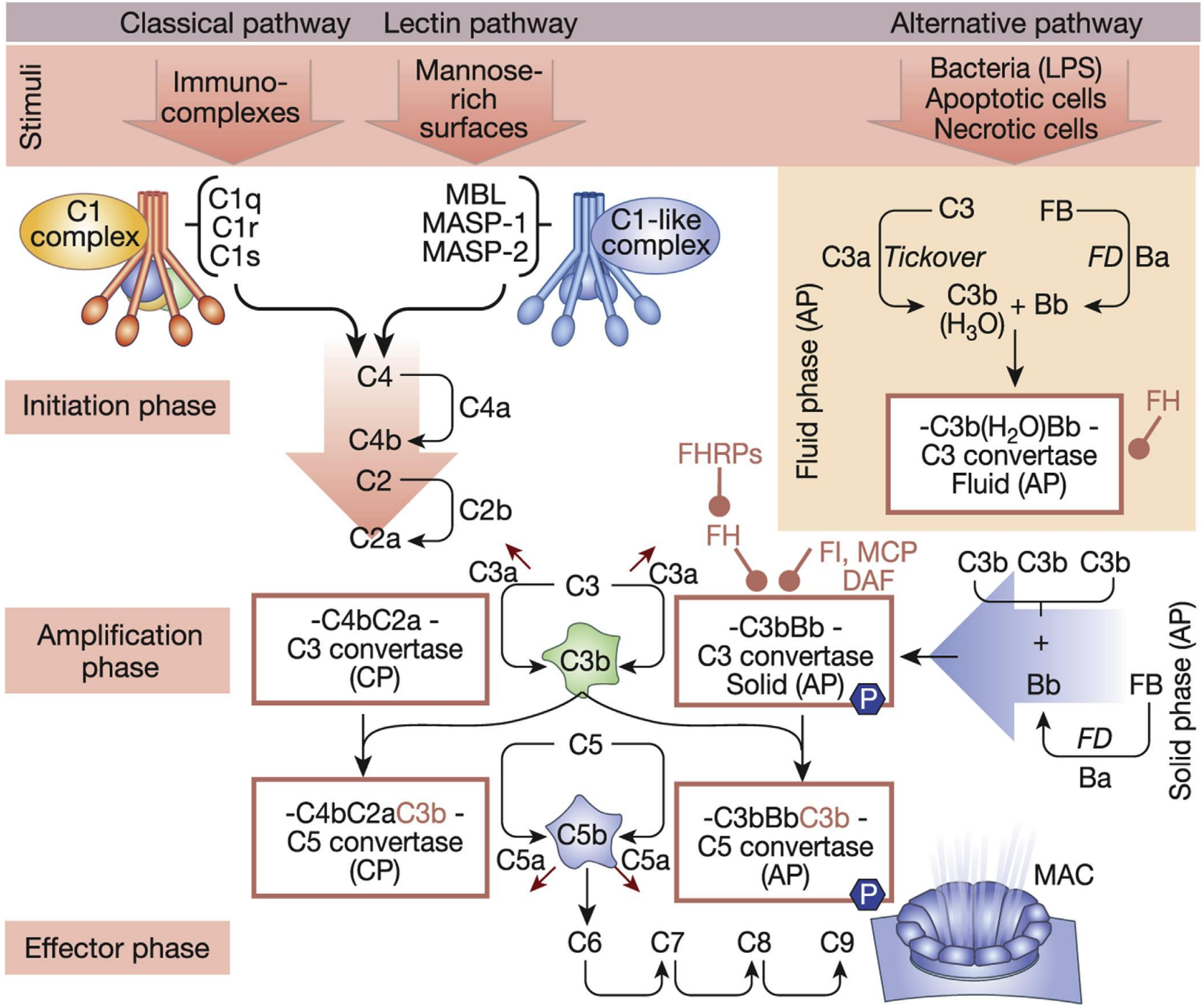
Complement – why all the interest?

What is complement?

- Essential part of innate immunity
- First-line defence against invading pathogens and abnormal self-derived components
- Proteolytic cascade, comprising more than 30 proteins, 4 where serine proteases activate each other
- Complement components are available in soluble form (fluid phase), or expressed on the cell membrane (solid phase)


Classical pathway
Lectin pathway
Alternative pathway
Stimuli
Immuno-complexes
Mannose-rich surfaces
Bacteria (LPS)
Apoptotic cells
Necrotic cells
C1 complex
C1q
C1r
C1s
MBL
MASP-1
MASP-2
C1-like complex
Initiation phase
C4
C4a
C4b
C2
C2b
C2a
C3
C3a
Tickover
FB
FD
Ba
C3b (H3O)
+ Bb
Fluid phase (AP)
-C3b(H2O)Bb - C3 convertase Fluid (AP)
FH
FHRPs
FH
FI, MCP DAF
Amplification phase
-C4bC2a - C3 convertase (CP)
C3b
-C3bBb - C3 convertase Solid (AP)
P
C3b C3b C3b
+
Bb
FB
FD
Ba
Solid phase (AP)
C5
-C4bC2aC3b - C5 convertase (CP)
C5b
C5a
C5a
-C3bBbC3b - C5 convertase (AP)
P
MAC
Effector phase
C6
C7
C8
C9

Complement pathway effector functions

- C5b-9 or membrane attack complex, which disrupts cell membranes and kills cells by forming lytic pores
- C3a and C5a, are powerful anaphylatoxins. Also C4a
  - Mediate local inflammation, promote chemotaxis, and activate cells through G protein–coupled receptors, C3aR and C5aR
- Opsonization occurs as a consequence of C3b labelling of target cells as foreign (bacteria) or nonviable (apoptotic cells).
  - Interactions with acquired immunity and scavenger systems then result in the removal of the opsonized cell.

Complement pathway regulation

- Complement factor I (FI)
- The proteolytic action of FI requires several cofactors:
  - Complement factor H (FH),
  - Membrane cofactor protein (MCP,CD46),
  - Decay-accelerating factor (DAF, CD55).
- DAF and MCP are membrane-bound regulators that accelerate the decay of the C3 convertase by facilitating the dissociation of Bb from C3bBb.
- FH is the most important regulator of the AP C3 convertase, both in the fluid phase and on cell surfaces.
- FH acts together with MCP in promoting the activity of FI and thus the proteolysis of C3b. It also competes with FB for binding to C3b and stimulates the decay of the C3bBb complex.

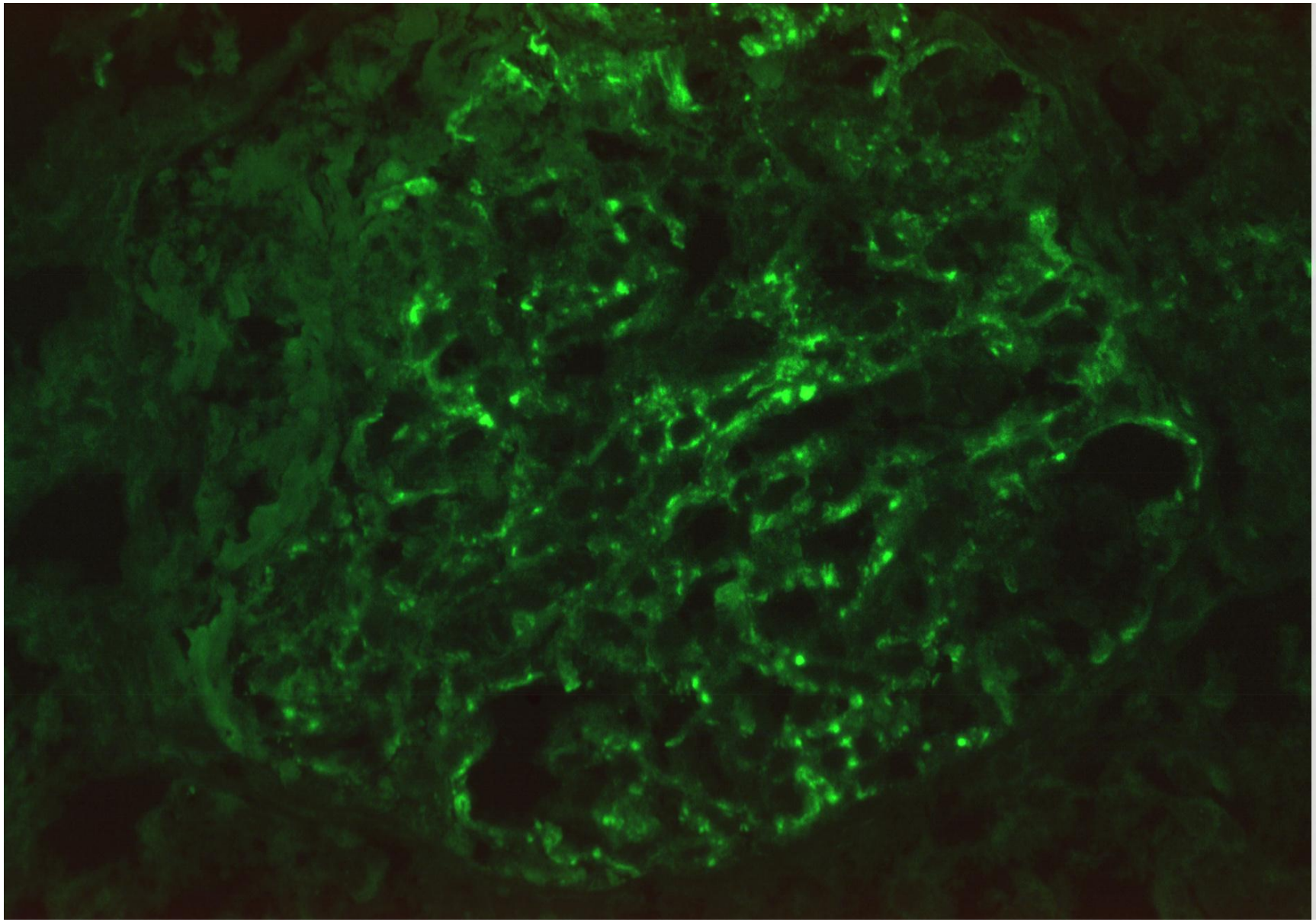
Complement in renal disease

Acute post infectious glomerulonephritis

- Low C3
- Normal or low C4
- Raised ASOT
- Probably secondary to immune complexes containing a streptococcal antigen being deposited in the affected glomeruli
- Evidence of alternative pathway activation later in the disease

IgG

C3

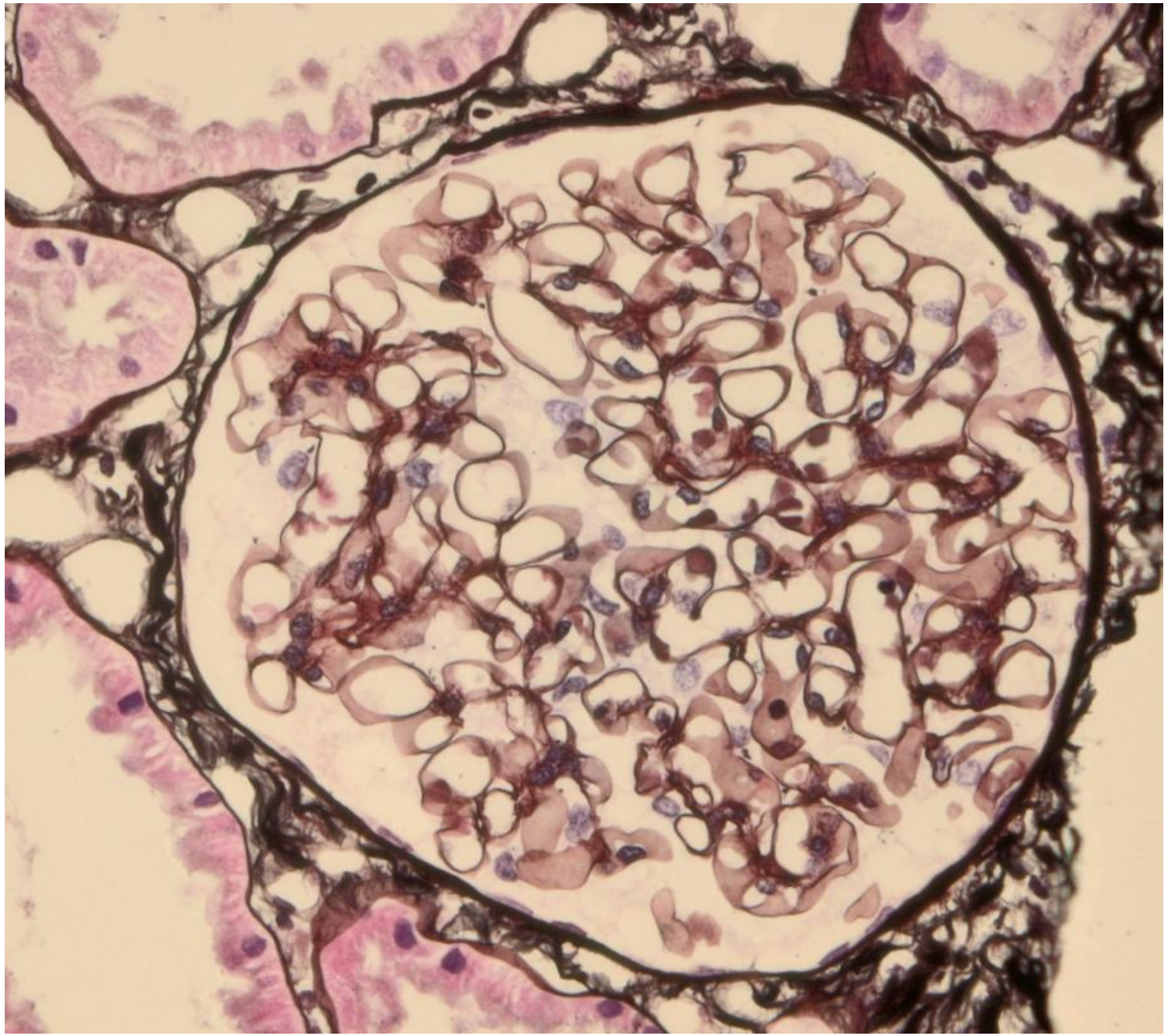


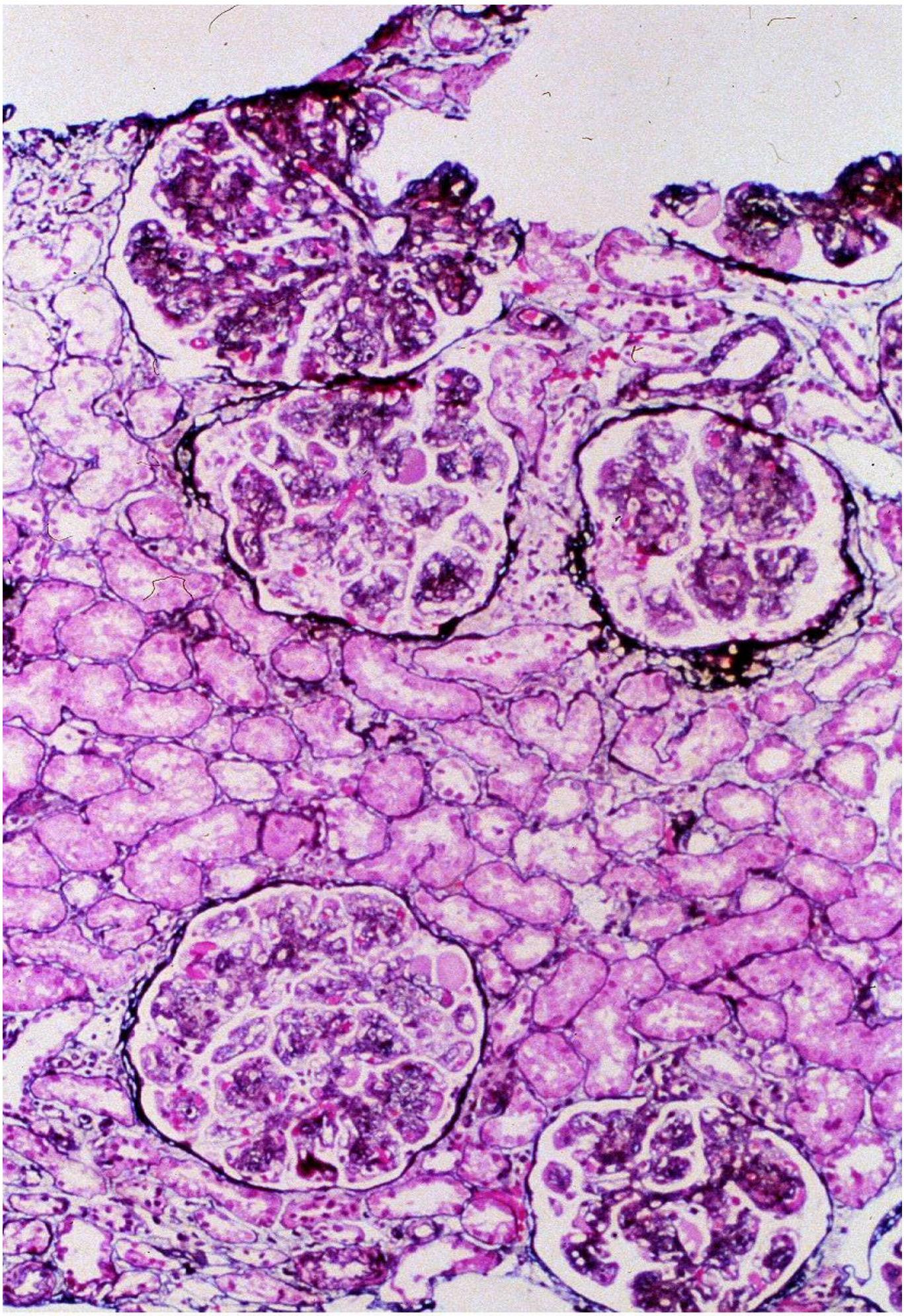
Persistent low C3 (> 8 weeks)

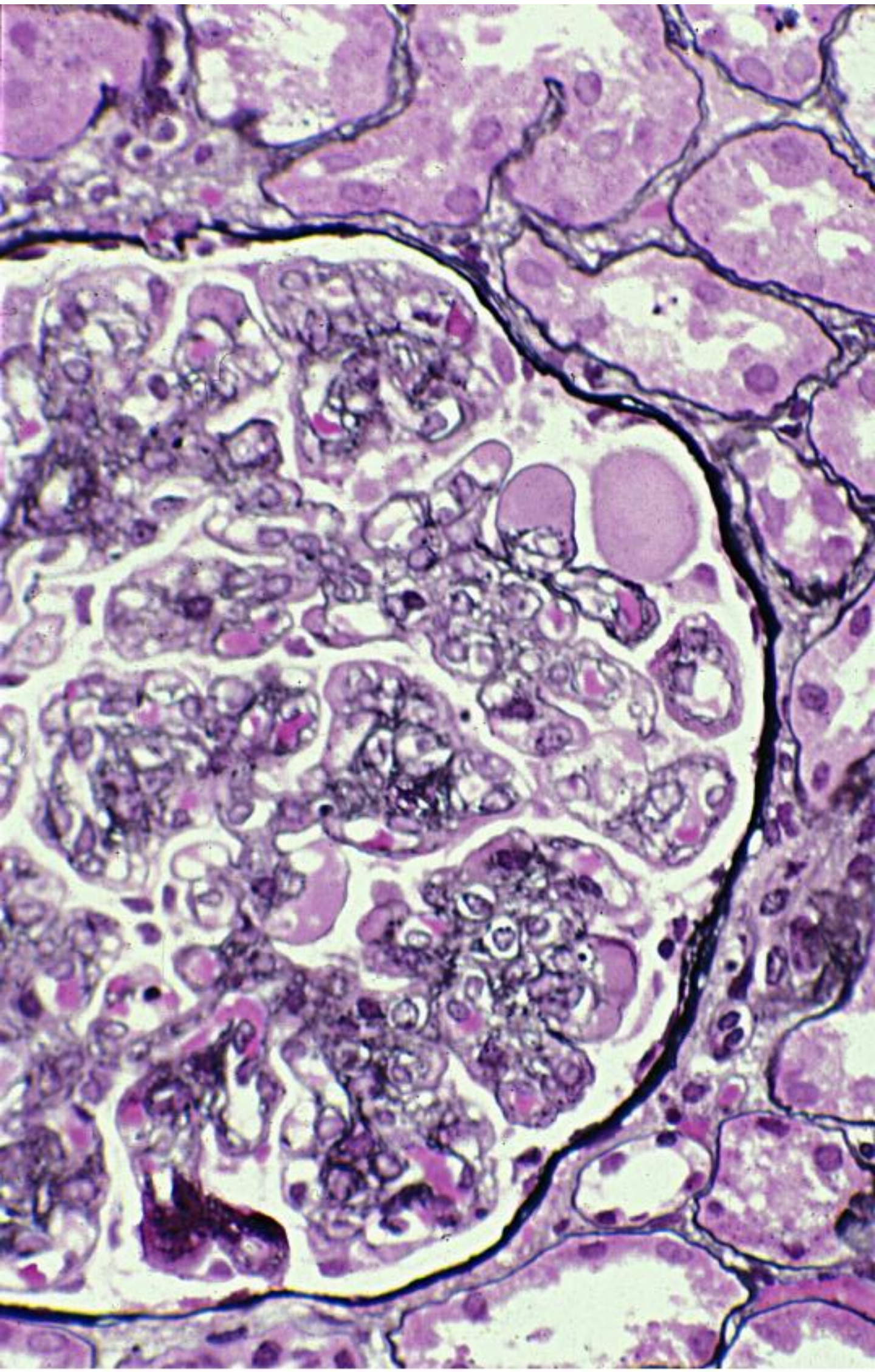
- Immune complex mediated MPGN
- Endocarditis
- Occult sepsis
- SLE
- Mutations in complement regulatory proteins

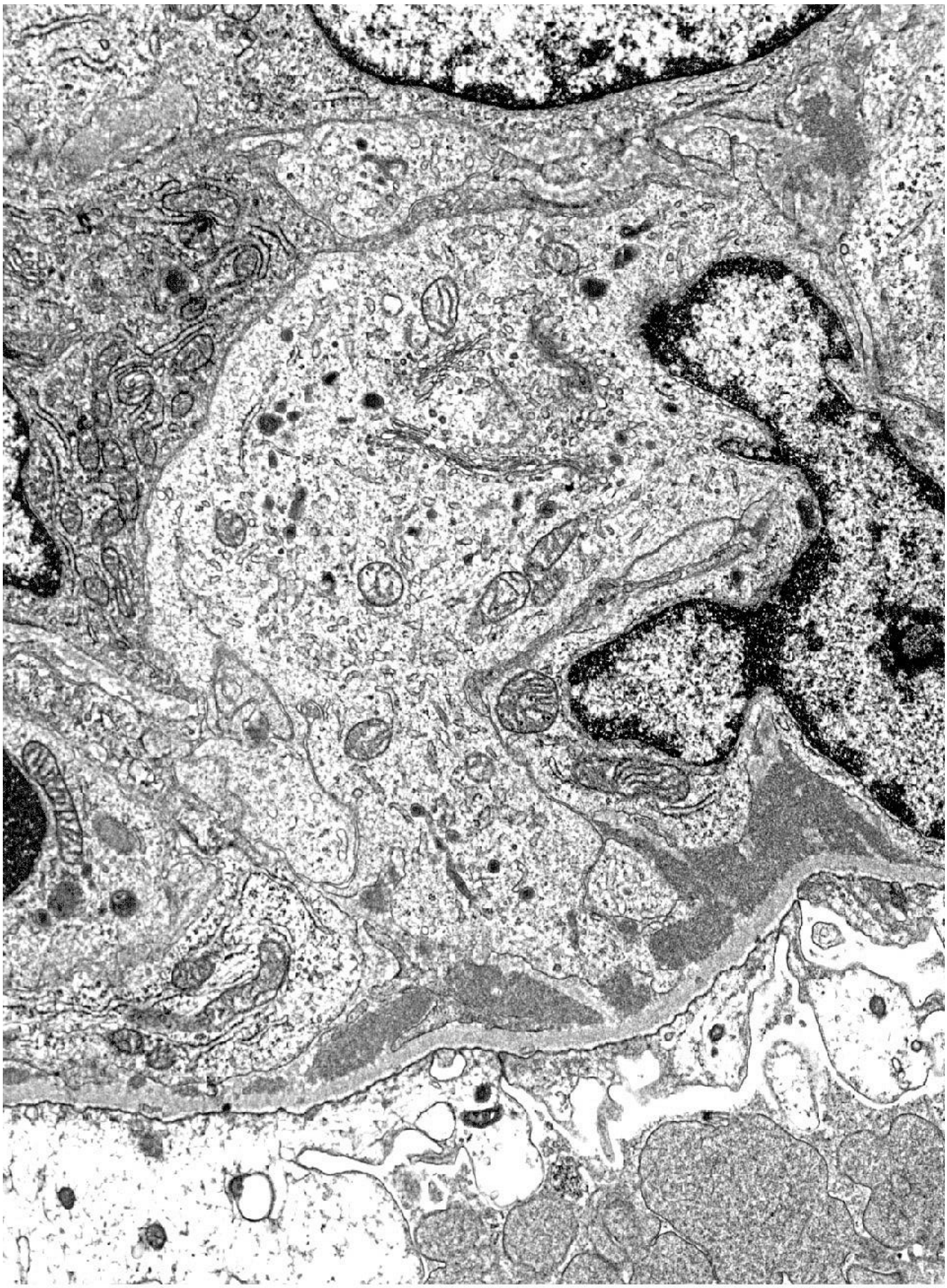
Membranoproliferative GN (MPGN)

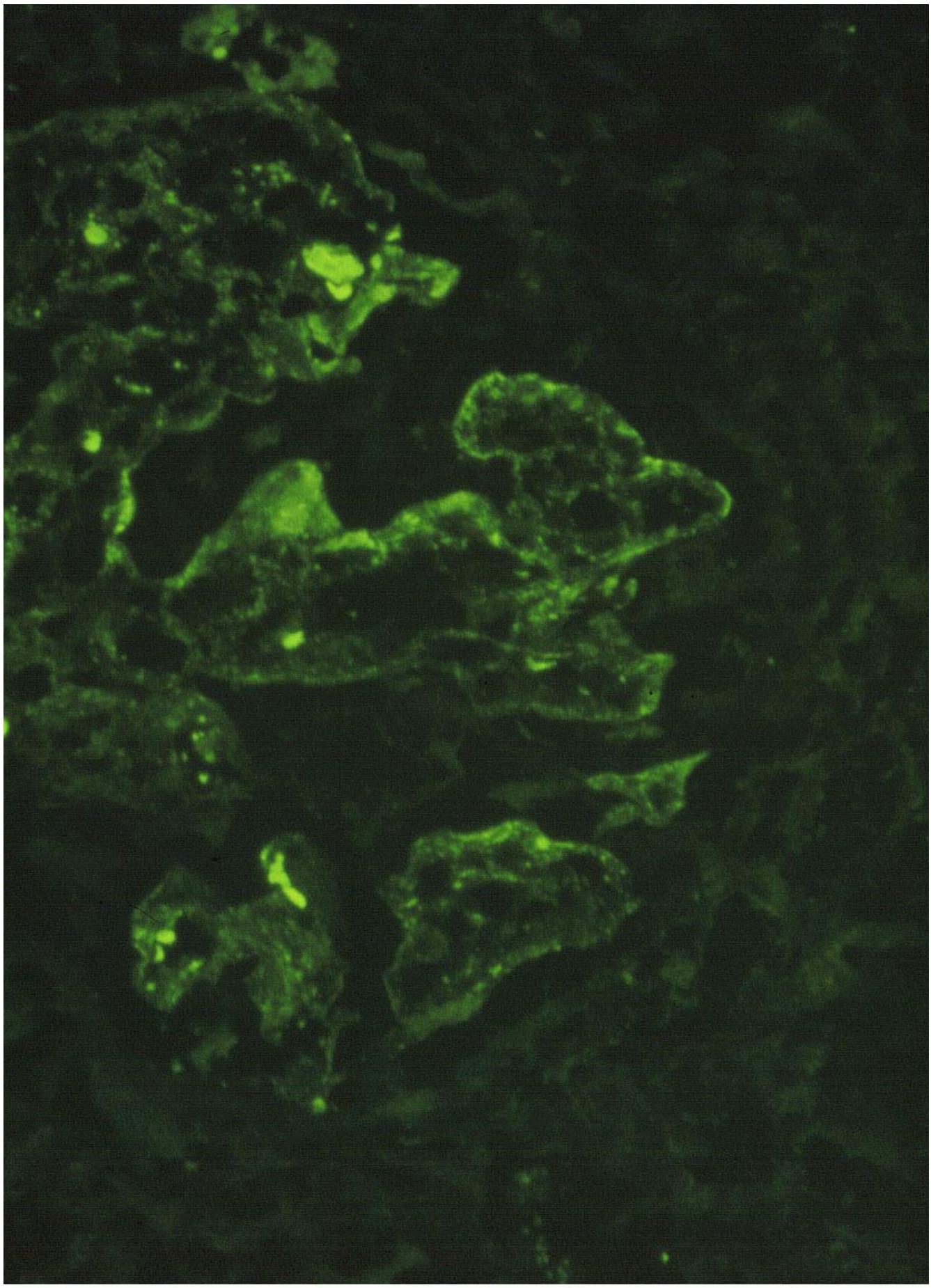
- Most commonly present in childhood
- Nephritic or nephrotic picture
- Historically
  - Type I – Primary MPGN
  - Type II – Dense deposit disease
  - Type III – Secondary MPGN (hepatitis C)

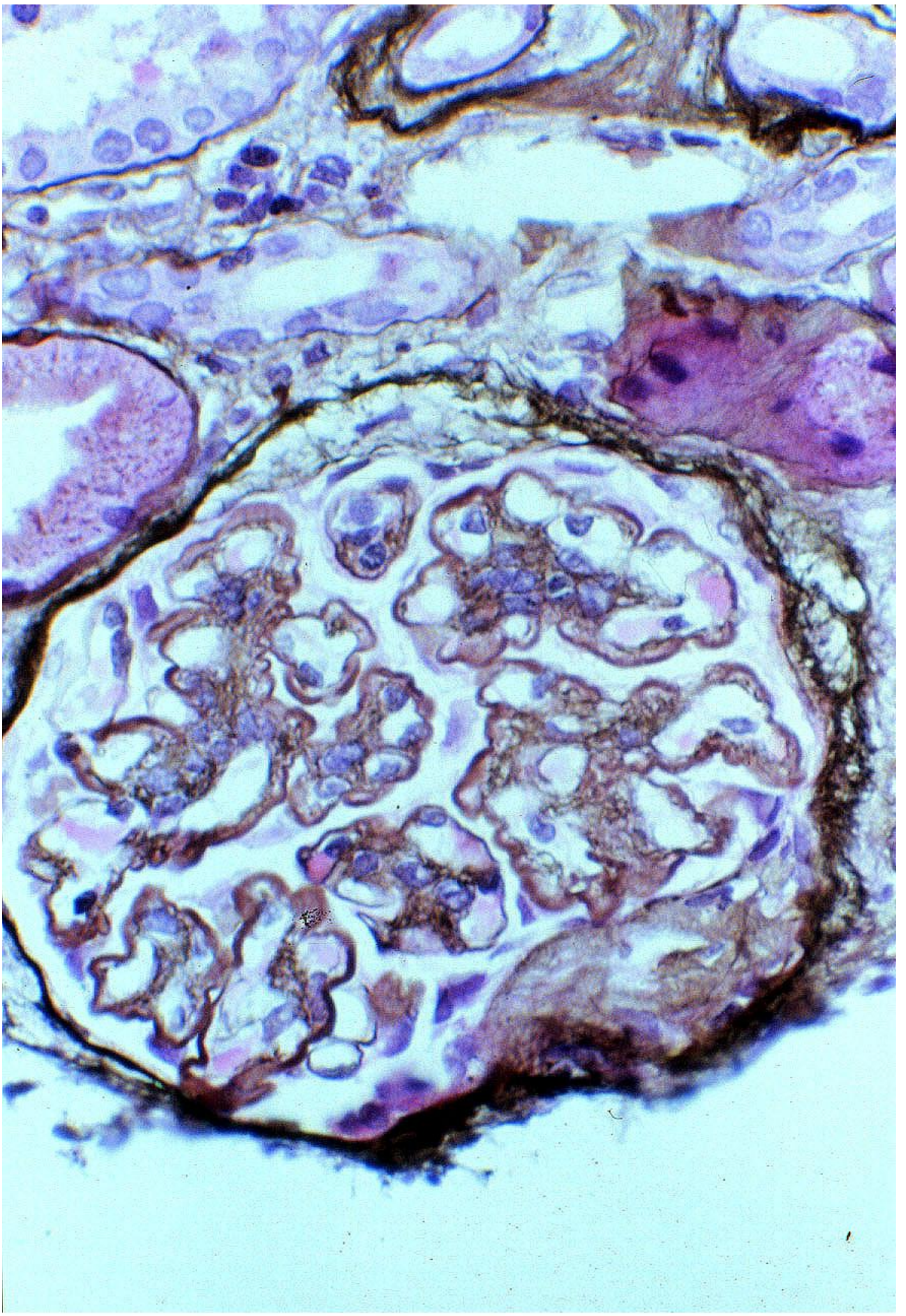


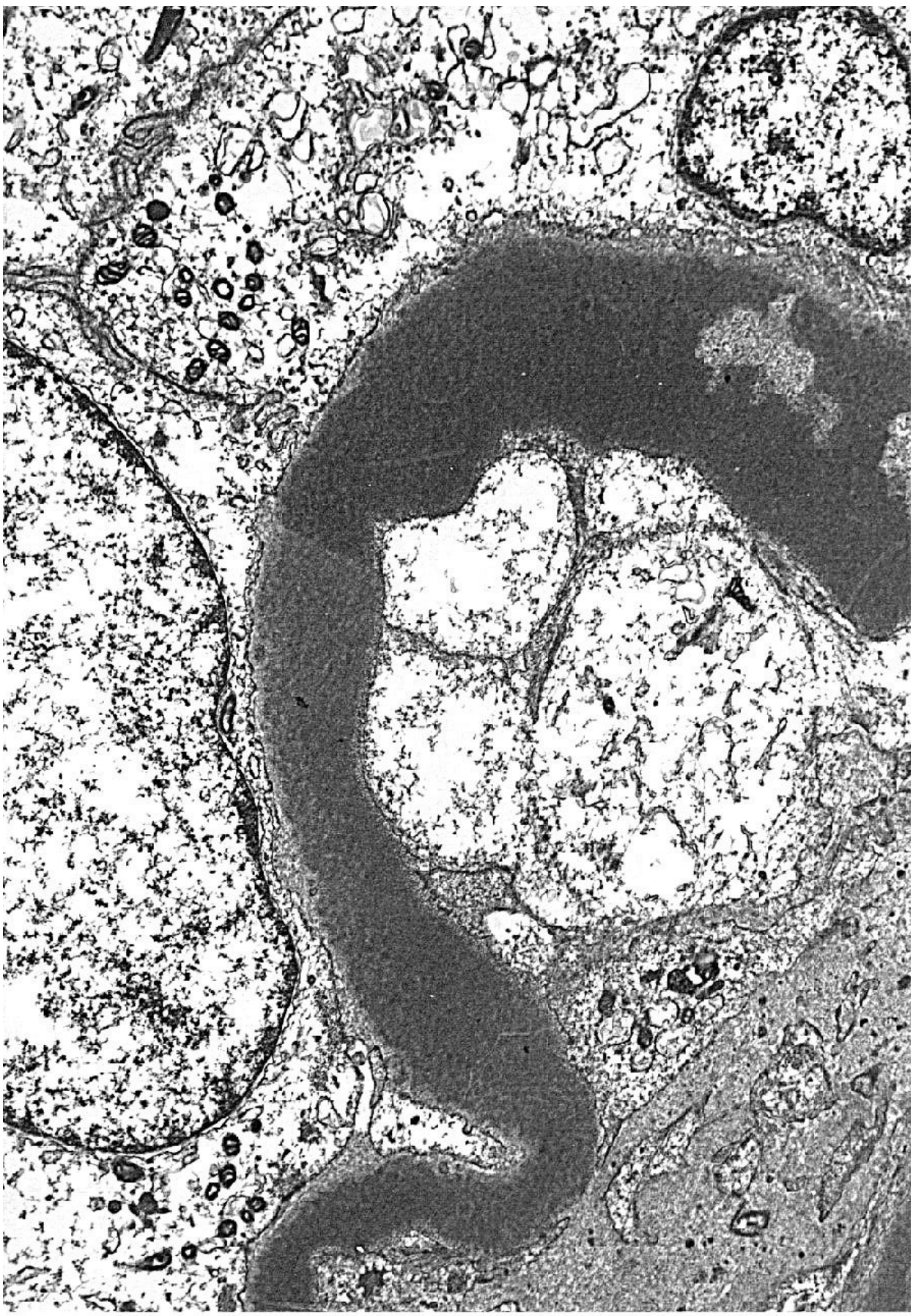


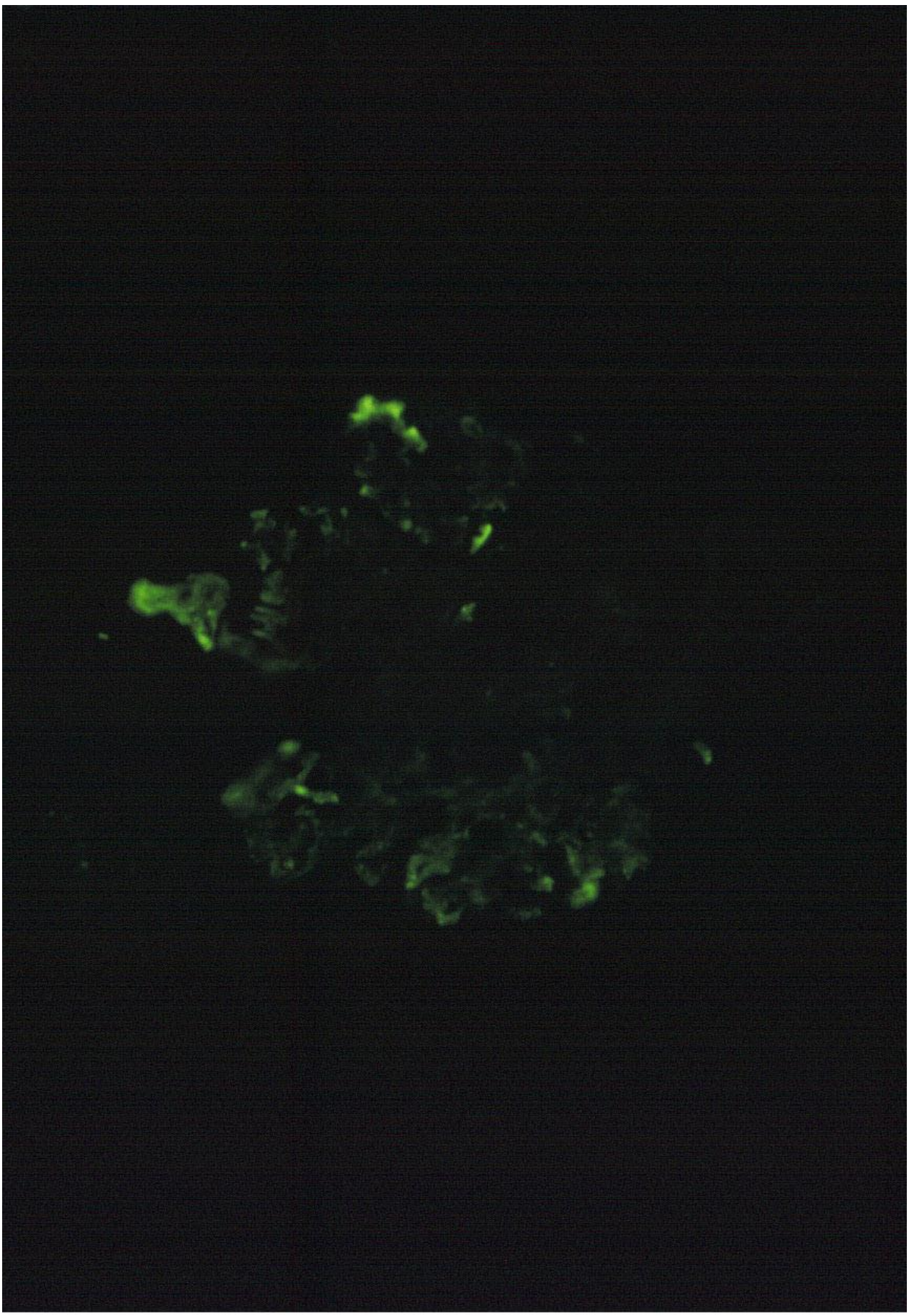


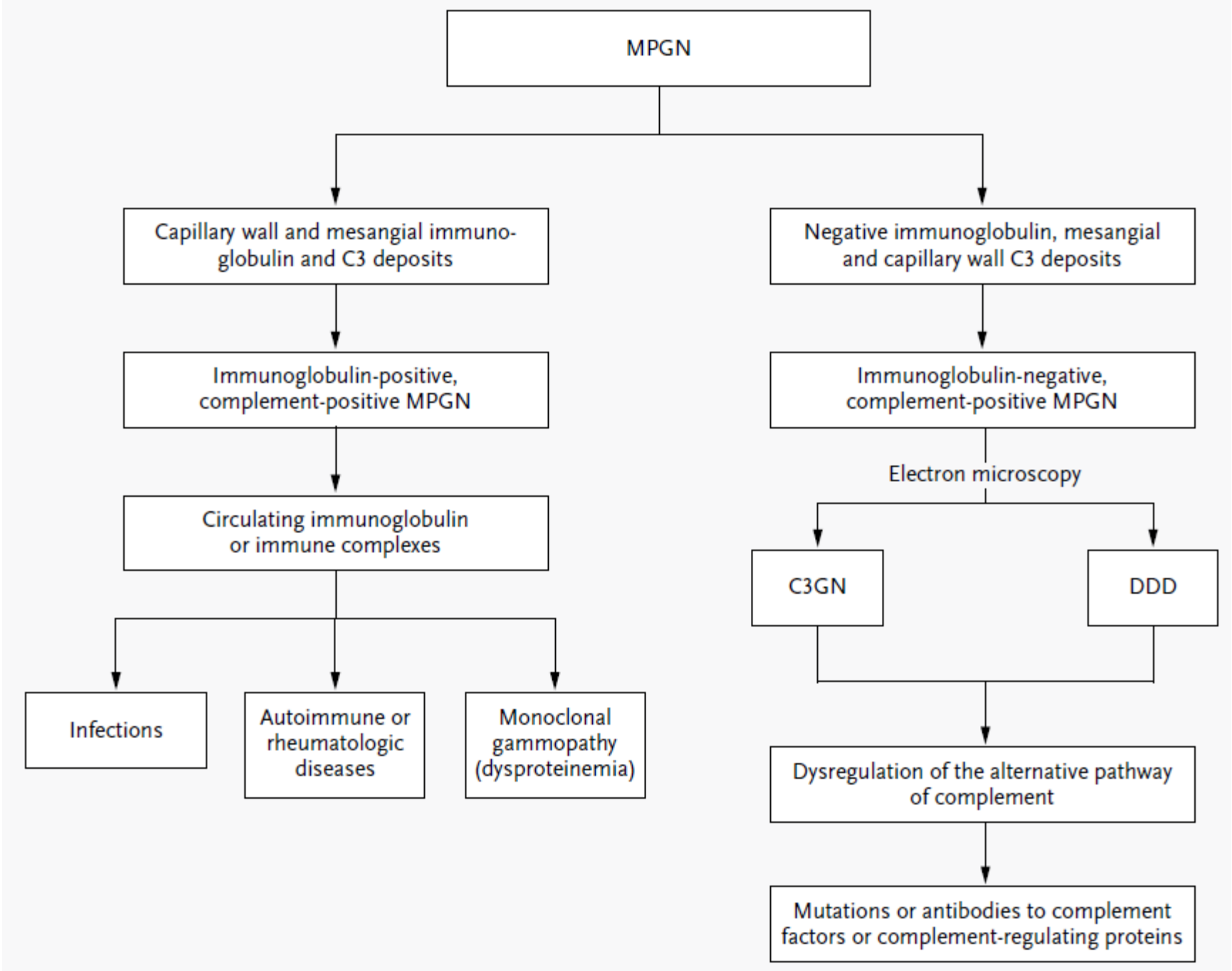











MPGN
Capillary wall and mesangial immuno-globulin and C3 deposits
Immunoglobulin-positive, complement-positive MPGN
Circulating immunoglobulin or immune complexes
Infections
Autoimmune or rheumatologic diseases
Monoclonal gammopathy (dysproteinemia)
Negative immunoglobulin, mesangial and capillary wall C3 deposits
Immunoglobulin-negative, complement-positive MPGN
Electron microscopy
C3GN
DDD
Dysregulation of the alternative pathway of complement
Mutations or antibodies to complement factors or complement-regulating proteins

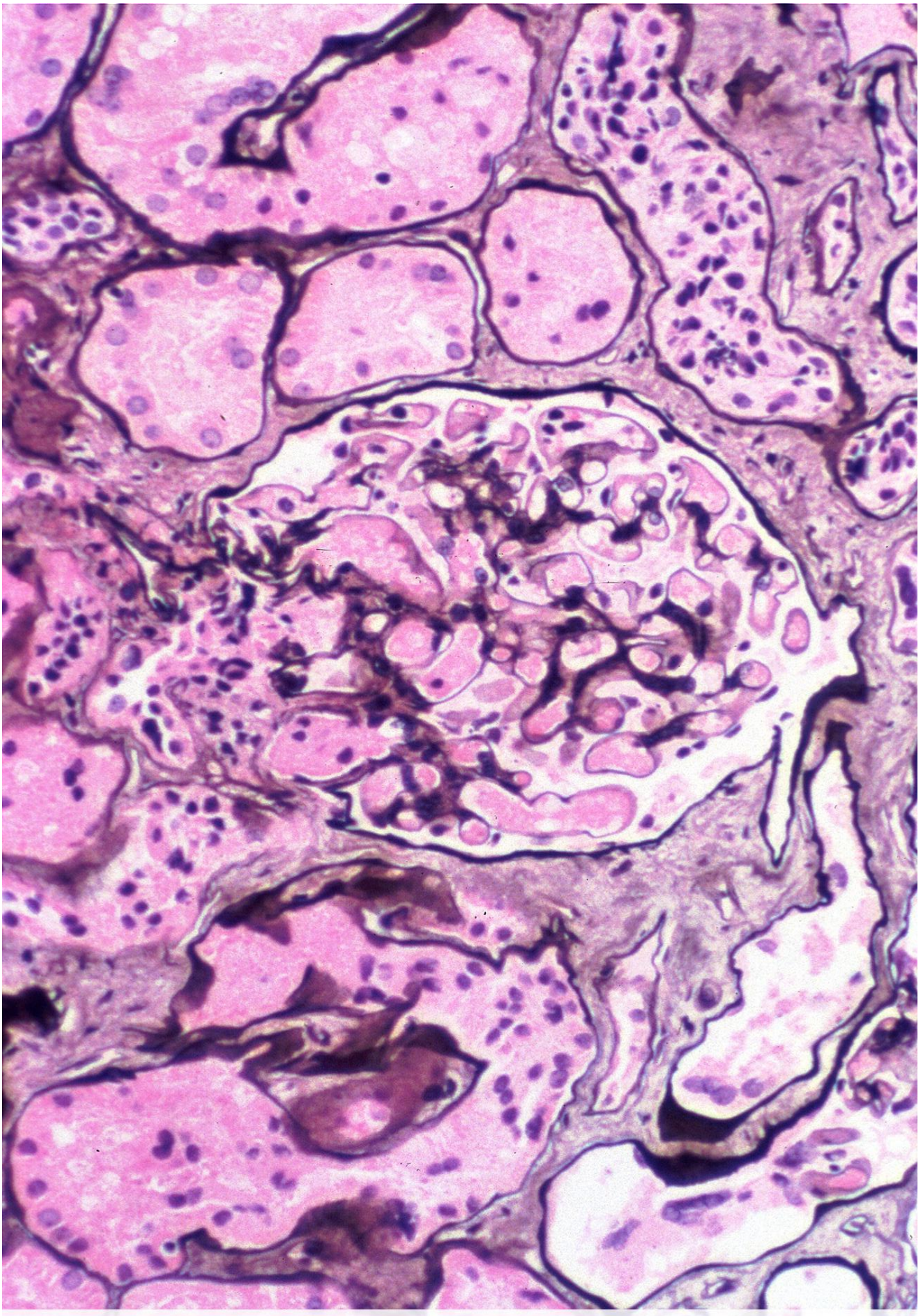
Protein	Disease associations
Control proteins	
Properdin	meningococcal infection
Factor H	hemolytic uremic syndrome (HUS), dense deposit disease
C1-INH	hereditary angioedema (HAE)
CD11a (LFA-1), CD11b (CR3), CD11c (CR4) /CD181	leukocyte adhesion deficiency type I (LAD I)
CD46 (MCP)	atypical hemolytic uremic syndrome (aHUS)
CD55, CD59 PIGA	paroxysmal nocturnal hemoglobinuria (PNH)

Overactivity of complement system

- Loss of regulatory proteins
- Antibodies versus regulatory proteins
- Activating mutations

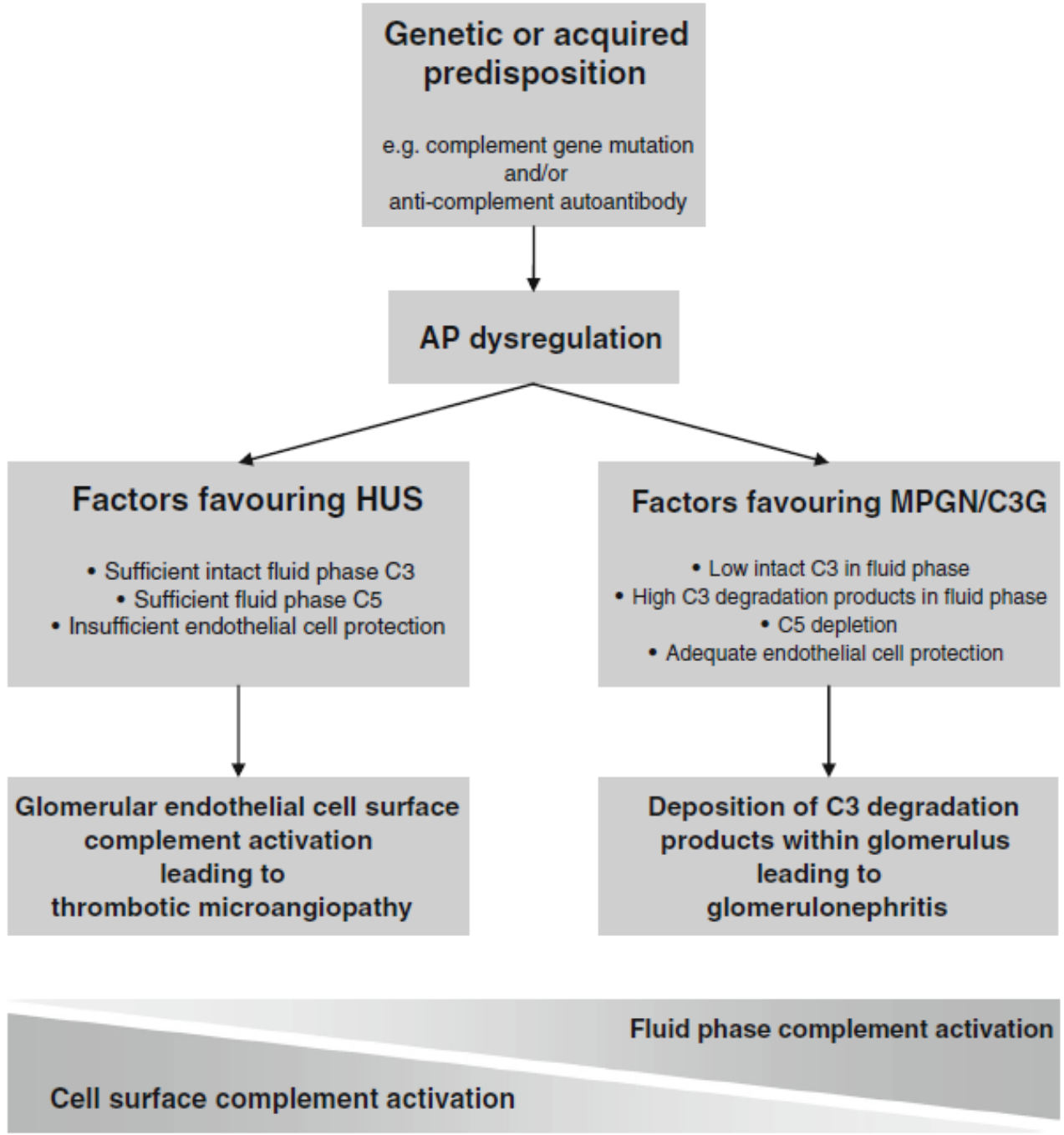
Renal diseases associated with mutations of complement proteins

- Atypical HUS (aHUS)
- C3 glomerulopathy
  - C3 glomerulonephritis (C3GN)
  - Dense deposit disease (DDD)

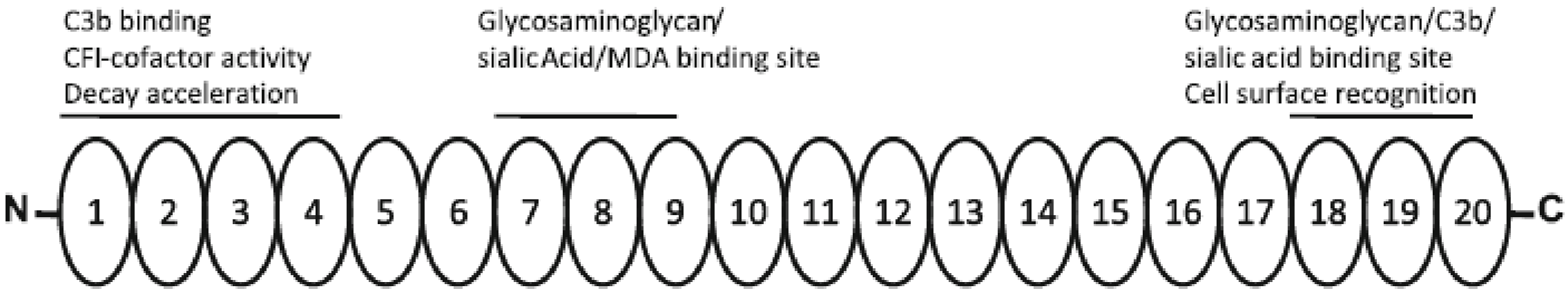


Genetic complement dysregulation

Complement protein	aHUS	DDD	MPGN type 1	C3GN
CFH mutation	20-30% of cases	+	+	+
MCP mutation	5-15% of cases	-		+
CFI mutation	4-10% of cases	-	+	+
C3 mutation	10% of cases	+		
CFB mutation	1-4% of cases			
Thrombomodulin mutation	3-5% of cases			
Antibody				
Anti CFH antibodies	6-10% of cases	+	+	
C3 nephritic factor			54% of cases	45% of cases
Anti CFI antibodies	?			
Anti CFB antibodies		?		


Genetic or acquired predisposition
e.g. complement gene mutation and/or anti-complement autoantibody
AP dysregulation
Factors favouring HUS
• Sufficient intact fluid phase C3
• Sufficient fluid phase C5
• Insufficient endothelial cell protection
Factors favouring MPGN/C3G
• Low intact C3 in fluid phase
• High C3 degradation products in fluid phase
• C5 depletion
• Adequate endothelial cell protection
Glomerular endothelial cell surface complement activation leading to thrombotic microangiopathy
Deposition of C3 degradation products within glomerulus leading to glomerulonephritis
Fluid phase complement activation
Cell surface complement activation

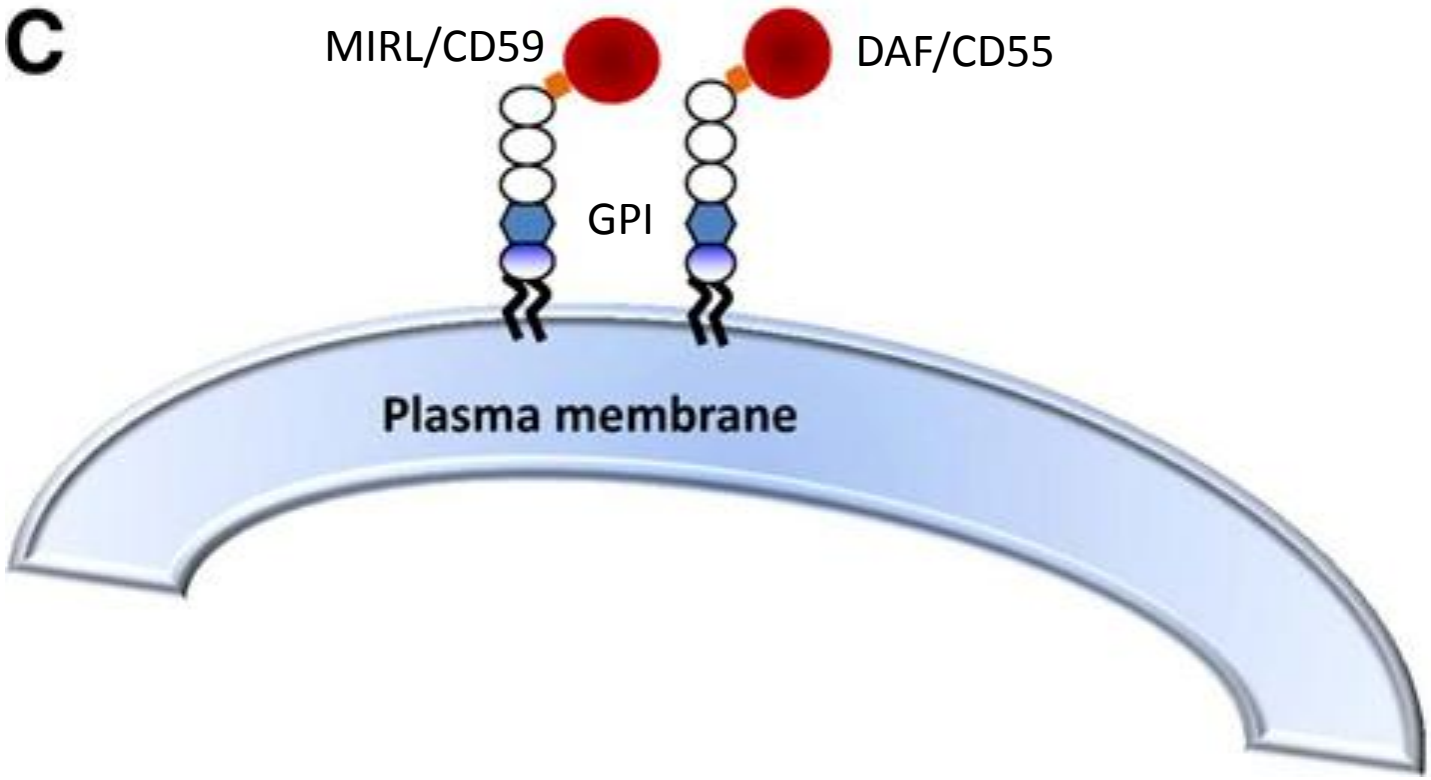
Complement Factor H



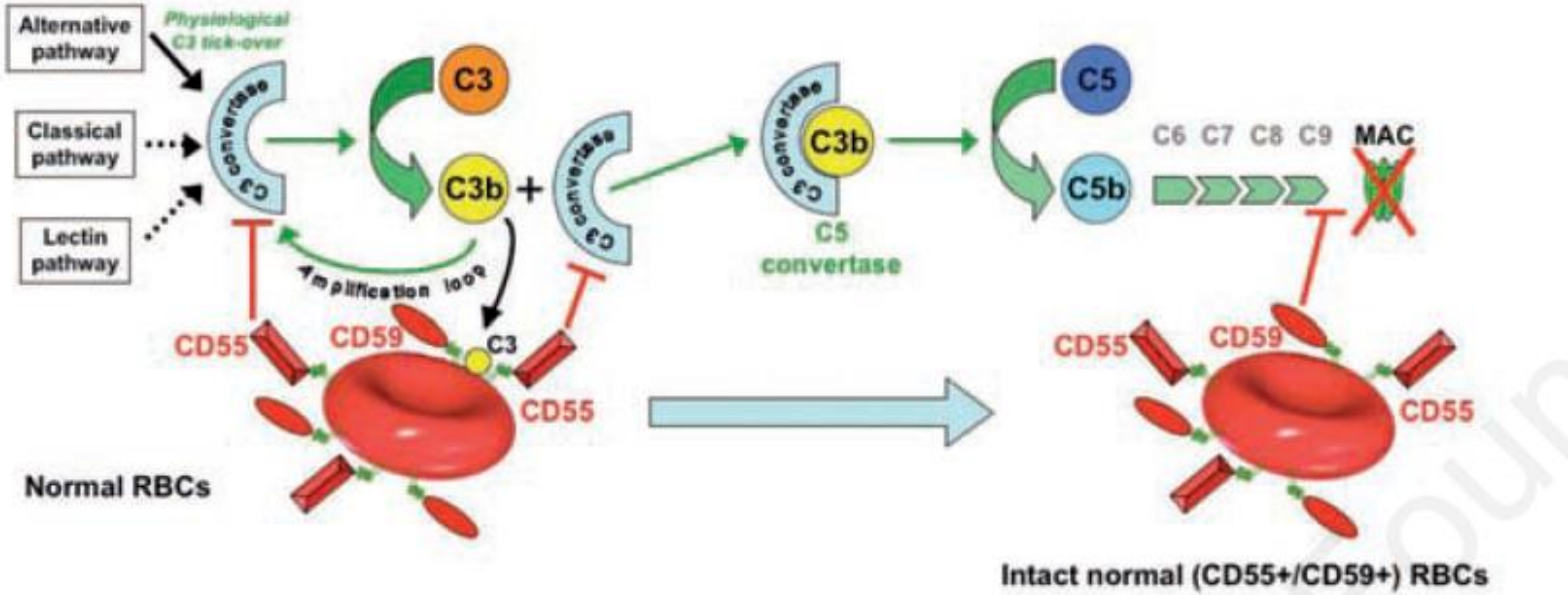
Paroxysmal nocturnal haemoglobinuria (PNH) Clinical manifestations

- Anaemia
  - Haemolysis
  - Bone marrow failure
- Thrombosis
  - Thrombophilia
  - Complement activation is prothrombotic
- Smooth muscle dystonia
  - Caused by free haemoglobin
- Chronic kidney disease
  - Renal tubular damage

GPI anchored protein on the plasma membrane

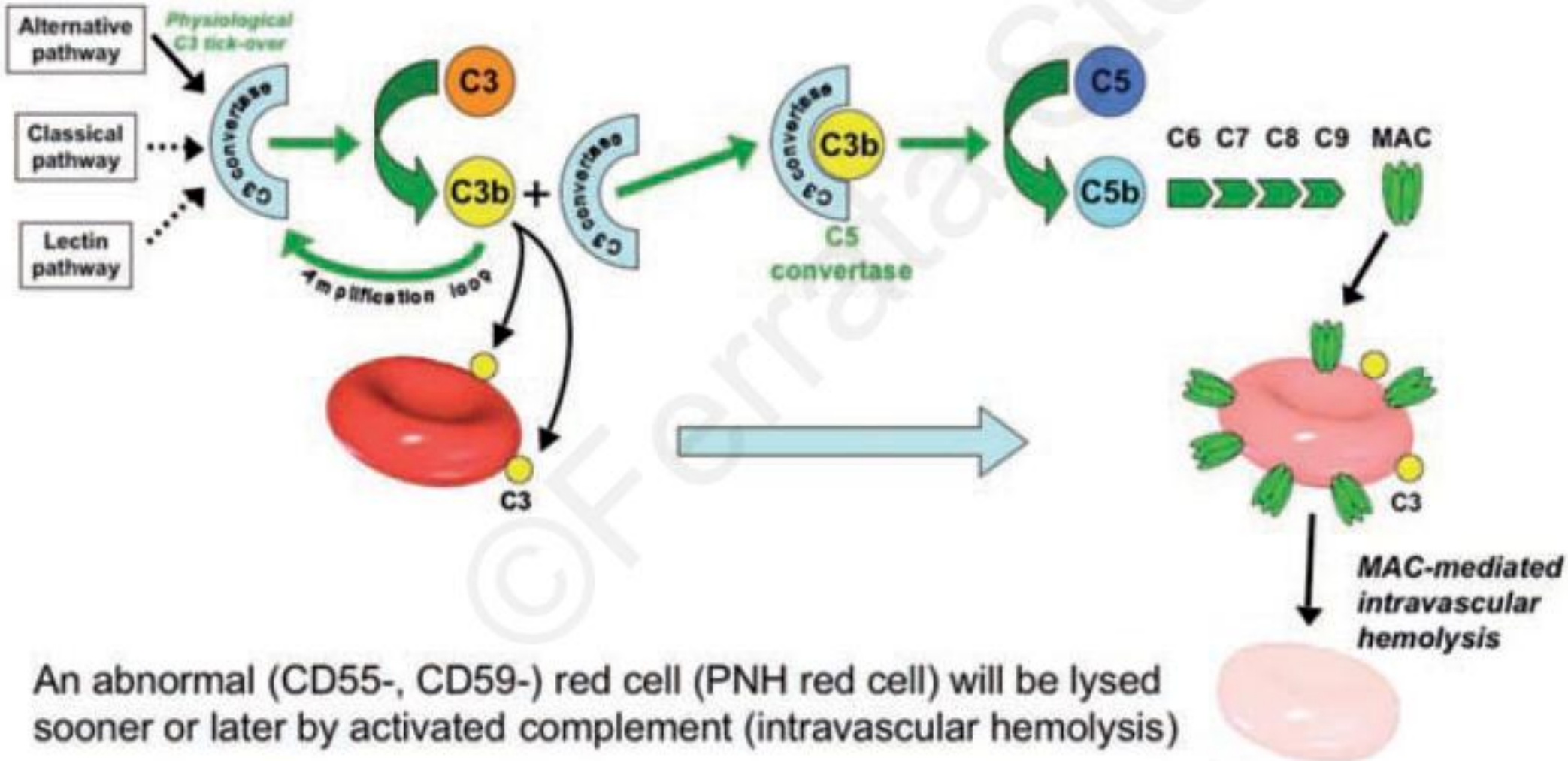


A Normal, steady state



A normal (CD55+, CD59+) red cell can withstand the hazard of complement activation

B PNH, steady state

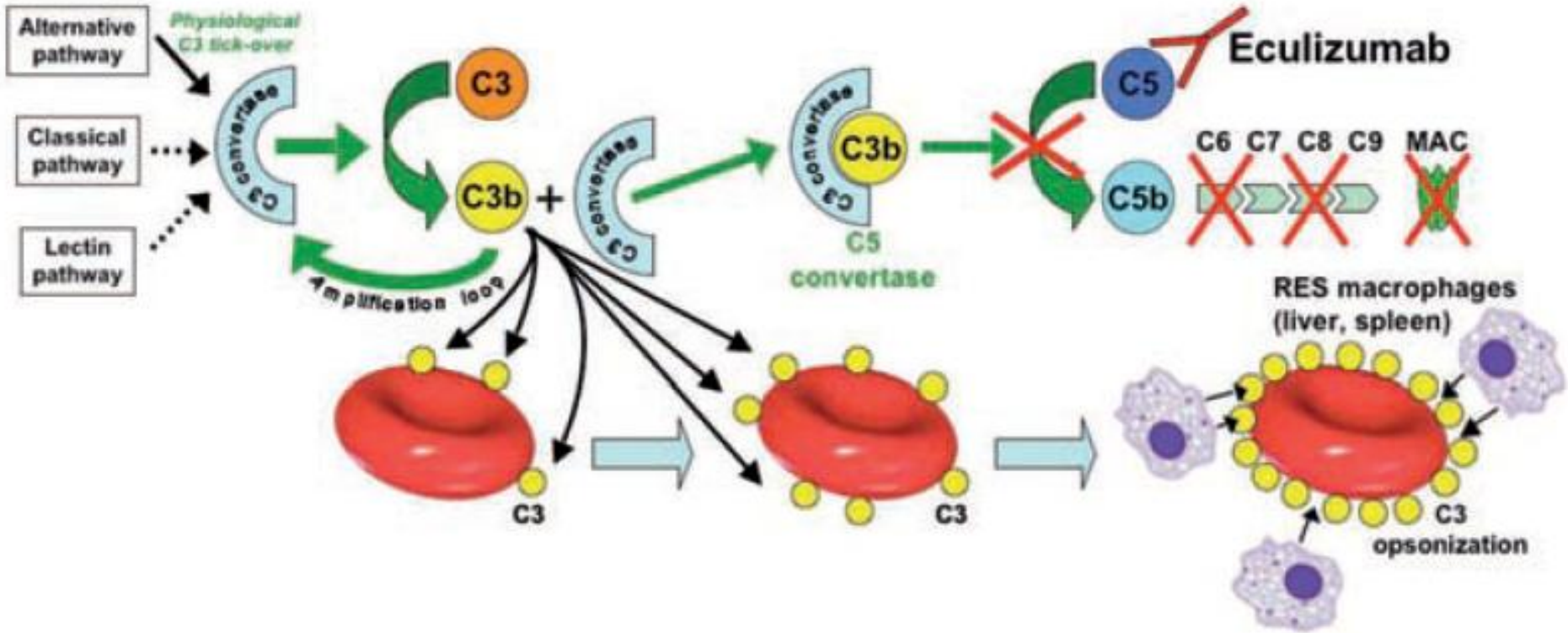


An abnormal (CD55-, CD59-) red cell (PNH red cell) will be lysed sooner or later by activated complement (intravascular hemolysis)

Eculizumab

- Humanized monoclonal antibody that blocks the terminal complement membrane attack complex by binding to C5
- Very expensive!
- £330,000 per year

C PNH, on eculizumab



With C5 blocked, a PNH red cell will be protected from undergoing intravascular hemolysis, but once opsonized by C3 it will become prey to macrophages

Eculizumab in renal disease

- Licensed for use in aHUS with complement mutations or anti-FH antibody.
- Case reports of benefit in C3G
- However C5 may not be the optimum target vs C3G as the renal pathology is dominated by deposition of C3 fragments.
- ?C3 inhibition but infection risk will be high.

Questions?