Diseases of the Immune System

AUTOIMMUNE DISEASES

Immunological Tolerance

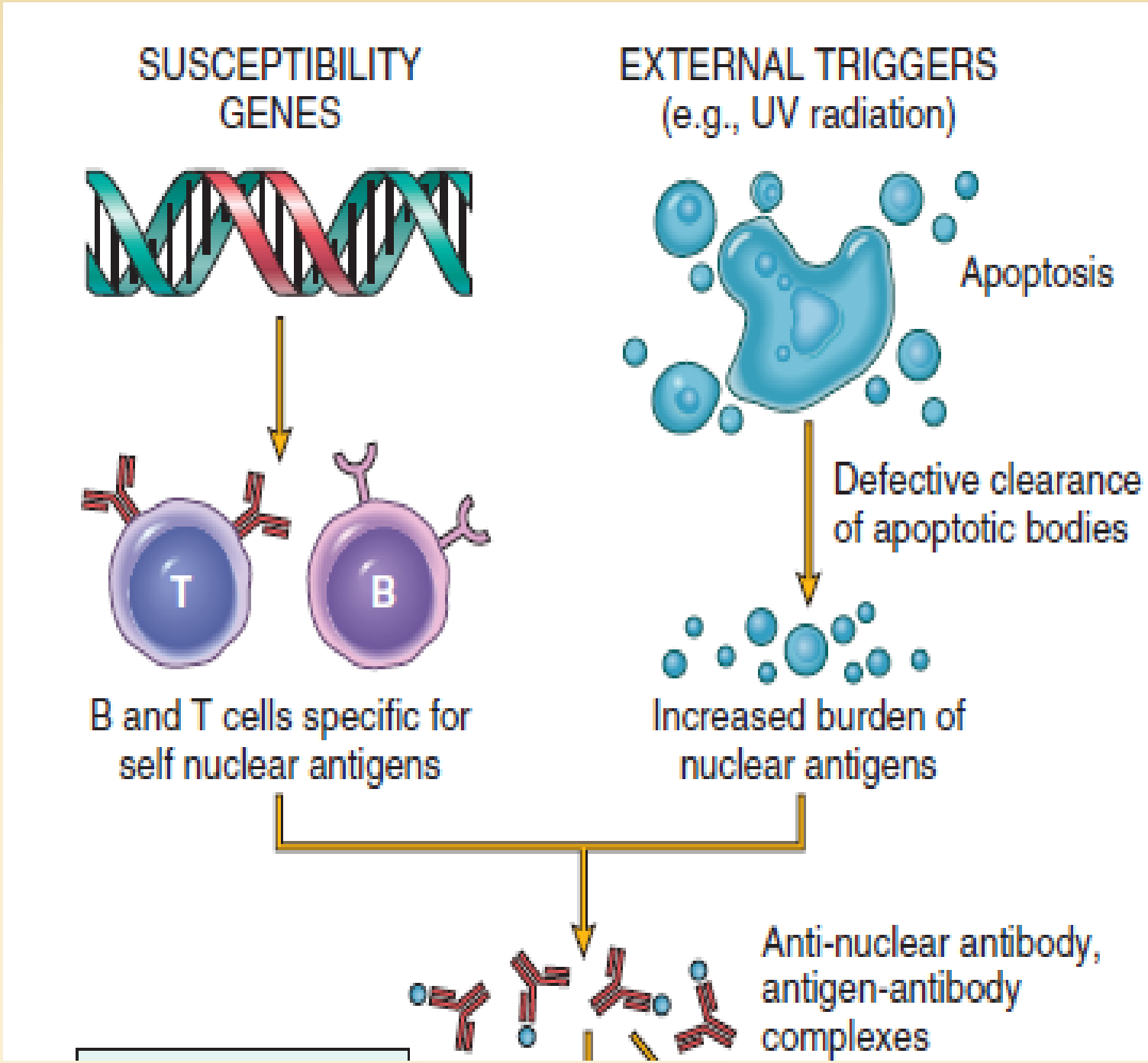
Mechanisms of Autoimmunity

Systemic Lupus Erythematosus

Pathogenesis

Pathogenesis

- *The fundamental defect in SLE is a* ***failure to maintain self-tolerance***
- causes remains unknown
  - as most autoimmune diseases
- genetic factors
- environmental factors


SUSCEPTIBILITY GENES
EXTERNAL TRIGGERS (e.g., UV radiation)
Apoptosis
T
B
Defective clearance of apoptotic bodies
B and T cells specific for self nuclear antigens
Increased burden of nuclear antigens
Anti-nuclear antibody, antigen-antibody complexes

Genetic Factors.

- Many lines of evidence:

- **Familial association**
- **HLA association.**
- **Other genes.**

Familial association

- Family members have an increased risk for SLE
- up to 20% of first-degree relatives have autoantibodies
- a high rate of concordance in monozygotic twins (25%) versus dizygotic twins (1-3%)

HLA association

- HLA-DR2 or HLA-DR3
  - - risk is 2-3
- Both haplotypes
  - - risk is 5

Other genes

- deficiencies of classical pathway complement proteins, C1q, C2, or C4 - 10%
  - defective clearance of immune complexes and apoptotic cells
  - failure of B cell tolerance
- A polymorphism in the inhibitory Fc receptor, FcγRIIb - some
  - inadequate control of B cell activation

Environmental Factors

- **Ultraviolet (UV) radiation**
- **Female gender**
- Drugs
- Cigarette smoking

Ultraviolet (UV) radiation & sun exposure

- development of SLE & exacerbates the lesions
  - apoptosis of host cells
    - increased burden of nuclear fragments
  - alter DNA and make it immunogenic
    - enhancing its recognition by TLRs
  - modulate the immune response
    - stimulating keratinocytes to produce IL-1, promotes inflammation

The gender bias

- an important influence
- **10 times more common** in women during reproductive years than in men
- partly attributable to sex hormones
- partly related to genes on the X chromosome

Drugs

- Procainamide
- Hydralazine
- D-penicillamine
  - can induce an SLE-like disease
  - Glomerulonephritis does not develop
  - cause demethylation of DNA

Immunologic Abnormalities

- Failure of self-tolerance in B cells
- CD4+ helper T cells escape tolerance
- **Type I interferons**
- **TLR signals**
- other cytokines

Failure of tolerance in B & T cells

- Defective elimination of self-reactive B cells in the bone marrow
- defects in peripheral B-cell tolerance
- CD4+ helper T cells specific for nucleosomal antigens also escape tolerance
- production of high-affinity pathogenic T cell–dependent autoantibodies, produced in germinal centers
- increased follicular helper T cells in the blood

Type I interferons

- Blood cells show effects of exposure to interferon-α (IFN-α), a type I interferon
- abnormally large amounts of IFN-α.
- produced mainly by plasmacytoid DCs

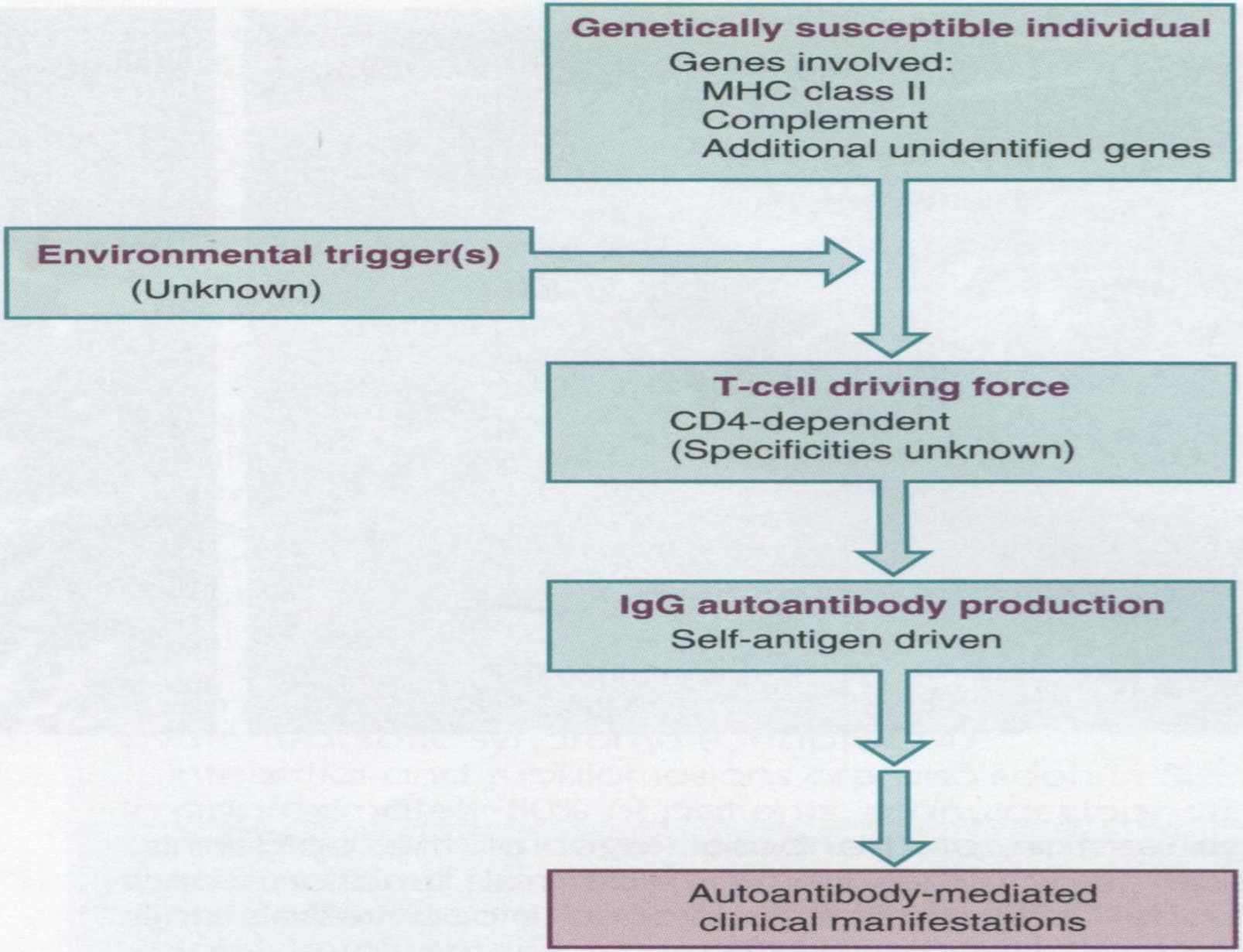
TLR signals

- TLRs recognize DNA and RNA
  - DNA-recognizing TLR9
  - RNA-recognizing TLR7
- Produce signals that activate B cells specific for self nuclear antigens.

BAFF

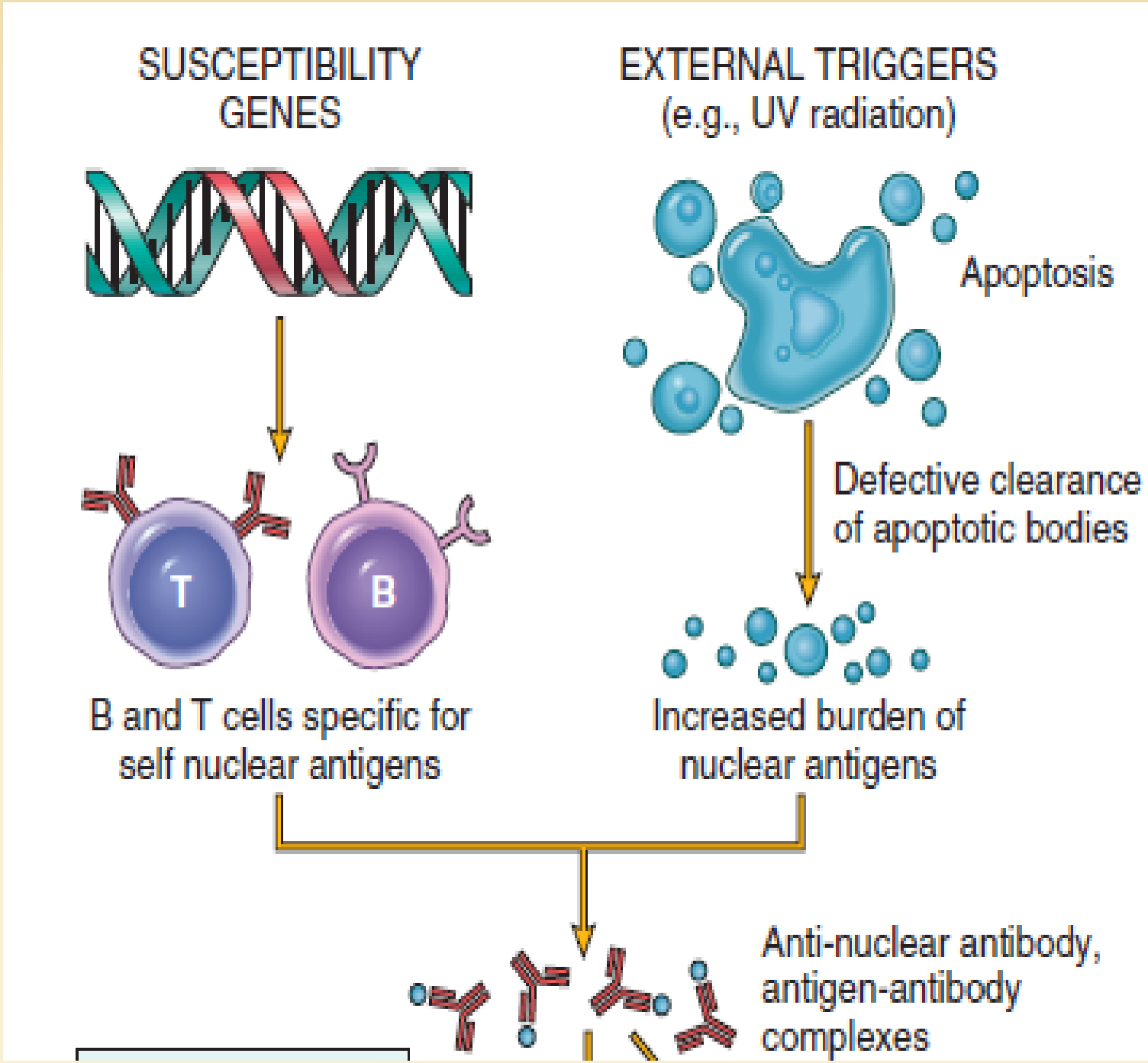
- TNF family member
- play a role in unregulated B-cell activation
- increased production
- promotes survival of B cells
- modest success of an antibody that blocks BAFF as a therapy for SLE

Model for pathogenesis of SLE


Genetically susceptible individual
Genes involved:
MHC class II
Complement
Additional unidentified genes
Environmental trigger(s)
(Unknown)
T-cell driving force
CD4-dependent
(Specificities unknown)
IgG autoantibody production
Self-antigen driven
Autoantibody-mediated
clinical manifestations

Model for pathogenesis of SLE

- UV and other environmental insults
- Apoptosis
- Inadequate clearance of the nuclei
- a large burden of nuclear antigens.
- defective self-tolerance
- The self-reactive B cells are stimulated
- antibodies are produced
- Complexes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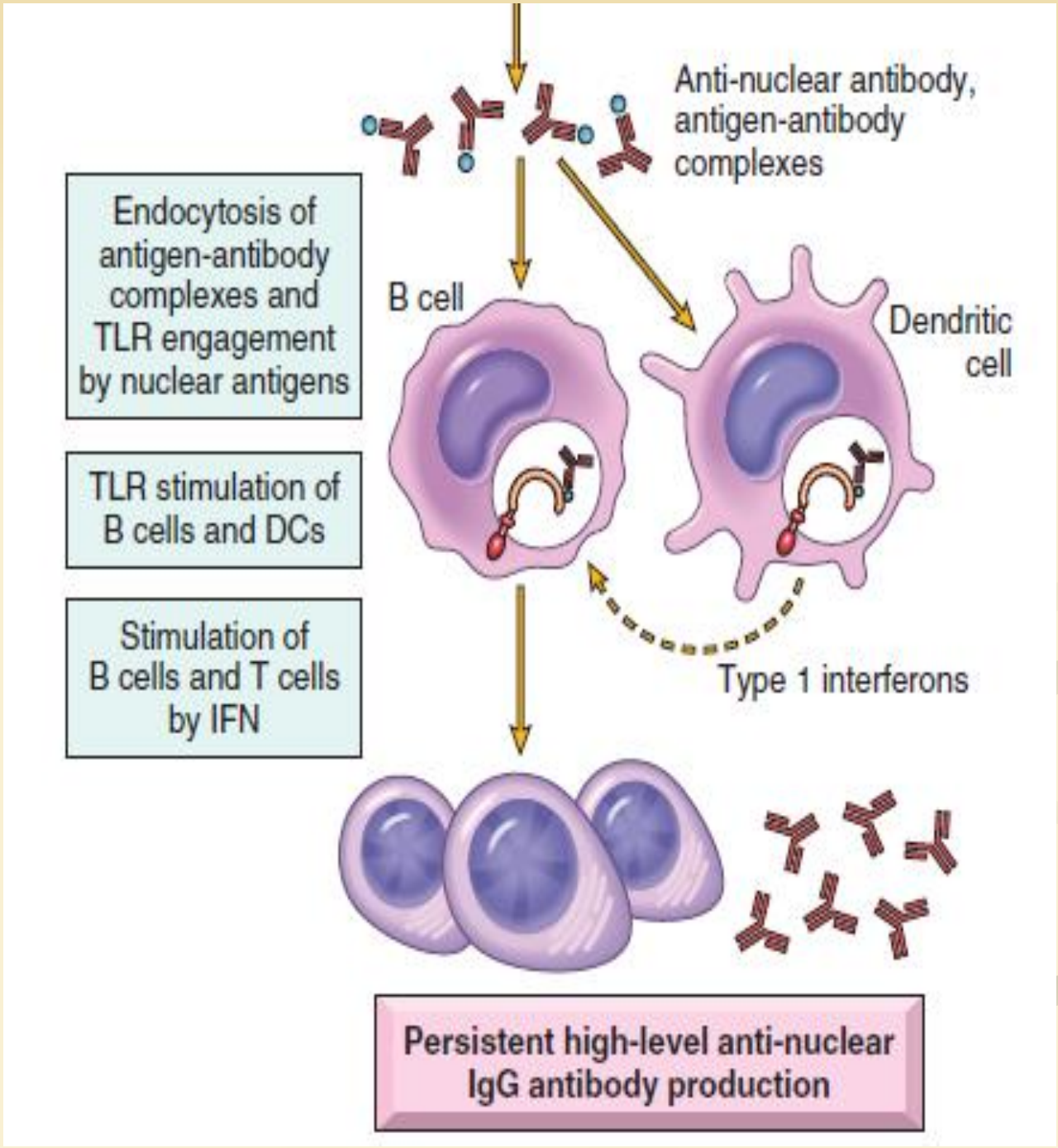
- Fc receptors on B cells and DCs
- nucleic acid components engage TLRs
  - stimulate B cells to produce autoantibodies
  - activate DCs
  - plasmacytoid DCs produce IFN-α
- Enhances the immune response
- a cycle of antigen release and immune activation resulting in the production of high-affinity autoantibodies.


Anti-nuclear antibody, antigen-antibody complexes
Endocytosis of antigen-antibody complexes and TLR engagement by nuclear antigens
B cell
Dendritic cell
TLR stimulation of B cells and DCs
Stimulation of B cells and T cells by IFN
Type 1 interferons
Persistent high-level anti-nuclear IgG antibody production

Mechanisms of Tissue Injury

organ damage in SLE

- type III hypersensitivity
  - diffuse and heavy granular deposits of complement, immunoglobulin in vessel wall and glomeruli
  - reduced serum levels of C3 &C4 at flares
  - T cell infiltrates

- type II hypersensitivity
- *Autoantibodies against red cells, white cells, and platelets* opsonize these cells
- lead to their phagocytosis
- cytopenias

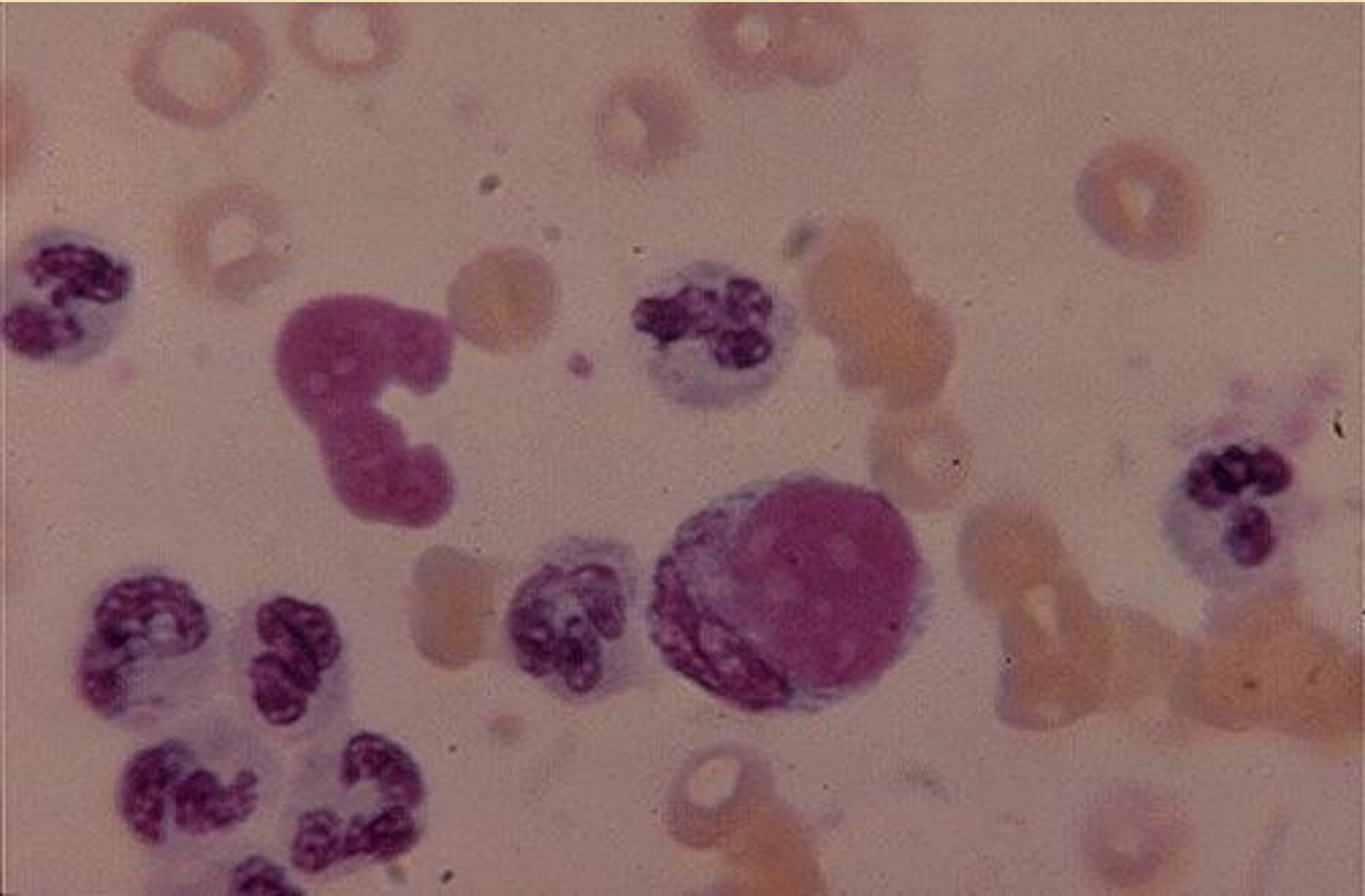
LE body
or *hematoxylin body*

- the ANAs cannot permeate intact cells
- if cell nuclei are exposed, the ANAs can bind to them
- In tissues, nuclei of damaged cells react with ANAs, lose their chromatin pattern, and become homogeneous

LE cell

- in vitro correlate of *LE body*
- a neutrophil or macrophage that has engulfed the denatured nucleus of another injured cell
- When blood is withdrawn and agitated, a number of leukocytes are sufficiently damaged to expose their nuclei to ANAs
- these opsonized nuclei are then readily phagocytosed
- is positive in as many as 70% of patients
- In pleural & pericardial fluid

NEVER order an LE cell test!!



Antiphospholipid antibodies

- react with a wide variety of proteins in complex with phospholipids
- Anti-cardiolipin, syphilis
- Lupus Anicoagulant
- **contribute to coagulation abnormalities:** antibodies against clotting factors, platelets, and endothelial cells

antiphospholipid antibody syndrome

- venous and arterial thrombosis
- Recurrent spontaneous miscarriages
- focal cerebral or ocular ischemia
- Thrombocytopenia
- in association with lupus, *secondary antiphospholipid antibody syndrome*
- without associated SLE, *primary anti-phospholipid antibody syndrome*

neuropsychiatric manifestations

- antibodies that cross the blood-brain barrier
- react with neurons or receptors for various neurotransmitters
- mechanisms involving other immune factors, such as **cytokines**, also may underlie the cognitive dysfunction and other CNS abnormalities

morphology

SLE morphology

- a systemic disease with protean manifestations
- extremely variable depending on:
  - the nature of the autoantibodies
  - the tissue in which immune complexes deposit
  - the course and duration of disease
- **immune complex deposition in blood vessels, kidneys, connective tissue, and skin**

Clinical Manifestation	Prevalence in Patients (%)*
Hematologic	100
Arthritis, arthralgia, or myalgia	80–90
Skin	85
Fever	55–85
Fatigue	80–100
Weight loss	60
Renal	50–70
Neuropsychiatric	25–35
Pleuritis	45
Pericarditis	25
Gastrointestinal	20
Raynaud phenomenon	15–40
Ocular	5–15
Peripheral neuropathy	15

acute necrotizing vasculitis

- small arteries and arterioles in any tissue
- necrosis and fibrinoid deposits within walls
- antibody, DNA, complement fragments, and fibrinogen
- transmural and perivascular leukocytic infiltrate
- In chronic stages, fibrous thickening with luminal narrowing

Kidney involvement

- **one of the most important clinical features**
- renal failure is the most common cause of death
- **50% clinically significant renal involvement**
- **virtually always by electron microscopy and immunofluorescence**

International Society of Nephrology/Renal Pathology Society morphologic classification

- class I, **Minimal mesangial lupus nephritis**
- **class II**, mesangial proliferative lupus GN
- **class III**, focal proliferative GN
- **class IV**, diffuse proliferative GN
- **class V**, membranous GN
- **class VI,** Advanced sclerosing lupus nephritis

Pathogenesis

- deposition of DNA/anti-DNA complexes
- inflammation
- proliferation (endothelial, mesangial and/or epithelial cells)
- necrosis
- **overlap within these classes**
- **may evolve from one class to another over time**
- **class I is the least common pattern**
- **class IV is the most common pattern**

Minimal mesangial lupus nephritis (class I)

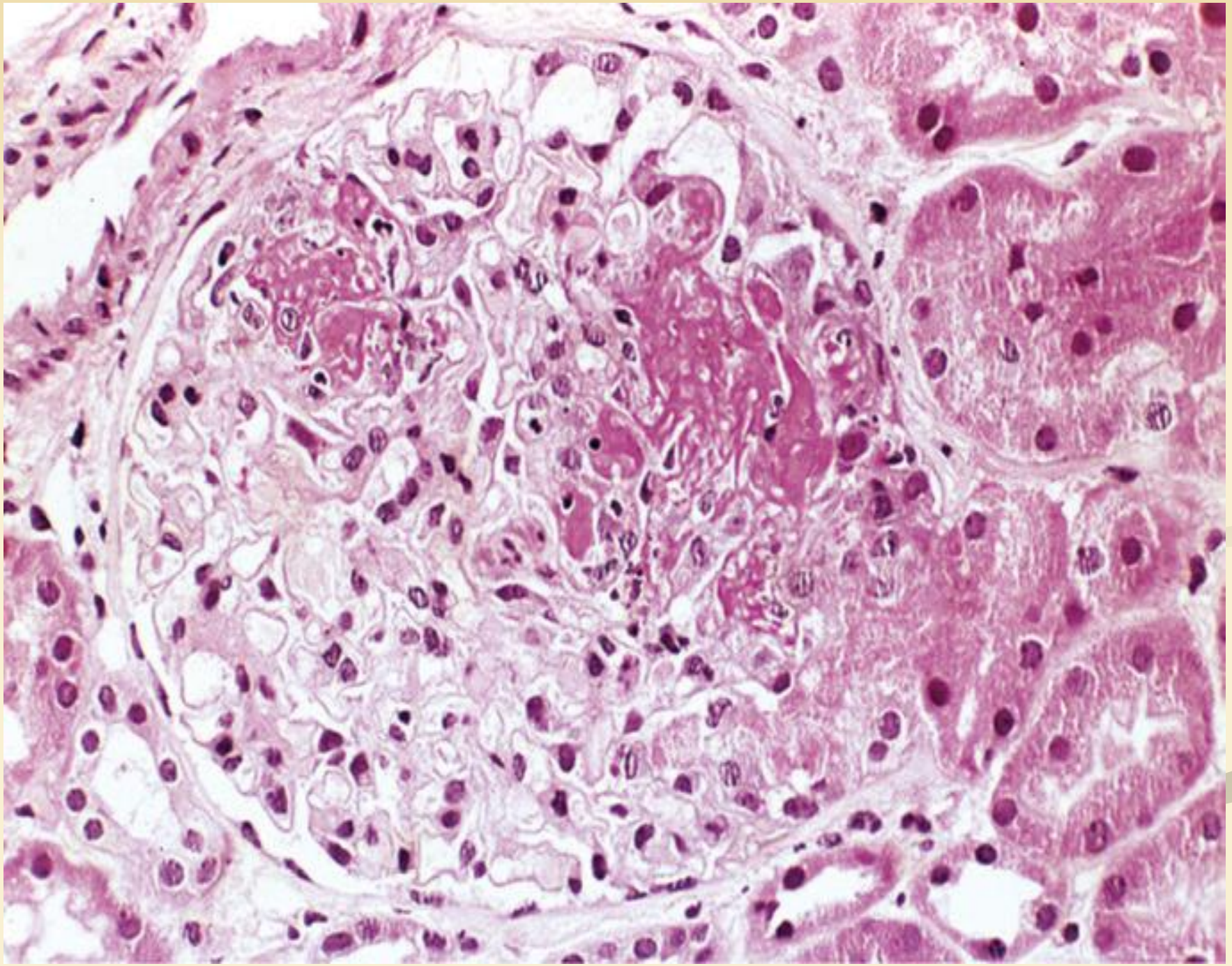
- very uncommon
- characterized by immune complex deposition in the mesangium
- identified by **immunofluorescence** and by **electron microscopy**, but without structural changes by light microscopy

Mesangial proliferative lupus glomerulonephritis **(class II)**

- 10% to 25%
- mild clinical symptoms
- IC and complement deposit in the mesangium
- **slight increase** in the mesangial matrix and cellularity
- **without involvement of capillaries**

Focal proliferative glomerulonephritis (class III)

- 20-35% of cases
- in fewer than half of all glomeruli
- **segmentally or globally within each glomerulus**
  - swelling and proliferation of endothelial and mesangial cells
  - neutrophils
  - fibrinoid deposits & necrosis in capillaries
  - capillary hyaline thrombi
  - extracapillary proliferation
  - focal necrosis and crescent formation

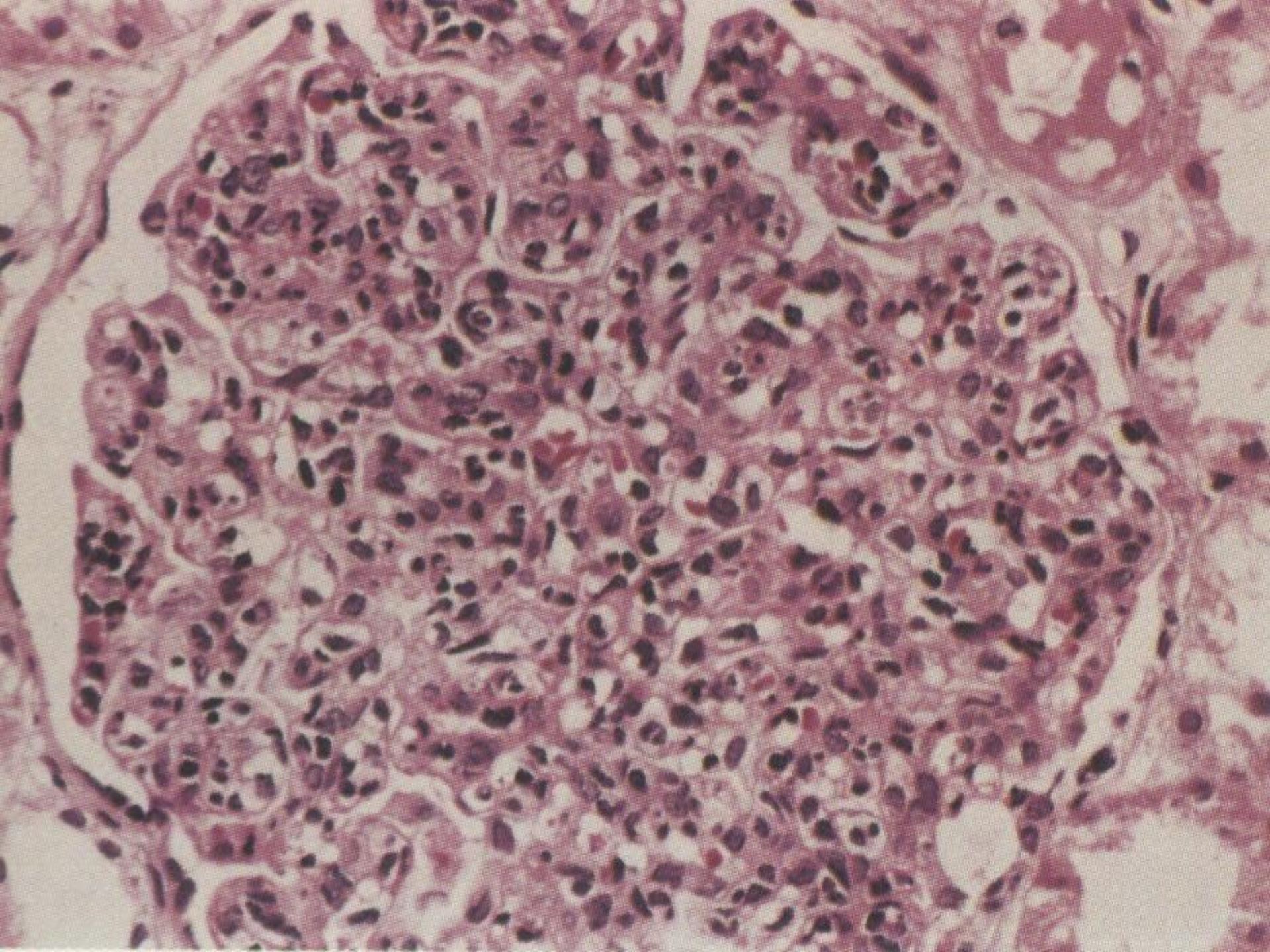


features

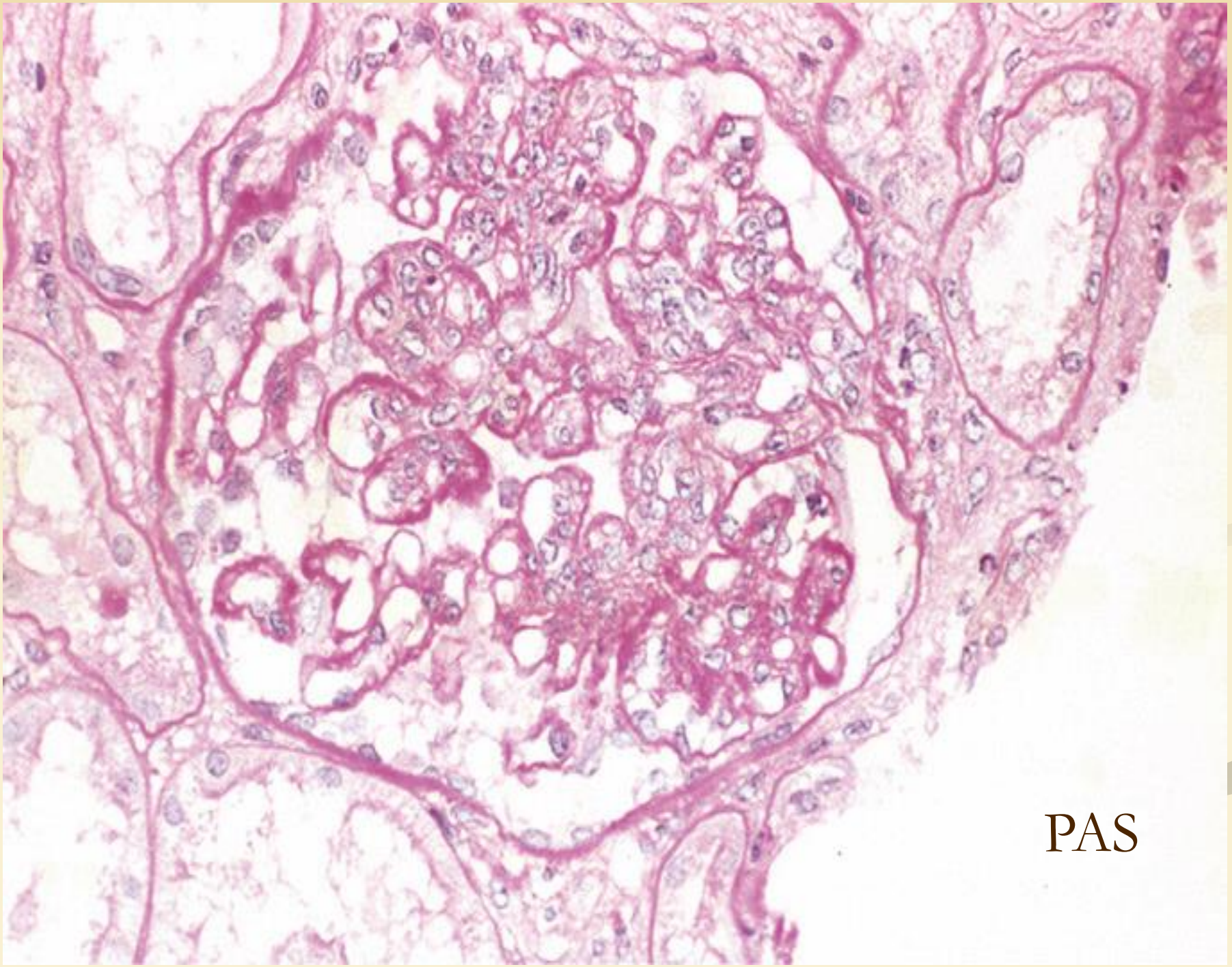
- mild microscopic hematuria & Proteinuria
- active urinary sediment
- red blood cell casts
- Up to acute, severe renal insufficiency
- Some progress to diffuse glomerulonephritis
- May heal completely
- Can lead to chronic global or segmental glomerular scarring

Diffuse proliferative glomerulonephritis (class IV)

- the most serious form of renal lesions
- the most common, 35-60%
- **half or more of glomeruli**
- **Identical to those in class III, but differ in extent**
- endothelial and mesangial proliferation affecting the entire glomerulus
- diffuse hypercellularity of the glomeruli



- proliferation of epithelial cells can cause **epithelial crescents** that fill Bowman's space
- When extensive, subendothelial immune complexes create a circumferential thickening of the capillary wall
- rigid "**wire loops**" on routine light microscopy

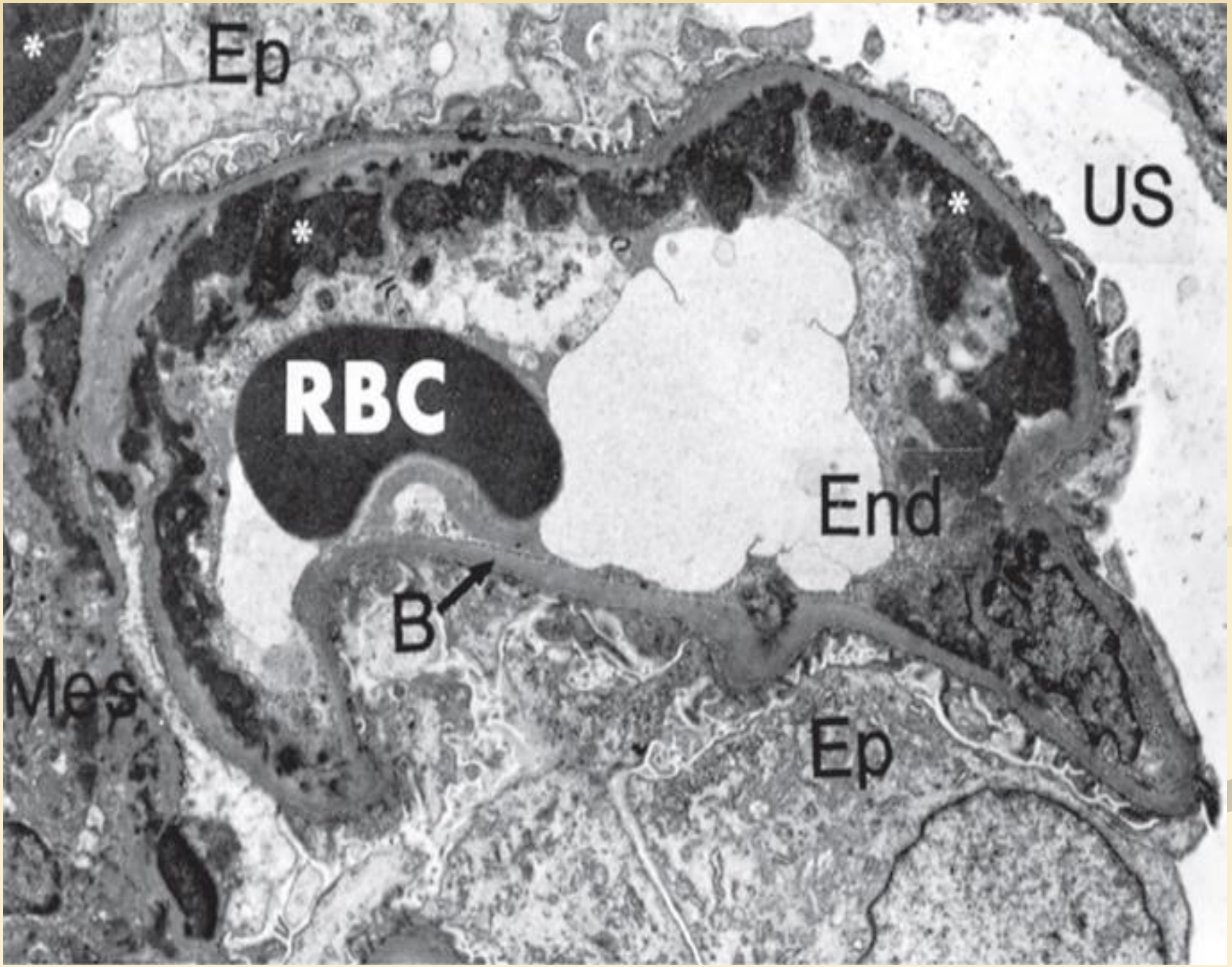

PAS

Electron microscopy

- prominent electron-dense subendothelial immune complexes

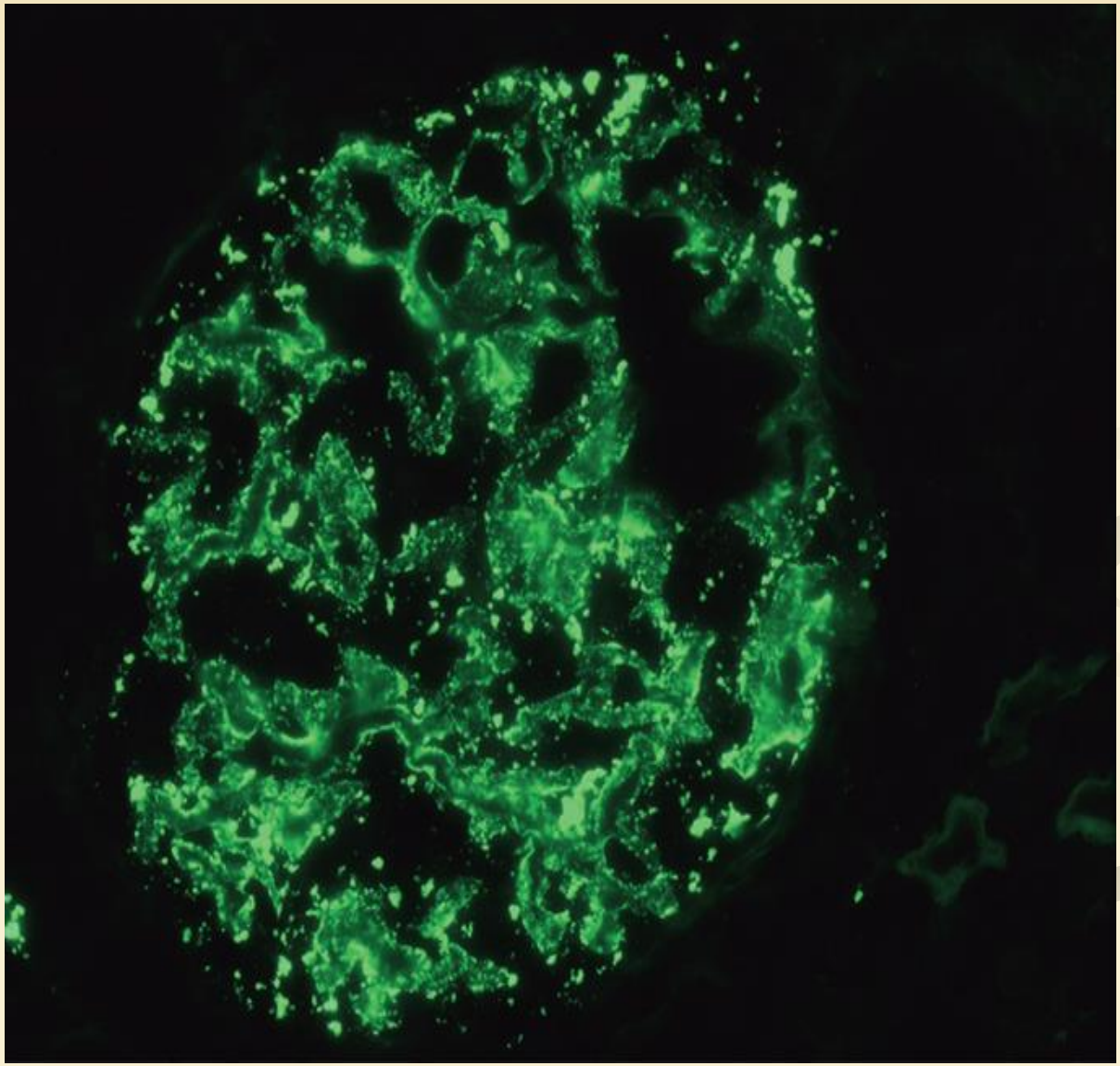
(between endothelium and basement membrane)

- immune complexes are also present in other parts of the capillary wall and in the mesangium.


Ep
US
RBC
End
B
Mes
Ep

- Immune complexes can be visualized by staining with fluorescent antibodies
- directed against immunoglobulins or complement
- a granular fluorescent staining pattern

Deposition of IgG antibody in a granular pattern, detected by immunofluorescence



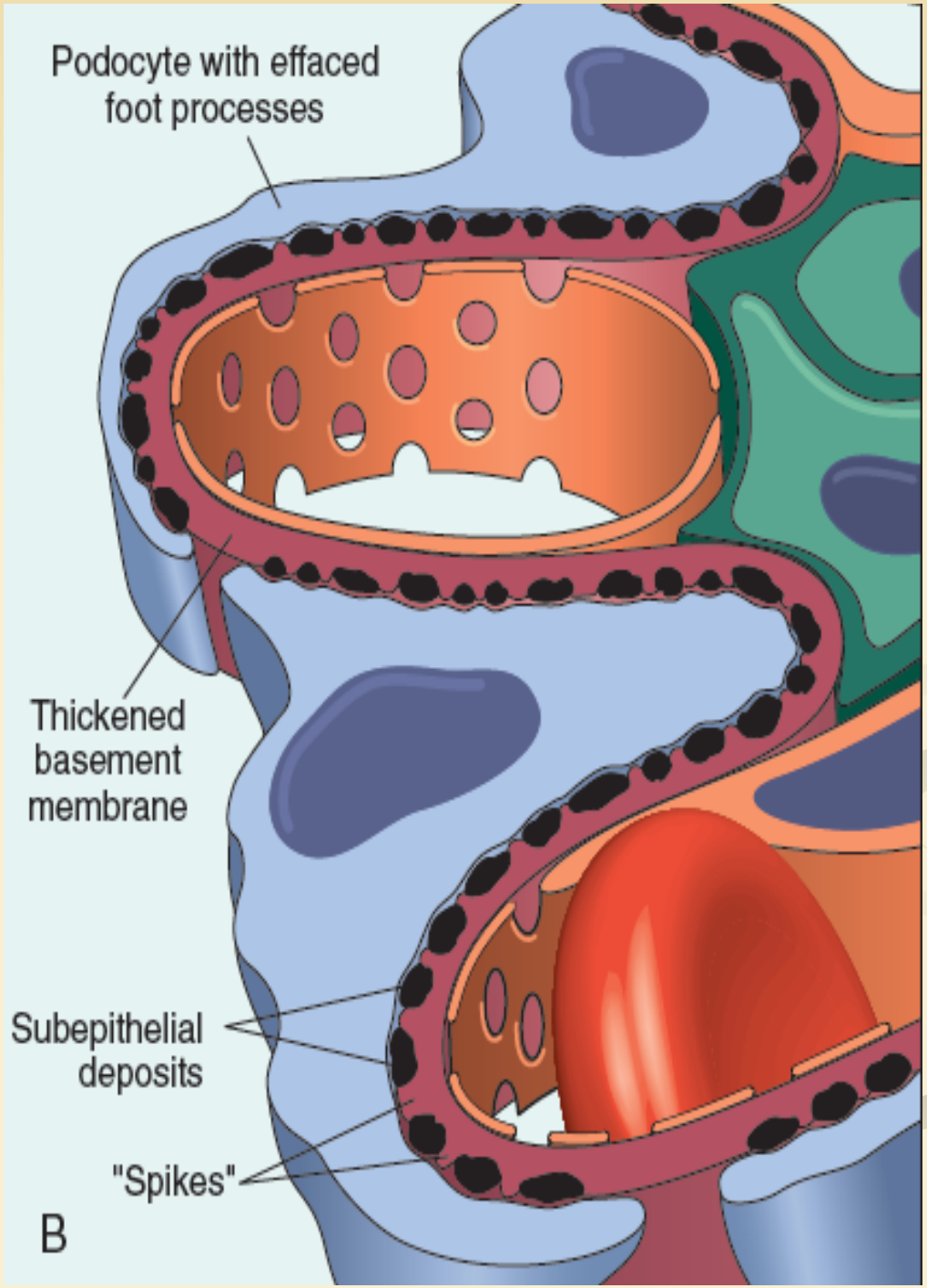
Most patients

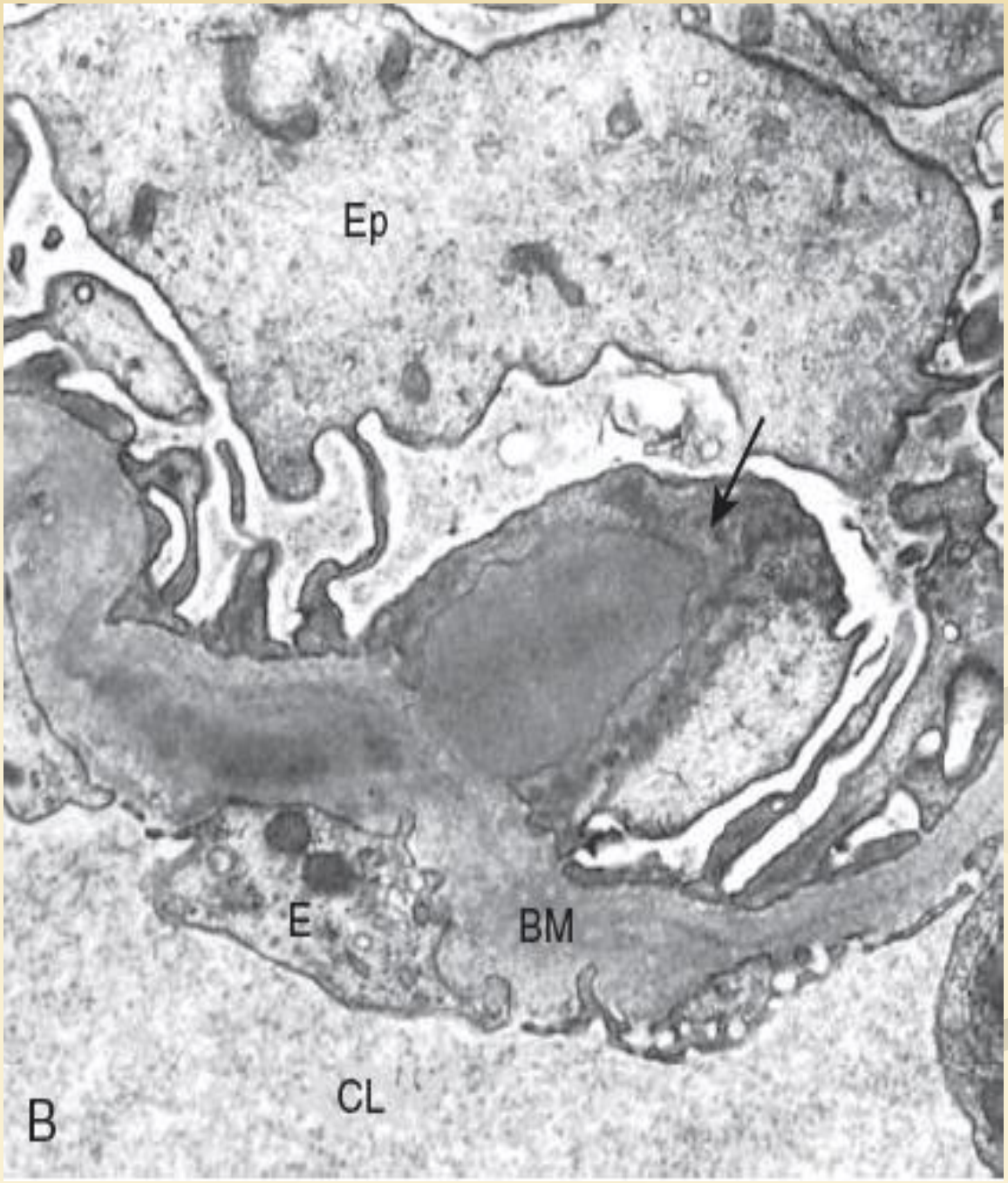
- hematuria
- moderate to severe proteinuria
- hypertension,
- renal insufficiency

- In due course, glomerular injury gives rise to scarring **(glomerulosclerosis)**

Membranous glomerulonephritis (class V)

- 10% to 15% of cases
- widespread thickening of the capillary wall
- increased deposition of basement membrane-like material
- **deposition of subepithelial immune complexes.**
- **"holes" and "spikes" on silver stain**
- Similar to idiopathic membranous nephropathy
- almost always have severe proteinuria with overt nephrotic syndrome

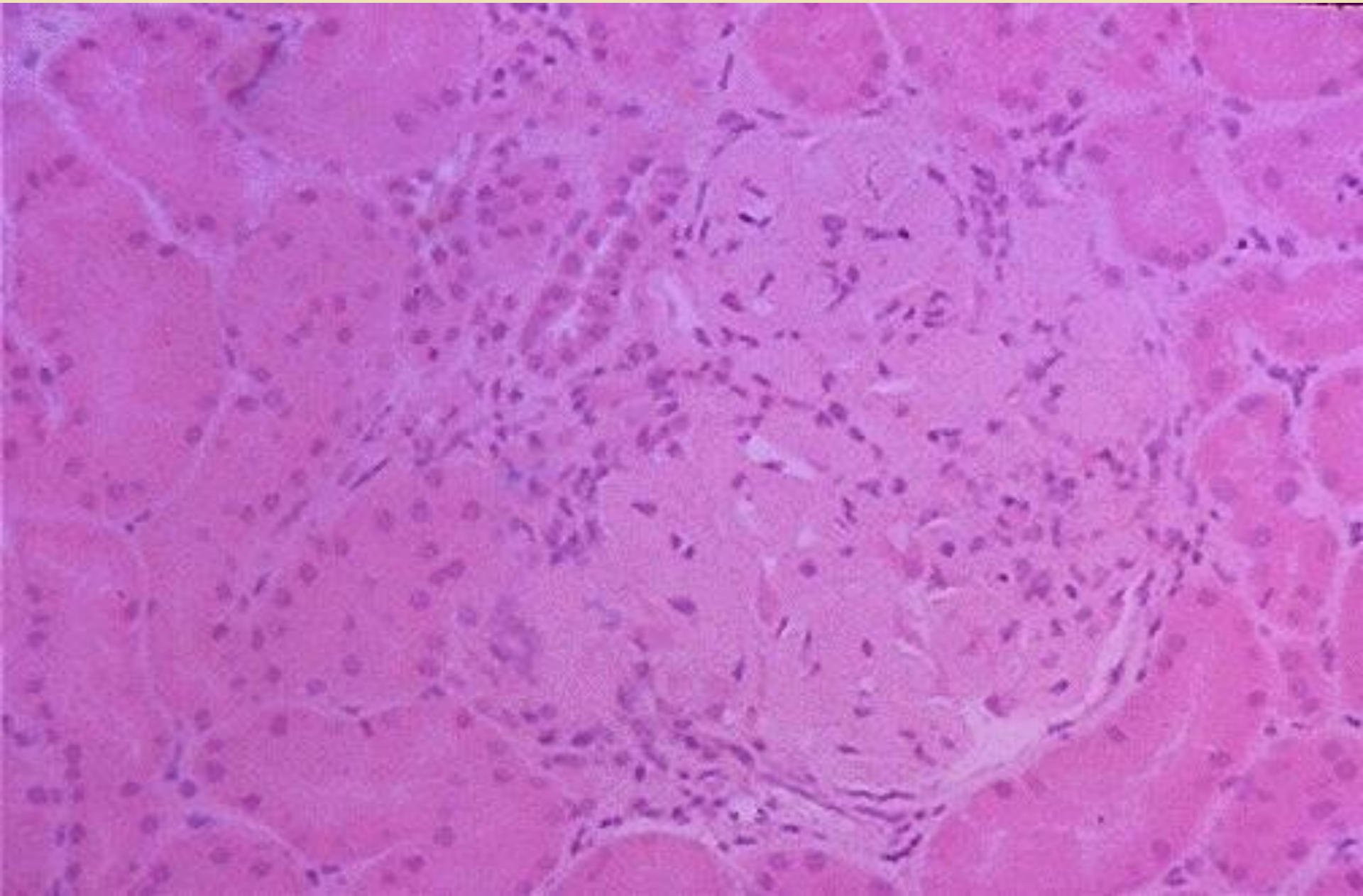

Podocyte with effaced foot processes
Thickened basement membrane
Subepithelial deposits
"Spikes"
B


Ep
E
BM
CL
B

Advanced sclerosing lupus nephritis (class VI)

- **complete sclerosis** of greater than 90% of glomeruli
- corresponds to clinical **end stage renal disease**

Glomerulo-sclerosis



Changes in the interstitium and tubules

- frequent
- Rarely may be the dominant
- Discrete immune complexes in the **tubular or peritubular capillary basement membranes**
- well-organized B-cell follicles
- plasma cells