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IN THE NAME OF GOD

RENAL PATHOLOGY

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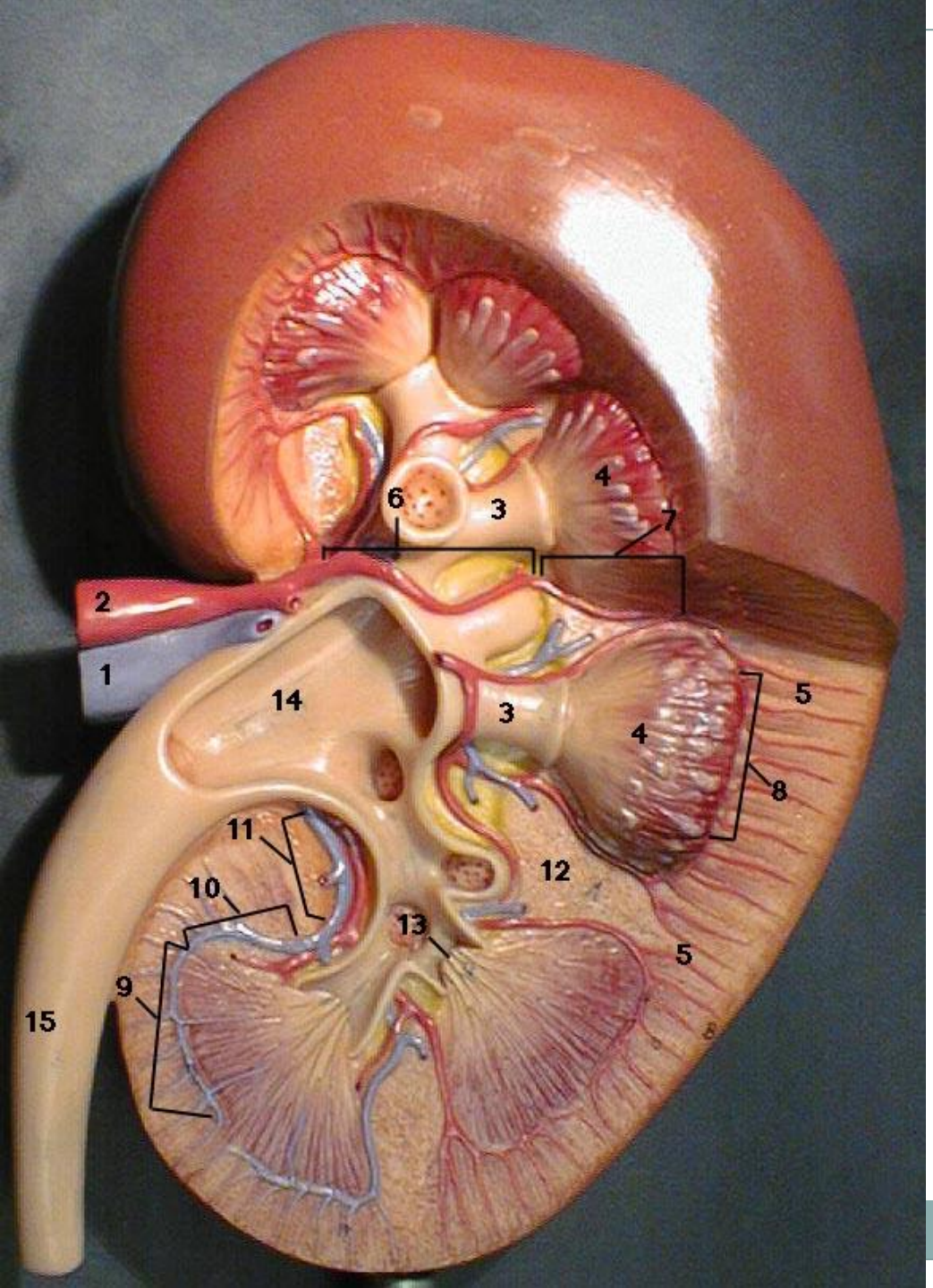
RENAL PATHOLOGY

- **NORMAL**
- **CONGENITAL Anomalies**
- **GLOMERULI**
- **Clinical Manifestations**
- **GN Classification**
- **Pathogenesis of Glomerular Disease/Injury**
  - **Nephritis Caused by Circulating Immune complexe**
  - **Injury from Ab reacting in-situ with glomerulus**
- **Cell mediated immune GN**
- **Other mechanisms of glomerular injury**

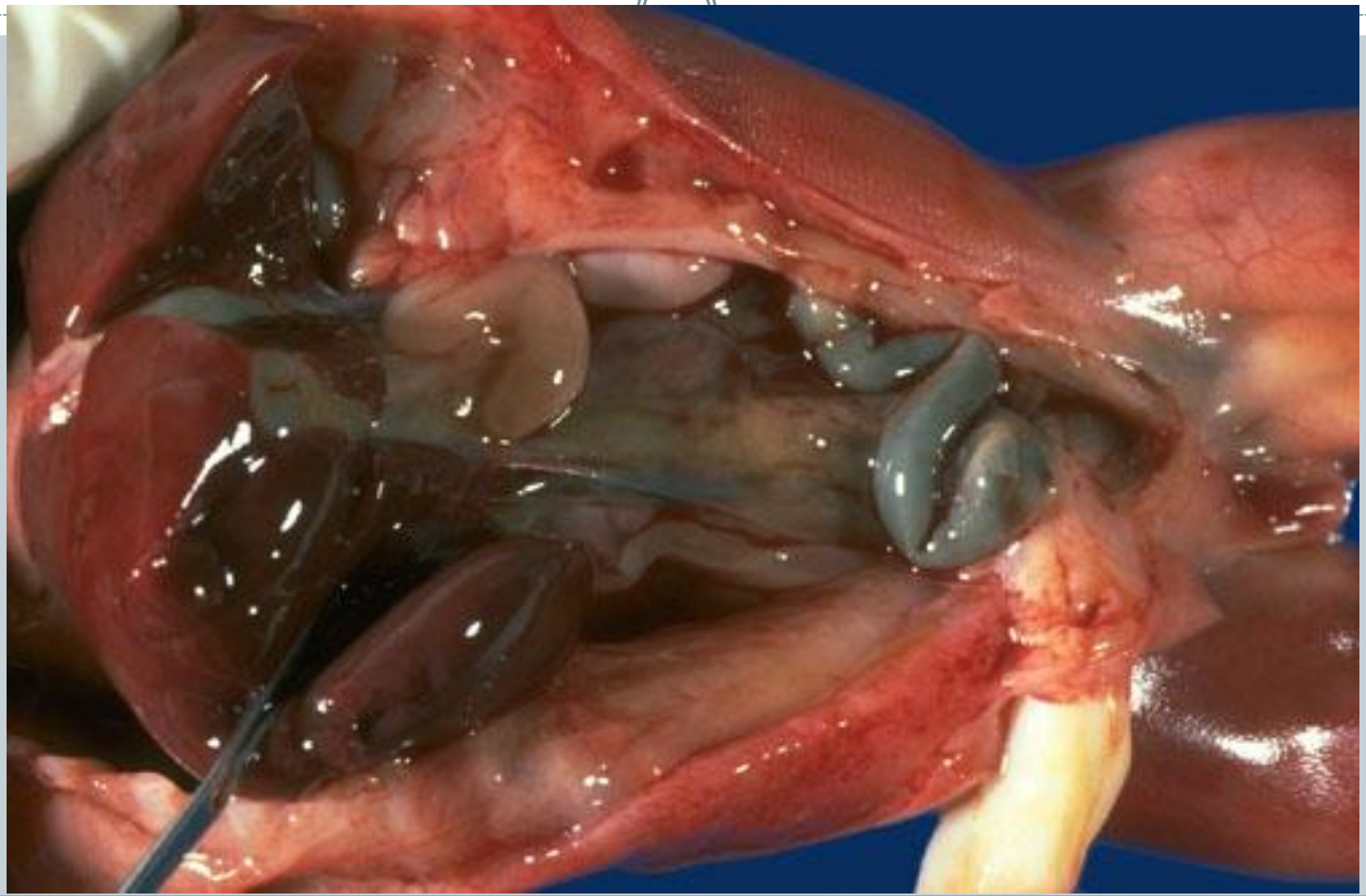


1. Renal Vein
2. Renal Artery
3. Renal Calyx
4. Medullary Pyramid
5. Renal Cortex
6. Segmental Artery
7. InterlobAR Artery
8. Arcuate Artery→ interlobular
9. Arcuate Vein
10. Interlobar Vein
11. Segmental Vein
12. Renal Column
13. Renal Papillae
14. Renal Pelvis
15. Ureter

CONGENITAL ANOMALIES

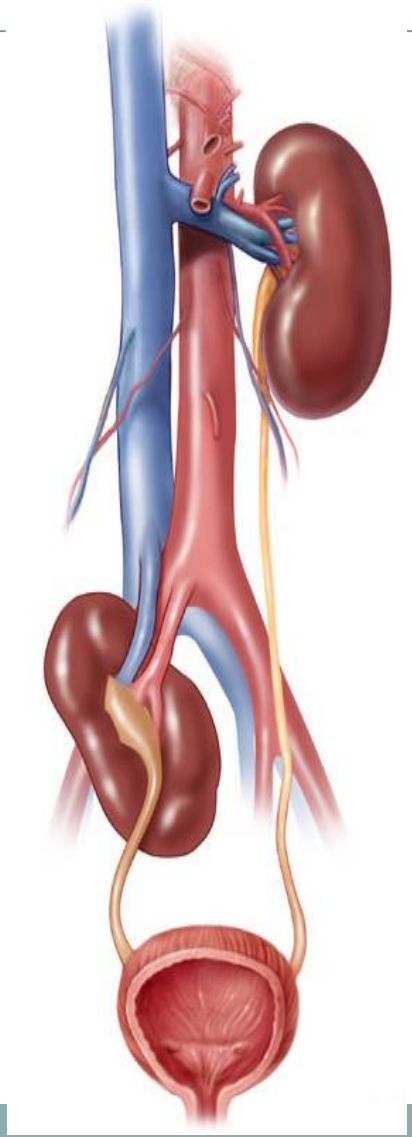
- AGENESIS
- HYPOPLASIA
- ECTOPIC KIDNEY
- HORSESHOE KIDNEY

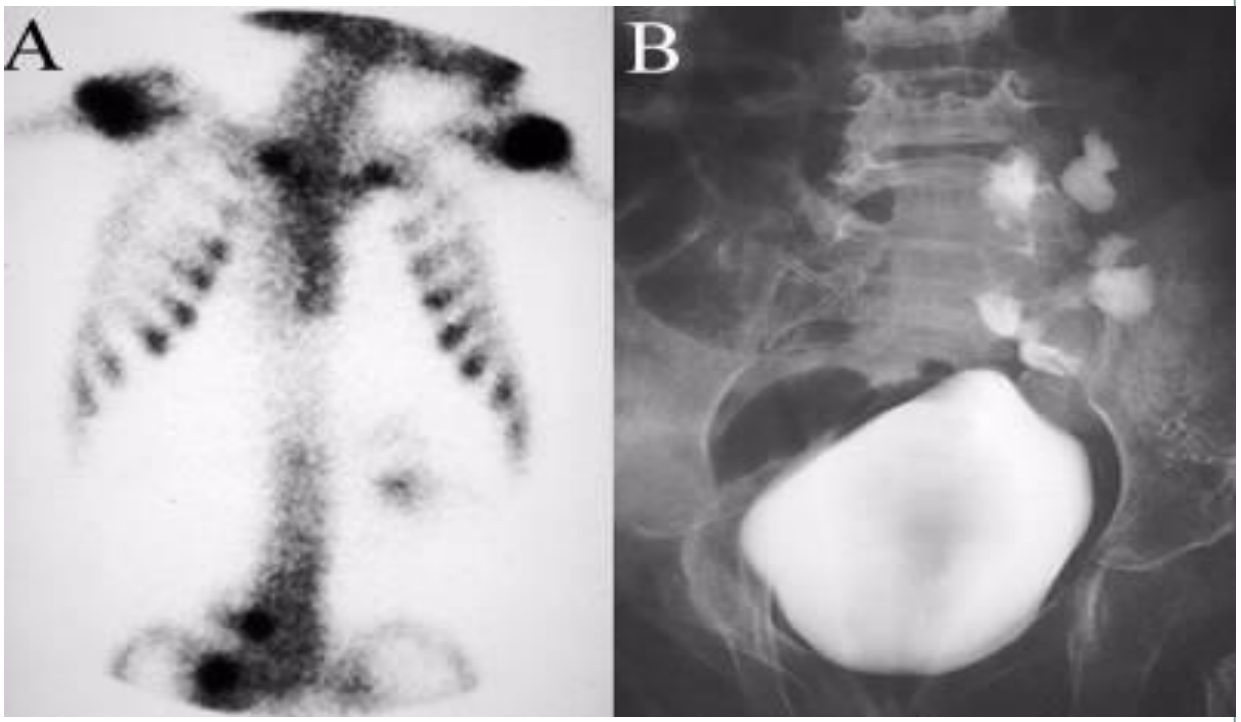
AGENESIS



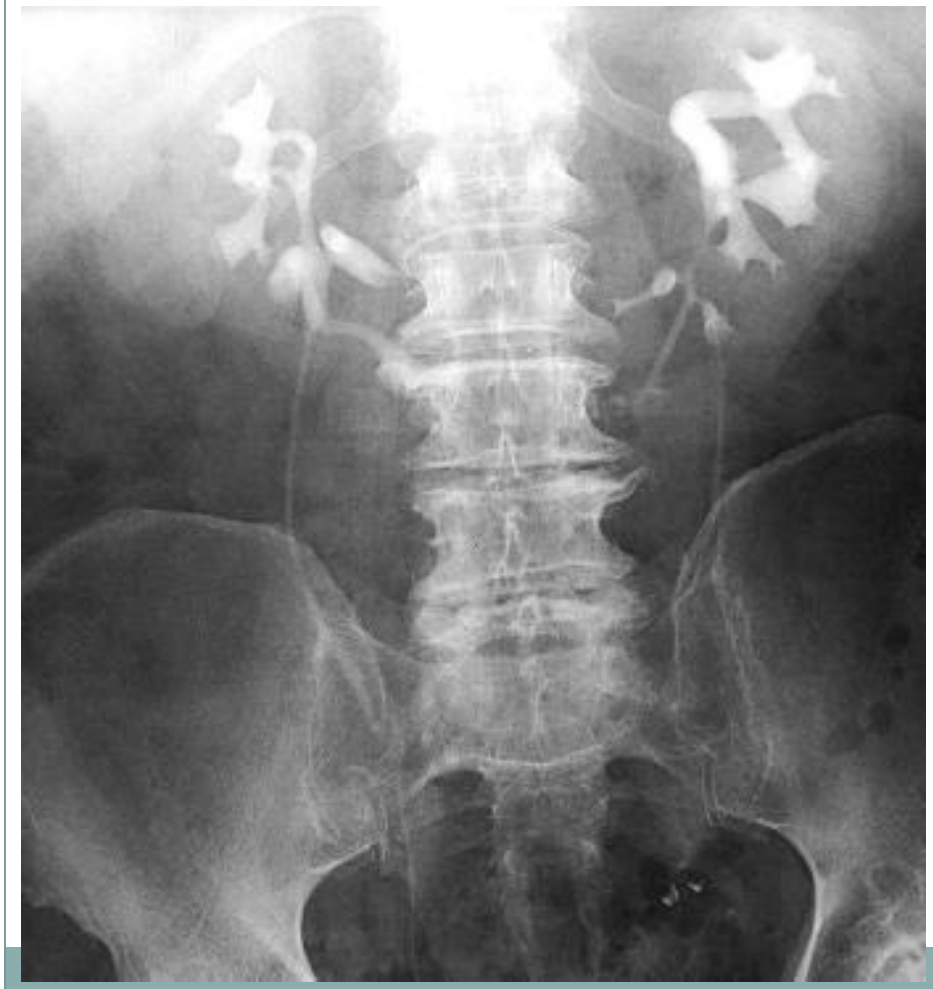
HYPOPLASIA

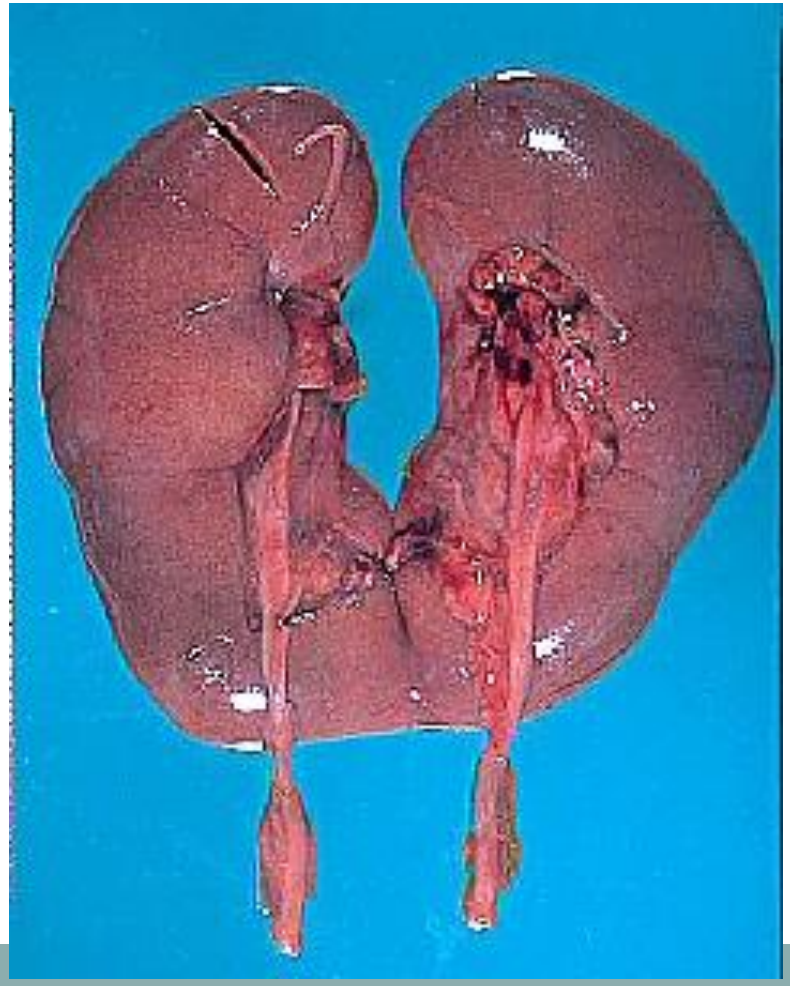
ECTOPIC (usually PELVIC)





HORSESHOE





Diseases Pathogenesis

a) glomeruli (often immunological)
b) tubules (toxic, infectious)
c) interstitium (toxic, infectious)
d) vascular

- **Disease in one area usually results in damage or disease on neighboring areas**

- **Large functional reserve**
  a) > 75% destruction before impairment

GLOMERULI

Network of capillaries

a) fenestrated endothelium

b) basement membrane

c) podocytes (“foot processes”)

d) mesangial cells

Glomeruli capillary wall

- a) fenestrated endothelium (70- 100 nm)
- b) glomerular basement membrane (GBM)
  - icollagen (type IV), heparan sulfate, laminin, glycoproteins
  - Type IV collagen forms network to which glycoprotein's attach

Glomeruli capillary wall

c) visceral epithelial cells (podocytes; "foot processes")

i) composed of interdigitating processes embedded to basement membrane

ii) adjacent foot processes are separated by 20-30 nm filtration bridged by thin diaphragm (nephrin)

Glomeruli capillary wall

- d) entire glomerulus is supported by mesangial cells
  - i) lying between capillaries
  - ii) phagocytic, contractile, proliferate, secretion of biologically active mediators
  - modified smooth muscle cells
  - iii) involved in many types of GN

Glomeruli

a) very permeable to H_2O and small solutes

b) impermeable to proteins (~ 70 kDa or larger; i.e., albumin)

c) "glomerular barrier function"

i) selective permeability based on:

- size
- charge: cationic more permeable

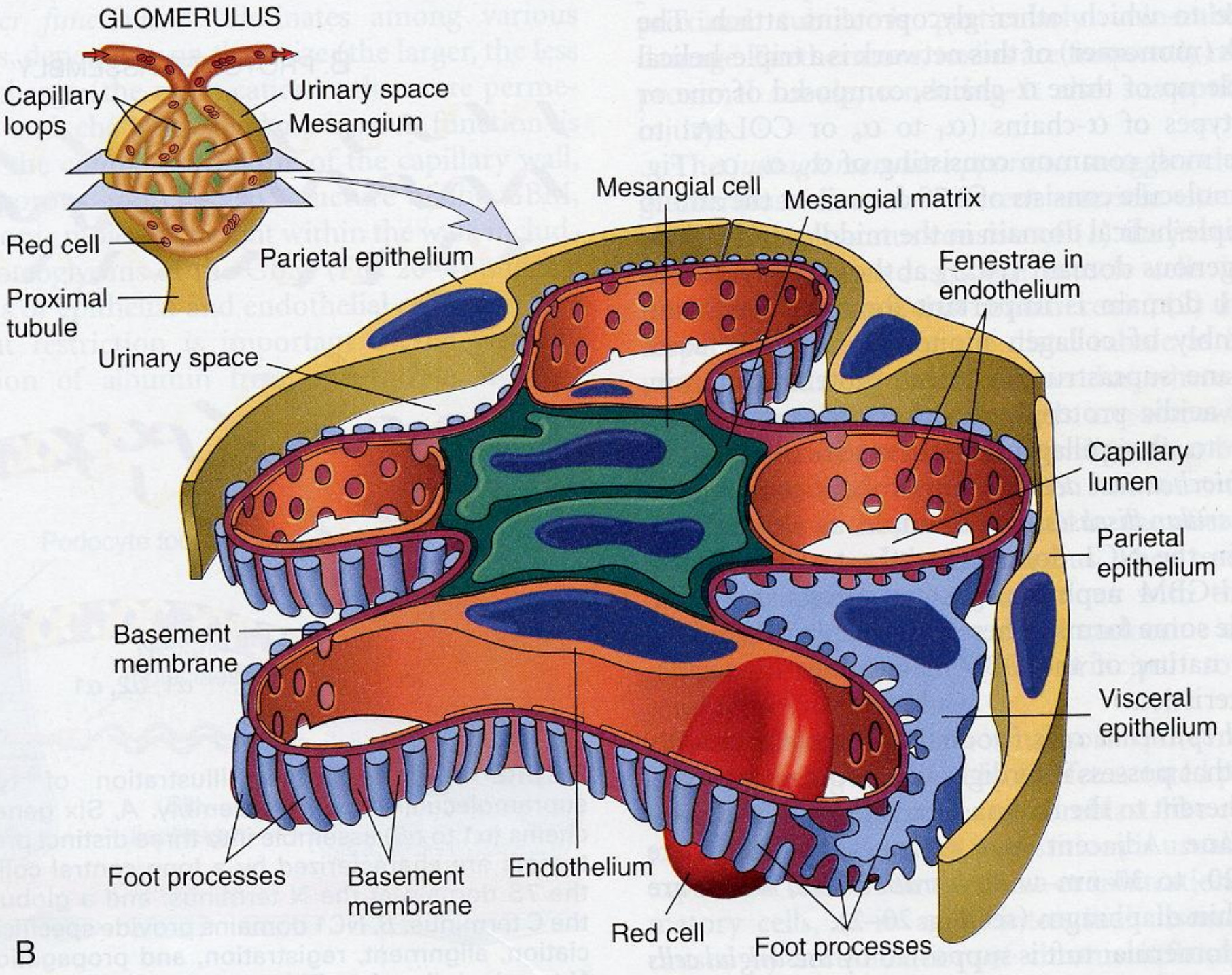
ii) podocytes important in maintaining this "function"

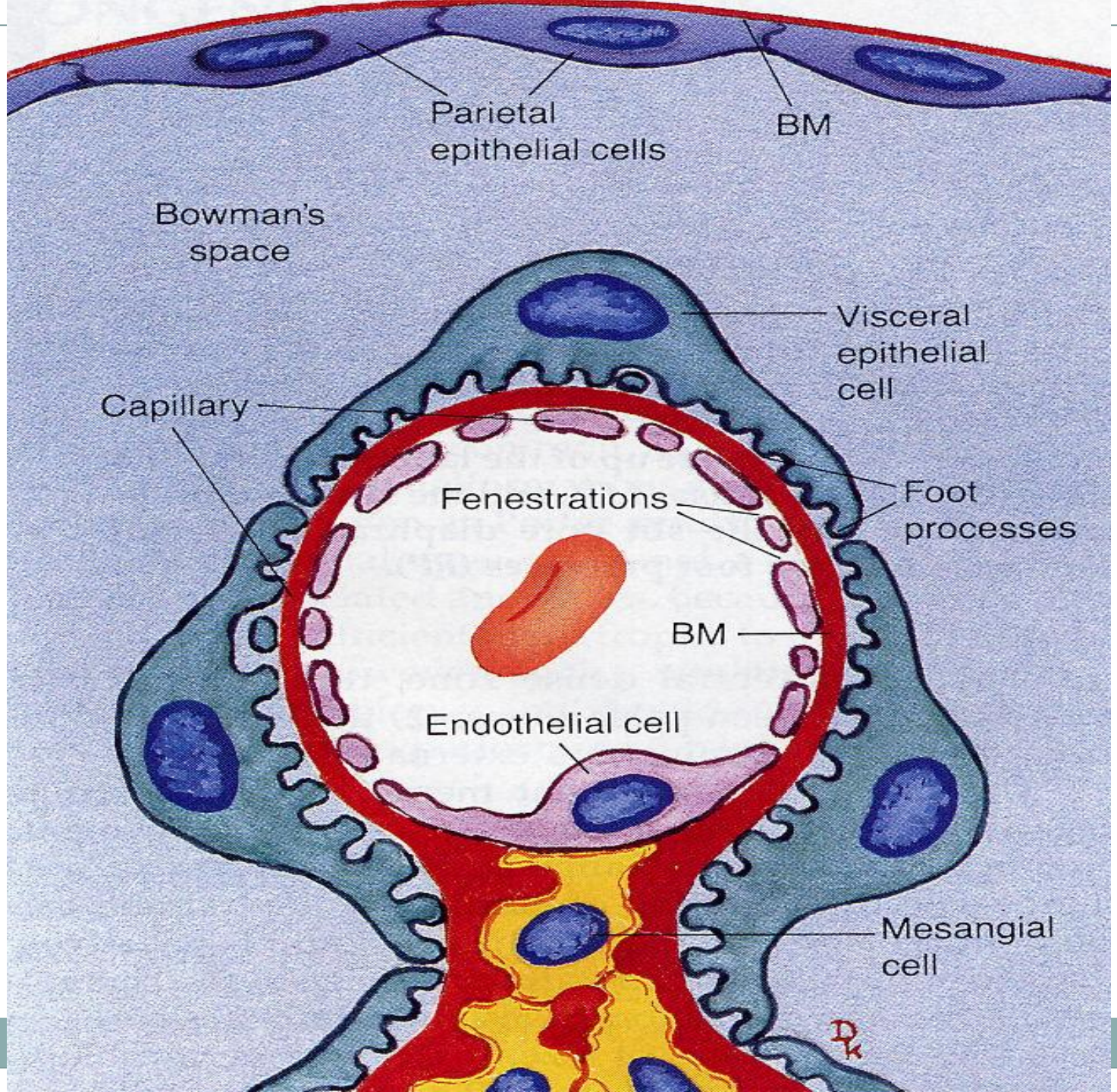
- slit diaphragm maintain size-selectivity by specific proteins

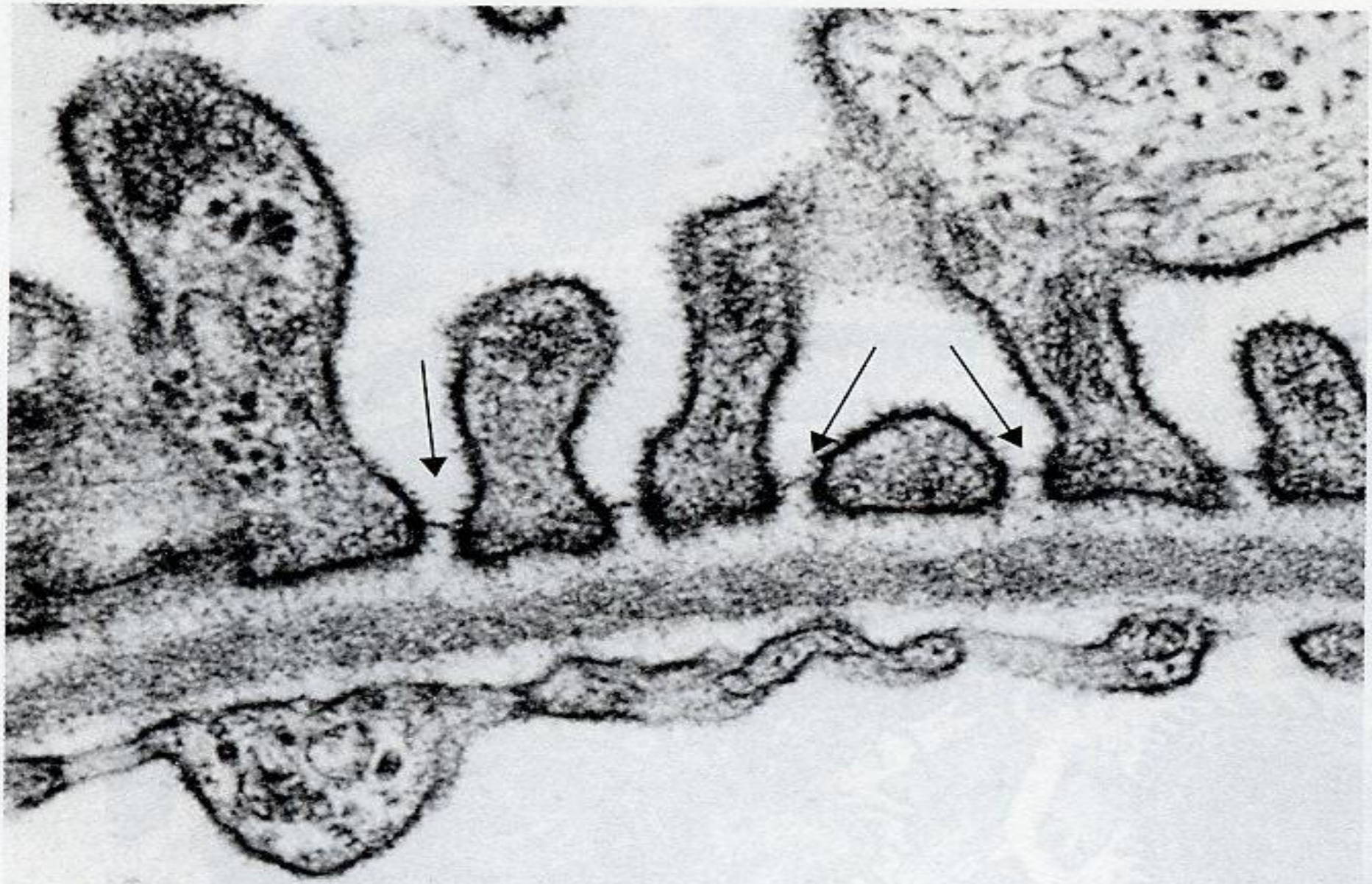
1.- NEPHRIN: extend towards each other from neighboring podocytes comprising the slit diaphragm !!

2.- PODOCIN: intracellular (podocyte) protein where nephrin attaches

mutations in genes encoding these proteins give rise to nephrotic syndrome (i.e., glomerular disease)


GLOMERULUS
Capillary loops
Urinary space
Mesangium
Red cell
Proximal tubule
Parietal epithelium
Mesangial cell
Mesangial matrix
Fenestrae in endothelium
Urinary space
Capillary lumen
Parietal epithelium
Basement membrane
Visceral epithelium
Foot processes
Basement membrane
Endothelium
Red cell
Foot processes
B


Parietal epithelial cells
BM
Bowman's space
Visceral epithelial cell
Capillary
Fenestrations
Foot processes
BM
Endothelial cell
Mesangial cell



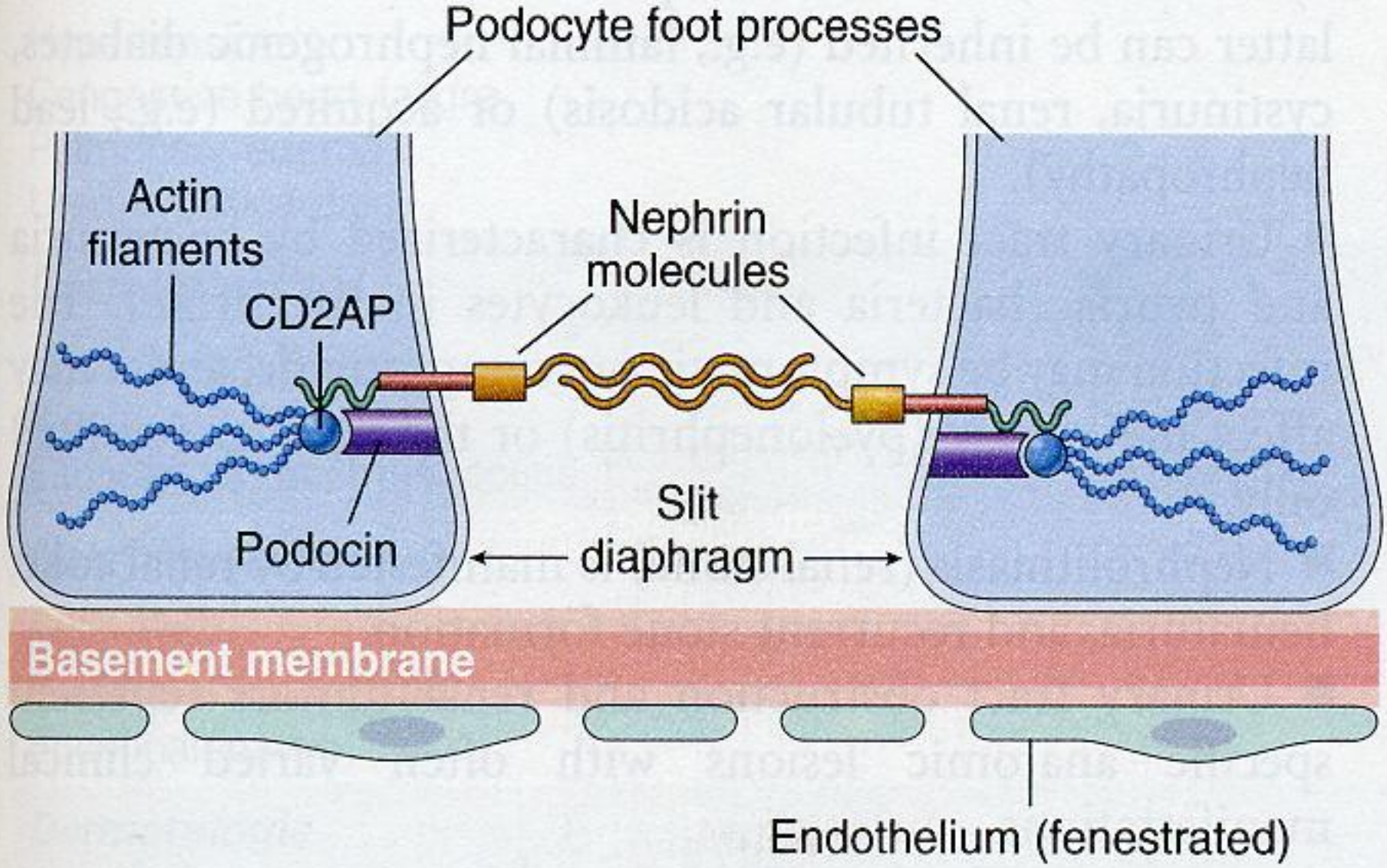


FIGURE 20–5 Schematic diagram of the proteins of the glomerular slit diaphragm. CD2AP, CD2-associated protein.

Clinical Manifestations

- **Termimology**

a) *Azotemia*: ↑ BUN and ↑creatinine

i) related to ↓ GFR

- prerenal azotemia: ↓ RBF, hypoperfusion w/out parenchymal damage
- postrenal azotemia: obstruction of urine flow below level of kidney

Clinical Manifestations

b) when azotemia becomes associated with a variety of clinical S & S and biochemical abnormalities → ***UREMIA***

CHRONIC RENAL FAILURE

Fluid and Electrolytes: Dehydration, Edema, Hyperkalemia, Metabolic acidosis

Calcium Phosphate and Bone: Hyperphosphatemia, Hypocalcemia, Secondary hyperparathyroidism, Renal osteodystrophy

Hematologic: Anemia, Bleeding diathesis

Cardiopulmonary: Hypertension, Congestive heart failure, Pulmonary edema, Uremic pericarditis

Gastrointestinal: Nausea and vomiting, Bleeding, Esophagitis, gastritis, colitis

Neuromuscular: Myopathy, Peripheral neuropathy, Encephalopathy

Dermatologic: Sallow (greenish-yellow) color, Pruritus, Dermatitis

Major Renal Syndromes

a) *Nephritic syndrome*: glomerular disease, hematuria, mild → moderate proteinuria azotemia, edema, ↑ BP

i) classic presentation of pos streptococcal GN

b) *Nephrotic syndrome*: heavy proteinuria (> 3.5g/day), hypoalbuminemia, severe edema, hyperlipidemia and lipiduria

Major Renal Syndromes

c) *Acute renal failure*: oliguria/anuria, recent onset of azotemia, can result from GN, tubular or interstitial disease

d) *Nephroliathiasis*: renal stones, renal colic, hematuria, recurrent stone formation

Major Renal Syndromes

e) *Chronic renal failure*: 4 stages

i) ↓ renal reserve: GFR ~ 50% normal BUN & creatinine normal, pt. asymptomatic, more susceptible to develop azotemia

ii) renal insufficiency: GFR 20-50% of normal, azotemia, anemia, ↑ BP, polyuria/nocturia (via ↓concentrating ability)

Major Renal Syndromes

iii) renal failure: GFR less than 20-25%
kidneys cannot regulate volume, ions:
edema, hypocalcemia,metabolic acidosis,
uremia with neurological, CV and GI
complications

iv) end stage renal disease: GFR < 5%
of normal, terminal stage of uremia

TABLE 20–4 The Glomerular Syndromes

Acute nephritic syndrome	• Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension
Rapidly progressive glomerulonephritis	• Acute nephritis, proteinuria, and acute renal failure
Nephrotic syndrome	• >3.5 gm proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria
Chronic renal failure	• Azotemia → uremia progressing for years
Asymptomatic hematuria or proteinuria	• Glomerular hematuria; subnephrotic proteinuria

Glomerular Disease

- **Chronic GN one of most common causes of chronic renal failure**
- **Glomerular disease often associated with systemic disorders such as:**
  - a) diabetes mellitus
  - b) SLE
  - c) amyloidosis
  - d) vasculitis
    - pts. with manifestations of glomerular disease should be considered for these systemic syndromes, etc.

Glomerular Disease

- **GN characterized by one or more of the following (inflammatory diseases of glomerulus)**

a) hypercellularity:
b) basement membrane thickening
c) hyalinization (hyalinosis) and sclerosis

Glomerular Disease

a) hypercellularity:

i) cell proliferation of mesangial cells or endothelial cells

ii) leukocyte infiltration (neutrophils, monocytes and sometimes lymphocytes)

iii) formation of crescents

- epithelial cell proliferation (from immune/inflammatory injury)
- fibrin thought to elicit this injury (TNF, IL-1, IFN-γ are others)

Glomerular Disease

b) basement membrane thickening

i) deposition of immune complexes on either the endothelial or epithelial side of GBM or w/in GBM itself

ii) thickening of GBM proper as with diabetes mellitus (diabetic glomerulosclerosis)

Glomerular Disease

- c) hyalinization (hyalinosis) and sclerosis

  i) accumulation of material that is eosinophilic and homogeneous

  - obliterates capillary lumen of glomerulus (sclerotic feature)

  -result of capillary or endothelial injury.

  -Usually end result of various forms of glomerular damage (intraglomerular thromboses, accumulation of other metabolic materials

GN Classification

Since etiology of primary GN is unknown, classification is based on histology.

Subdivided:

a) diffuse (all glomeruli)

b) global (entire glomerulus)

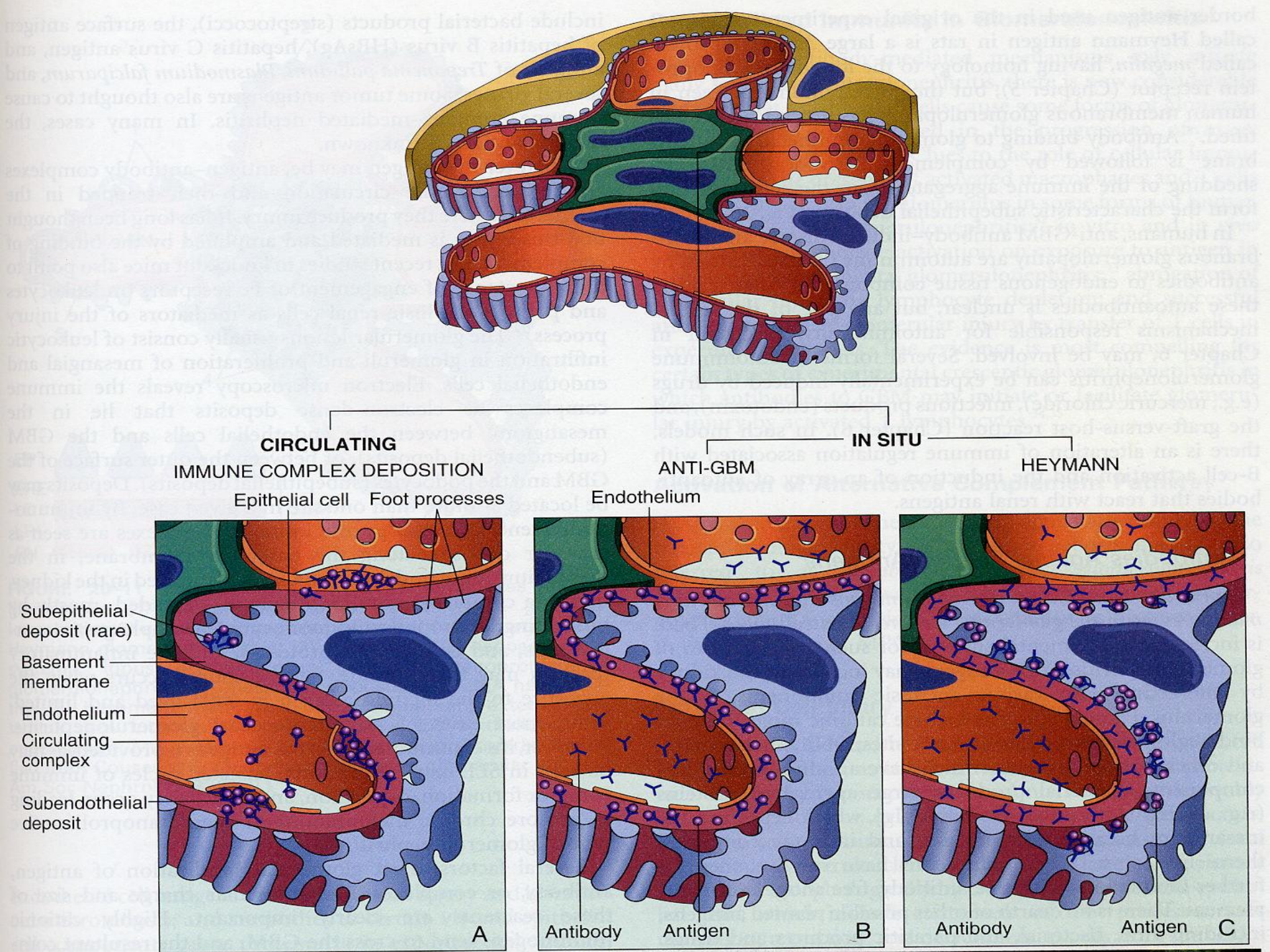
c) focal (portion of glomeruli)

d) segmental (part of each glomerulus)

e) mesangial (affecting mesangial region)

Pathogenesis of Glomerular Disease/Injury

- Antibody-associated injury :
  - (1) deposition of soluble circulating antigen-antibody complexes in the glomerulus,
  - (2) injury by antibodies reacting in situ within the glomerulus,
    - insoluble fixed (intrinsic) glomerular antigens
    - molecules planted withinthe glomerulus (Fig. 14-3).
- Cell mediated immune GN


CIRCULATING
IMMUNE COMPLEX DEPOSITION
IN SITU
ANTI-GBM
HEYMANN
Epithelial cell
Foot processes
Endothelium
Subepithelial deposit (rare)
Basement membrane
Endothelium
Circulating complex
Subendothelial deposit
Antibody
Antigen
A
B
Antibody
Antigen
C

Nephritis Caused by Circulating Immune Complexes

- glomerulus :"innocent bystander“ because it does not incite the reaction.
- The antigen is not of glomerular origin:
  - Endogenous :
    - SLE
  - Exogenous :
    - certain bacterial (streptococcal),
    - viral (hepatitis B),
    - parasitic *(Plasmodium falciparum* malaria),
    - spirochetal *(Treponema pallidum)* infections.

Nephritis Caused by Circulating Immune Complexes

- produce injury large part through the activation of complement and the recruitment of leukocytes.
- glomerular lesions usually consist of
  - leukocytic infiltration (exudation) into glomeruli
  - variable proliferation of endothelial, mesangial, and parietal epithelial cells.

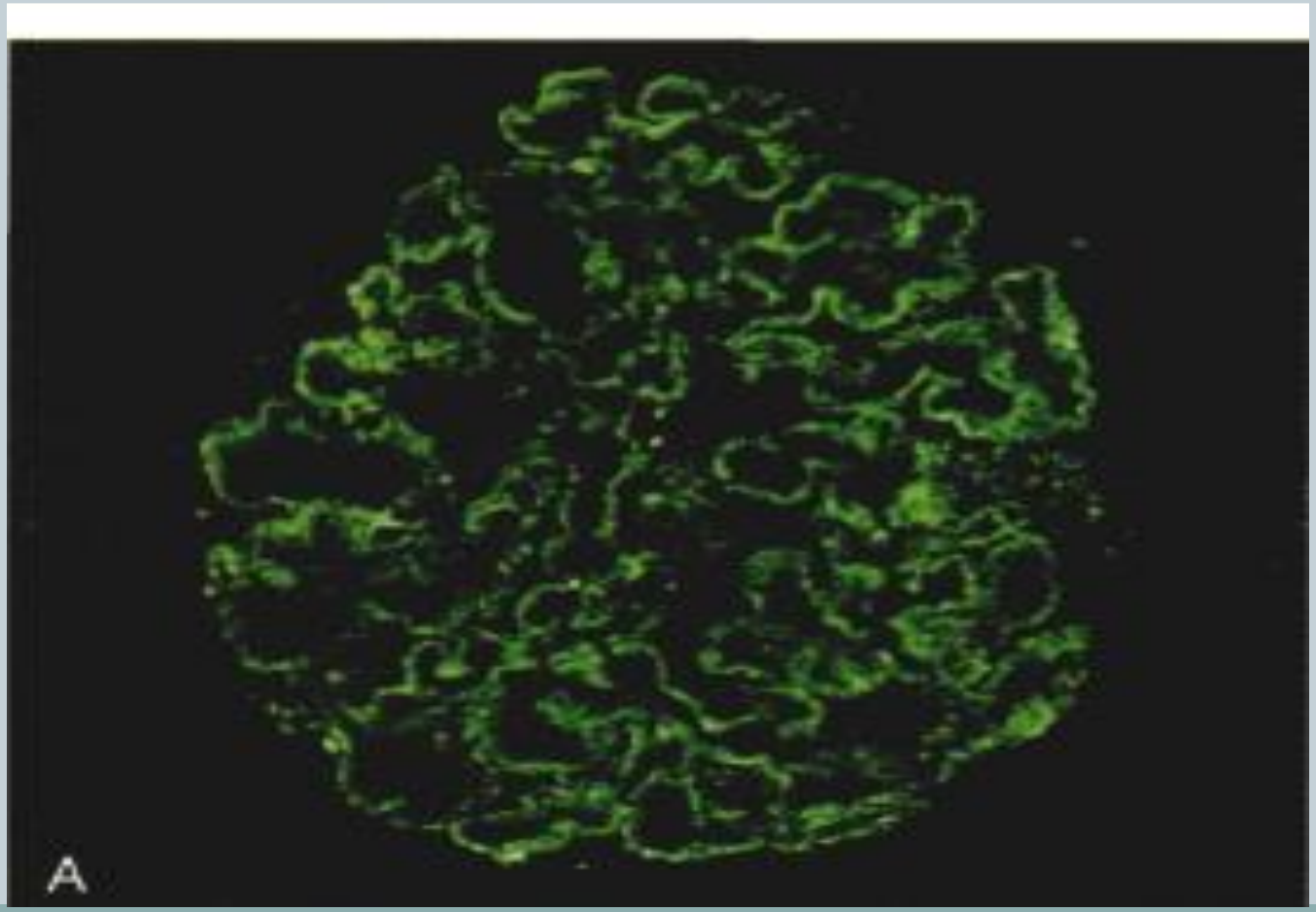
Nephritis Caused by Circulating Immune Complexes

- Electron microscopy : immune complexes as electron-dense deposits or clumps that lie at one of three sites:
  - in the mesangium,
  - Between the endothelial cells and the GBM (subendothelial deposits),
  - between the outer surface of the GBM and the podocytes (subepithelial deposits)
- Deposits may belocated at more than one site in a given case.

Nephritis Caused by Circulating Immune Complexes

- *When fluoresceinated anti-immunoglobulin or anti-complement antibodies are used, the immune complexes are seen as granular deposits in the glomerulus* (Fig.14-4A).

Nephritis Caused by Circulating Immune Complexes



Nephritis Caused by Circulating Immune Complexes

- short-lived and limitedexposure to the inciting antigen :
- immune complexes may eventually be degraded or phagocytosed, mostly by infiltrating leukocytes and mesangial cells, and the inflammatory changes may then subside (most cases of poststreptococcal or acute infection-related GN).

Nephritis Caused by Circulating Immune Complexes

- Continuous shower of antigens :
- repeated cycles of immune complex formation, deposition, and injury may occur, leading to chronic GN.
  - source of chronic antigenic exposure is clear
    - hepatitis B virus infection
    - self nuclear antigens in SLE.
  - antigen is unknown.

Pathogenesis of Glomerular Disease/Injury

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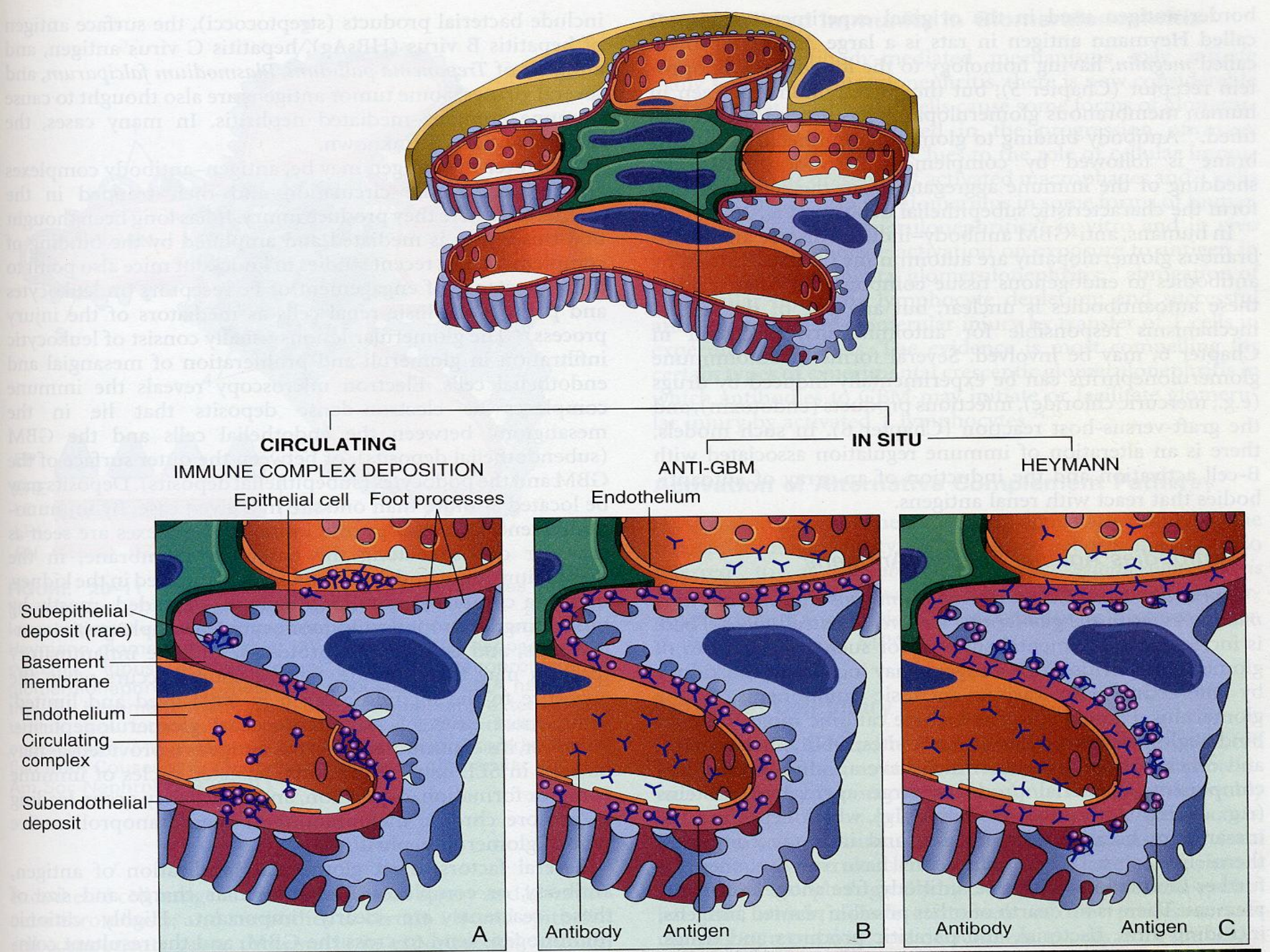
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In Situ Immune Complex Deposition

a) *anti-GBM Ab-induced nephritis*

- Ab directed against fixed Ag in GBM
- in humans spontaneous AGBM

nephritis is autoimmune disease

- Ab bind along GBM forming a "linear pattern"
- sometimes AGBM Ab cross react with BM of lung ▪ "GOODPASTURE SYNDROME"
- < 1% of GN cases
- some cases show severe glomerular damage and rapidly progressive crescentic GN

b) *Heymann nephritis*

- a form of membranous GN
- Ab bind along GBM in "granular pattern"

Ab can react with "planted" Ag in GBM

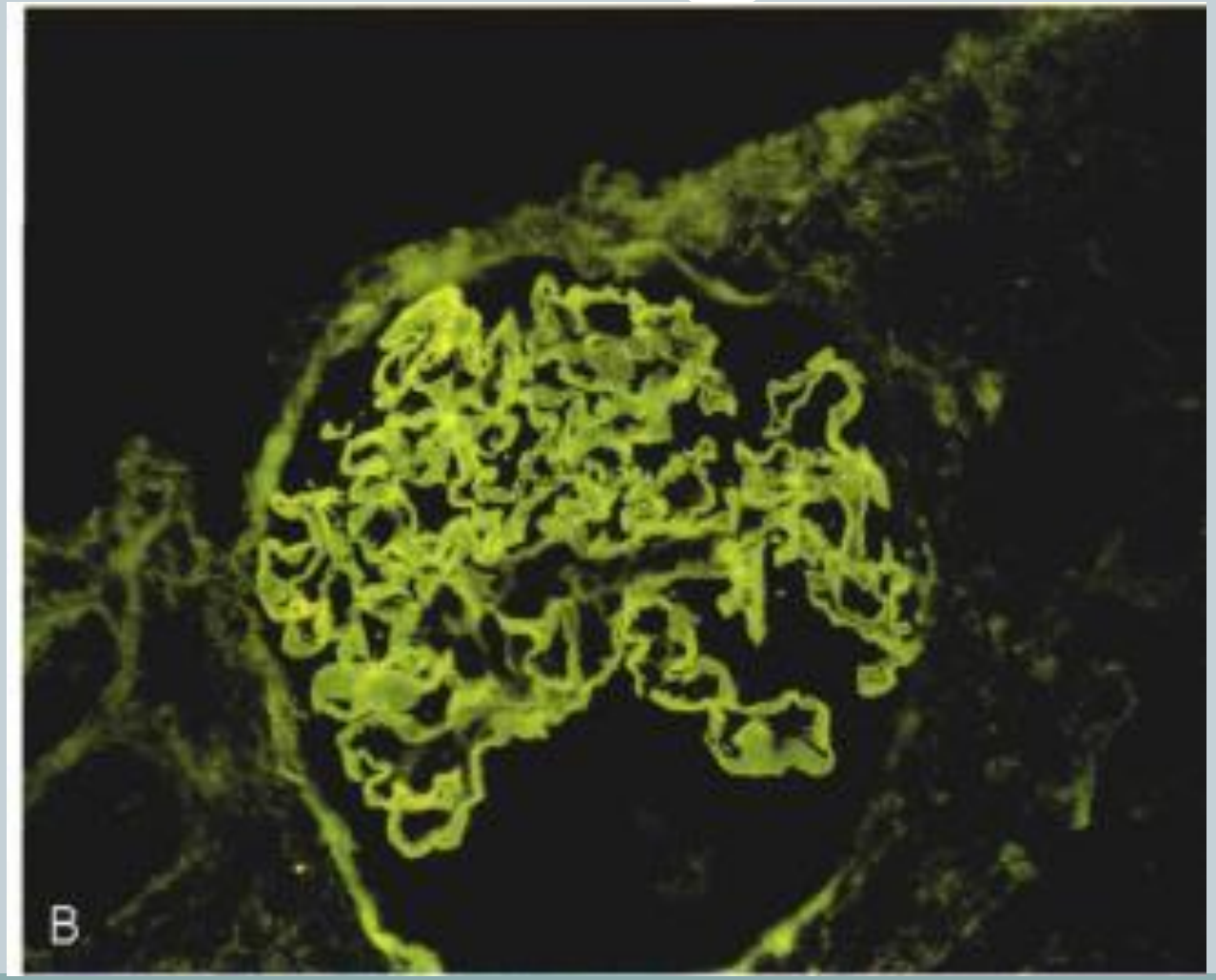
a) cationic Ag binding to anionic GBM sites

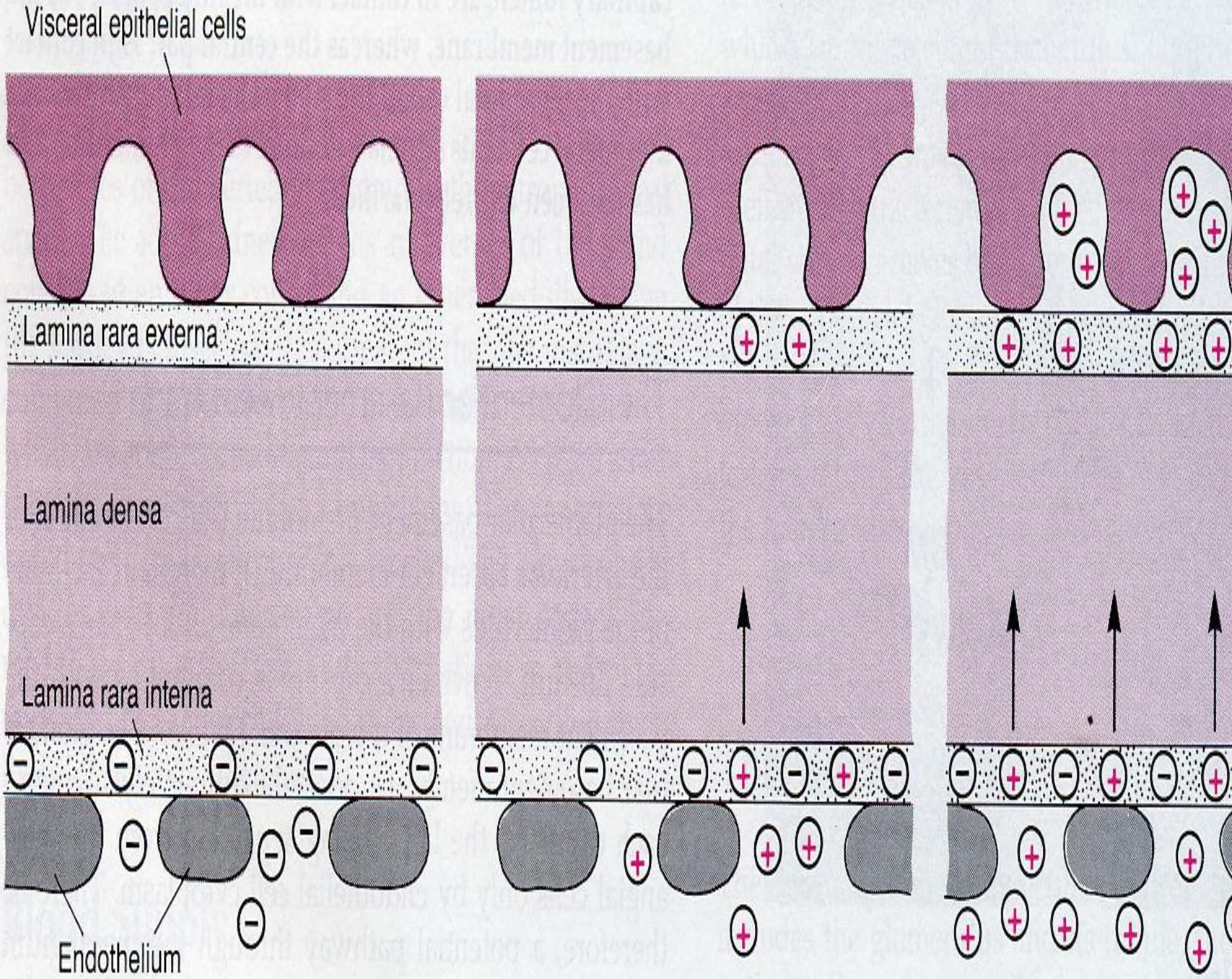
b) bacterial byproducts

c) IgG deposition in mesangium

c) Trigger for induction of autoimmune Ab is unclear

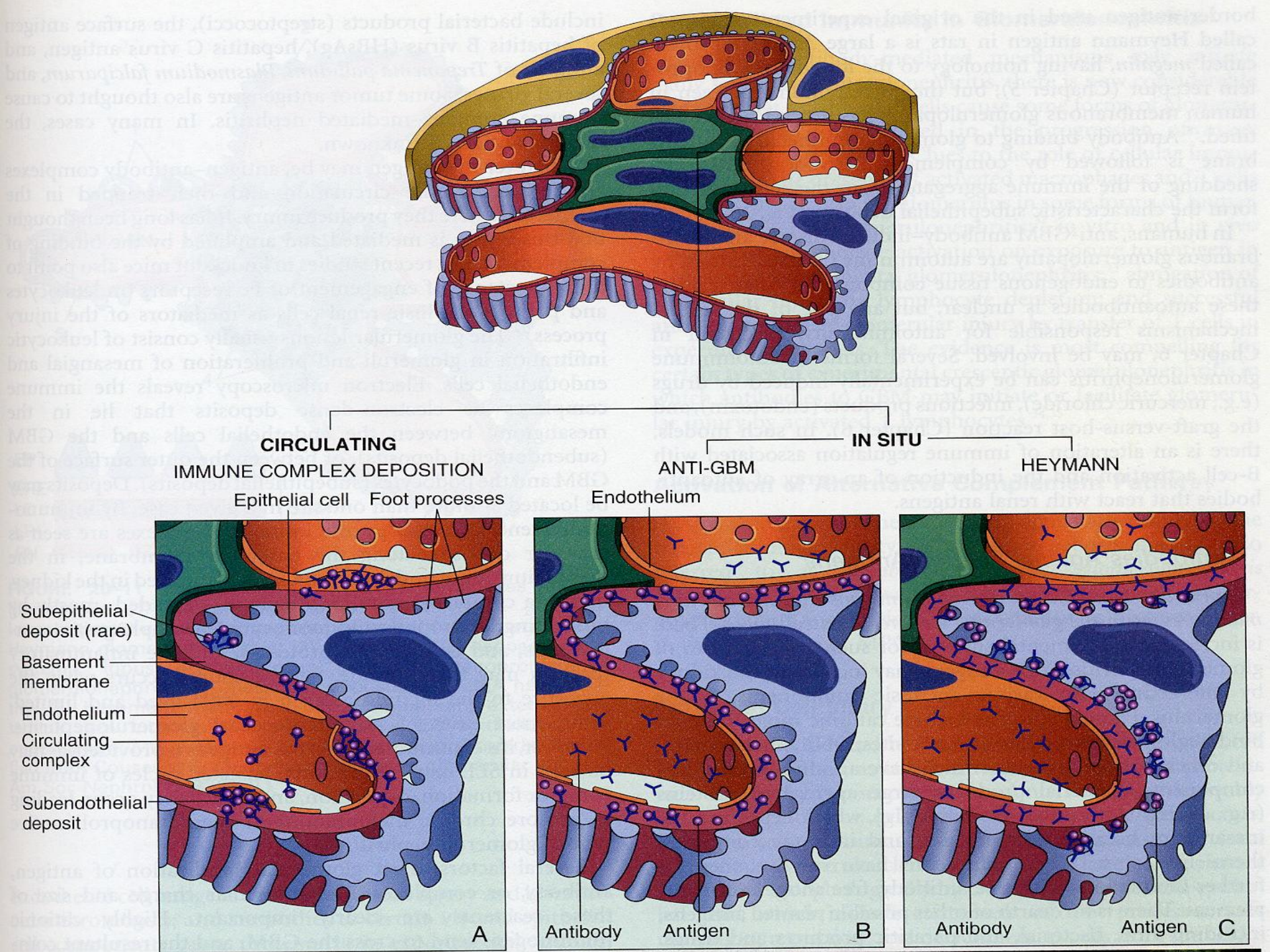
GOODPASTURE SYNDROME




Visceral epithelial cells
Lamina rara externa
Lamina densa
Lamina rara interna
Endothelium

- ***re: Ab-mediated injury → Ag-Ab deposition in GBM is major pathway of glomerular injury !!***
    a) largest proportion of cases of GN are granular immune pattern along the GBM or mesangium

- **Cell mediated immune GN**
    a) sensitized T cells can cause glomerular injury, in absence of immune deposits
        i) may occur in some forms of rapidly progressive GN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A
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Mediators of immune injury

•Complement-leukocyte mechanism

a) well established

i) activated complement (C5a) → neutrophils and monocytes

- release proteases → degrade GBM

ii) ROS

iii) neutrophil-independent- C5-C9 (lytic component; membrane attack complex)

Membrane attack complex stimulate growth factors (TGF) → GBM thickening

iv) direct cytotoxicity

Other mechanisms of glomerular injury

a) epithelial cell injury

i) can be induced by Ab to visceral epithelial cell Ag

ii) toxins

iii) cytokines

iv) loss of foot processes

- caused by alterations in nephrin

Other mechanisms of glomerular injury

b) renal ablation GN

i) any renal disease → ↓ GFR (30-50% of normal)

- lead to end stage renal failure

ii) patients develop proteinuria and diffuse glomerulosclerosis

- initiated by unaffected glomeruli → hypertrophy to maintain function → single nephron hypertension → damage

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