Immune Complex Nephritis

Dr.Hend NOTES

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Extra Explanation

EXTRA

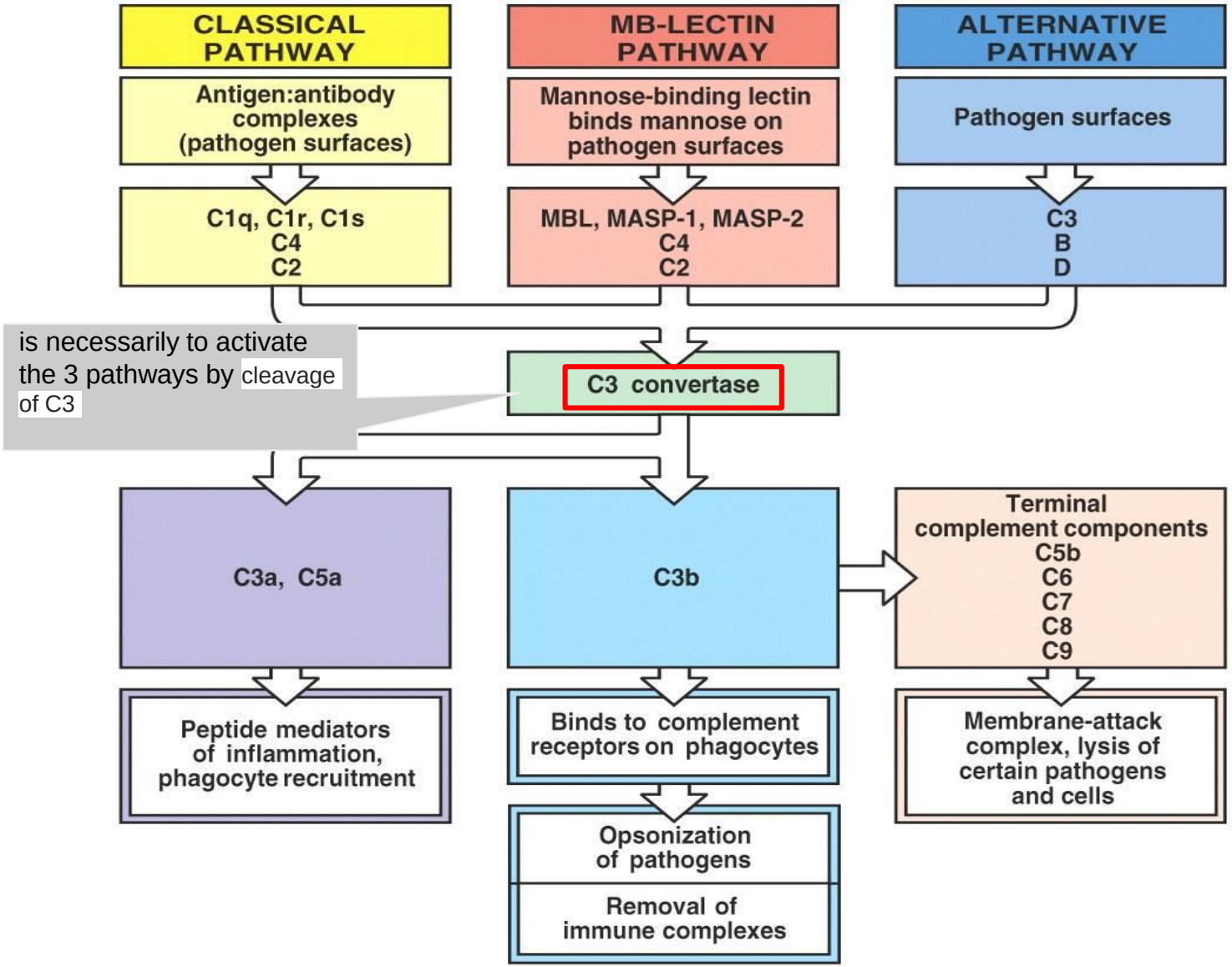


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

EXTRA

types of hypersensitivity reactions

Type	Name	Mechanism	Disease examples
Type I	Immediate hypersensitivity	IgE-mediated degranulation of mast cells following antigen binding and cross-linking of IgE	Allergic asthma, allergic rhinitis, anaphylaxis
Type II	Antibody-mediated hypersensitivity	IgM/IgG antibody:antigen interactions on target cell surfaces	Drug-induced thrombocytopenia, myasthenia gravis, Graves disease, haemolytic anaemia of newborn
Type III	Immune complex-mediated hypersensitivity	Immune complex formation and deposition in tissues leading to local or systemic inflammatory reactions	Rheumatoid arthritis, SLE, Goodpasture's syndrome, Arthus reaction, serum sickness
Type IV	Delayed-type hypersensitivity	Sensitized T_H1 cells activated to release cytokines upon binding to antigen, resulting in macrophage and cytotoxic T cell accumulation	Contact dermatitis, chronic transplant rejection

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.

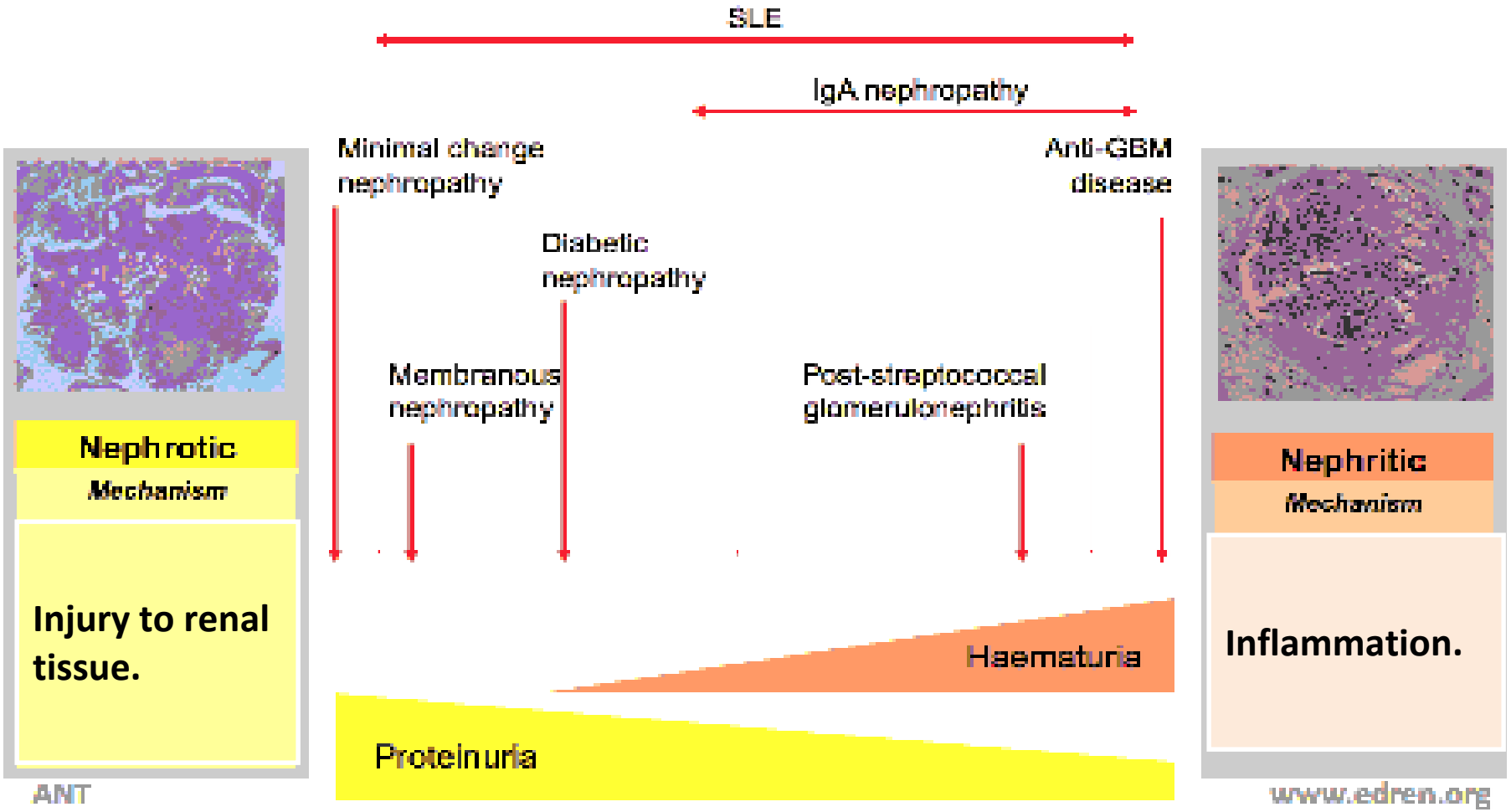
Complexes of antibody with various microbial OR self antigens induce type II or III hypersensitivity reactions in the kidney :

Hematuria can either be (gross) seen by the pt. Or after sending it to the lab.

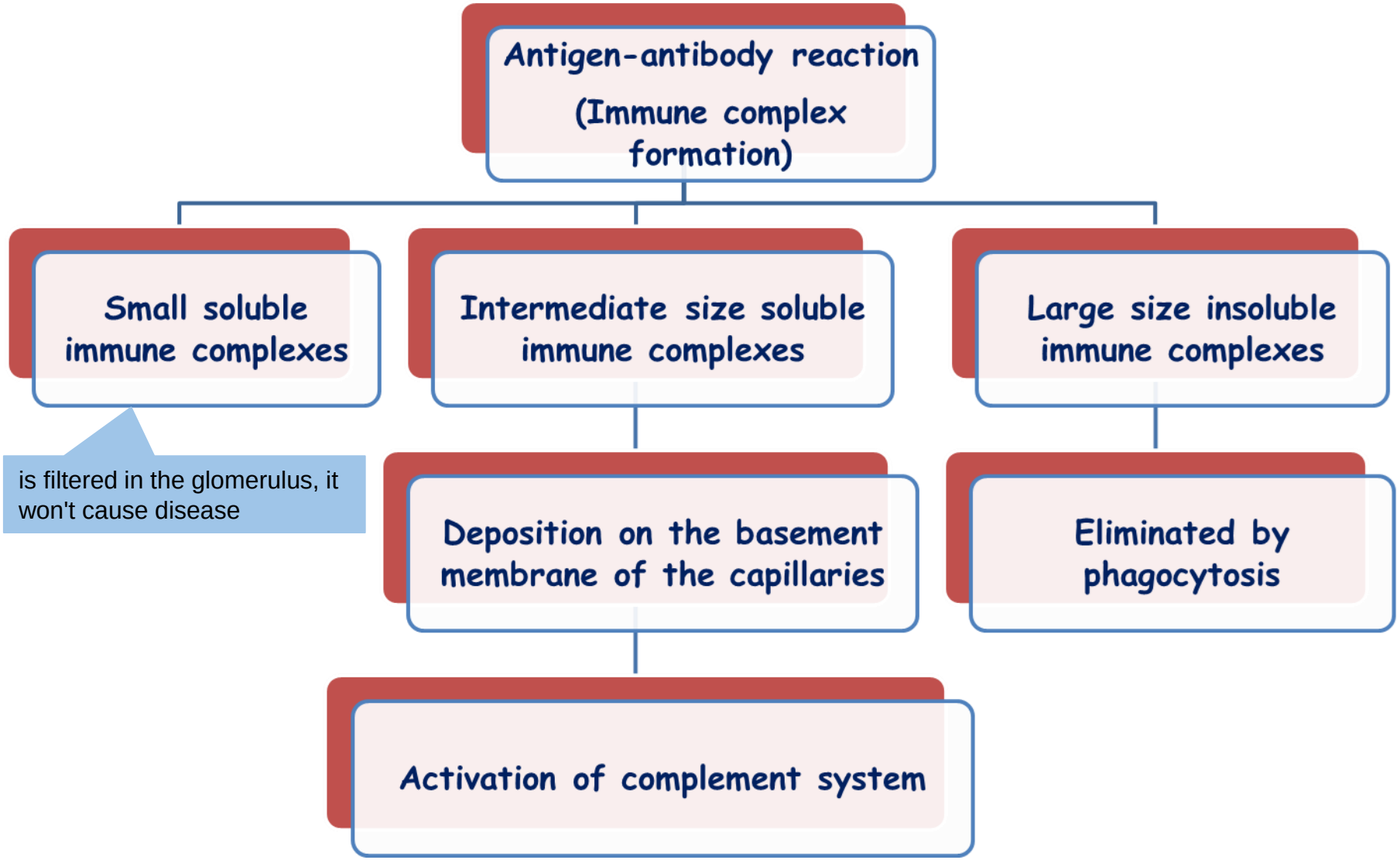
*Inflammation (Nephritis)>Hematuria

*Nephrotic > Proteinuria

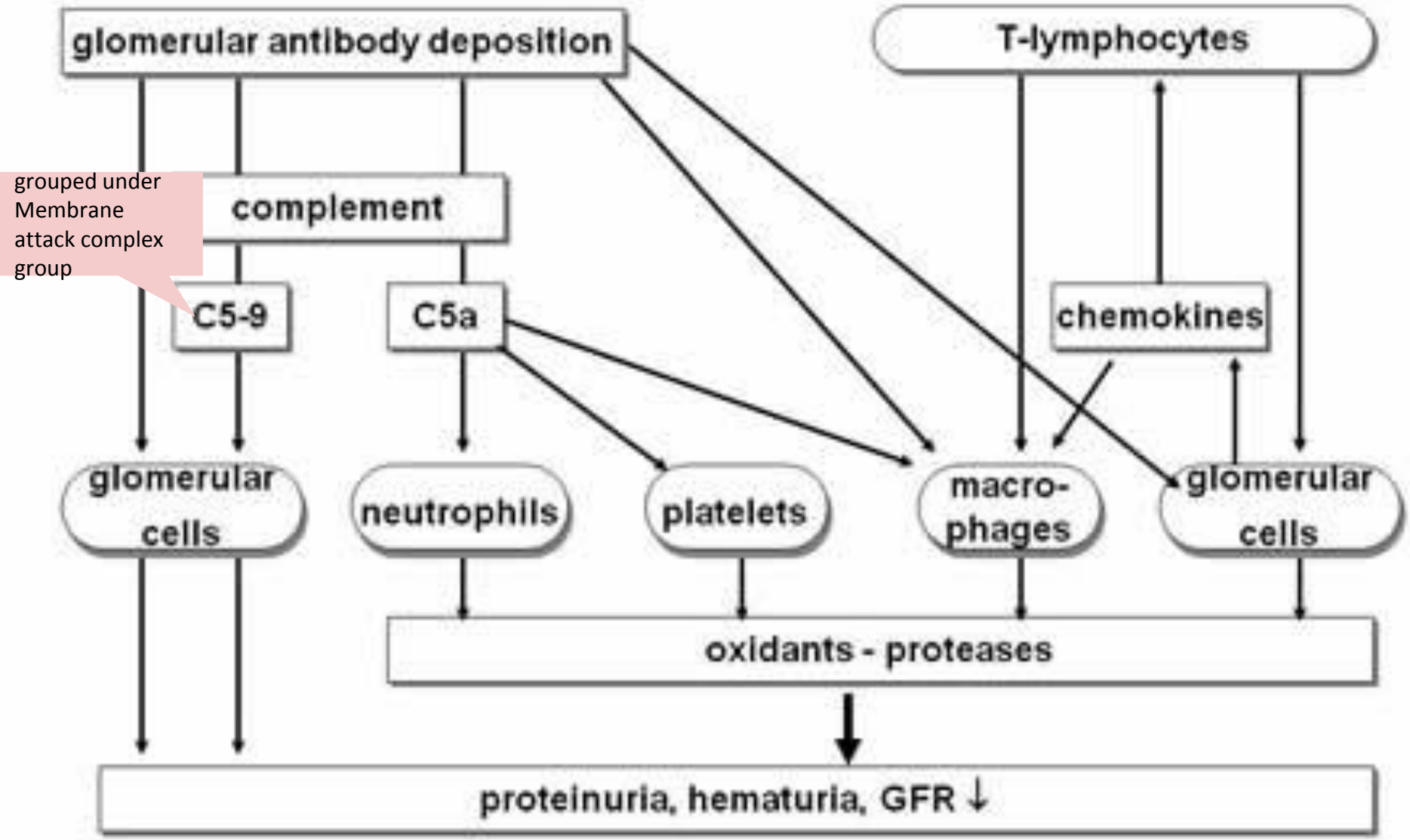
The spectrum of glomerular diseases



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)

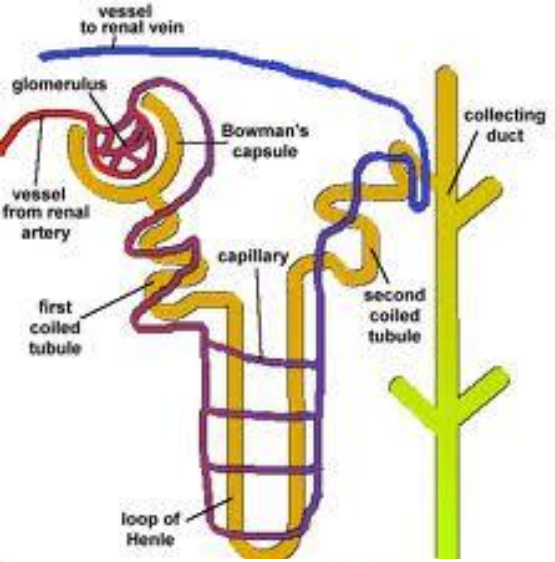
CR41 (complement receptor) exists in the endothelim , kidneys and synovials. That's why we see such manifestations in these areas.

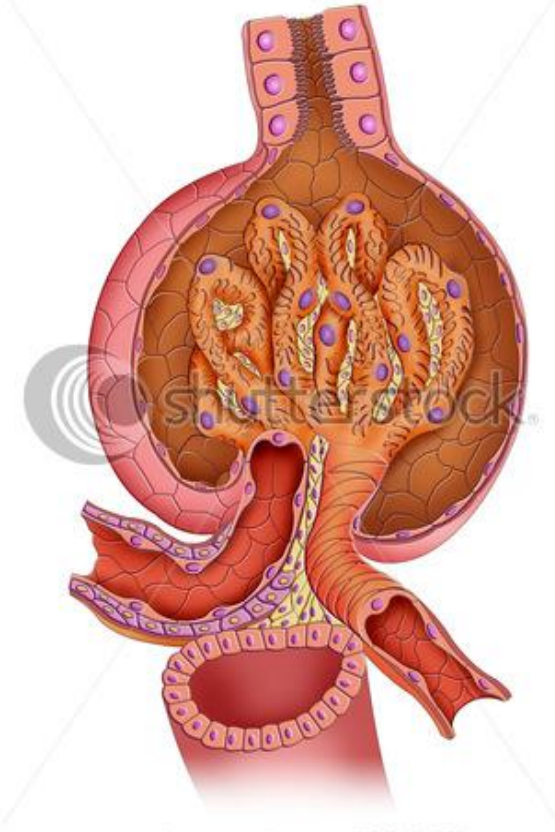
بسبب كثرة وجود,لماذا هذي الأماكن اكثر عرضه

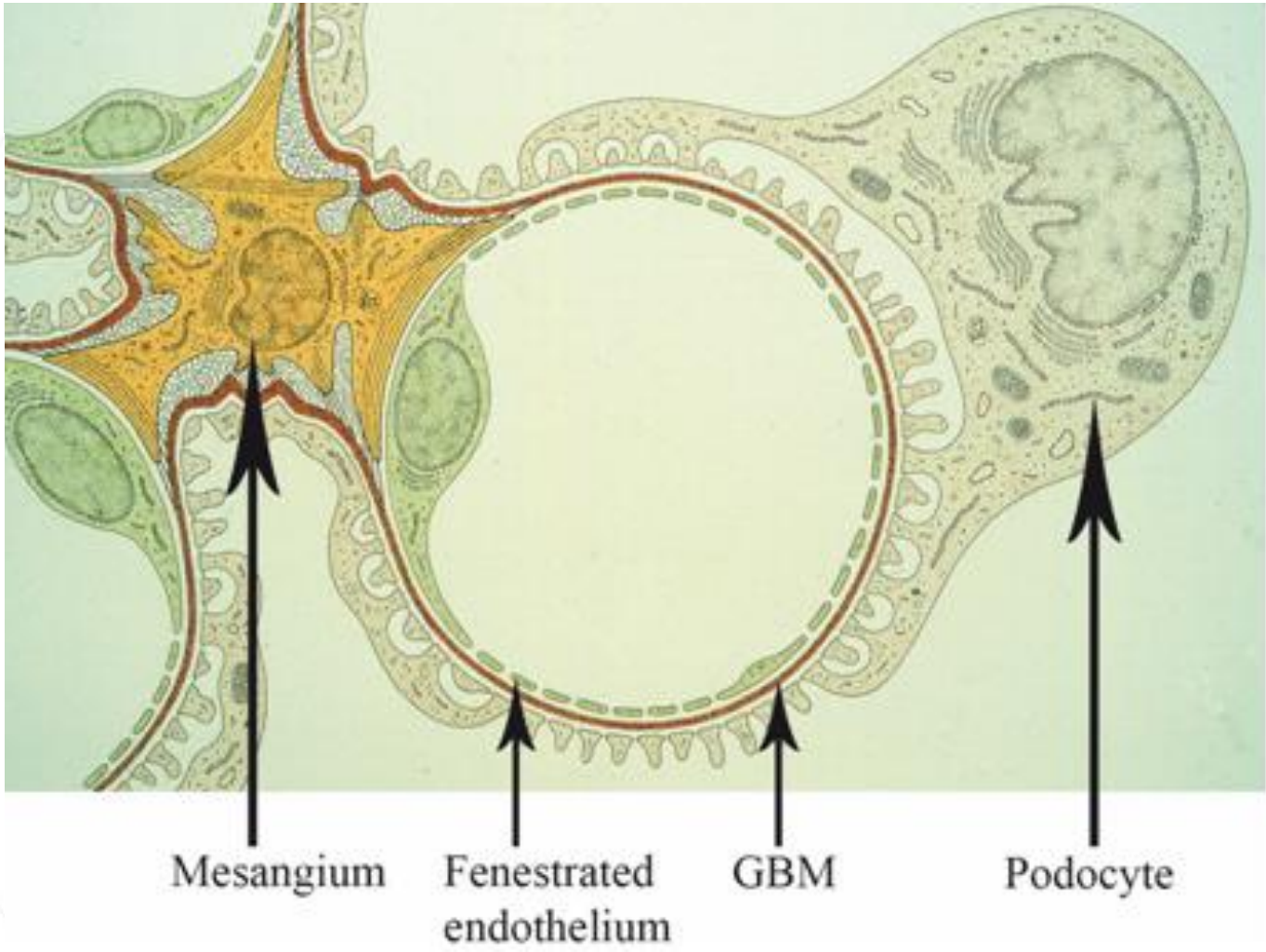
Complement receptor

فيها أكثر من غيرها

Nephron and glomerulus







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

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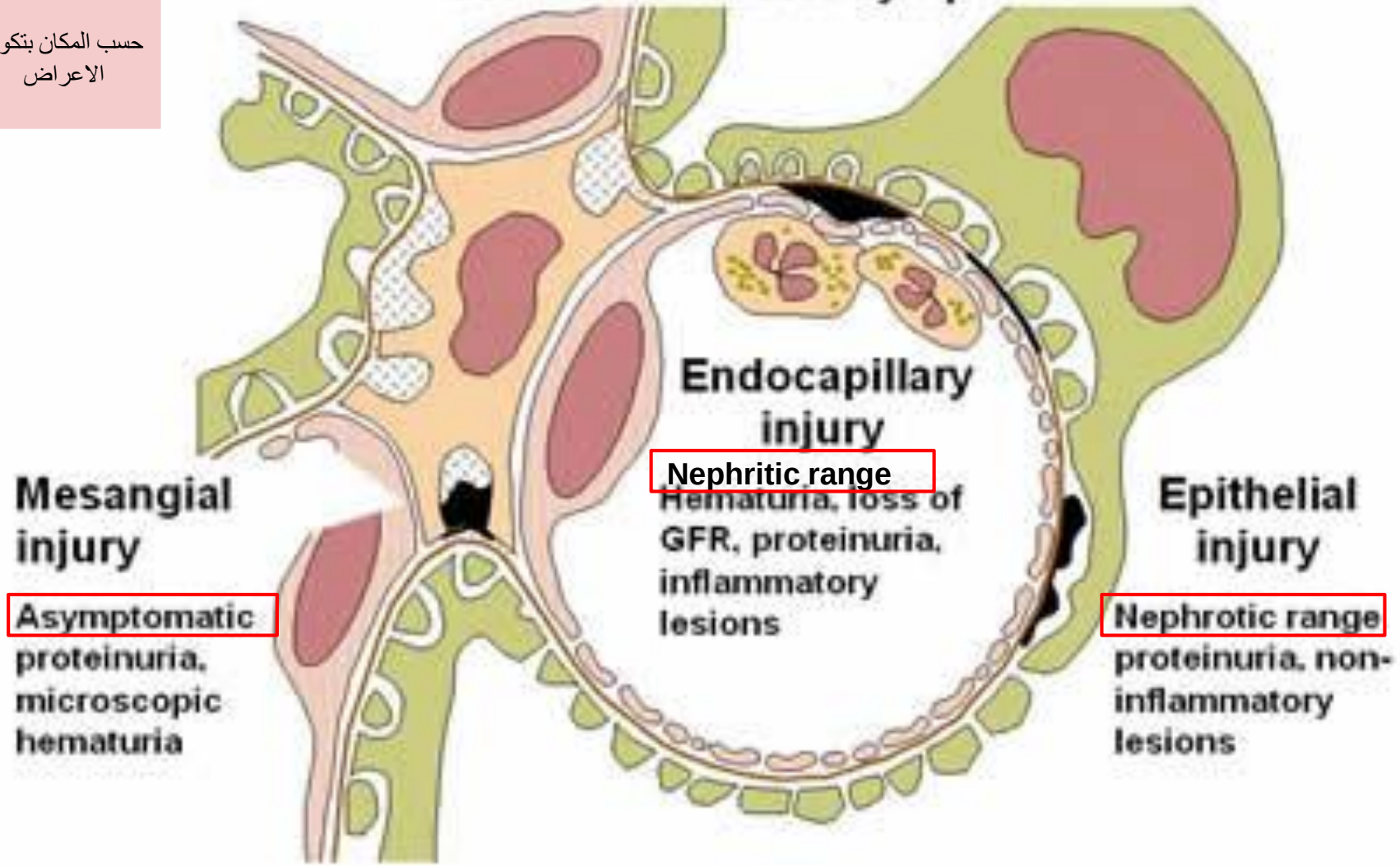


Types of immune-mediated renal injury:

- 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* **strept** pharyngitis.
- 14-21 days *after* (skin infection)

until the microorganism and the symptoms of its infection disappear

in skin infections it takes longer time

these can lead to Abrupt onset (Acute nephritic syndrome)

after a period of time when there is no more symptoms of the post infection , a sudden onset of the antibody mediated disease post infectious glomerulonephritis

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**

caused by only certain strains of streptococci, designated as

mostly negative if skin infection

- In most children bacterial culture will be negative
- Anti –streptolysin-O antibody(ASO) will be the only evidence

you are trying to prove that the infection is indeed strept, not staph or anything else at all

ASO=blood test to measure antibodies against streptolysin O

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

Diffuse proliferative GN (PGN)

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

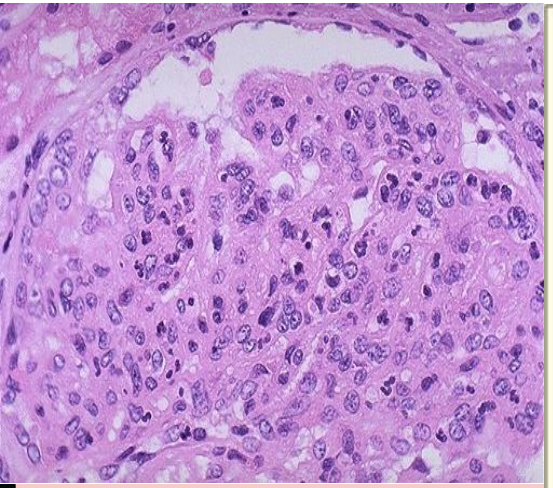
➢ Typical features of immune complex disease :

- Hypocomplementemia

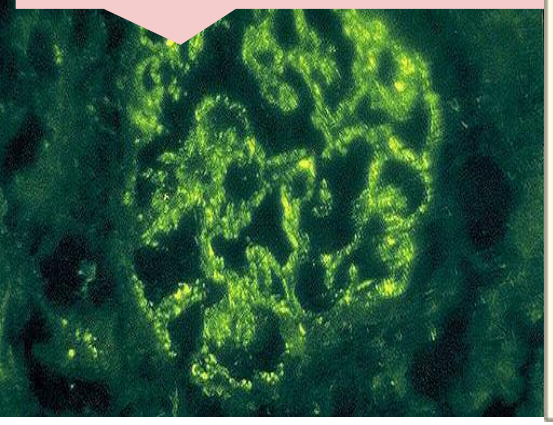
less complements in the circulation because they got deposited (consumed) on glomerular basement membrane

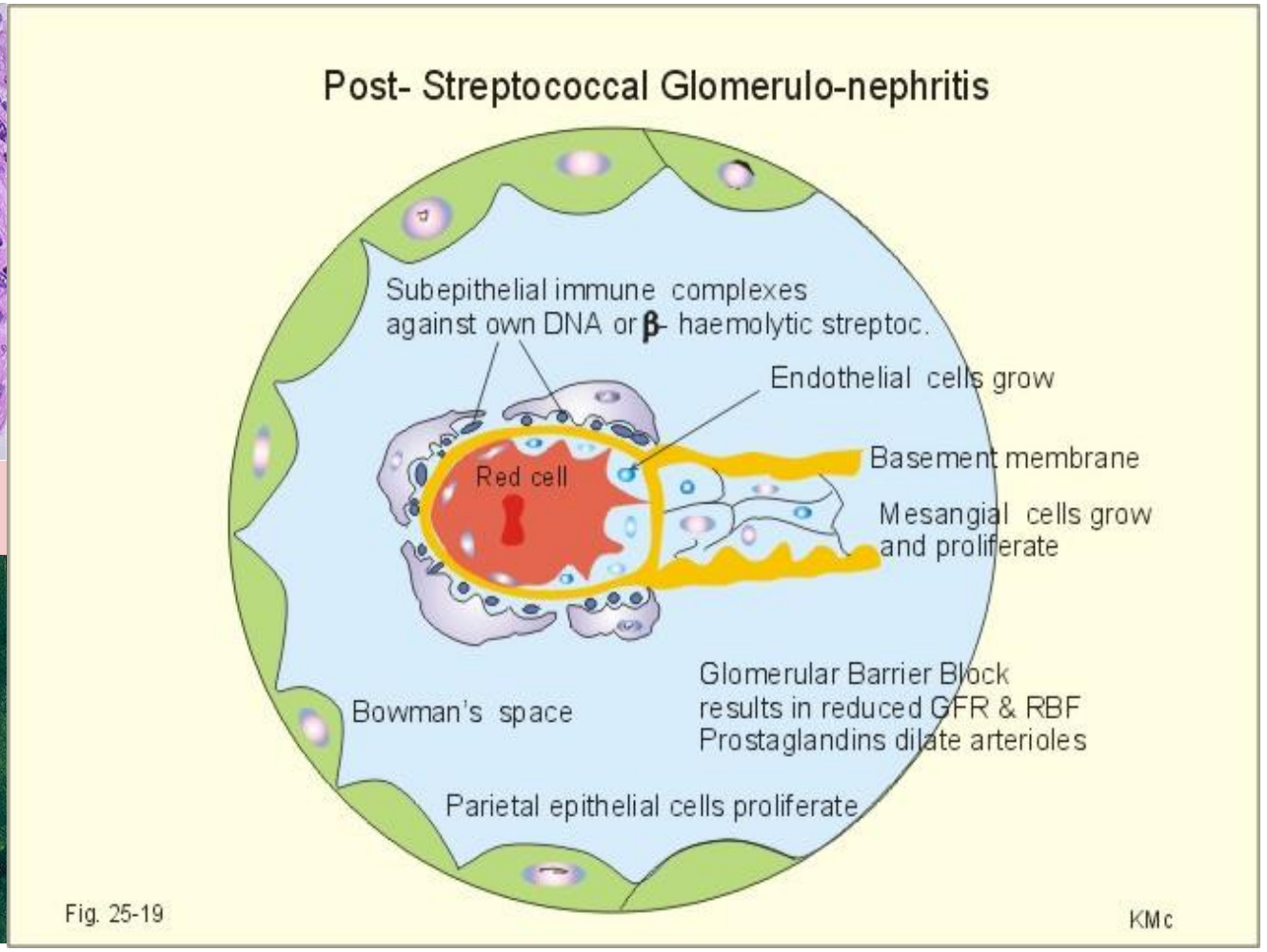
- Granular deposits of IgG & complement on GBM

Post streptococcal GN. Diffuse Proliferative GN (Generalized damage to glomeruli)



immunofluorescent dye (directly applied on sample)





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

2. Membranous Glomerulonephritis (Membranous nephropathy)

- A slowly progressive disease

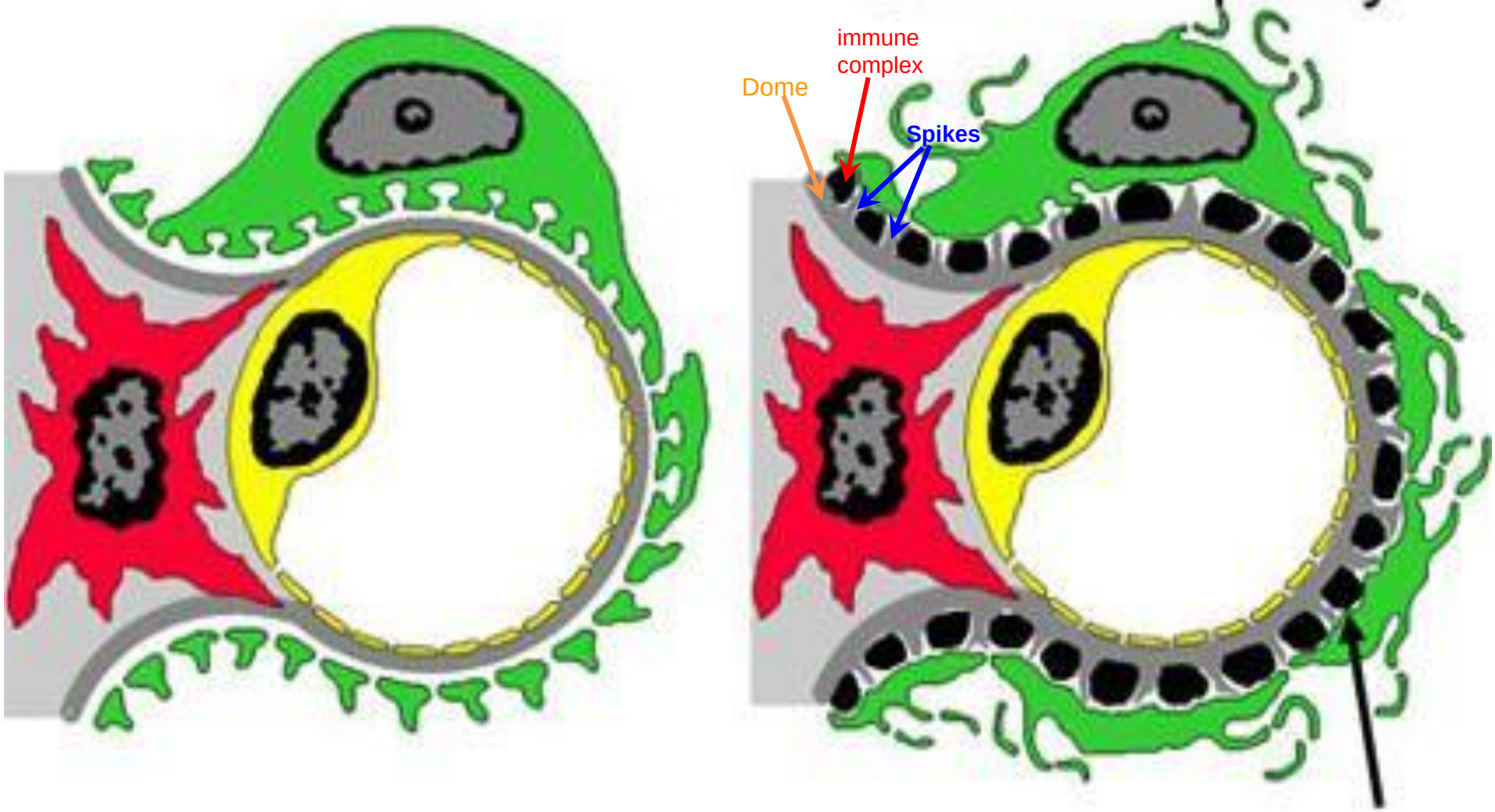
- A form of chronic immune-complex nephritis

- Most common between 30 - 50 years

Immune complexes are deposited in a thickened basement membrane creating a "spike and dome" appearance on electron microscopy only

Normal Capillary

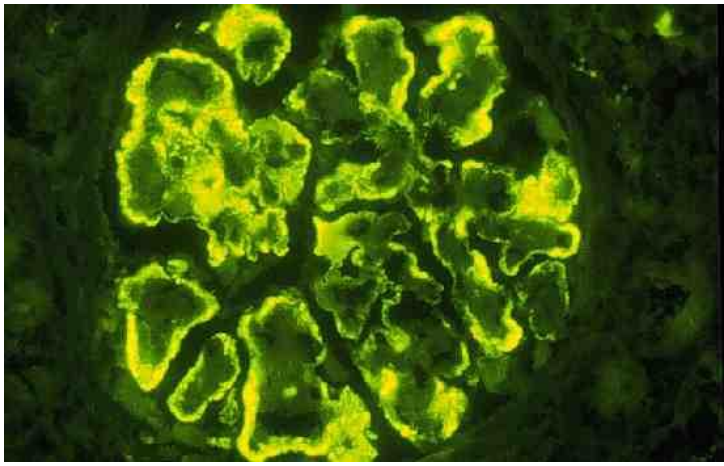
Membranous Glomerulopathy



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

Type II MPGN

Also known as : **dense deposit disease** .

The fundamental abnormality is :

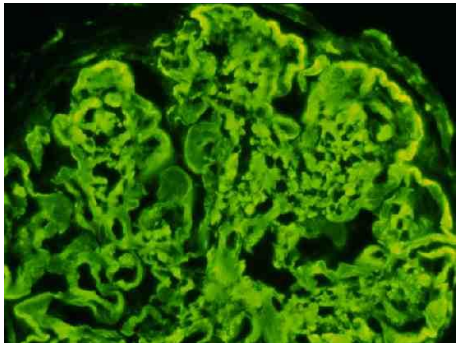
- Excessive complement activation.

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

C3 convertase is responsible for activating complement systemes by cleavage of C3

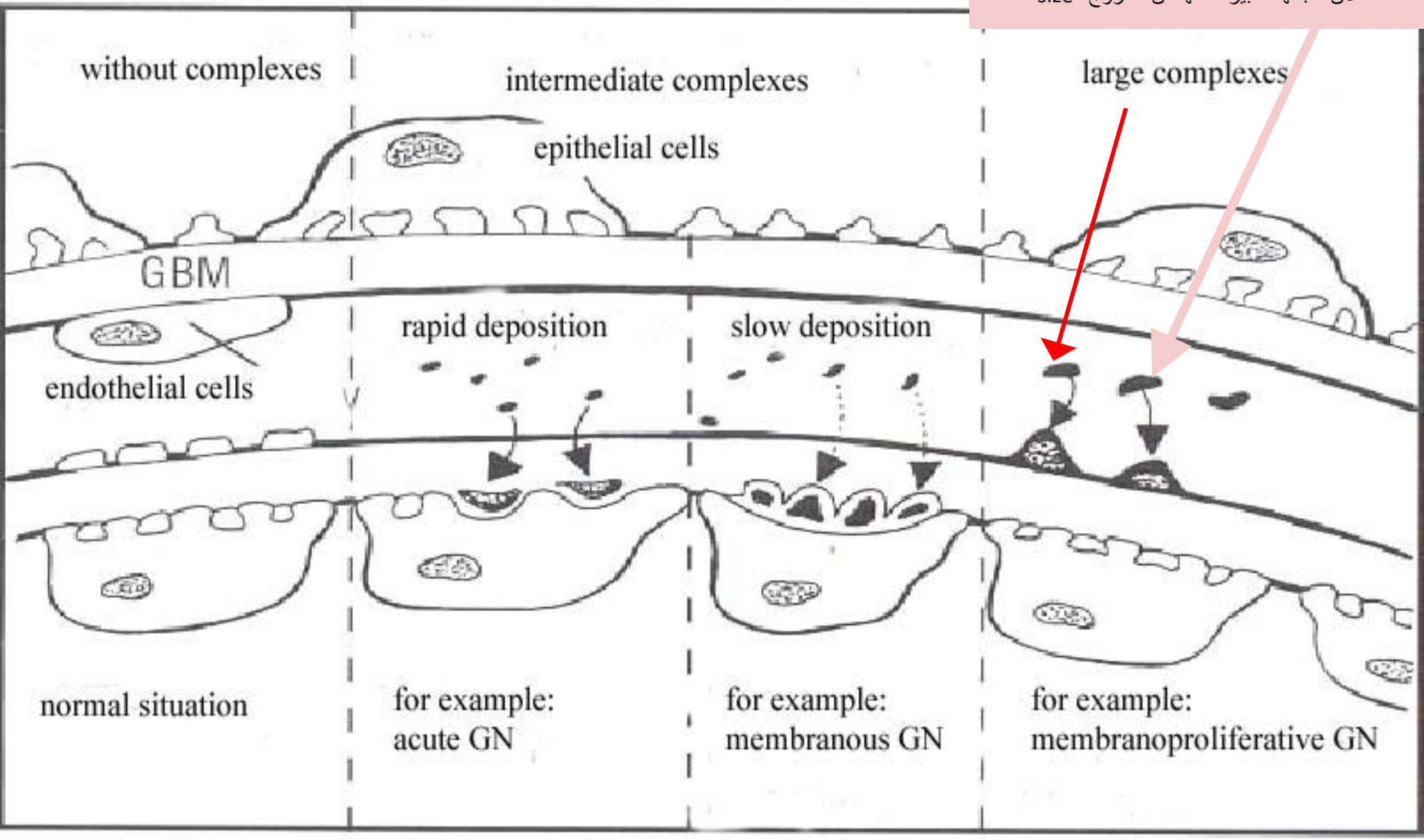
C3 nephritic factor=
which is believed to stabilize the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway.These abnormalities result in excessive complement activation. more marked in dense deposit disease,

- Characterized by **intramembranous dense deposits**



Membranoproliferative GN

the complex is large because it has a lot of antibodies or a lot of complement and it can't pass through the glomeruli so it affects the mesangial cell only "the affected Tissue is small because of complex's large size" لأن حجمها الكبير اعاقها من الخروج



4. IgA Nephropathy (Berger disease)

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

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

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

IgA Nephropathy

- The pathogenic hallmark is :

- Deposition of IgA & complement C3 in the mesangium

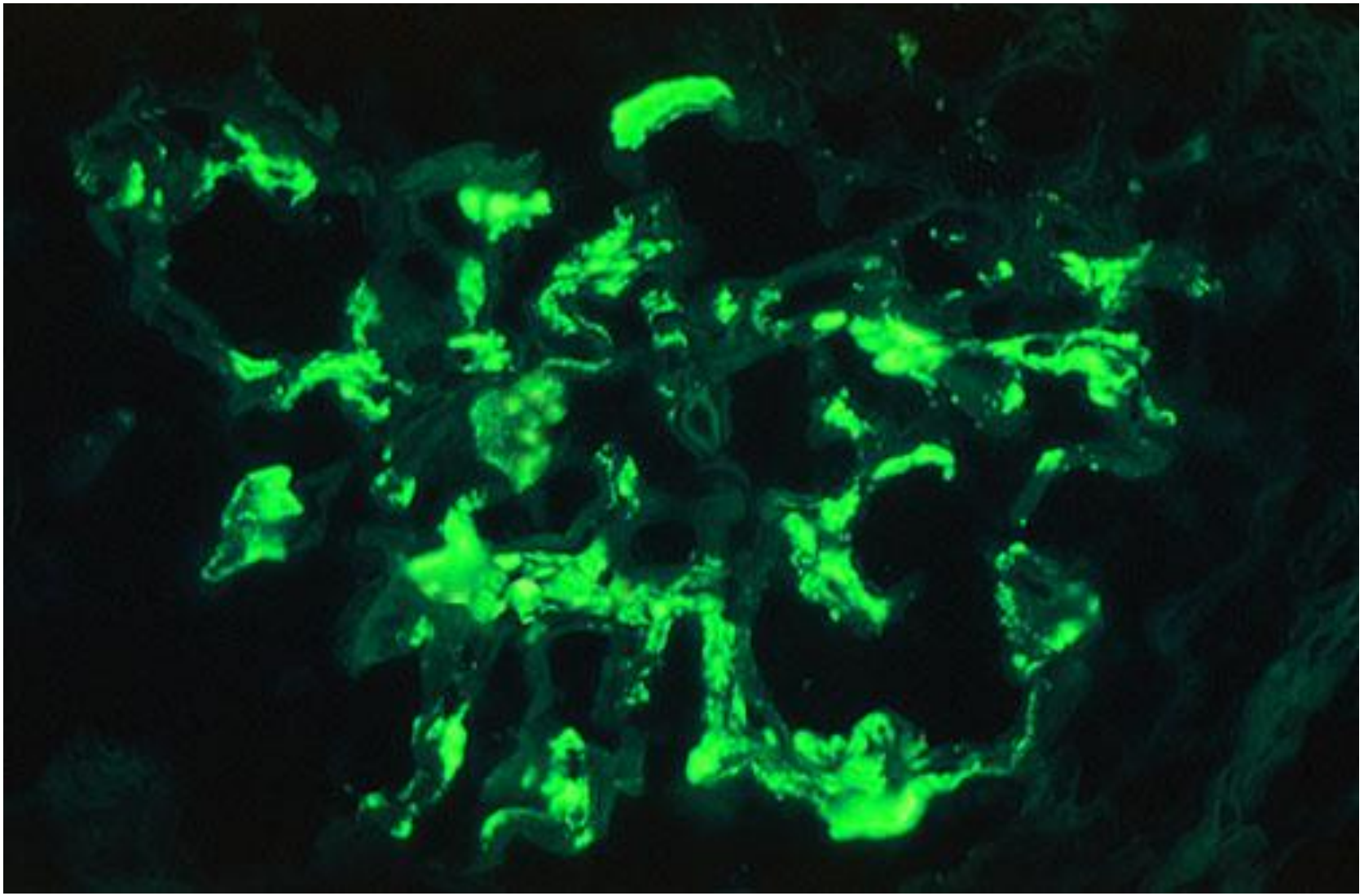
- There is evidence of :

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

”because it’s faster pathway

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

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)

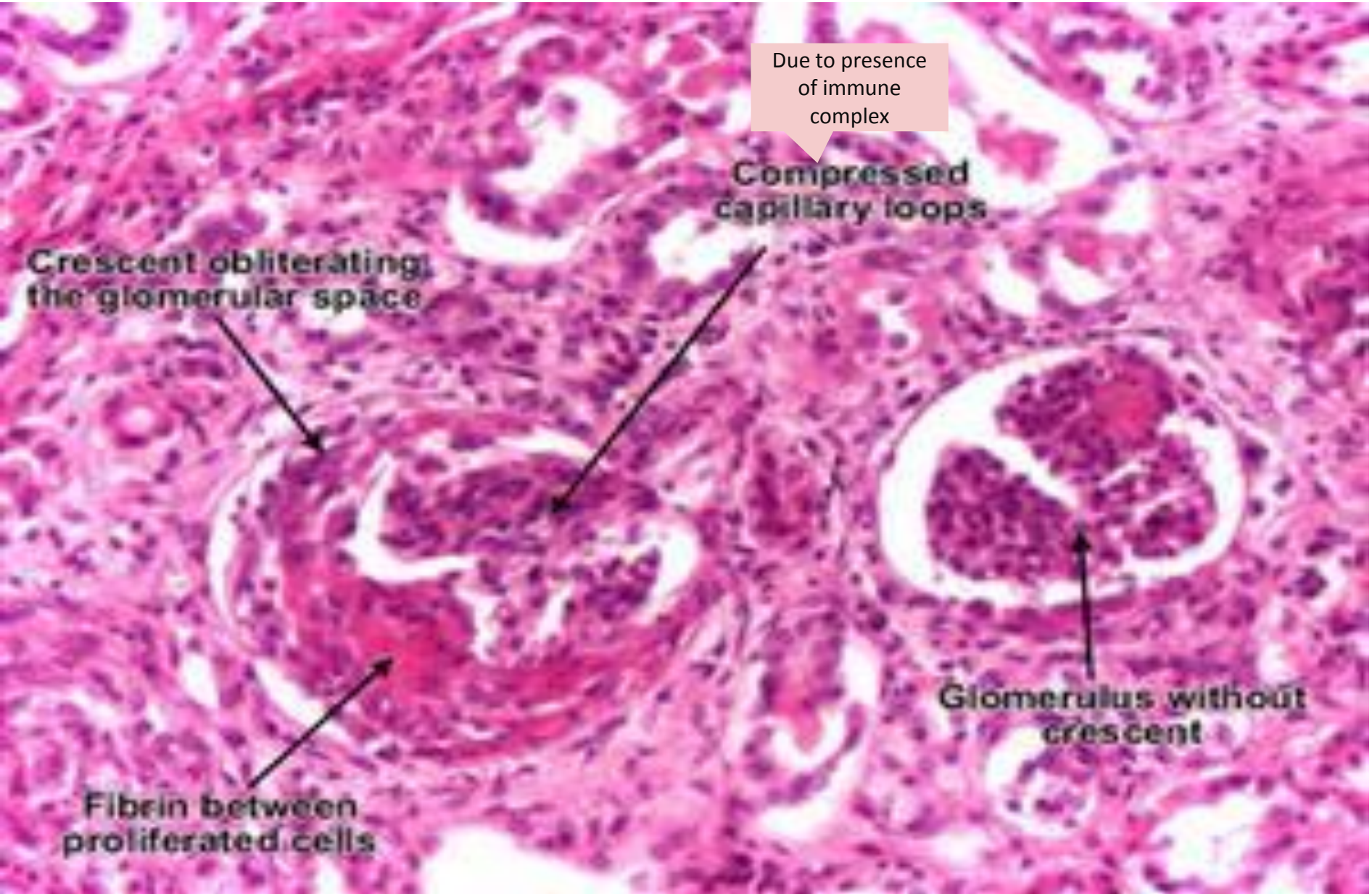
defined as any glomerular disease characterized by extensive crescents as the principal histologic finding and by a rapid loss of renal function

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

In most cases the glomerular injury is immunologically mediated

A practical classification divides CrGN into three groups on the basis of immunologic findings

Rapidly Progressive (Cresentic) Glomerulonephritis



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

Characterized by linear deposition of IgG and C3 on the GBM

Associated with

- **Goodpasture syndrome:**

  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

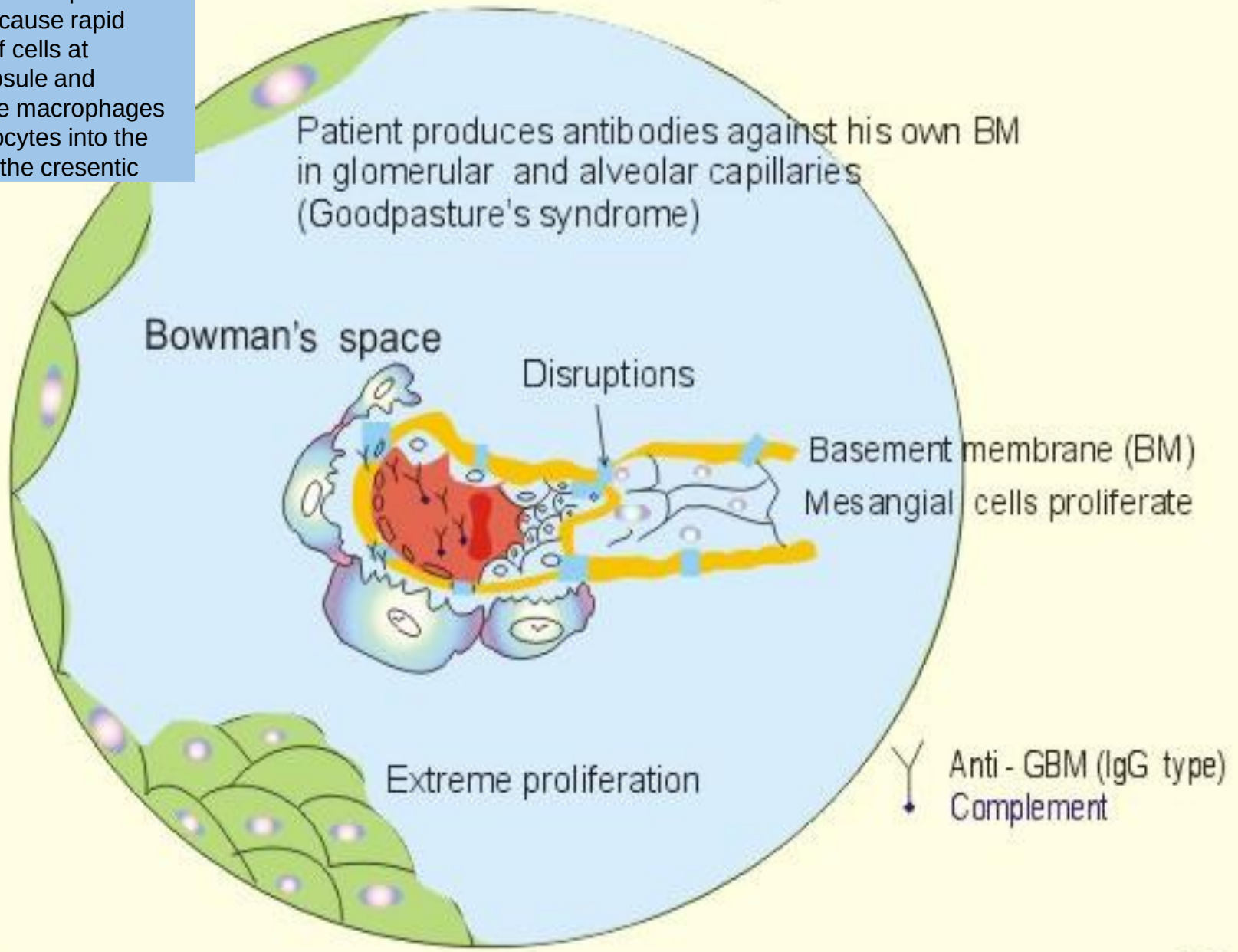


Fig. 25-20

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Type II
(Immune complex - mediated Cresentic GN)

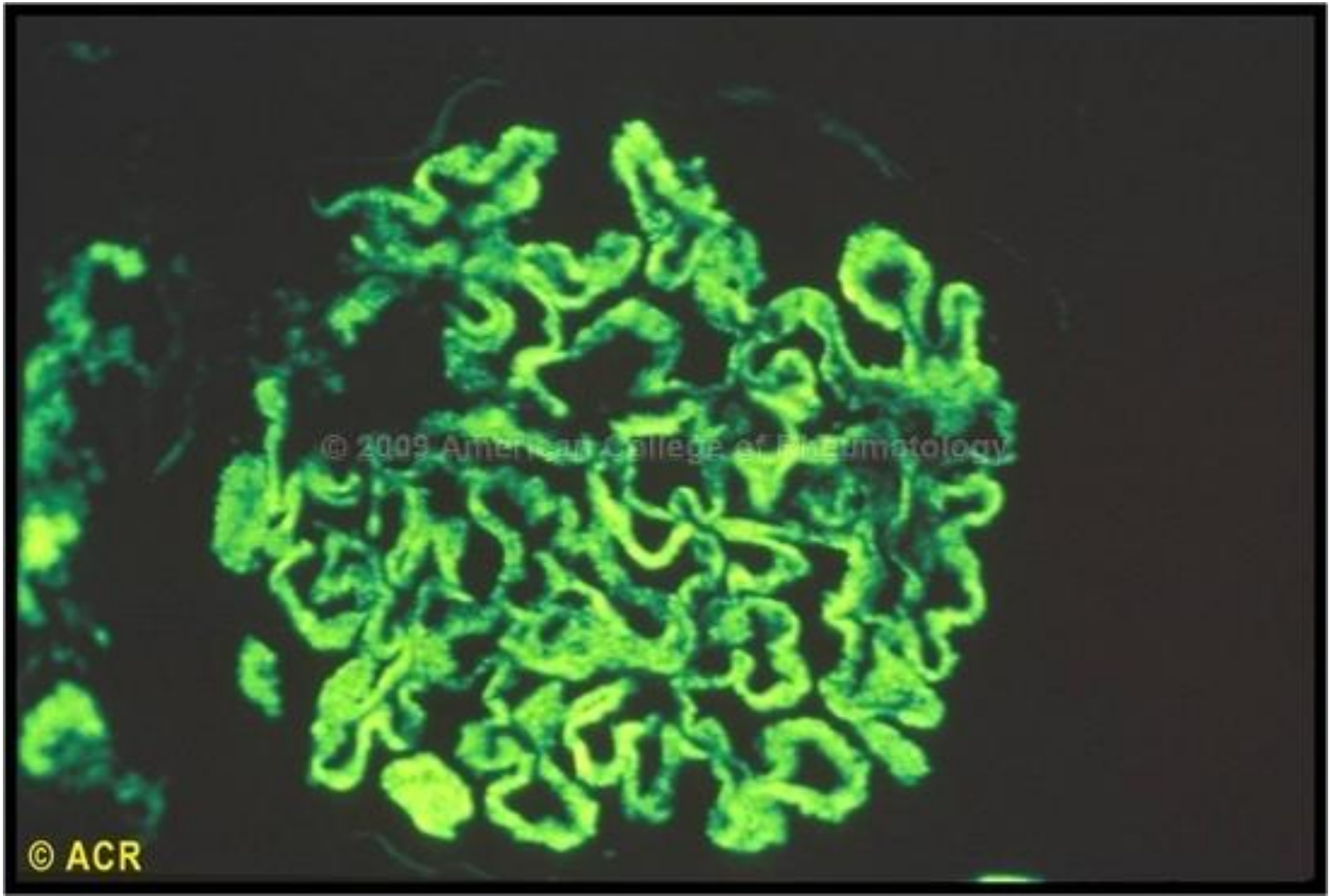
- May occur as a complication of any of the immune complex nephritides

it is not a primary disease of its own, it's a result of other diseases.

  - 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



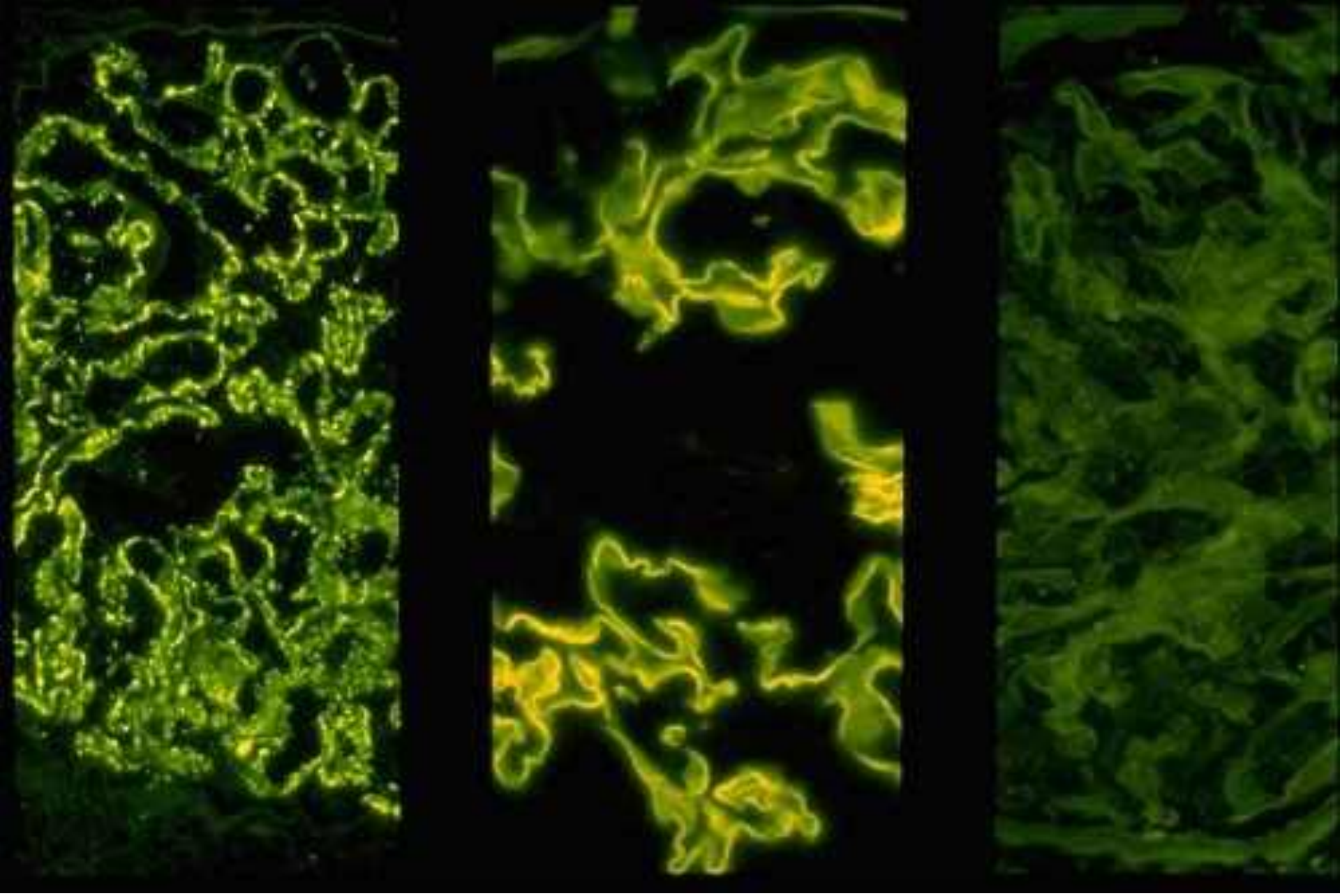
Pauci= قليل

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

*__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)

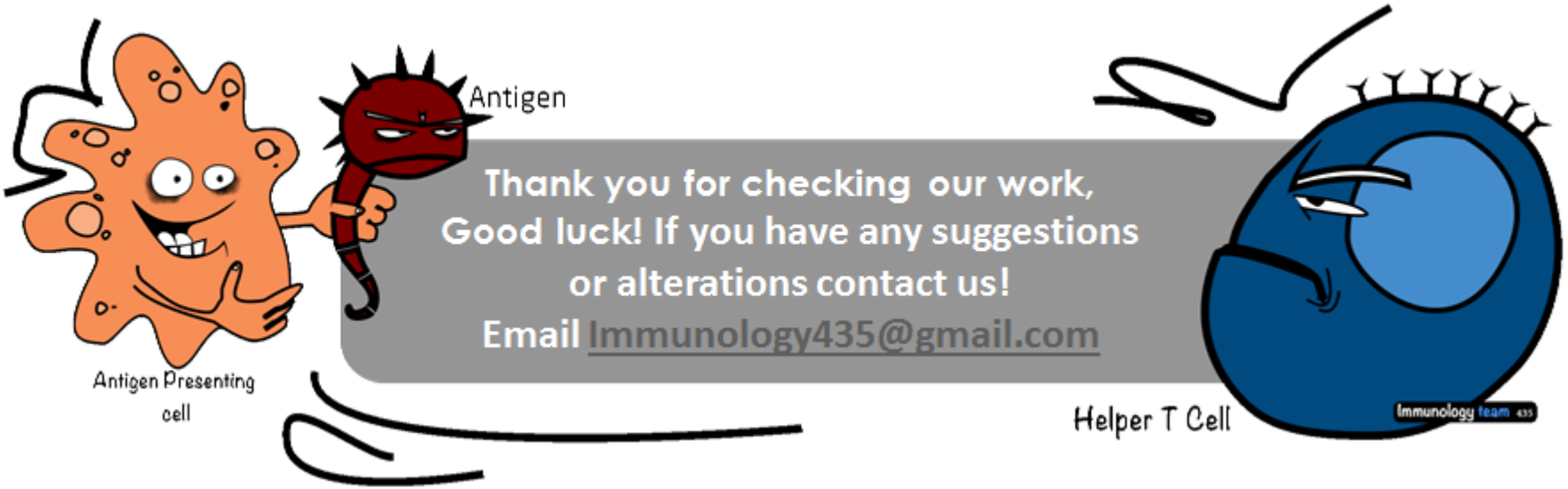
No antibody staining
(Pauci associated with vasculitis)

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.



sources:
-robbins basic pathology
-medscape