Immune Complex Nephritis

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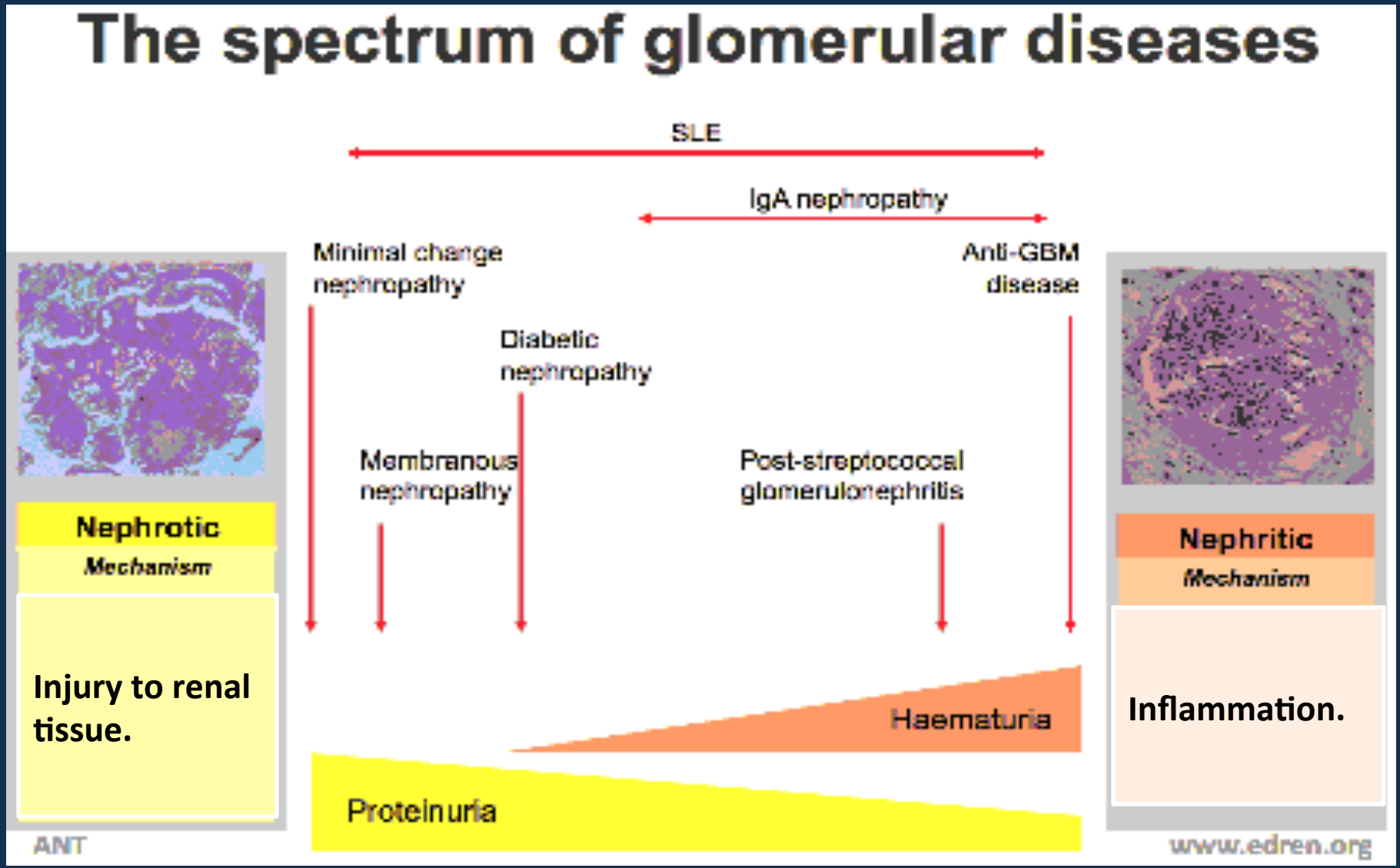
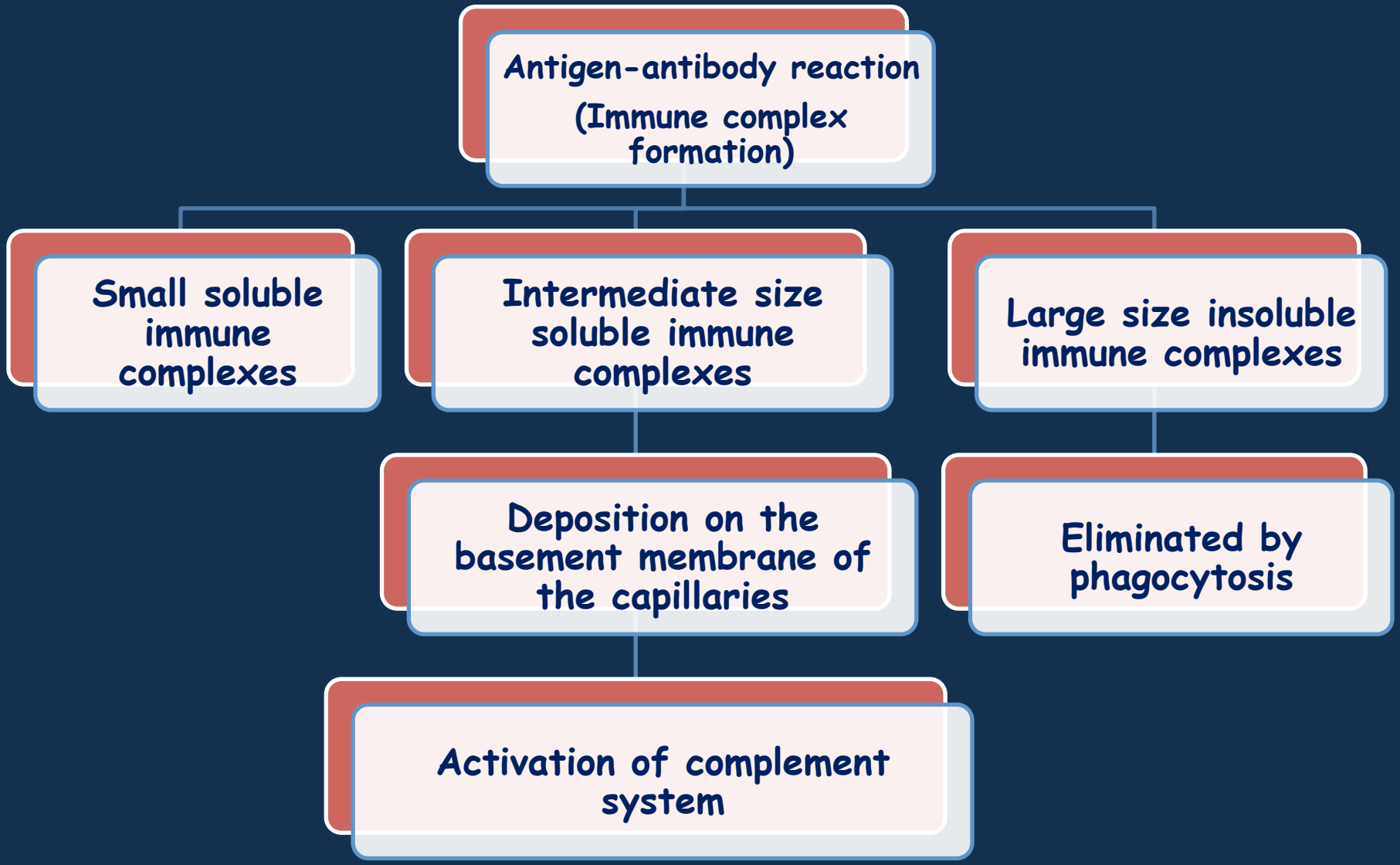
Objectives

- 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.

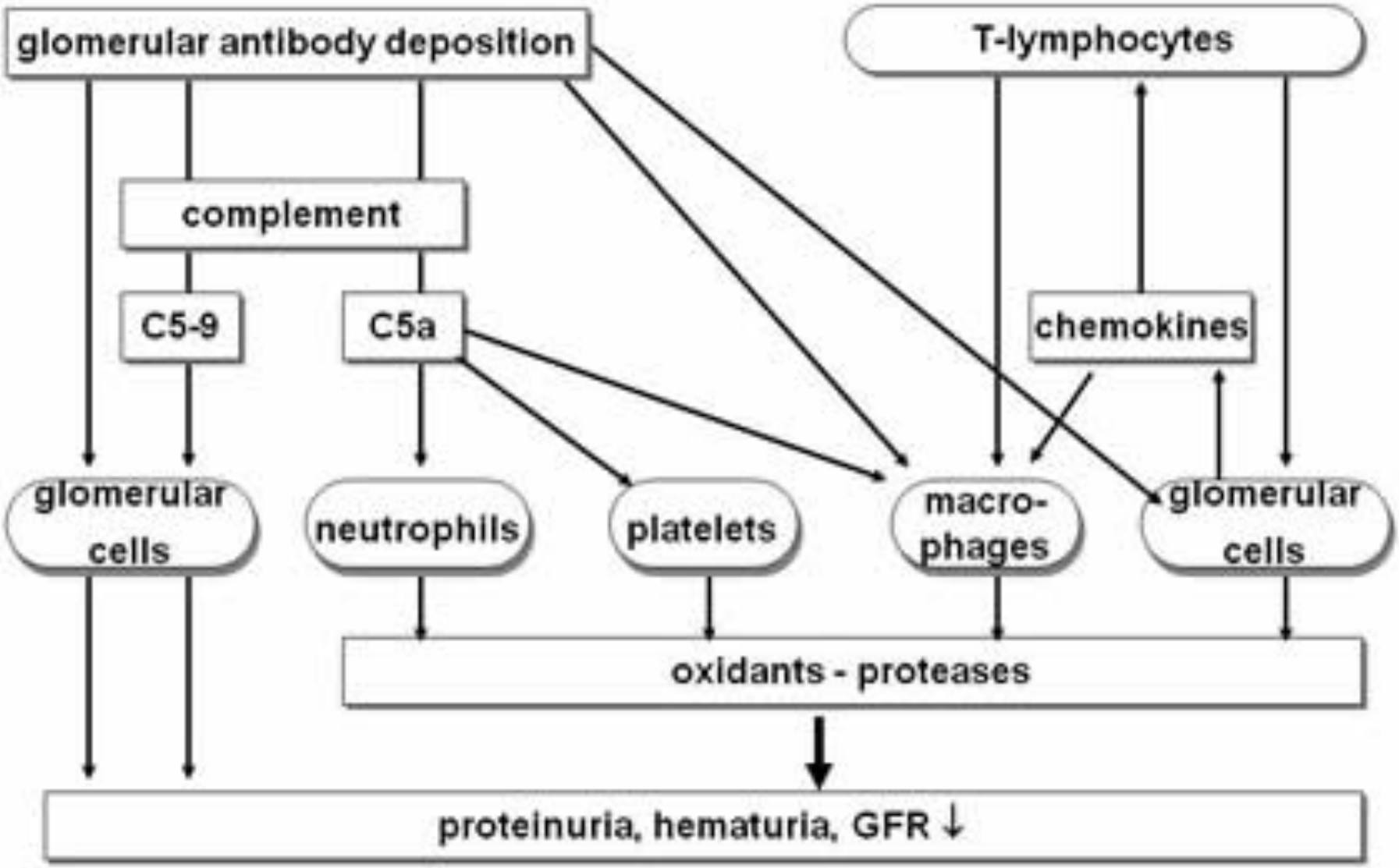
Complexes of antibody with various microbial OR self antigens induce type II or III hypersensitivity reactions in the kidney :



Pathogenesis of immune-complex nephritis (Type III hypersensitivity reactions)



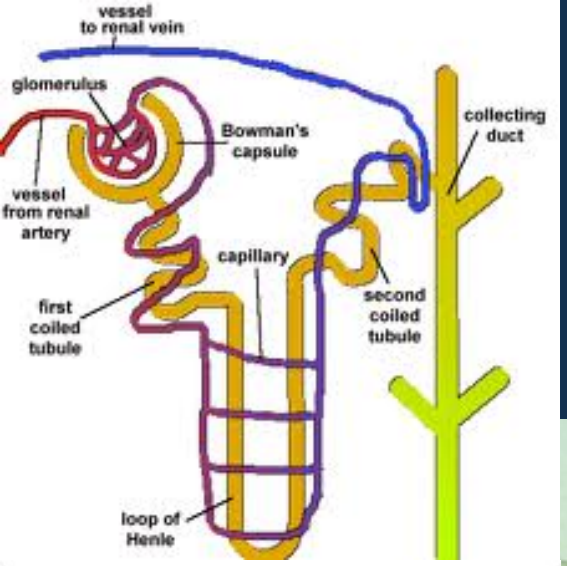
Immune-mediated glomerular injury

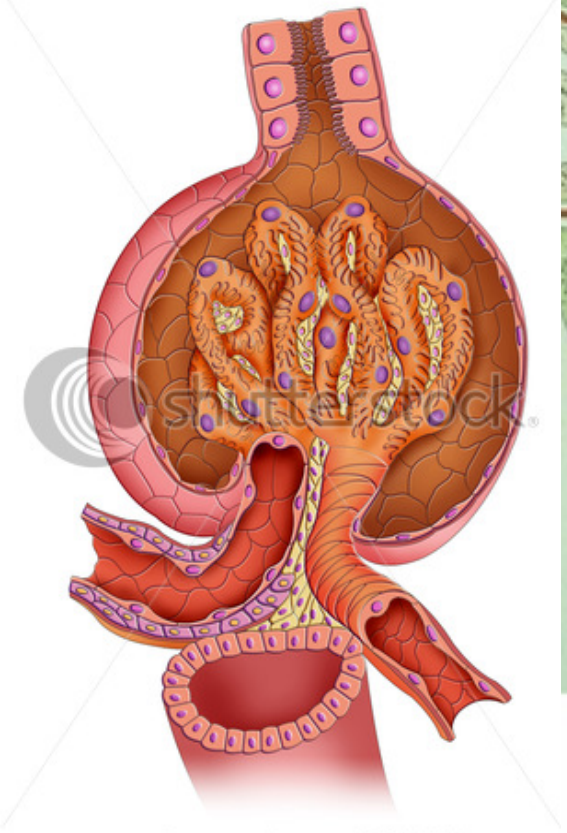


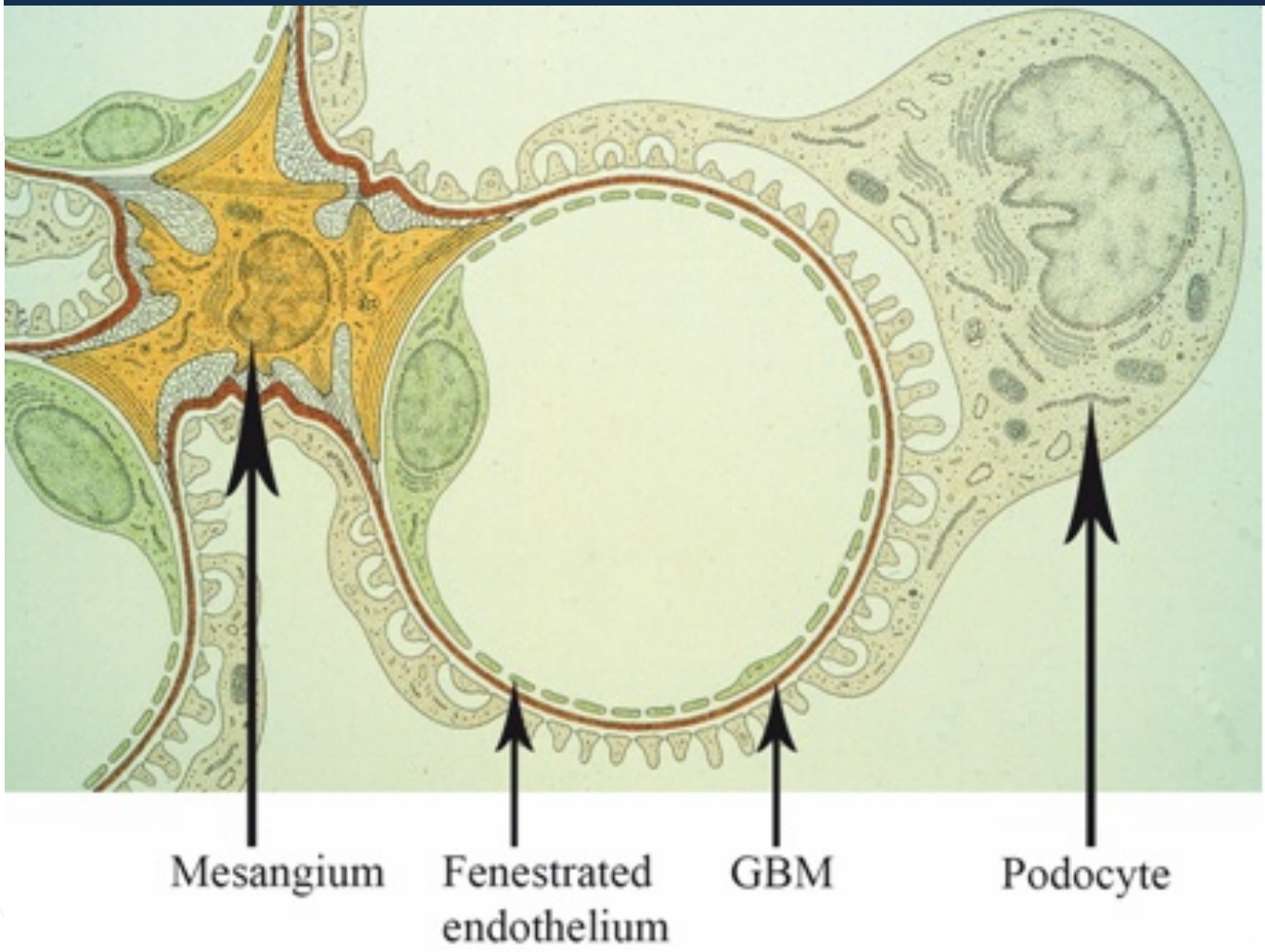
Site of deposition:

- 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)

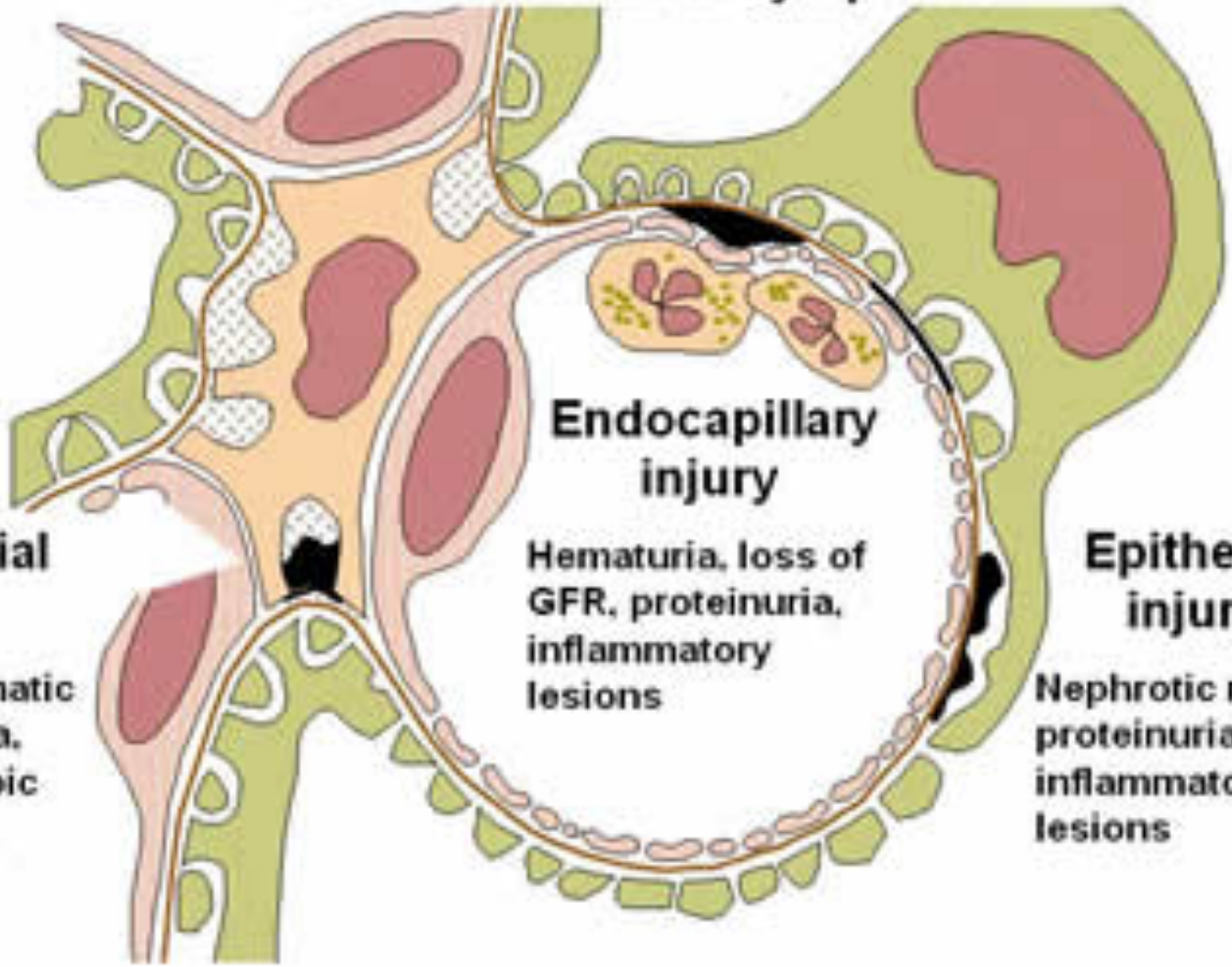
Nephron and glomerulus







Glomerular injury is determined by immune complex localization as are the clinical symptoms



Mesangial injury

Asymptomatic proteinuria, microscopic hematuria

Endocapillary injury

Hematuria, loss of GFR, proteinuria, inflammatory lesions

Epithelial injury

Nephrotic range proteinuria, non-inflammatory lesions

Types of immune-mediated renal injury:

- Antibody-mediated Injury:
  - Membranous glomerulonephritis
  - IgA nephropathy
  - Membranoproliferative glomerulonephritis
  - Post infectious glomerulonephritis
  - Antiglomerular basement membrane disease

1. Post Infectious Glomerulonephritis (GN) (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

Poststreptoccal 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

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 glomerulonephritis

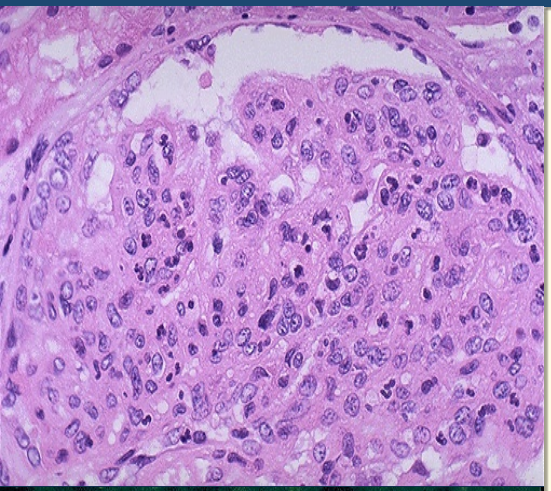
Diffuse proliferative GN (PGN)

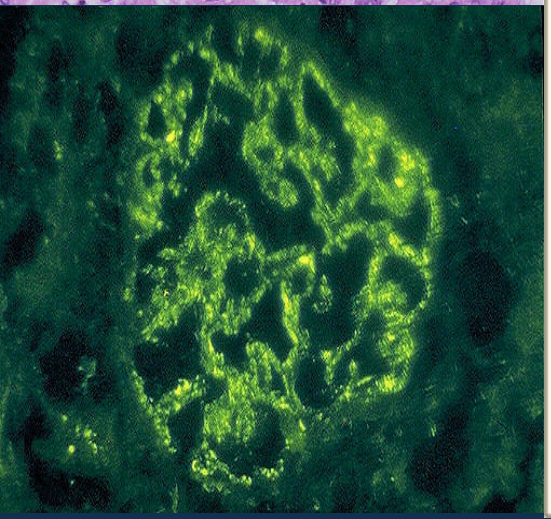
- Diffuse proliferation of glomerular cells and frequent infiltration of leukocytes (especially neutrophils)

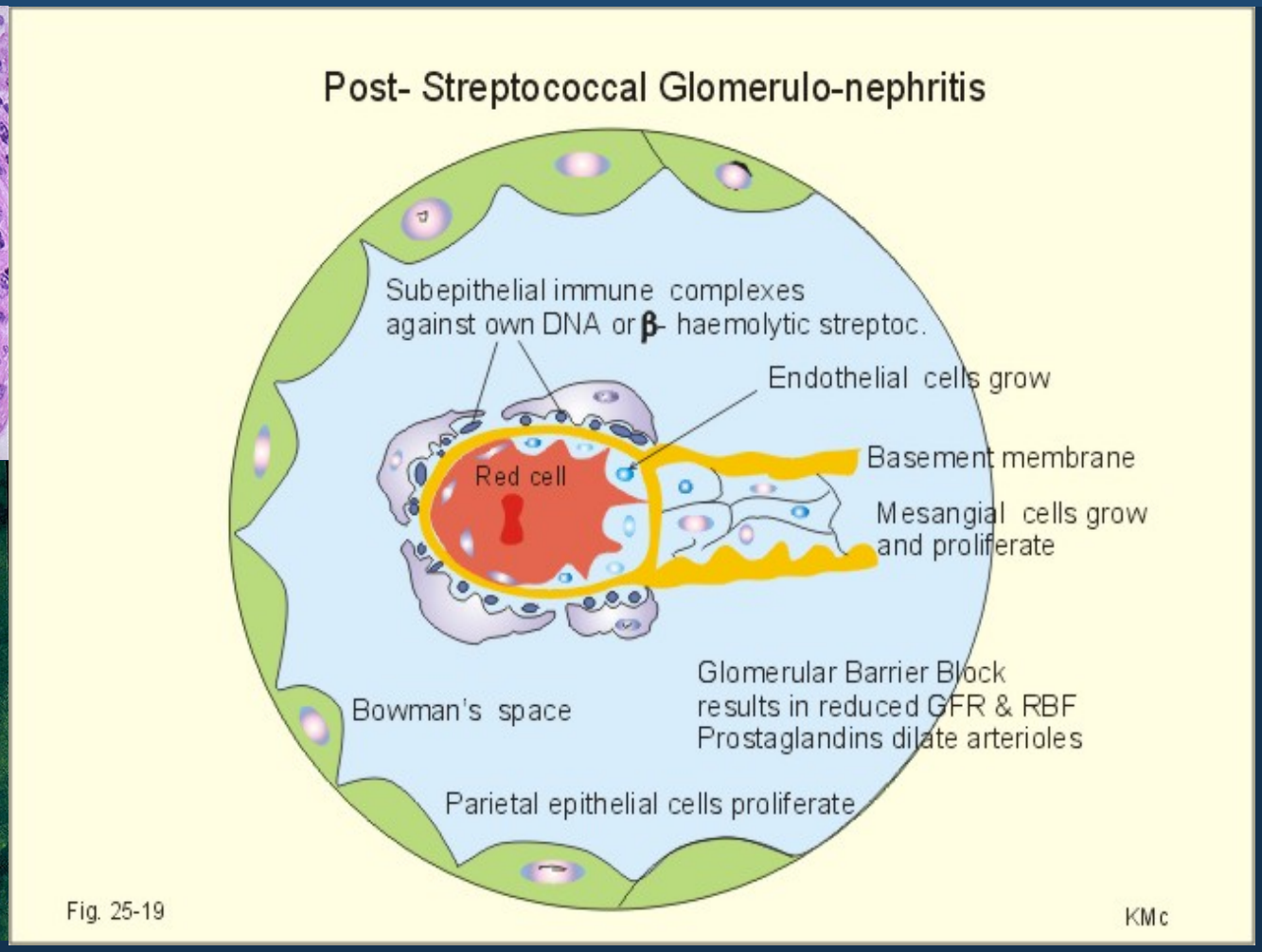
- Typical features of immune complex disease :

  - Hypocomplementemia
  - 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.

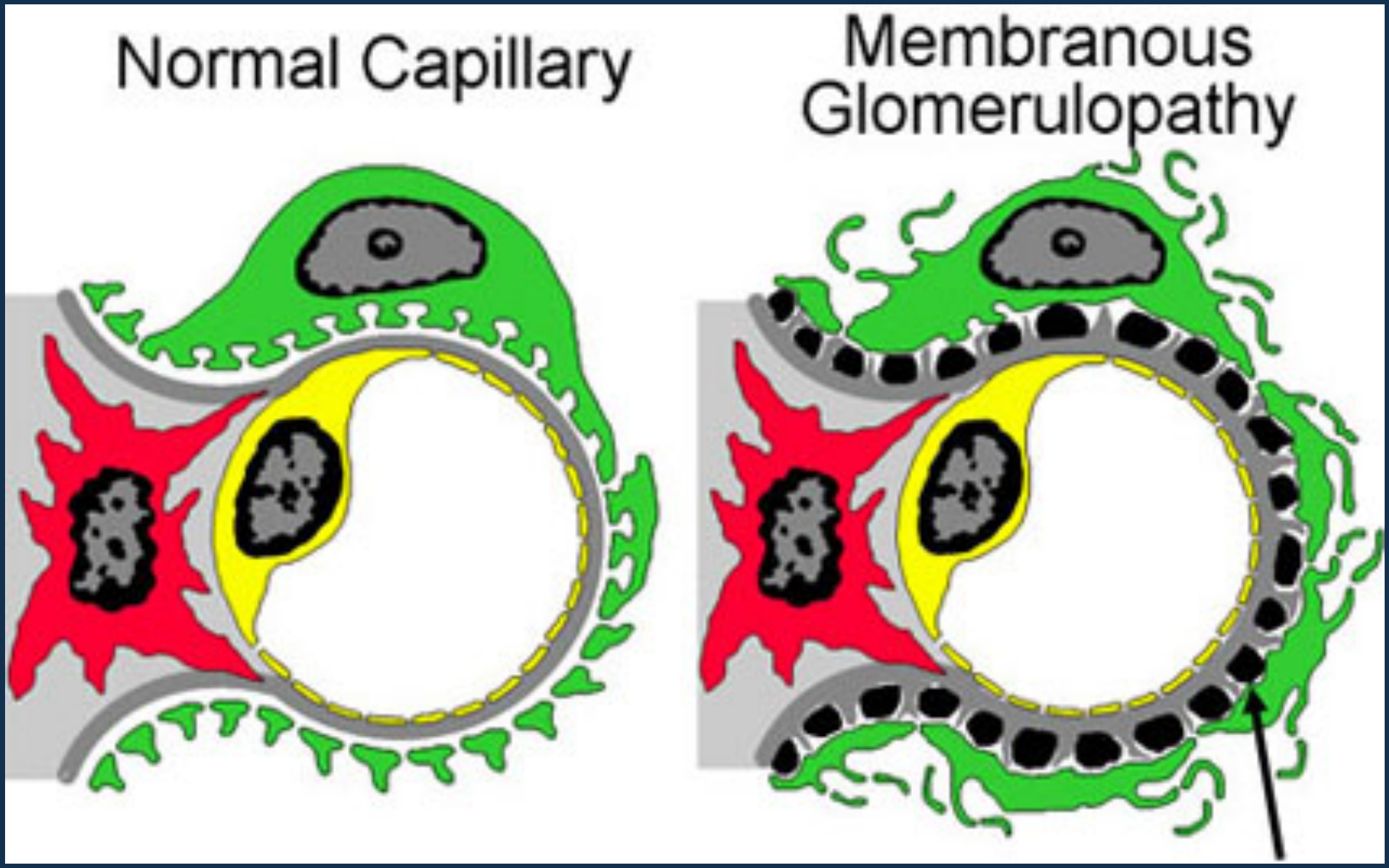
2. Membranous Glomerulonephritis (Membranous nephropathy)

- A slowly progressive disease
- A form of chronic immune-complex nephritis
- Most common between 30 - 50 years but rare in children
- 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 A_2 receptor 1 (PLA_2R) represents the major target antigen in primary membmranous nephropathy

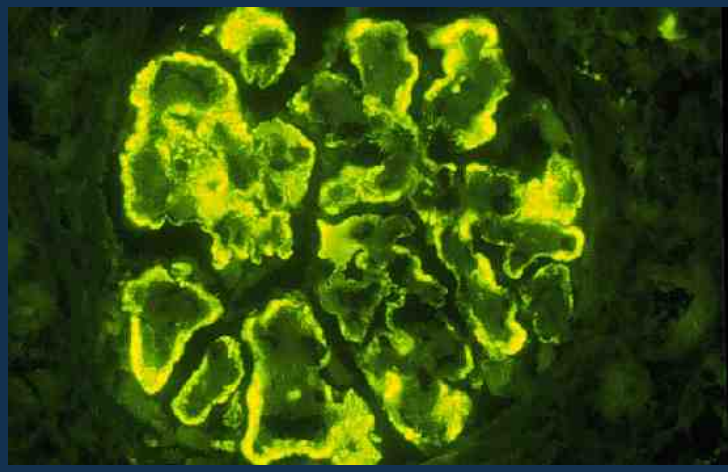
- Anti-PLA_2R antibodies are present in 70%-80% of patients with primary membranous nephropathy


Normal Capillary
Membranous Glomerulopathy

3. Membranoproliferative Glomerulonephritis (MPGN) OR Mesangiocapillary GN

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

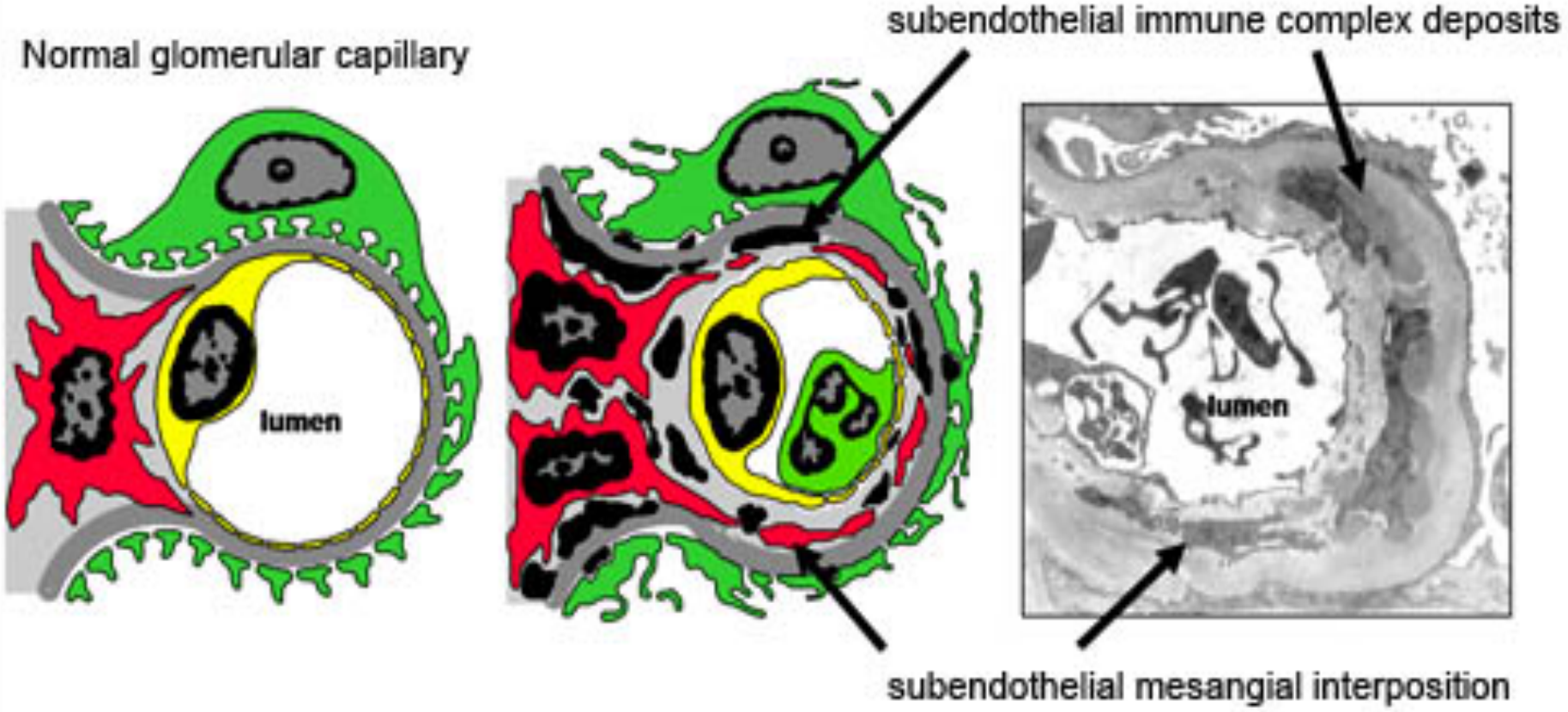
2 main types :



Type I MPGN (80% of cases)

- Circulating immune complexes have been identified
- May occur in association with hepatitis B&C antigenemia, extra-renal infections or SLE
- Characterized by subendothelial and mesangial deposits

Membranoproliferative Glomerulonephritis Type I
Capillary Viewed by Electron Microscopy



Type II MPGN

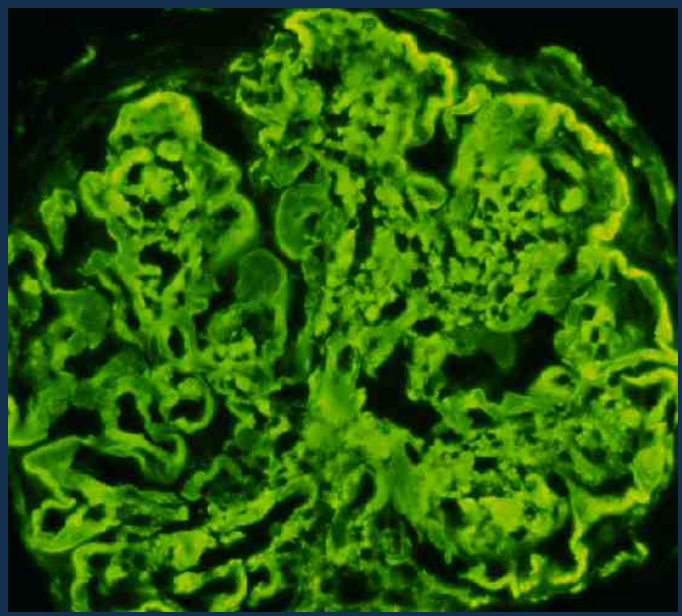
Also known as : dense deposit disease .

The fundamental abnormality is :

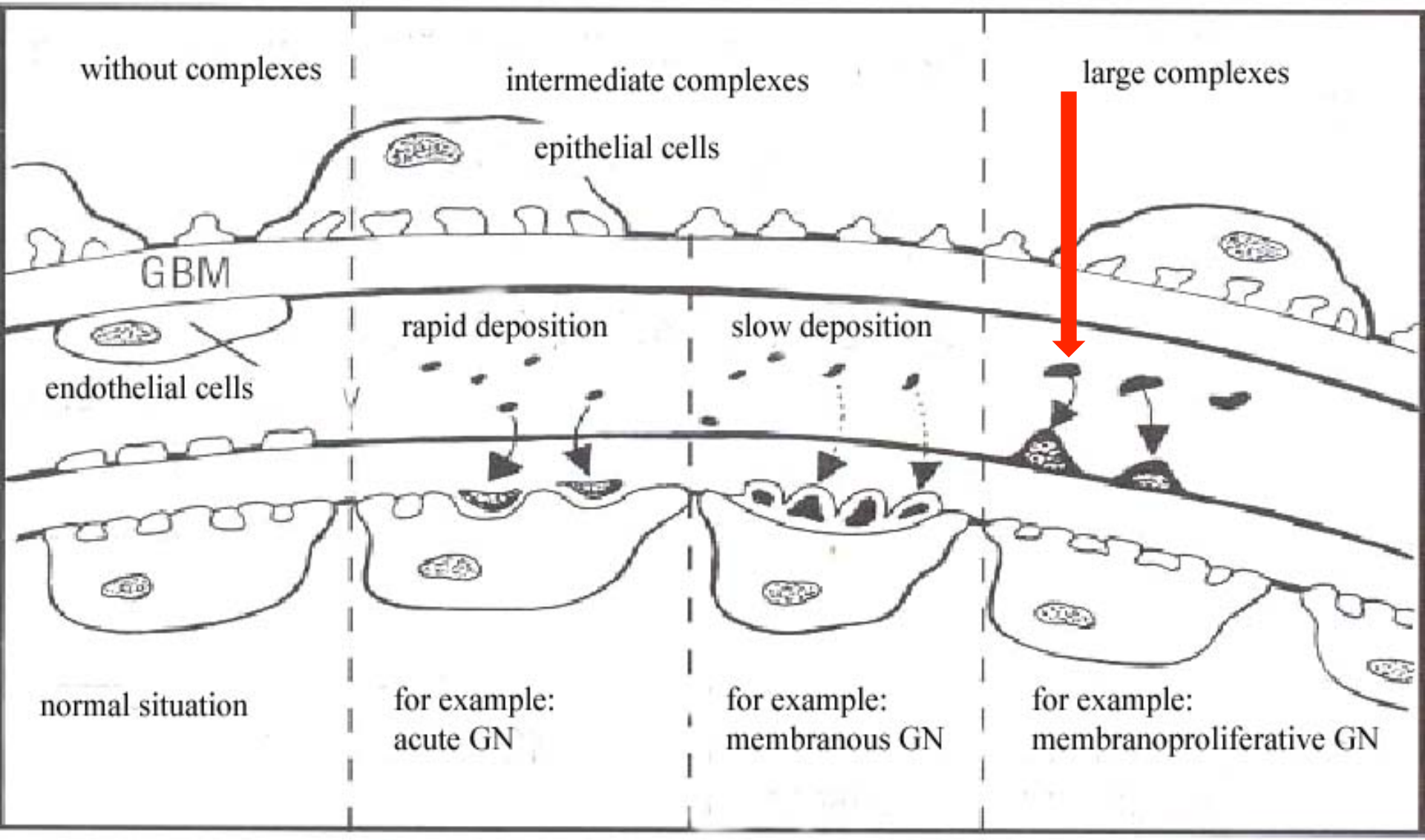
- Excessive complement activation.

- Some patients have autoantibody against C3 convertase called: C3 nephritic factor.

- Characterized by intramembranous dense deposits



Membranoproliferative GN



4. IgA Nephropathy (Berger disease)

The most common from 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

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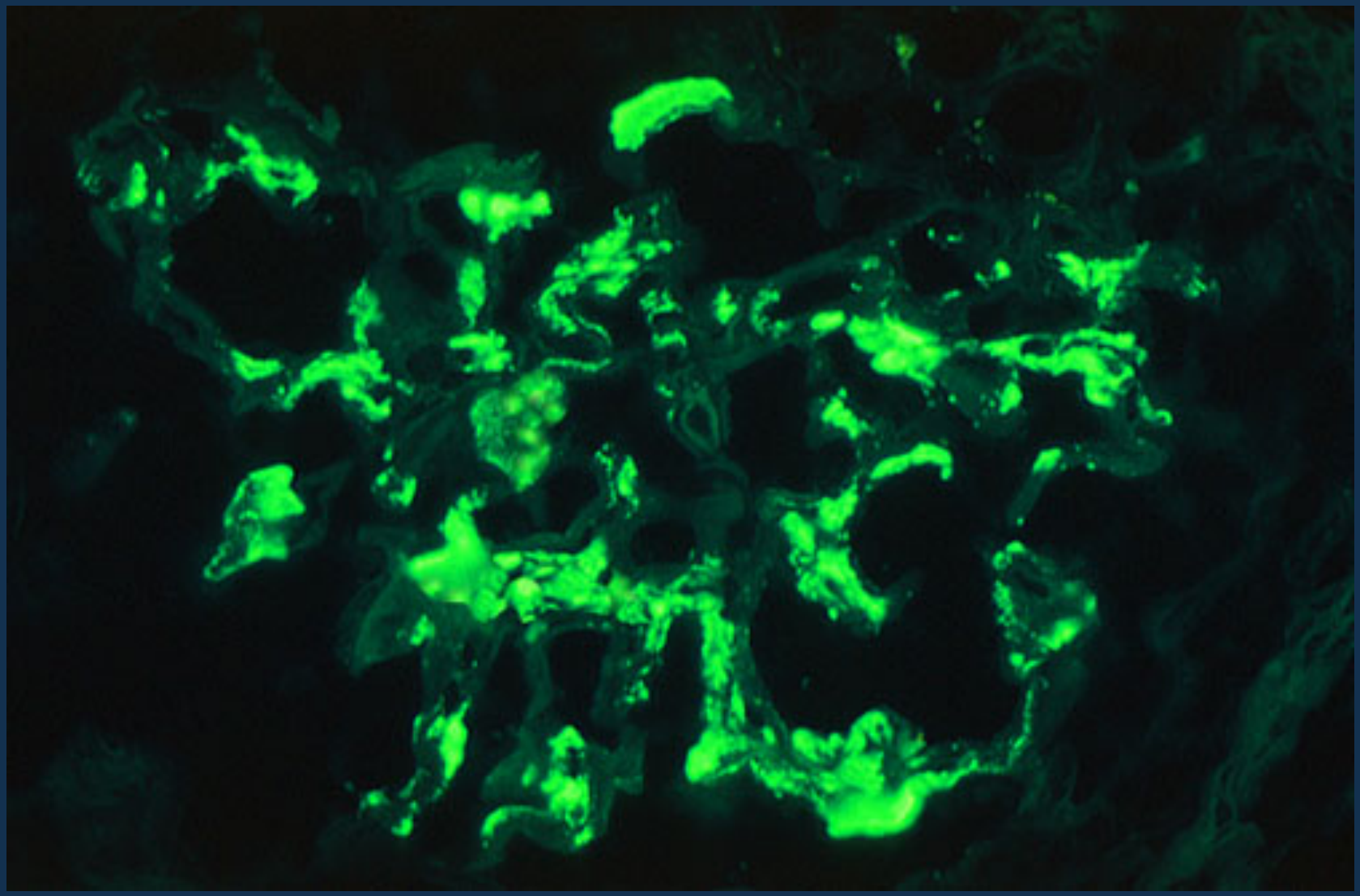
IgA Nephropathy

- The pathogenic hallmark is the production of aberrantly glycosylated IgA and development of autoantibodies against those under-lycosylated IgA antibodies.
- The immune complexes are deposited in the masangium.
- Histology findings: Deposition of IgA & complement C3 in the mesangium
- There is evidence of :

  Activation of complement by the alternative pathway (serum complement C2 and C4 will be normal)

IgA Nephropathy

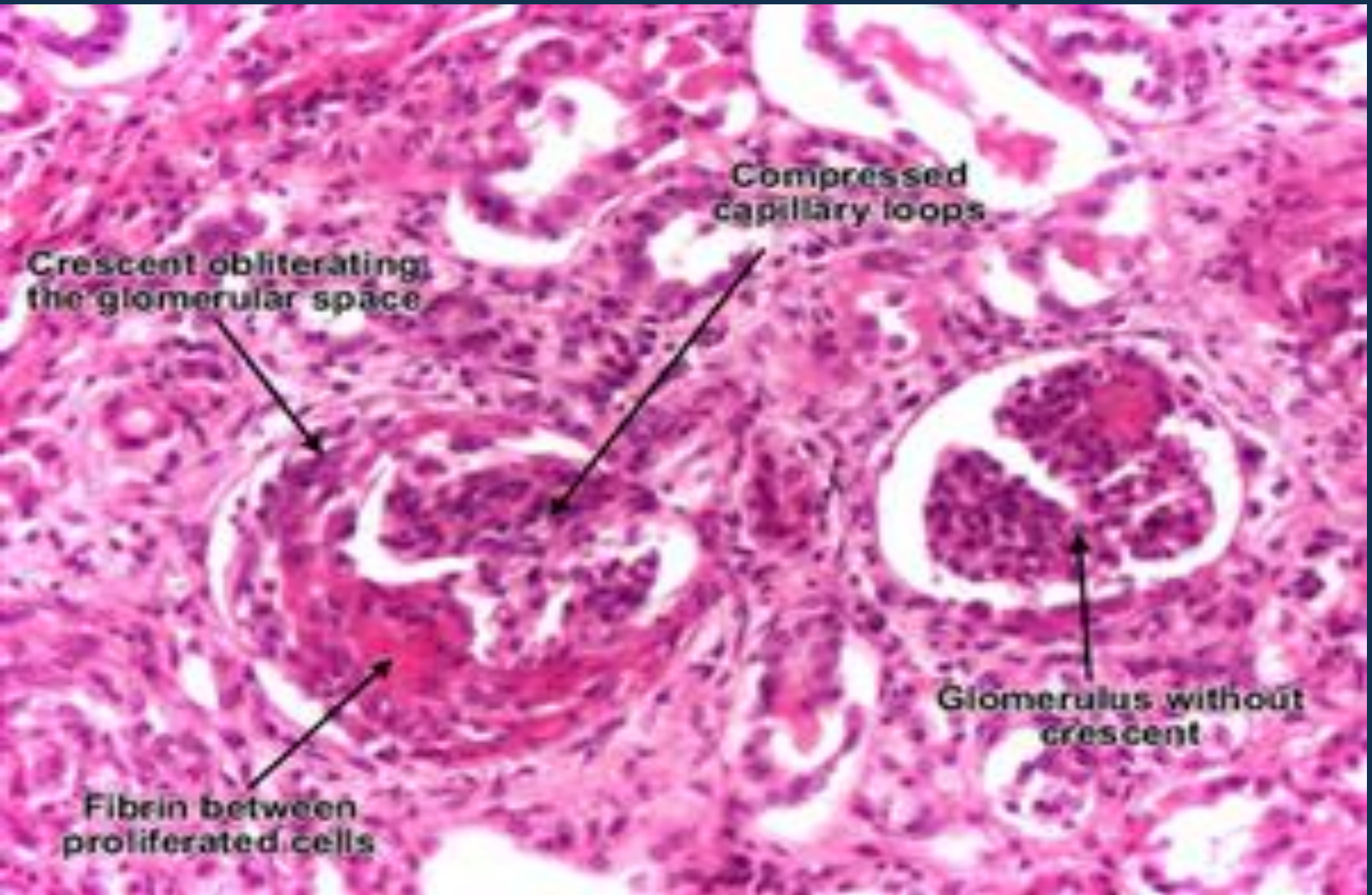


This immunofluorescence pattern demonstrates positivity with antibody to IgA. The pattern is that of mesangial deposition in the glomerulus. This is IgA nephropathy.

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

Rapidly Progressive (Cresentic) Glomerulonephritis



-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

Type I (Anti-GBM antibody) (Cresentic GN)

Characterized by linear deposition of IgG and C3 on the GBM

- Goodpasture syndrome

  Antibodies bind also in the pulmonary alveolar capillary basement membranes

Anti - Gbm Glomerulo - Nephritis

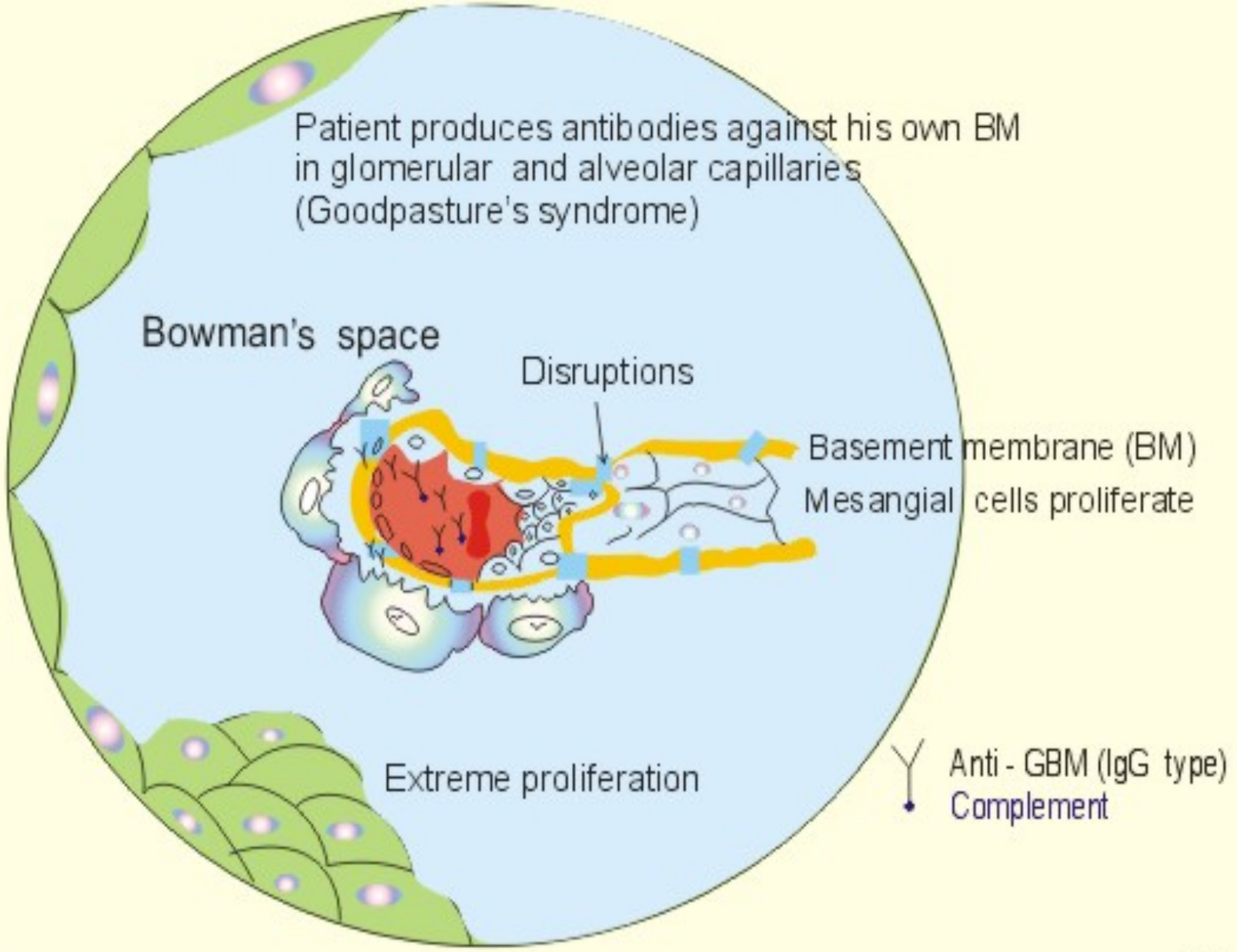


Fig. 25-20

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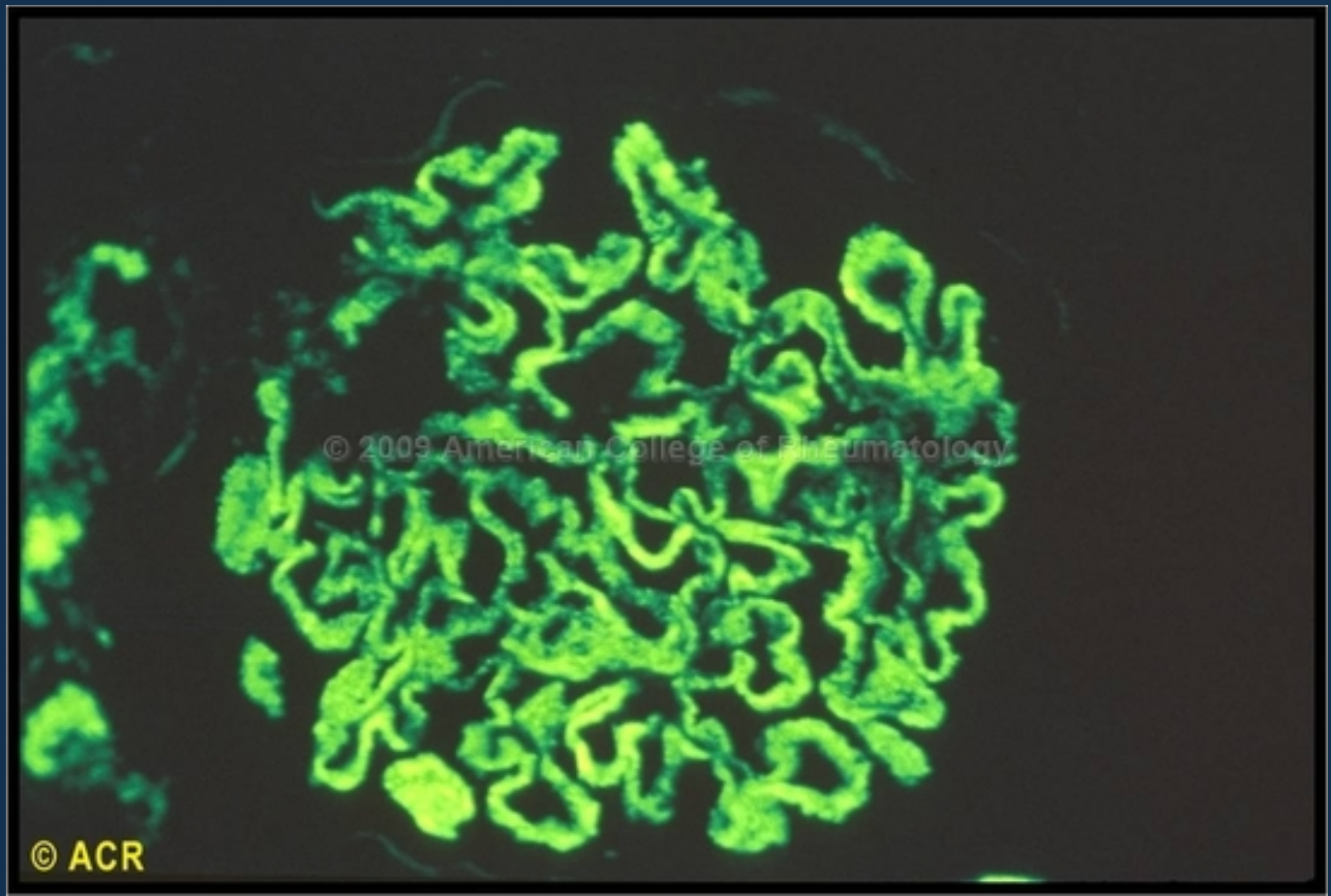
Type II
(Immune complex - mediated Cresentic GN)

- 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.

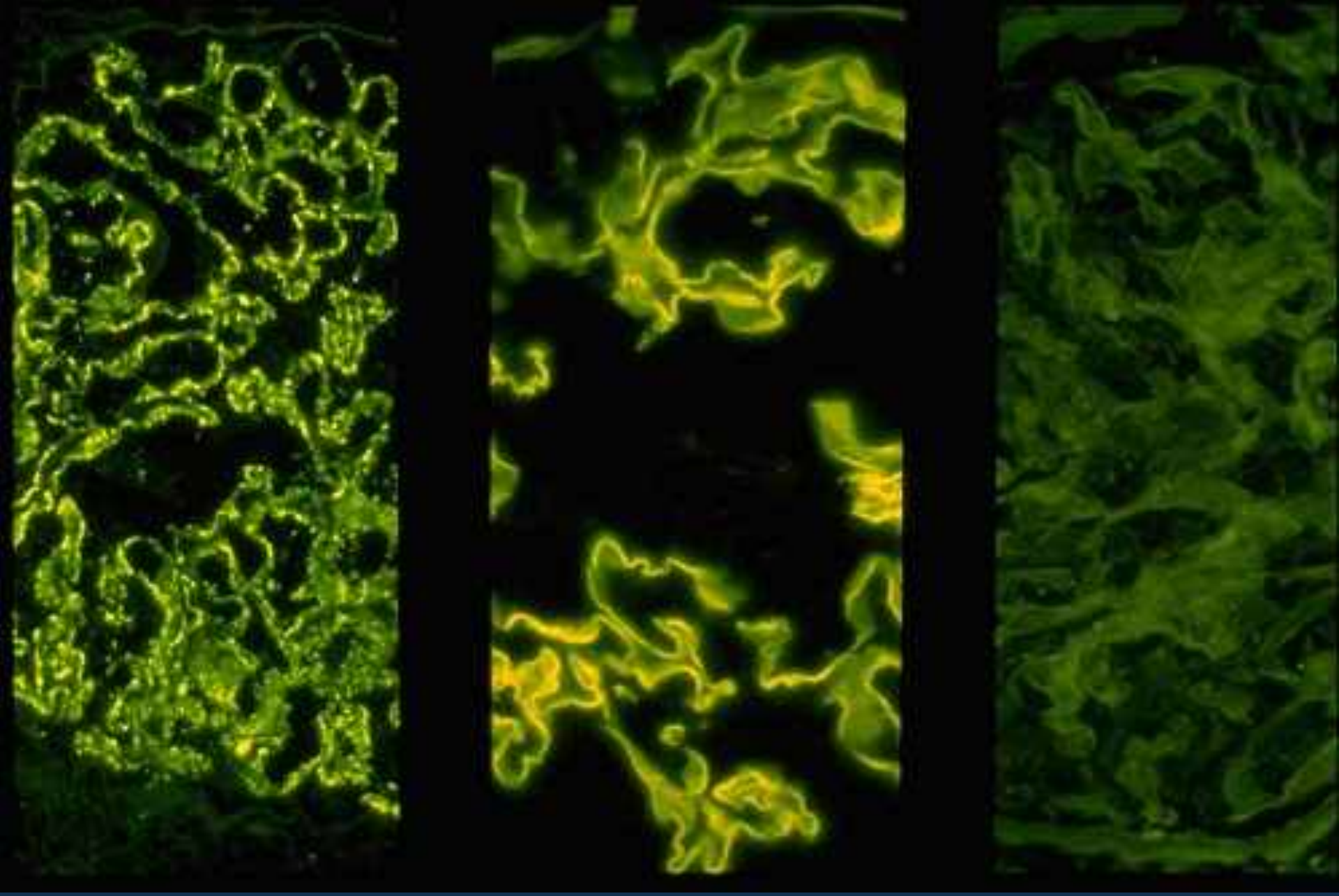
A lumpy-bumpy pattern of staining of the GBM



Type III (Pauci-immune) Cresentic GN

- Defined by the lack of anti-GBM antibodies.

- Most cases are associated with:
  Anti-neutrophil cytoplasmic antibodies in serum (ANCA) and systemic vasculitis



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.