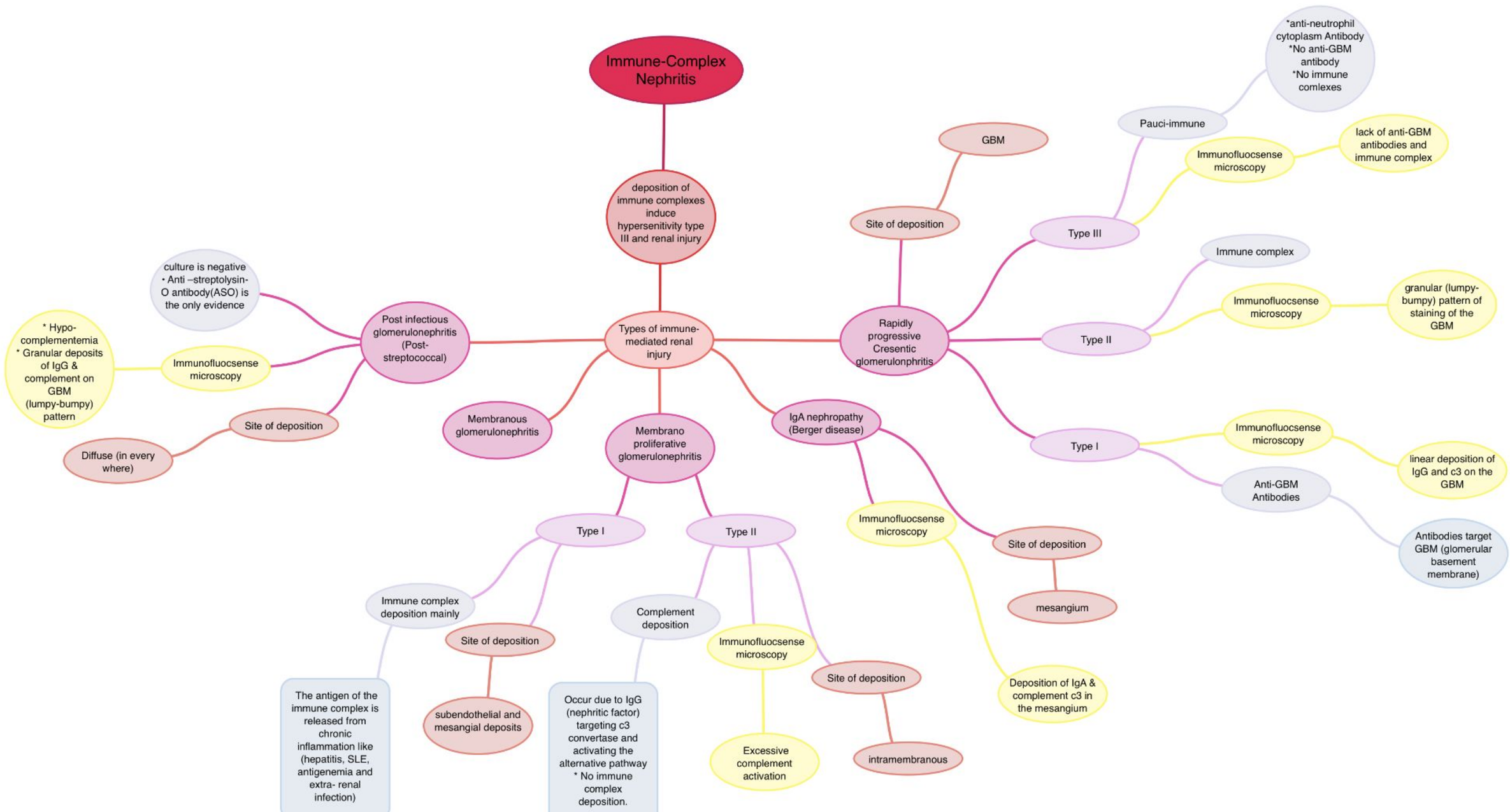
IMMUNOLOGY
436's TEAMWORK

Objectives:

- Understand the importance of **immune complexes** in the **pathogenesis** of renal injury.
- Learn that immune complexes form **in the circulation and may deposit** in different tissues.
- Understand the **dynamics of deposition** of complexes which depend on the size and rate.
- Identify the different types of **renal disease based on the site** of deposition of the immune complexes.

- **Important.**
- **Extra notes.**
- **Doctors' notes**

Before you start, please note that in order to get the concept of immune-mediated renal injury please watch all the videos we've added. they are must-see!



Recall: types of hypersensitivity

Descriptive	Name	Cause	Time Course	Characteristic Cells Involved
Type I	Immediate hypersensitivity	IgE on sensitized cells' membranes binds antigen, causing degranulation	Seconds to minutes	Mast cells, basophils, and eosinophils
Type II	Cytotoxic hypersensitivity	Antibodies and complement lyse target cells	Minutes to hours	Red blood cells
Type III	Immune complex–mediated hypersensitivity	Nonphagocytized immune complexes trigger mast cell degranulation	Several hours	Neutrophils
Type IV	Delayed hypersensitivity	T_C cells attack the body's cells	Several days	Activated T cells

I = Allergic Anaphylaxis and Atopy

II = antiBody

III = immune Complex

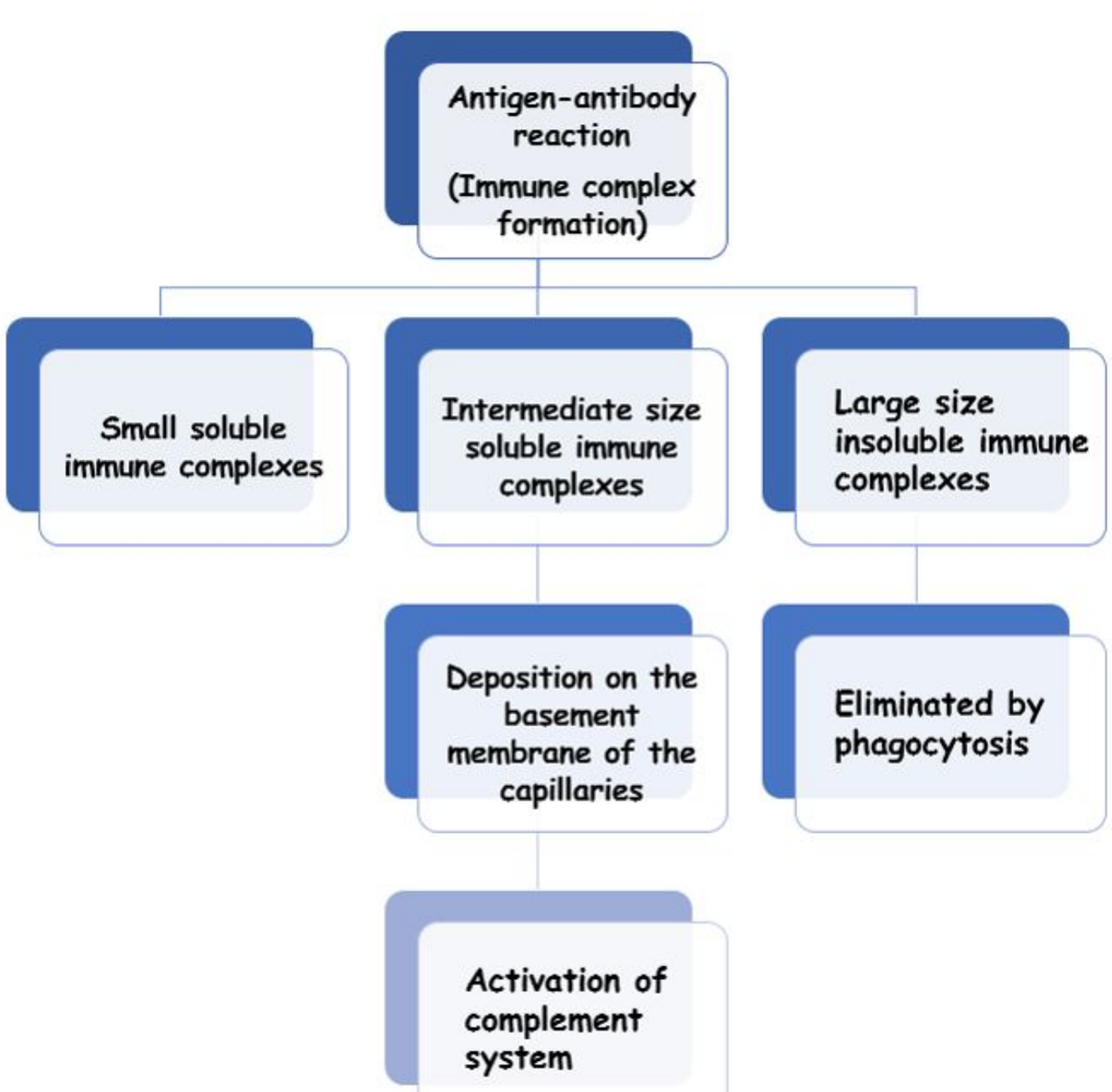
IV = Delayed

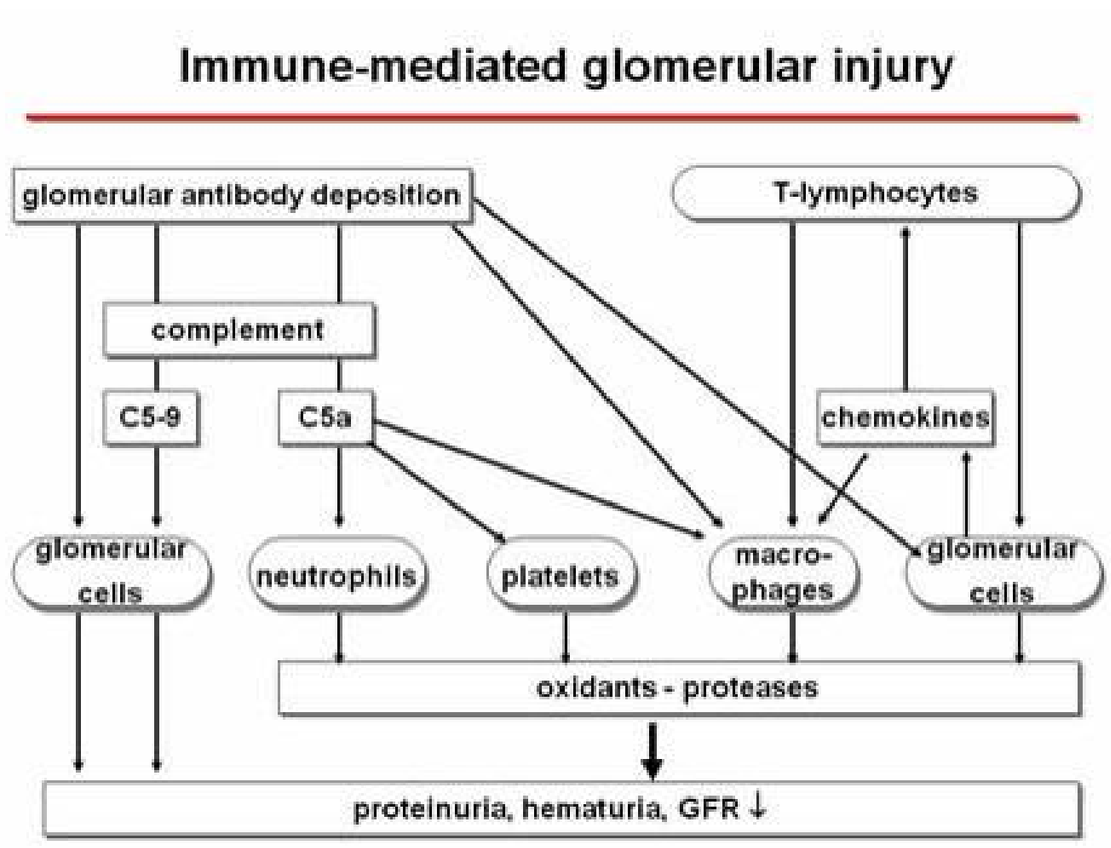
Very quick review for type III hypersenetivity

Pathogenesis of Immune-Complex Nephritis

(Type III hypersensitivity reactions)

Complexes of **antibody** with various **microbial** or **self antigens** induce type II or **III hypersensitivity** reactions in the kidney.



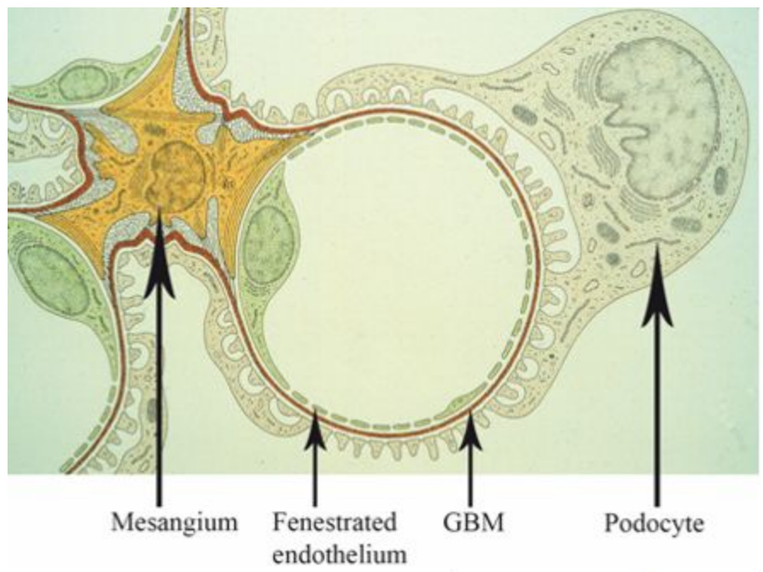


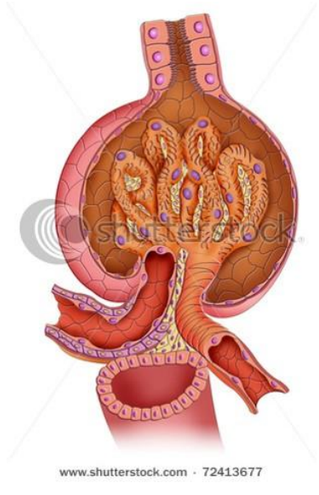
Site of Deposition:

- Complexes accumulate in tissues where **filtration** of plasma occurs.

  This explains the high incidence of:

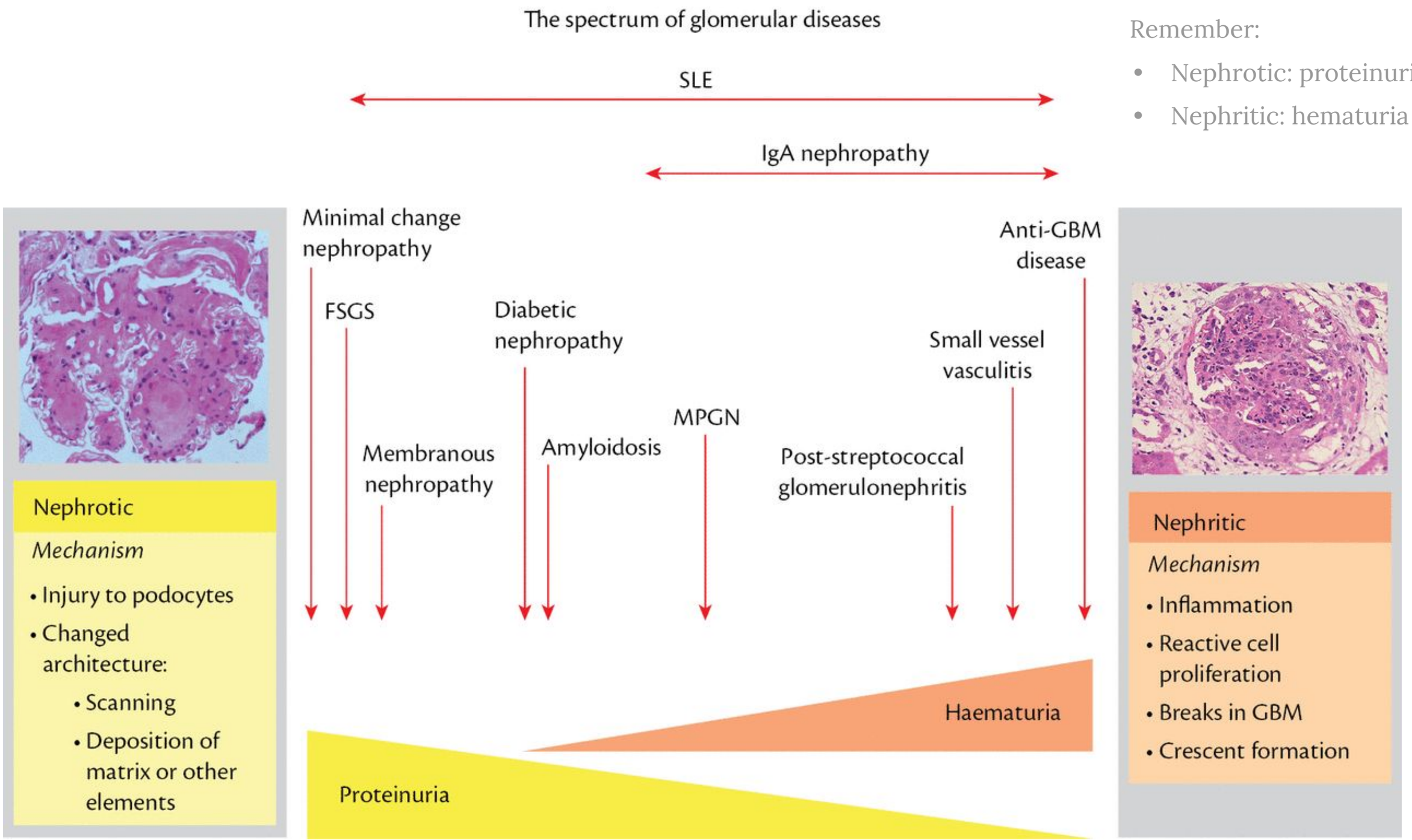
  - Glomerulonephritis (deposition in the **kidney**)
  - Vasculitis (deposition in the **arteries**)
  - Arthritis (deposition in the **synovial joints**)

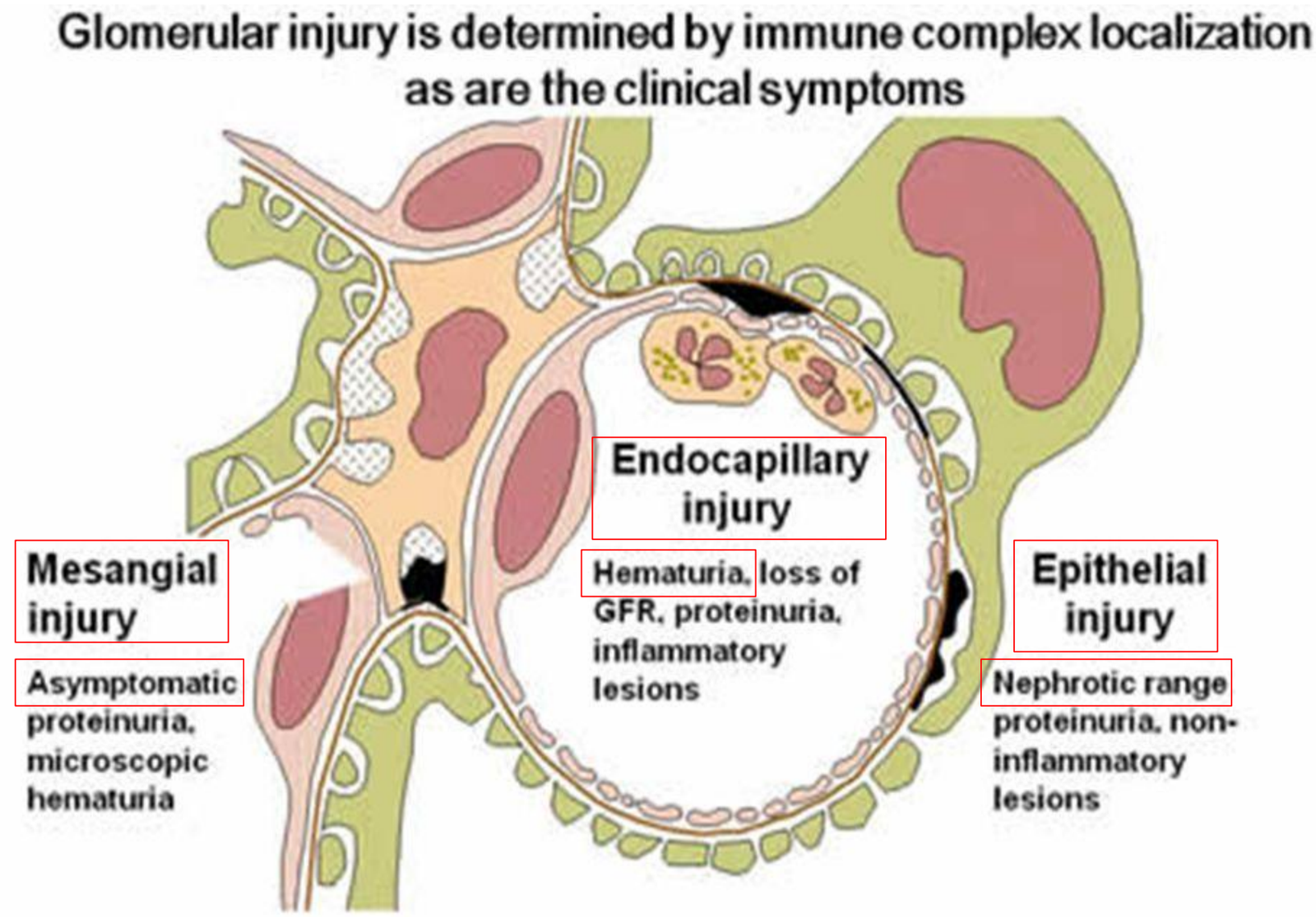




Remember:

- Nephrotic: proteinuria
- Nephritic: hematuria





Types of Immune-Mediated Renal Injury

- Antibody-mediated Injury:

  1- Post infectious glomerulonephritis (nephritic syndrome)

  2- Membranous glomerulonephritis (nephrotic syndrome)

  3- Membranoproliferative glomerulonephritis (nephrotic syndrome and could be nephritic)

  4- IgA nephropathy (nephritic syndrome)

  5- Antiglomerular basement membrane disease (nephritic syndrome)

1- Post Infectious Glomerulonephritis (GN)

Postinfectious Glumerulonephritis

(Post-streptococcal)

Presentation:

- 7-14 days after **pharyngitis.**
- 14-21 days after **(skin infection)**
- Abrupt onset **(Acute nephritic syndrome)**
- Strep antigens trigger antibodies that cross-react to glomeruli
- Circulating immune complexes during filtration in the glomerulus deposit in the kidney
- Immune complexes activate complement

Poststreptococcal GN:

- Caused by known streptococcal types called: **nephritic strains**
- In most children bacterial culture will be **negative**
- Anti –streptolysin-O antibody(ASO) will be the only evidence → ASO=blood test to measure antibodies against streptolysin O which is an enzyme produced by streptococcus
- The anti-DNAse B titre is a **better** indicator of streptococcal skin sepsis than the ASO titre.
- Cholesterol and lipids in skin suppress the ASO antibody response but **not** the anti-DNAse B antibody titre.

Features of Acute Glomerulunephritis:

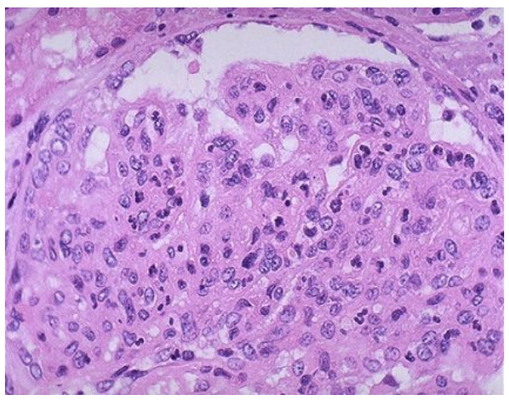
1- Diffuse proliferative GN (PGN) : Diffuse proliferation of glomerular cells and frequent infiltration of leukocytes (especially neutrophils) in light microscope, there is increased cellularity caused by both proliferation and swelling of endothelial and mesangial cells and by infiltrating neutrophils and monocyte.

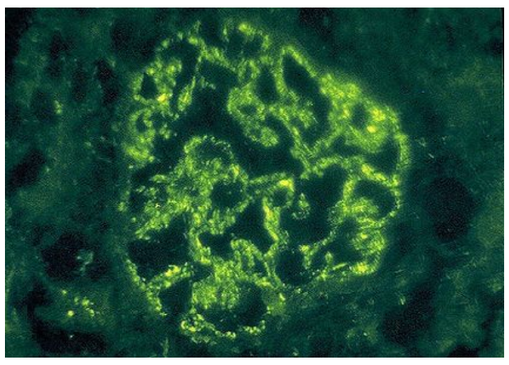
2- Typical features of immune complex disease:

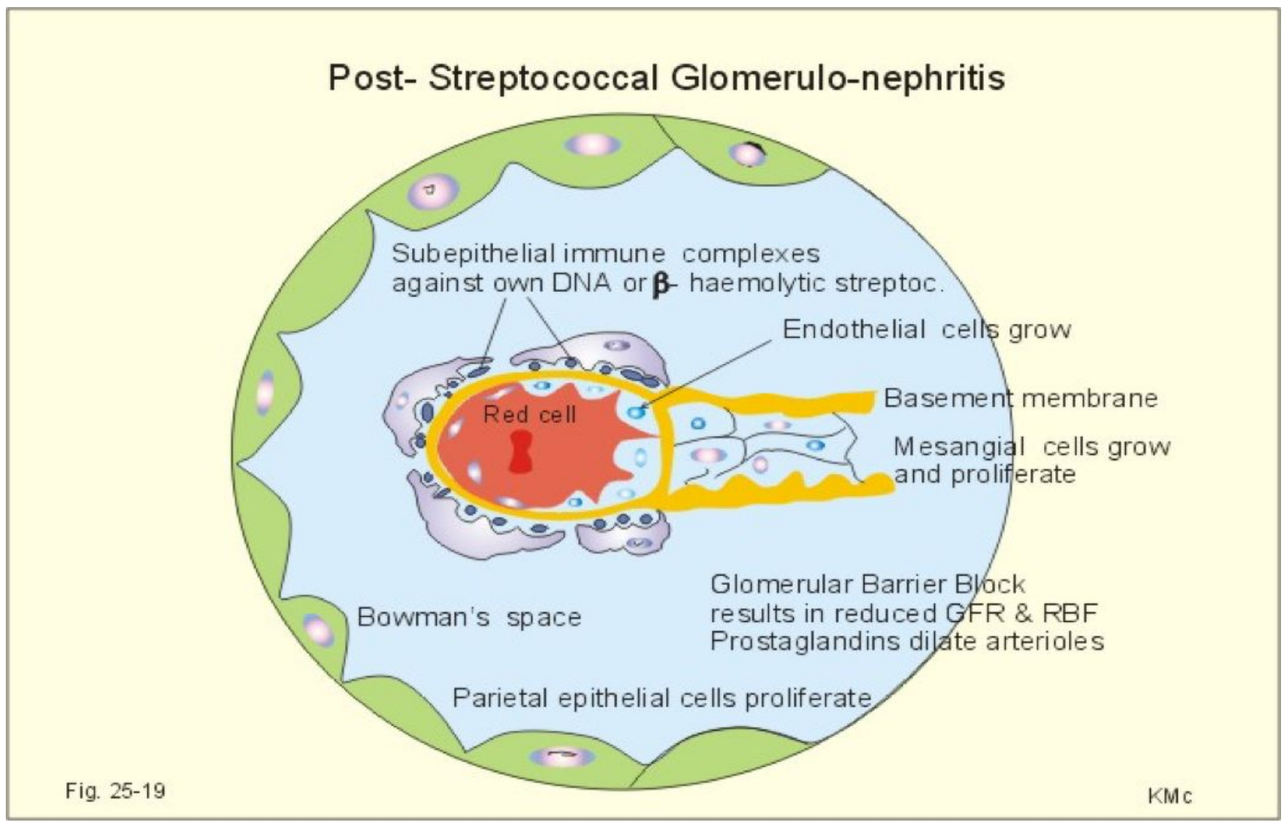
- Hypocomplementemia (decrease in c3 and c4)
- Granular deposits of IgG & complement on GBM

Post streptococcal GN. Diffuse Proliferative GN

(Generalized damage to glomeruli)





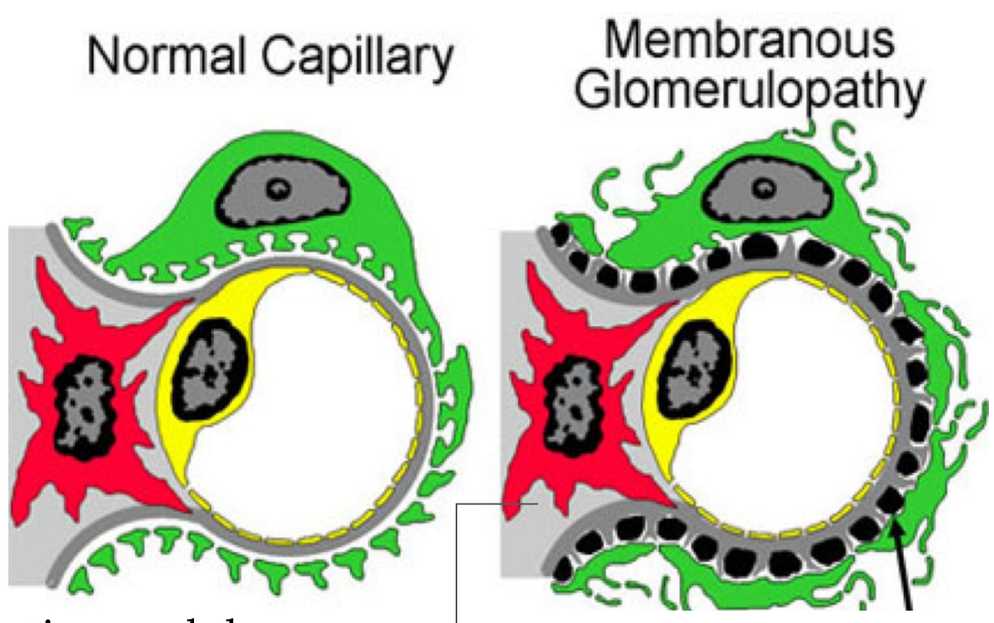


The immune deposits are distributed in the capillary loops in a granular, bumpy pattern because of the focal nature of the deposition process.

2- Membranous Glomerulonephritis

(Membranous nephropathy)

Membranous glomerulonephritis



- A **slowly** progressive disease
- A form of **chronic** immune-complex nephritis
- Most common between **30 - 50 years**
- Most **common cause** of primary **nephrotic** syndrome in Caucasian adults above 40 years
- **60%** of cases are **primary** whereas the remaining cases are secondary to conditions such as cancer, infection and drugs
- It was shown recently that the M-type phospholipase A2 receptor 1 (PLA2R) represents the major target antigen in primary membranous nephropathy
- Anti-PLA2R antibodies are present in 70%-80% of patients with primary membranous nephropathy

it's characterized morphologically by the presence of subepithelial immunoglobulin-containing deposits along the GBM

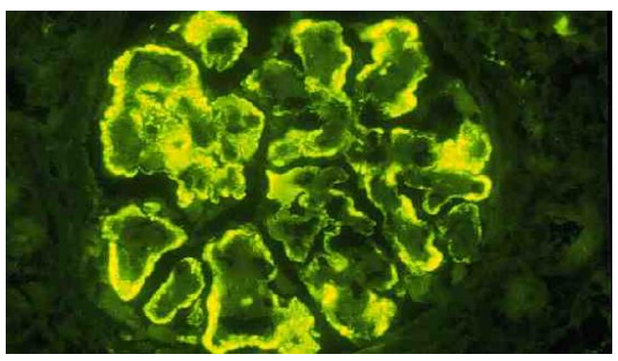
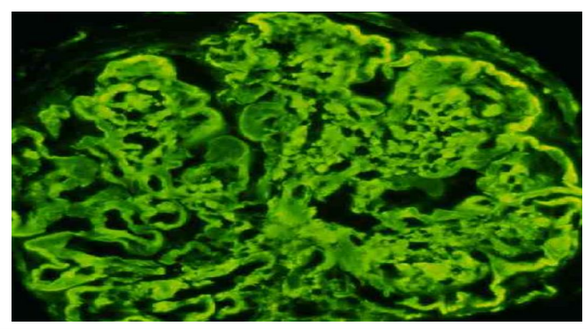
3- Membranoproliferative Glomerulonephritis (MPGN) OR Mesangiocapillary GN

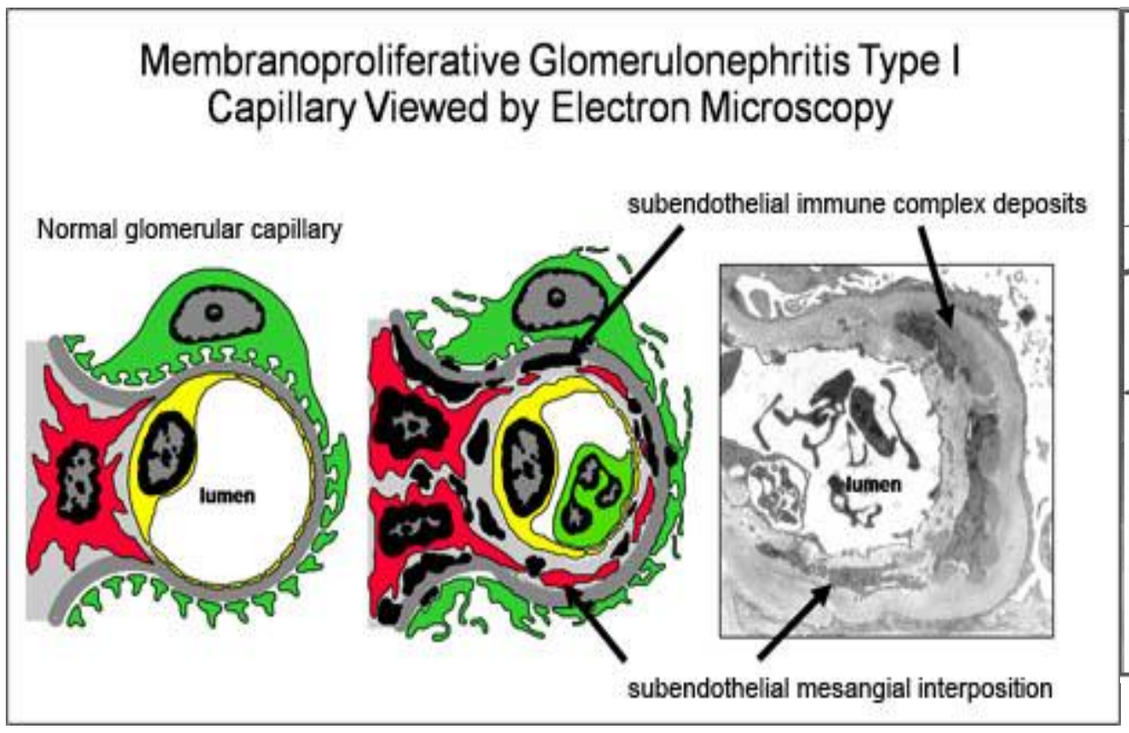
It is a **chronic progressive** glomerulonephritis that occurs in older children and adults

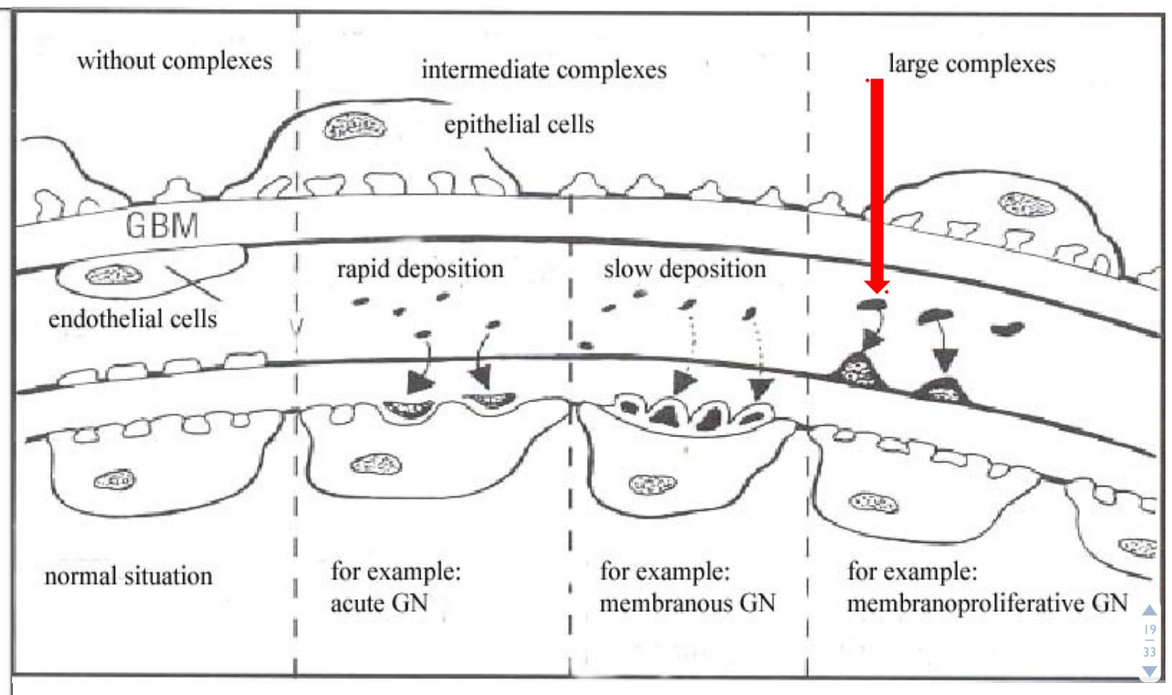
2 main types: (it is an alternation in the GBM and mesangium and a proliferation of glomerular cells.)

- Type I MPGN
- Type II MPGN

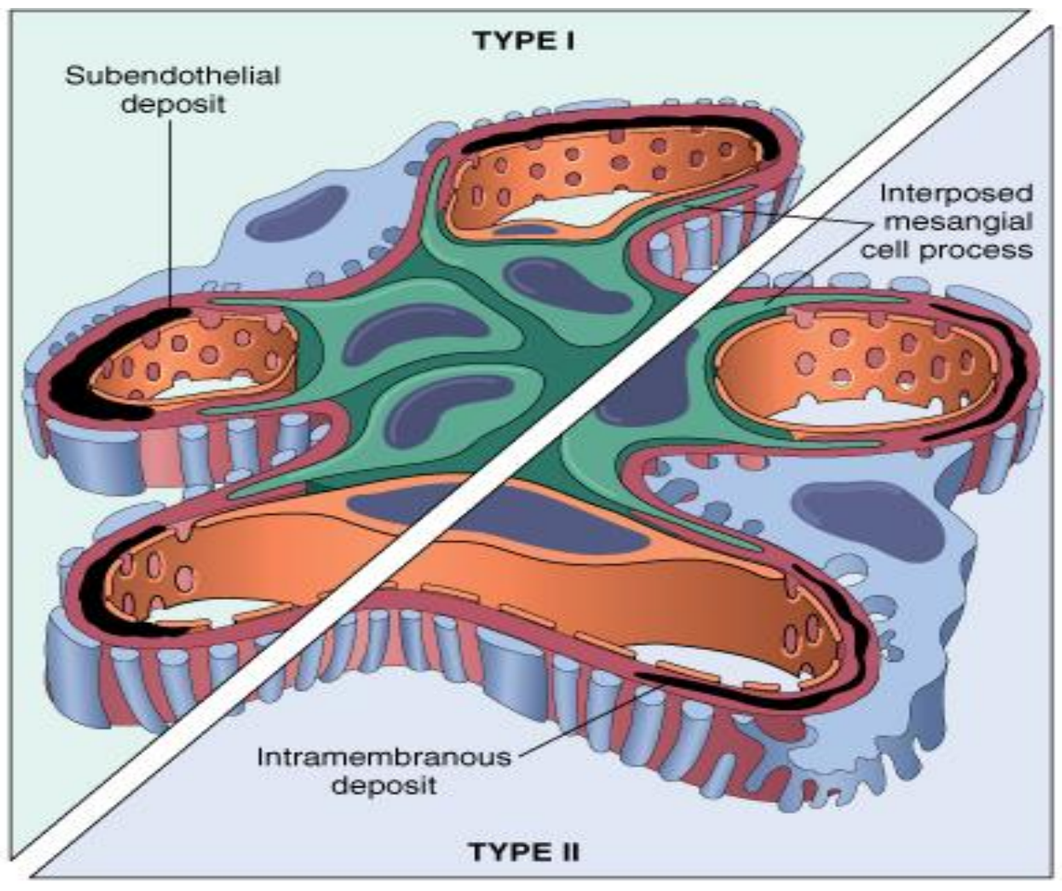
Membranoproliferative glomerulonephritis (MPGN)

Type I MPGN (80% of cases)	**Type II MPGN** Also known as: **Dense Deposit Disease**
- Circulating immune complexes (which is composed of antibody + antigen. The antigen is released from a chronic inflammation like hepatitis and SLE) - May occur in association with hepatitis B&C antigenemia, extra-renal infections or SLE - Characterized by **subendothelial and mesangial** deposits 	The fundamental abnormality is: - Excessive **complement activation** (IgG which is called nephritis factor binds to 3c convertase and allow it to keep on converting c3 to c3a and c3b which will lead to **complement deposits not immune complexes deposits**) - Some patients have autoantibody against C3 convertase called: C3 nephritic factor. - Characterized by **intramembranous dense deposits** 





EXTRA picture to show the difference between type I and type II



B

Extra (435):Not to be confused with Thromboangiitis obliterans (also known as Buerger's disease)

Extra (435):When it occurs in combination with vacuities and multi-organ involvement then is referred to as Henoch-Schonlein purpura (Small vessel vacuities)

4- IgA Nephropathy (Berger disease)

(IgA has 2 subclasses: IgA1 in the serum + IgA2 in mucus. It's composed of amino acid and sugar molecules. IgA nephropathy develops when IgA becomes galactose-deficient and be no longer recognized by the body as self, in response body generates IgG and target the abnormal IgA1 creating a complex (abnormal IgA1+IgG) that circulates in the body and deposits in the mesangium. This will lead to alternative complement pathway activation and finally glomerulr injury)

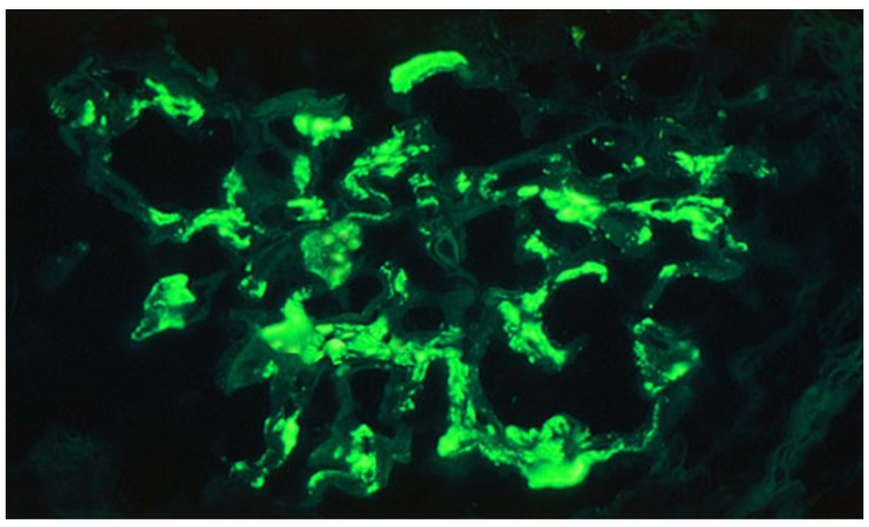
- The **most common** form of primary glomerulonephritis in the world
- Affects children and young adults
- Begins as an episode of gross hematuria that occurs within 1-2 days of a non-specific upper respiratory tract infection

- **The pathogenic hallmark is:**

  It's the production of aberrantly glycosylated IgA and development of autoantibodies against those under-lycosylated IgA antibodies.

- The immune complexes are deposited in the **mesangium**.
- Histology findings: Deposition of IgA & complement C3 in the mesangium
- There is evidence of : Activation of complement by the <u>alternative</u> pathway. (serum complement C2 and C4 will be normal)

Extra(435):
As we took on foundation block Alternative pathway“activated by bacterial products “ : it includes C3,c5,c6,c7,c8,c9 so that’s why C2 & C4 are normal because they belong to the classical pathway Not the alternative!!



This immunofluorescence pattern demonstrates **positivity** with antibody to **IgA**. The pattern is that of **mesangial deposition** in the glomerulus.
This is IgA nephropathy.

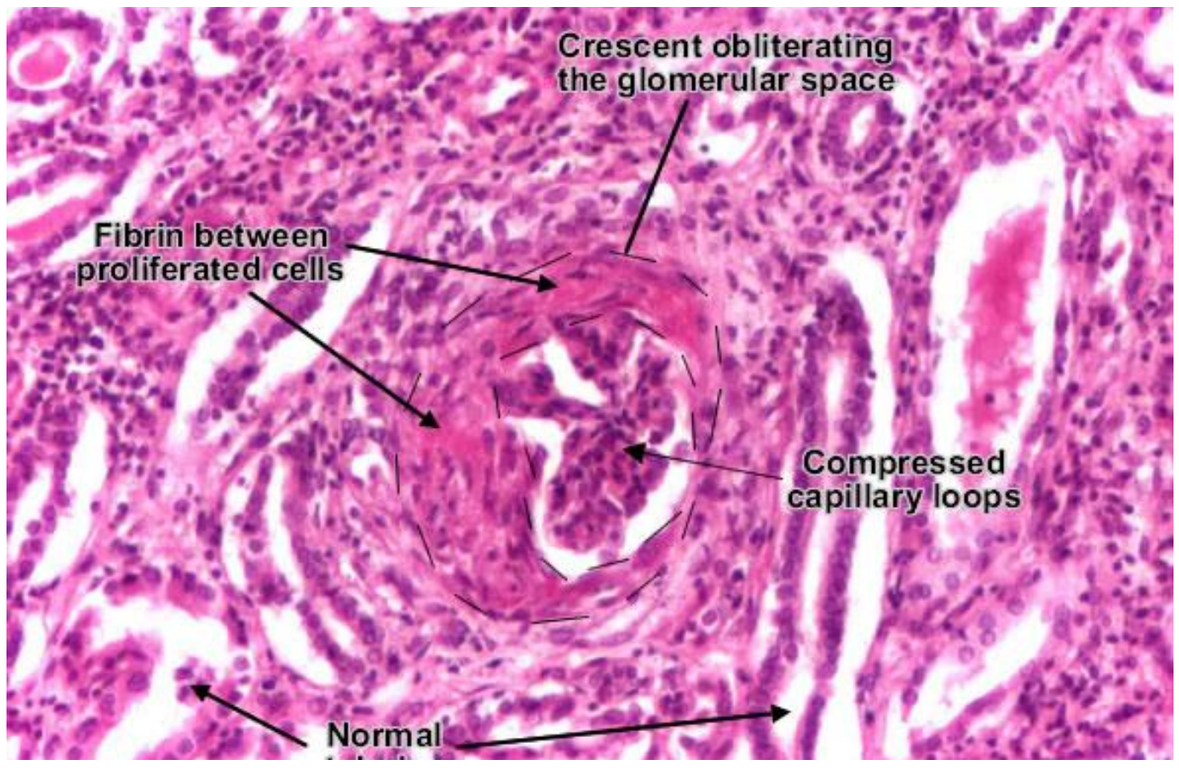
IgA nephropathy (Berger disease)

5- Rapidly Progressive (Cresentic) Glomerulonephritis (RPGN)

- RPGN is a clinical syndrome and **not a specific form of GN**

Crescents are defined as the presence of **two or more layers** of cells in the Bowman space.

- The presence of crescents in glomeruli is a marker of severe injury.
- In most cases the glomerular injury is immunologically mediated
- A practical classification divides CrGN **into three groups** on the basis of immunologic findings



The initiating event is the development of a physical disruption in the GBM.

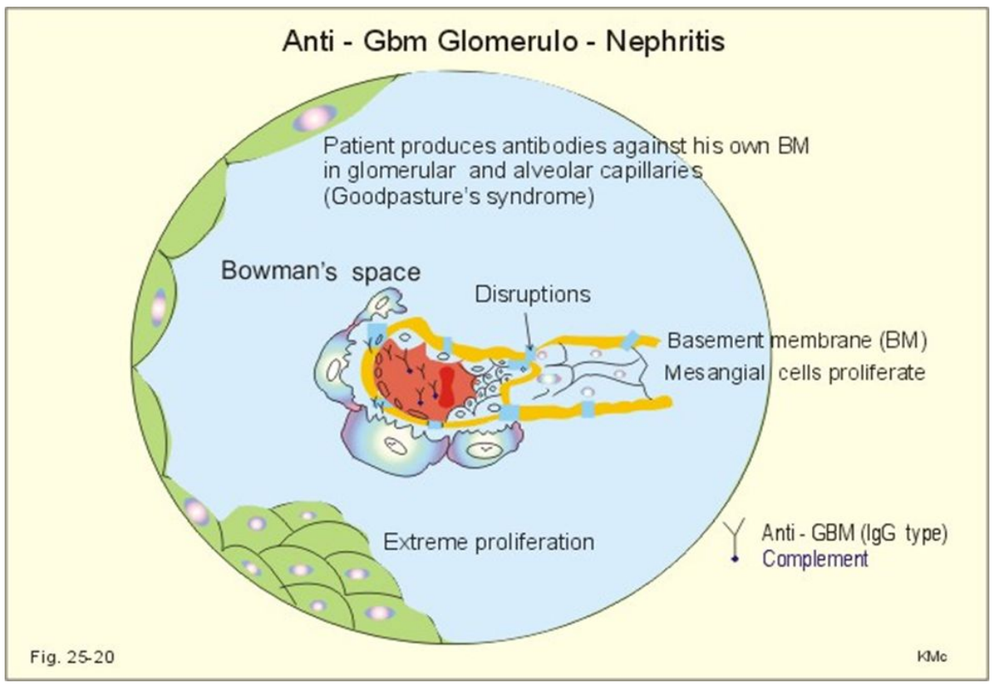
- The lesions are mediated by processes involving macrophages and cell-mediated immunity.
- Following disruption of the glomerular capillary, circulating cells, inflammatory mediators, and plasma proteins pass through the capillary wall into the Bowman space.
- CrGN is classified into three groups based on immunological findings

A. Type I (Cresentic GN)

(Anti-GBM antibody)

Generated antibodies against the glomerular basement membrane characterized by **linear** deposition of **IgG** and **C3** on the GBM

Associated with **Goodpasture syndrome** which is characterized by Antibodies bind also in the pulmonary alveolar capillary basement membranes



This picture shows the destruction of the membrane leakage of blood components (fibrin) this will cause rapid multiplication of cells at Bowman 's capsule and infiltration of the macrophages and the lymphocytes into the space causing the cresentic

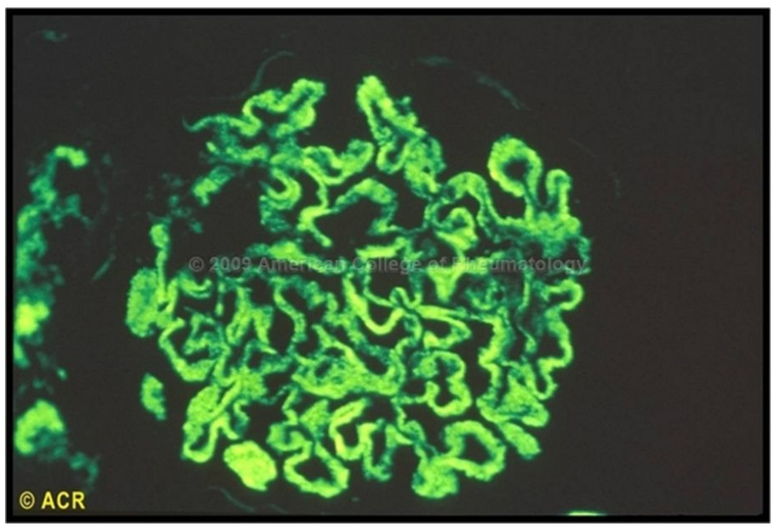
Rapidly progressive glomerulonephritis

B. Type II of Cresentic GN

(Immune complex - mediated)

- May occur as a **complication** of any of the immune complex **nephritides**
  - Post infectious
  - SLE
  - IgA nephropathy

Characteristic granular (lumpy-bumpy) pattern of staining of the GBM for immunoglobulin & complement



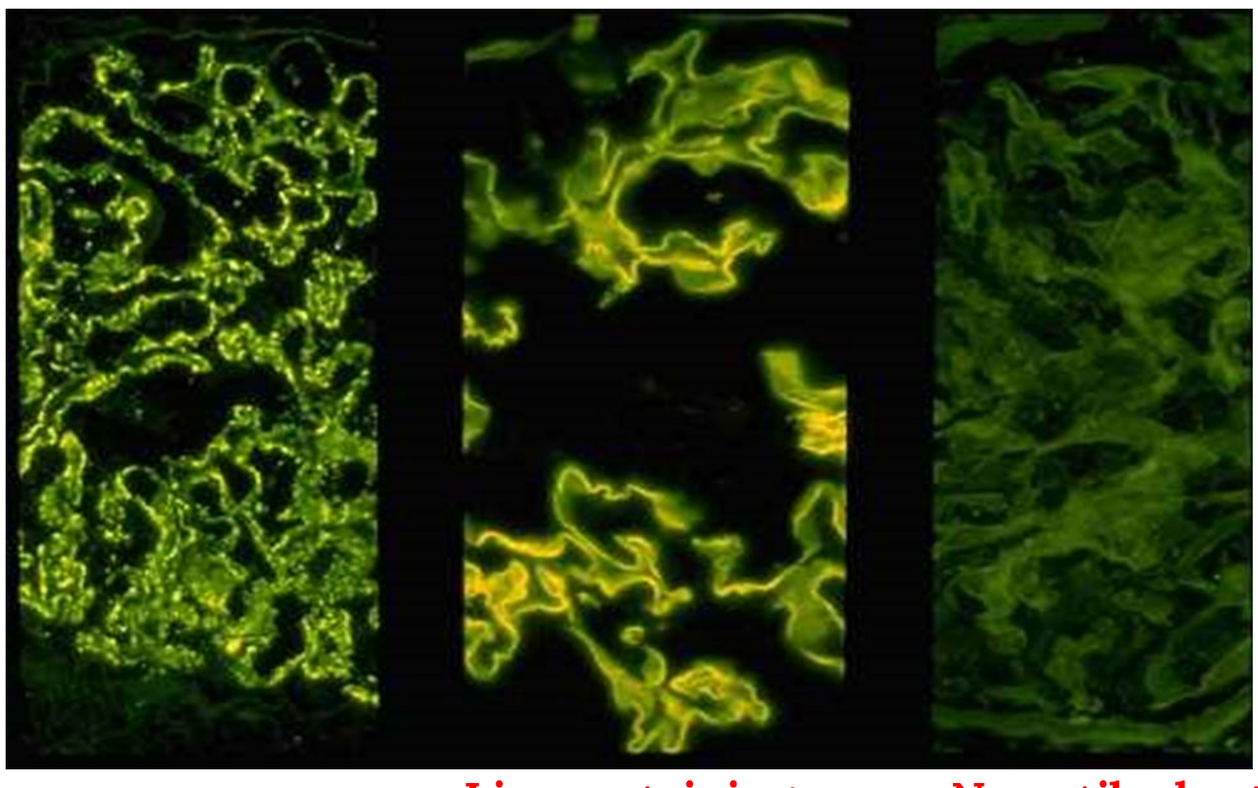
A lumpy-bumpy pattern of staining of the GBM

C. Type III of Cresentic GN

(Pauci-immune) Pauci = قليل

- Defined by the **lack** of **anti-GBM** antibodies and lack of immune complexes.
- Instead most cases are associated with **Anti-neutrophil cytoplasmic antibodies** in serum (**ANCA**) and systemic vasculitis

(435) How ANCAs are activated? is an unknown mechanism But two assumptions are made one in which they bind to PMNs activate them so they can attack and destroy the basement membrane. Or its presence of already activated neutrophils activates these ANCAs and they cause the damage



Granular staining (Immune complex)

Linear staining (Anti-GBM)

No antibody staining (Pauci associated with vasculitis)

Take home message

- Immune complexes underlie the pathogenesis of many of the glomerulo-nephritides.
- Activation of the complement system is an integral part of the process, and measurement of the complement proteins help in diagnosis and follow-up of patients.
- Immunofluoresence of renal biopsy demonstrate the presence of immune complexes and confirm the diagnosis.

MCQs

1- Immune complex nephritis is considered to be which type of hypersensitivity:

a) type 1 b) type 2 c) type 3 d) b and c

2- Poststreptococcal GN is caused by known streptococcal types called:

a) Nephritic strains b) Nephrotic strains c) a and b d) none

3- Which of the following is a type| (anti-GBM antibody) crescentic GN:

a) Post infection b) SLE c) IgA nephropathy d) Goo. d pasture syndrome

4- Which of the following may occur with hepatitis B or C?

a) Membranous glomerulonephritis b) IgA nephropathy

c) Membrano-proliferative glomerulonephritis d) Crescentic glomerulonephritis

5- Post Infectious Glomerulonephritis occurs 7-14 days after which of the following?

a) Nephritic Syndrome b) Pharyngitis

c) Skin Infection d) Antiglomerular basement membrane disease

6- The site of immune complexes deposition in Membranous glomerulonephritis is:

a) Mesangium b) Basement membrane

c) a and b d) Parietal layer of bowman's capsule

7- What is type II Crescentic GN characterized by:

a) IgA nephropathy b) SLE c) Post-infections d) all of them

1-c
2-a
3-d
4-c
5-b
6-b
7-d

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