IN THE NAME OF GOD

RENAL PATHOLOGY

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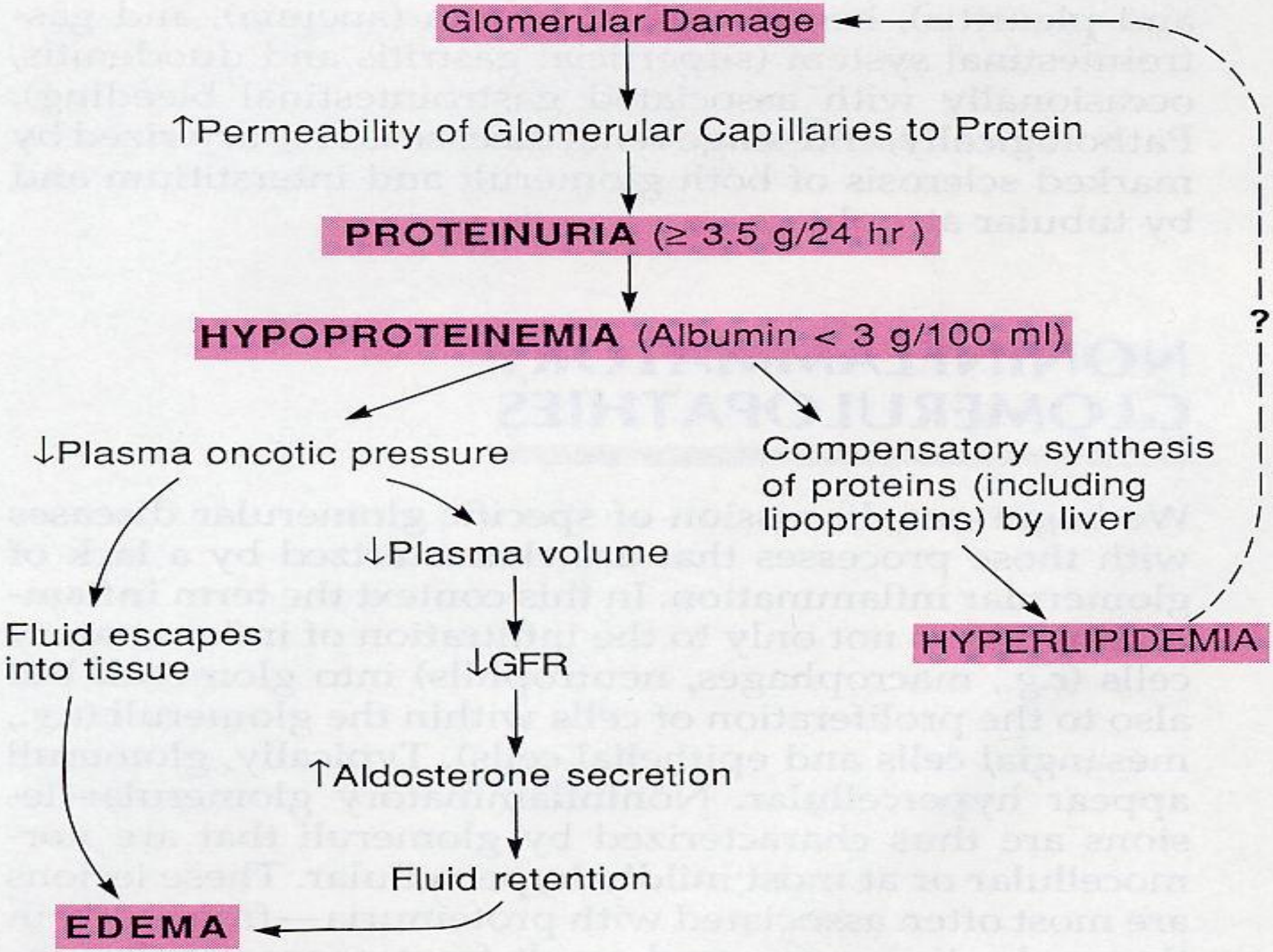
TABLE 20–4 The Glomerular Syndromes

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 Syndromes and Disorders

Nephrotic Syndrome

a) massive proteinuria (> 3.5 g/day)
b) hypoalbuminemia
c) generalized edema
d) hyperlipidemia and lipiduria


Glomerular Damage
↑Permeability of Glomerular Capillaries to Protein
PROTEINURIA (≥ 3.5 g/24 hr)
HYPOPROTEINEMIA (Albumin < 3 g/100 ml)
↓Plasma oncotic pressure
Compensatory synthesis of proteins (including lipoproteins) by liver
↓Plasma volume
Fluid escapes into tissue
↓GFR
HYPERLIPIDEMIA
?
↑Aldosterone secretion
Fluid retention
EDEMA

Nephrotic Syndrome

Initial event is derangement of GBM →

increasing permeability and progressive

loss of plasma proteins → hypoalbuminemia → decrease in plasma volume → ↓ plasma colloid osmotic pressure → ↑ aldosterone ↓ ANP, GFR → edema →

↑ water and solute retention by

kidney → exacerbation of edema (anasarca;

massive amounts of edematous fluid);

hypoalbuminemia → ↑ lipoprotein production

by the liver

Nephrotic Syndrome

- In children < 15 yrs, nephrotic syndrome almost always caused by primary renal disease (~ 98 %)

- In adults nephrotic syndrome may often be associated with secondary renal disease

Minimal change disease
(Lipoidnephrosis; Epithelial cell disease)

a) major cause of nephrotic syndrome in children < 15 yrs;

b) → peak 2-6 yrs

i) also in adults with nephrotic syndrome (~ 20 %)

c) *effacement of "foot" processes*

d) glomeruli show only "minimal" changes

Minimal change disease (Lipoidnephrosis; Epithelial cell disease)

e) most patients are boys who usually present prior to 6 yrs of age

i) selective proteinuria (albumin)

ii) history of recent Ag exposure ??

f) idiopathic (sometimes follows respiratory infection or routine immunizations)

Minimal change disease (Lipoidnephrosis; Epithelial cell disease)

g) T cell involvement suggested

i) patients present w/ similar S & S

ii) epithelial cell diseases have altered T ell function

h) loss of lipoproteins through the glomeruli

→ accumulates lipids in proximal tubule cells → foamy cytoplasm ,together with lipids in the urine → LIPOID NEPHROSIS

i) remission w/in 8 weeks with use of corticosteroid use (very dramatic response is one hallmark of this disease)

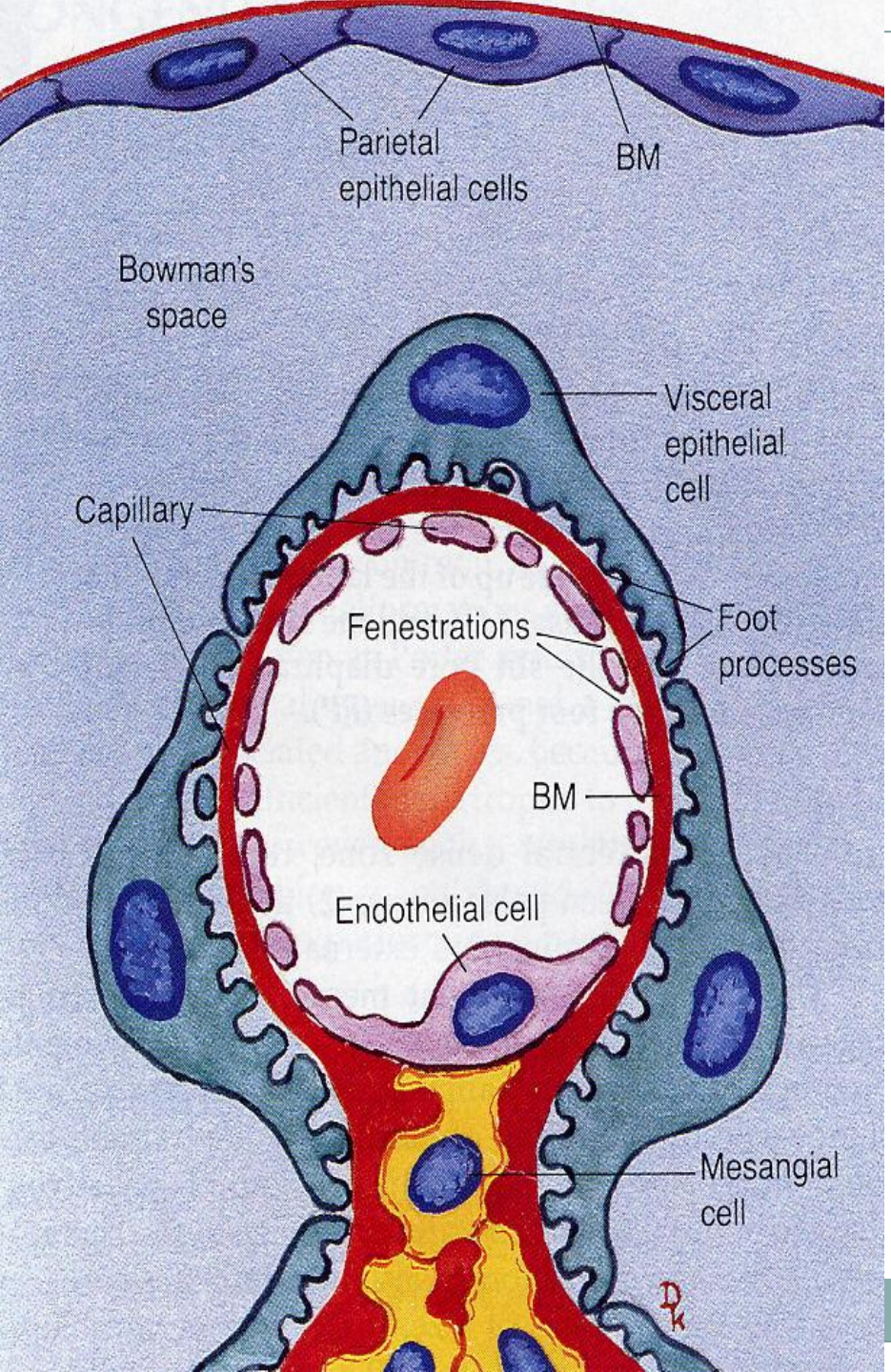
Minimal change disease (Lipoidnephrosis; Epithelial cell disease)

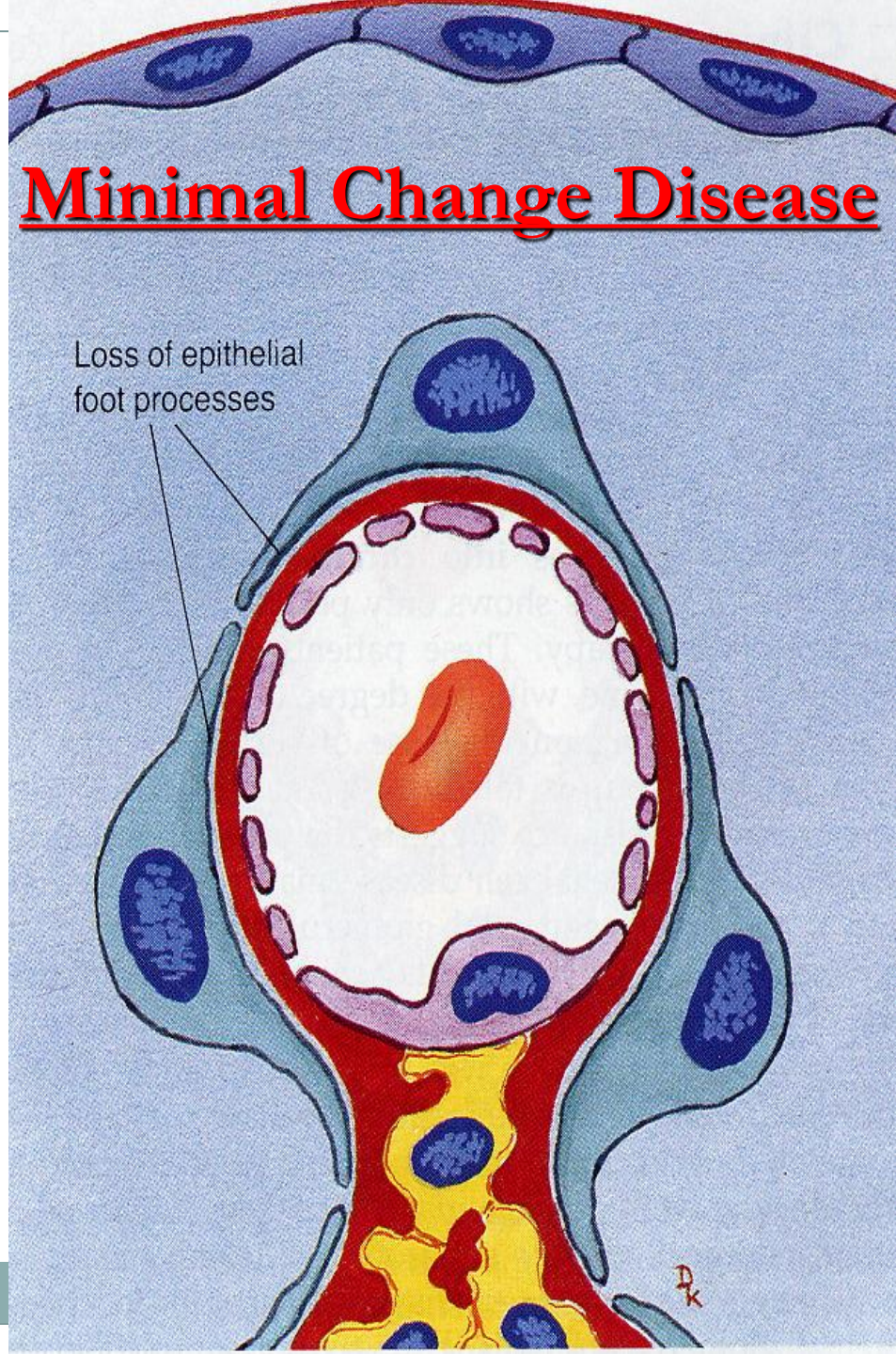
j) relapses do not tend to progress to chronic renal failure

k) development of azotemia should suggest incorrect diagnosis of minimal change disease

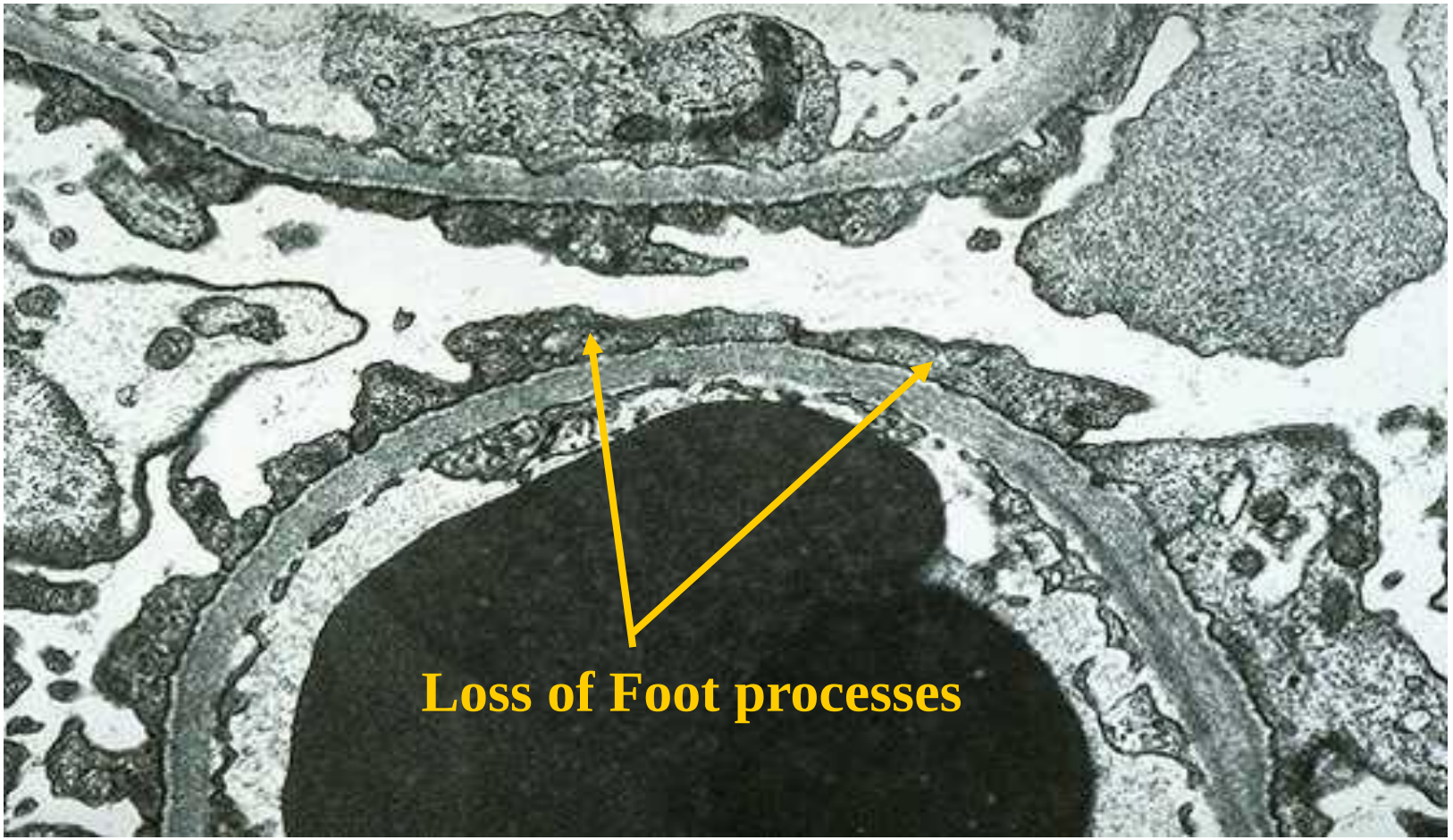
l) in absence of complications, outcome of patients with epithelial cell disease is same as general population

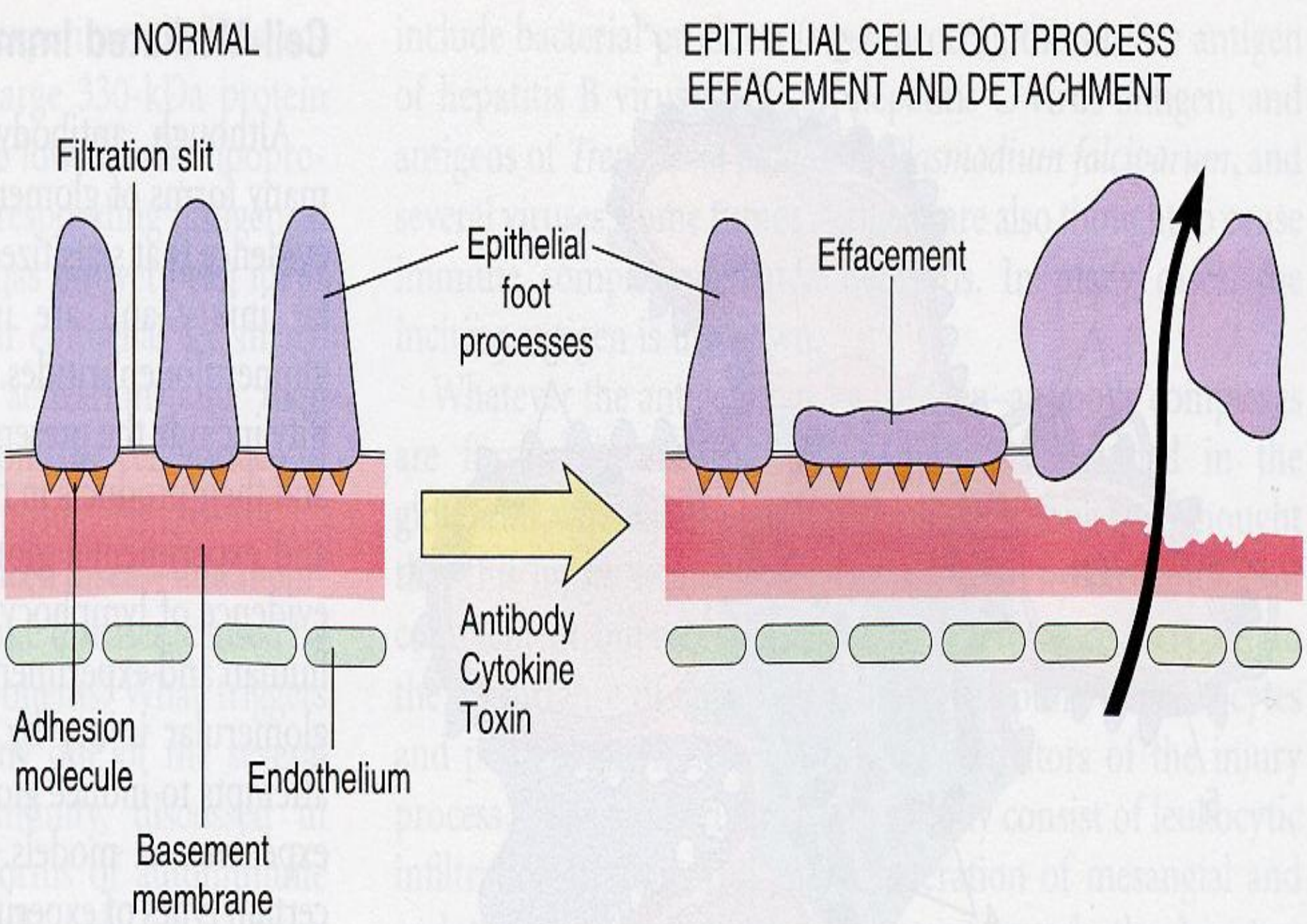
Minimal Change Disease





Minimal Change Disease:




NORMAL
EPITHELIAL CELL FOOT PROCESS EFFACEMENT AND DETACHMENT
Filtration slit
Epithelial foot processes
Effacement
Antibody
Cytokine
Toxin
Adhesion molecule
Endothelium
Basement membrane

Membranous Glomerulopathy (epithelial cell and BM disease)

a) most common cause of nephrotic syndrome in adults (C5-C9 cytotoxic)
b) diffuse thickening of glomerular capillary wall !!
c) most cases are idiopathic
    i) most believed to be autoimmune
d) most glomeruls are normocellular or only mildly hypercellular

Membranous Glomerulopathy (epithelial cell and BM disease)

e) **believed to be caused by**

i) deposition of immune complexes w/in capillary wall

- IgG and C3

ii) formation of *in situ* immune complexes

iii) refer to Heymans nephritis

iv) classified as non inflammatory since there is NO cellular proliferation

Membranous Glomerulopathy (epithelial cell and BM disease)

f) In adults, a frequent association is with carcinoma !! (i.e., melanocarcinoma, lung and colon Cancer)

g) associated with systemic infections and disease

i) HBV

ii) SLE

h) associated with certain drug treatments

i) gold, penicillamine, NSAID

Membranous Glomerulopathy (epithelial cell and BM disease)

- **Clinical**

a) variable

i) spontaneous remission

ii) renal failure w/in 10-15 yrs

b)persistent proteinuria w/ normal function

c) better response to corticosteroids in children vs. adults

Membranous Glomerulopathy (epithelial cell and BM disease)

d) Progression of disease

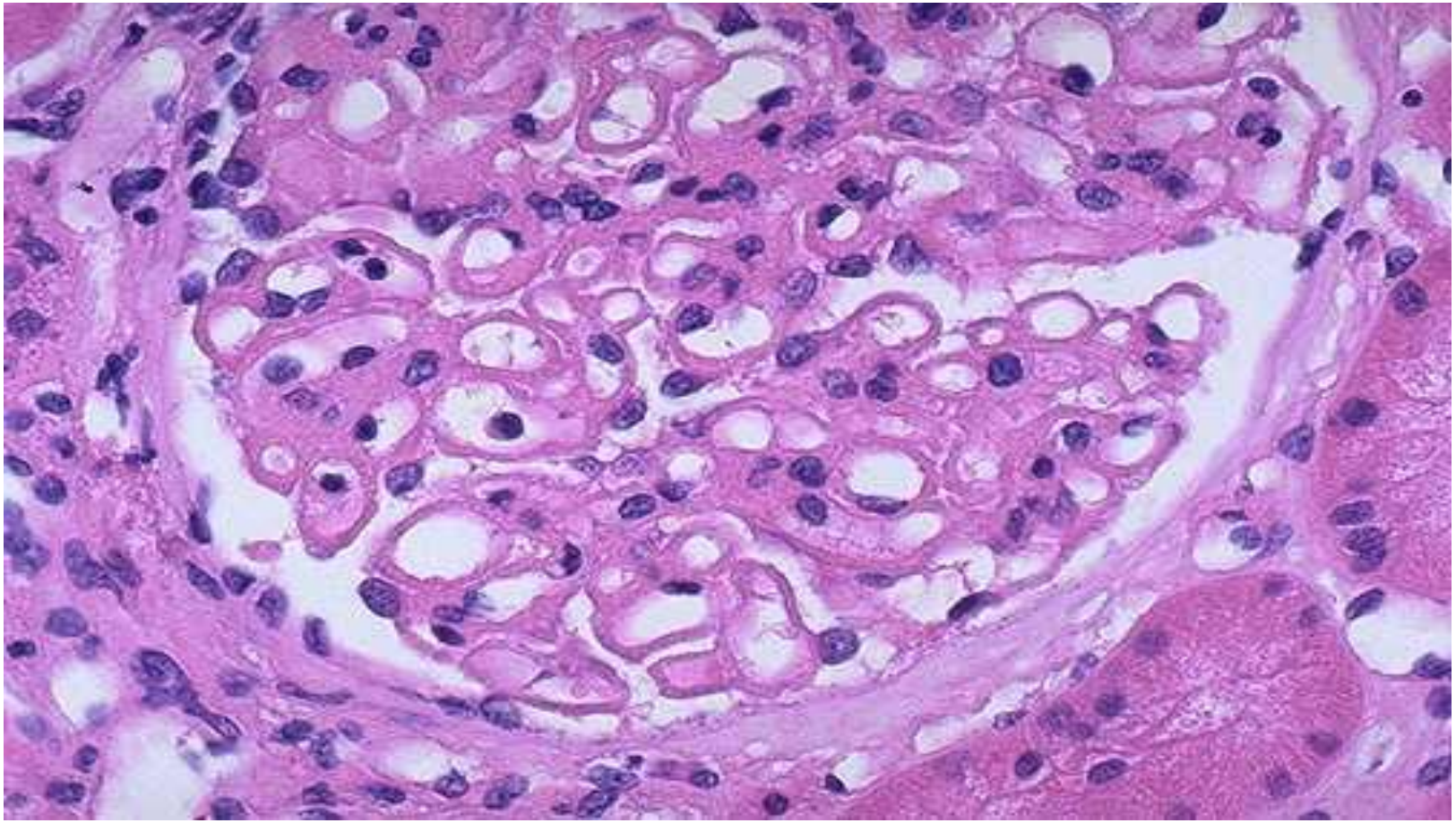
i) stage I: small granular subepithelial deposits

i) stage II: "spikes" of BM protrude between deposits of electron dense material (e.g., IgG, C3)

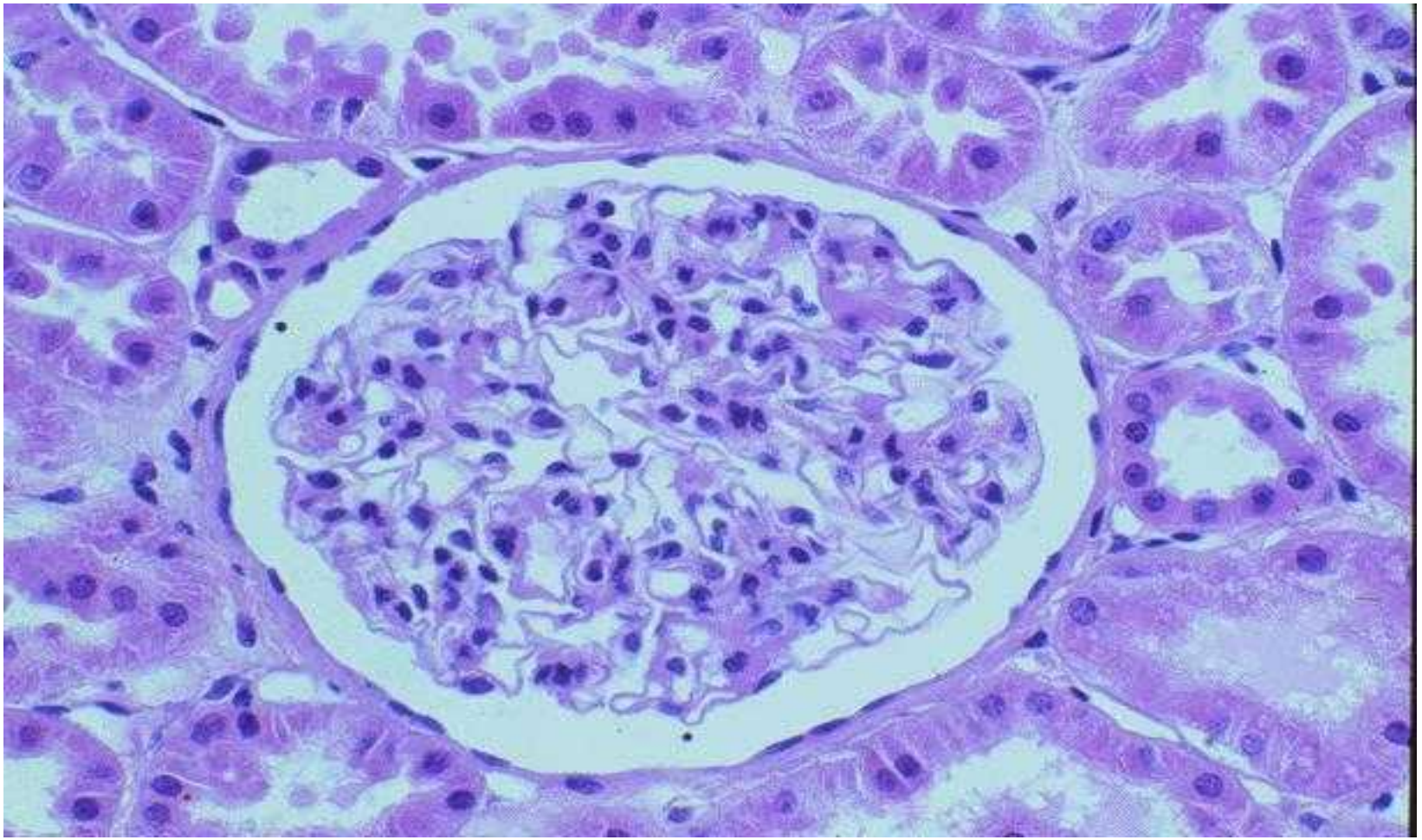
iii) stage III: deposits of electron dense material are incorporated into GBM

iv) stage iv: GBM very distorted and damaged

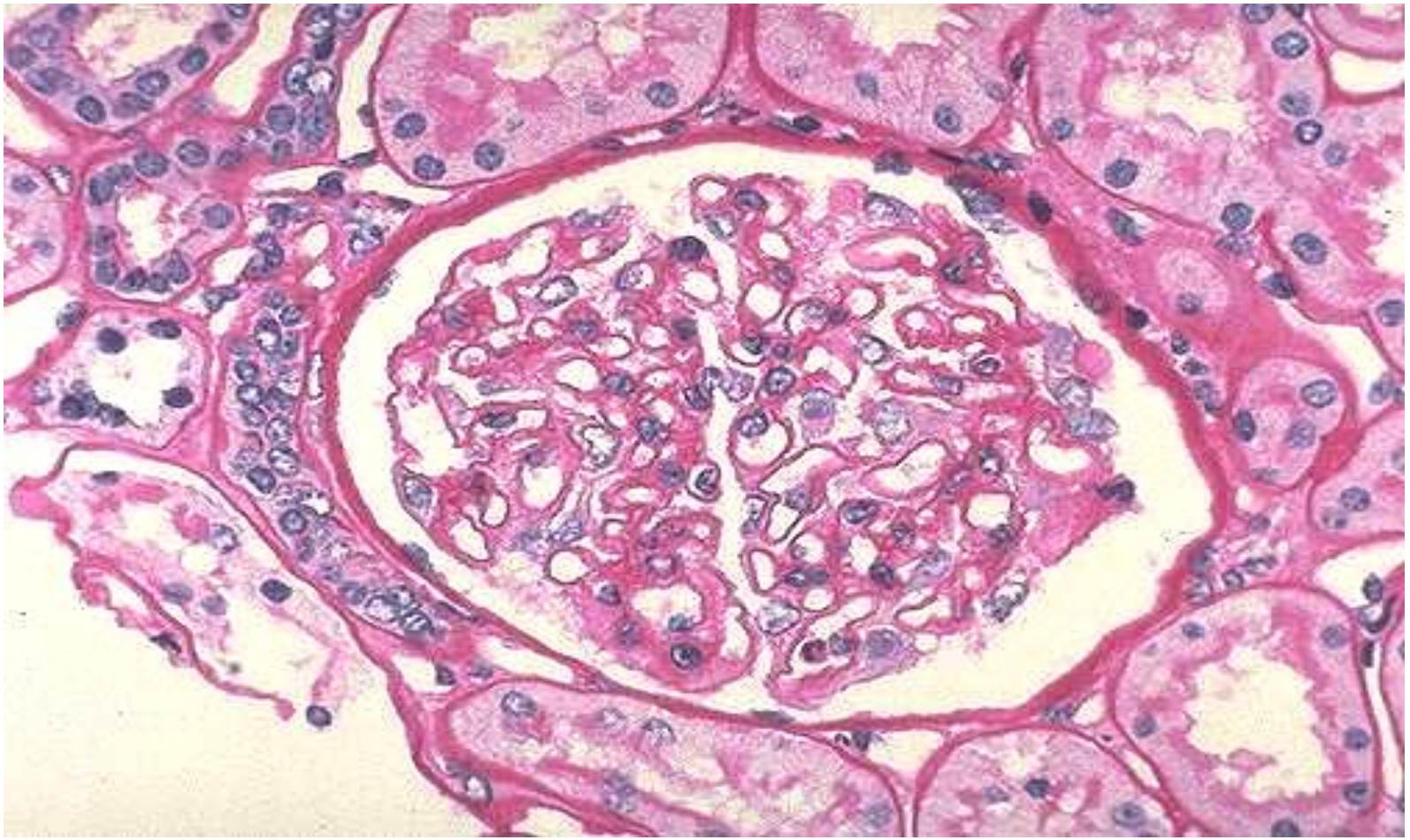
Membranous GN :



Normal Kidney:



Normal Glomerulus (PAS)



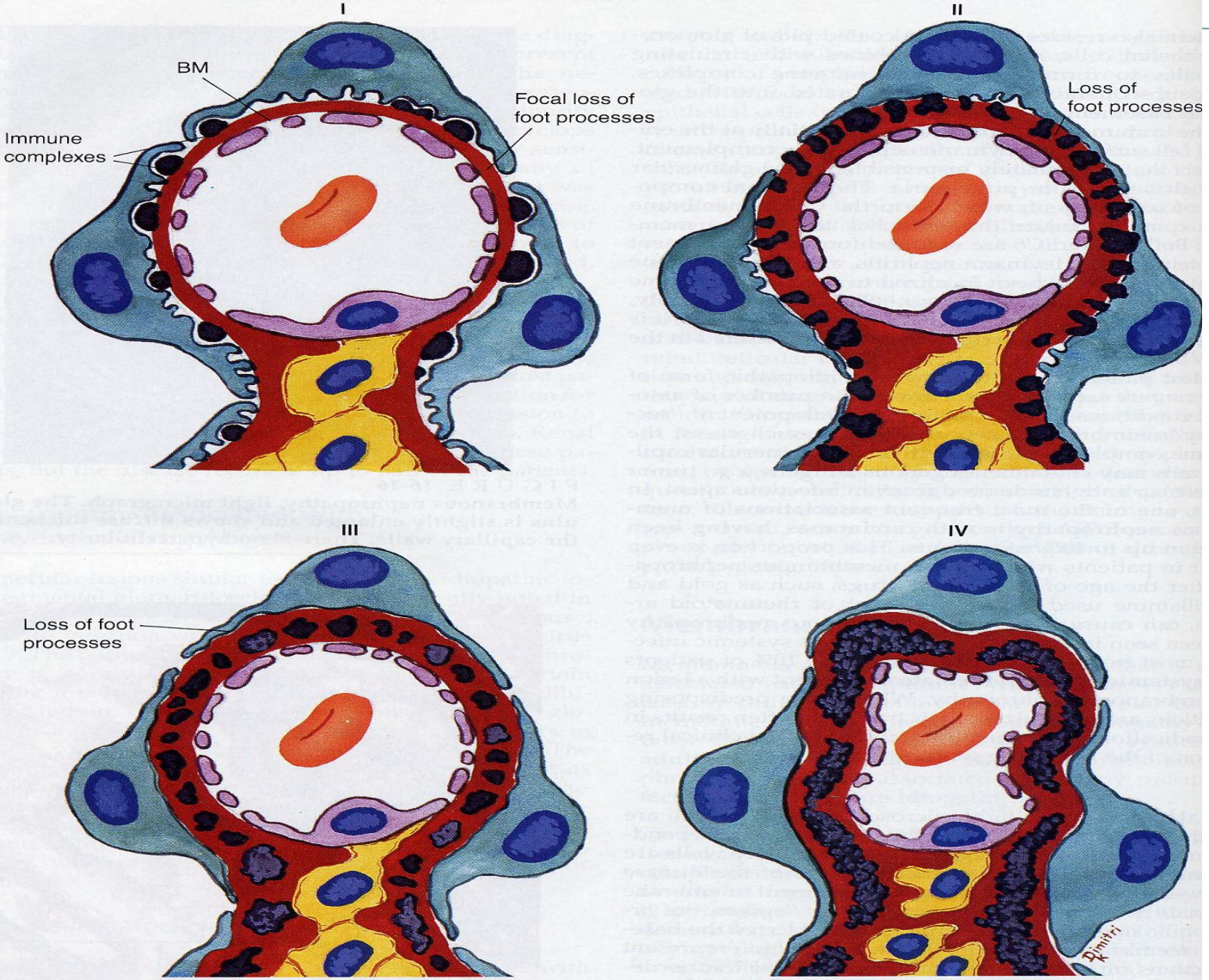


FIGURE *16-18*
Membranous nephropathy. Membranous nephropathy is related to the extracapillary deposition of immune complexes and the accompanying changes in the basement membrane. Stage I exhibits marked, diffuse subepithelial deposits in both the peripheral capillaries and the stalk. The outer contour of the basement membrane remains smooth and foot process effacement is focal. Stage II disease has a spike and dome pattern. The domes are the deposits that gradually extend into the basement membrane. Reactive spikes of newly formed basement membrane tent up the epithelial cells, the foot processes of which are extensively effaced. In Stage III disease newly formed basement membrane has sequestered intramembranous deposits. Variations in density of trapped deposits relate to light areas where the deposit has disappeared, leaving the spongy-appearing and thickened basement membrane. With Stage IV disease there is further loss of deposits and even greater widening of the now diffusely spongy basement membrane.

Focal segmental glomerulosclerosis (epithelial cell and BM disease)

a) some glomeruli exhibit segmental areas of sclerosis whereas others are normal

b) nephrotic syndrome

i) most common cause of nephrotic syndrome in USA

Focal segmental glomerulosclerosis (epithelial cell and BM disease)

c) occurs in the following setting:

i) associated with other conditions

- HIV
- heroin addiction
- sickle cell disease
- morbid obesity

ii) secondary event

- IgA nephropathy

iii) adaptive process to loss of kidney

- renal ablation
- advanced stages of other renal diseases (e.g.hypertension)

iv) primary disease (e.g., idiopathic focal segmental glomerulosclerosis)

Focal segmental glomerulosclerosis (epithelial cell and BM disease)

d) differs from minimal change disease

i) higher incidence of hematuria, reduced GFR, and hypertension

ii) poor response to corticosteroids

iii) proteinuria is non selective

iv) progression to chronic glomerulosclerosis

v) IgM and C3 trapping on sclerotic segments

Focal segmental glomerulosclerosis (epithelial cell and BM disease)

vi) whether this is a specific disease or
is an evolution of minimal change disease is unresolved !!

- degeneration of visceralepithelial cells hallmark of FSGN
- similar cell damage as seen in minimal change disease

Focal segmental glomerulosclerosis (epithelial cell and BM disease)

vii) genetic basis

-NPHS1 gene →

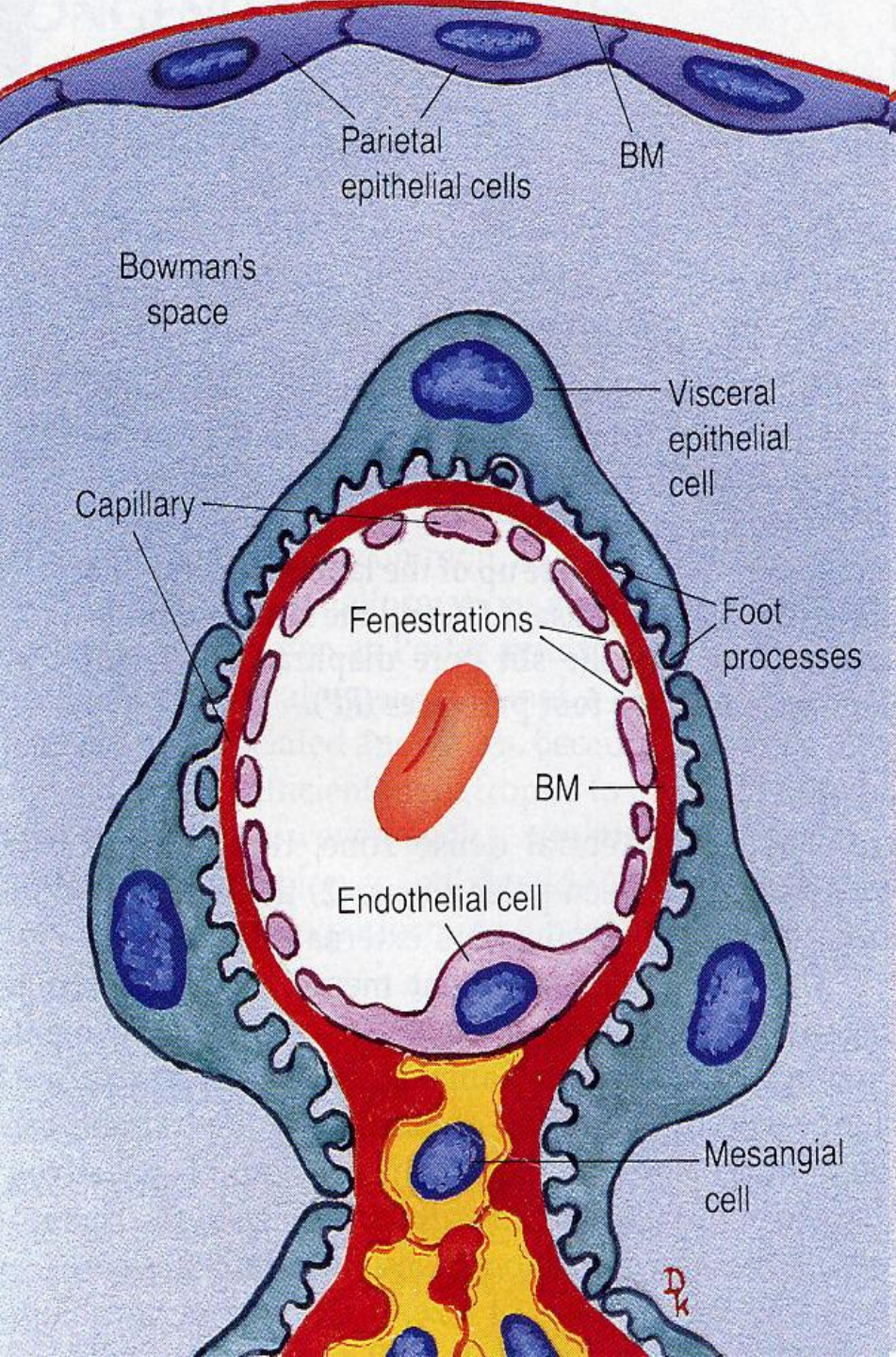
-encodes nephrin

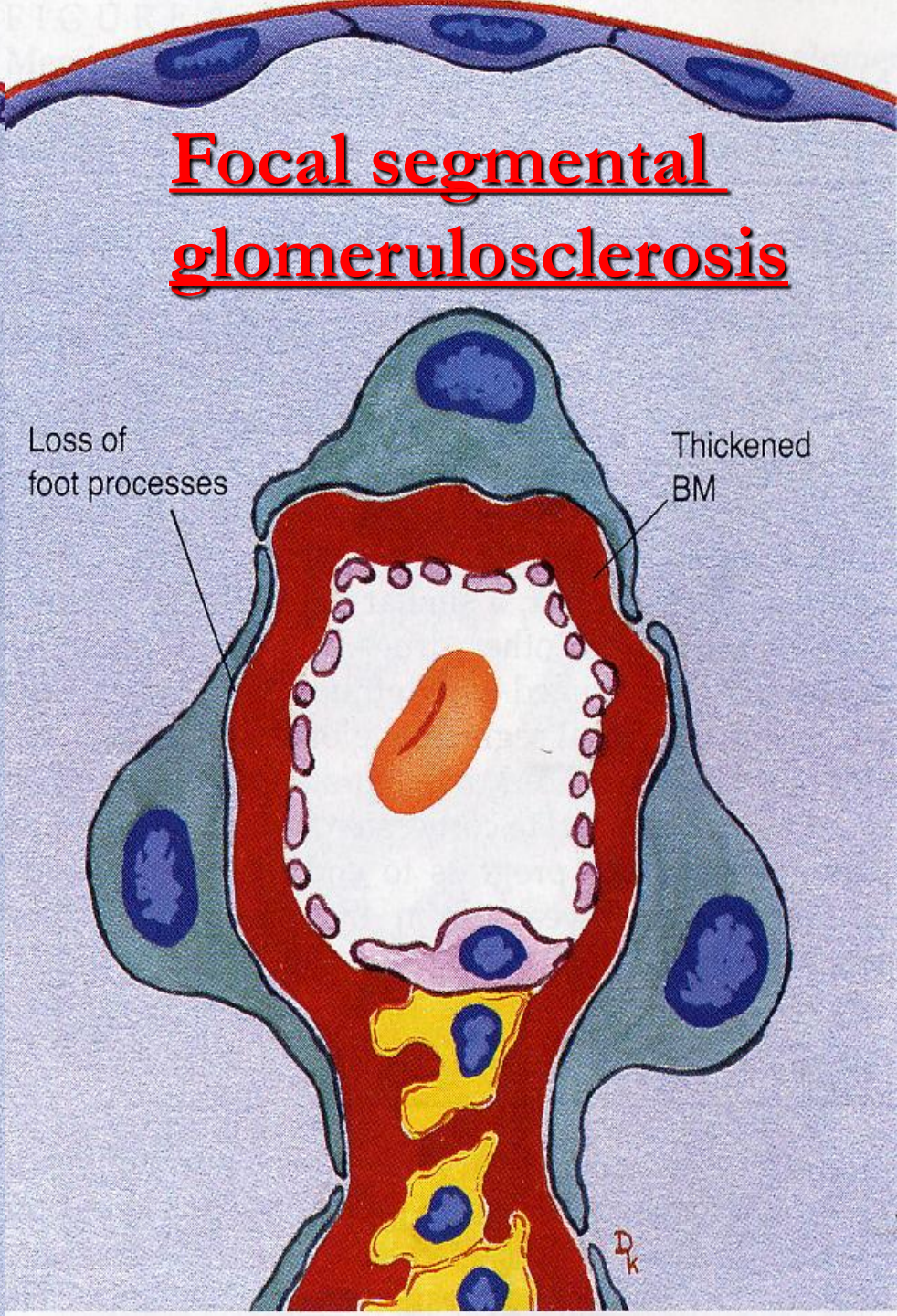
- several mutations of this gene give rise to congenital nephrotic syndrome of the Finnish type (CNF)

-NPHS2 gene

- encodes to podocin
- mutations give rise to steroid resistant nephrotic syndrome in children

Focal segmental glomerulosclerosis





Membranoproliferative GN

a) characterized by GBM thickening (i.e., “membrano”) + mesangial cell proliferation (“proliferative ”)

b) two major groups: Types I and II (+ III)

i) Type I: majority of cases are idiopathic.

Associations with

- HBV
- HCV
- bacterial endocarditis
- strep infections
- granular deposition of Ig (IgG, IgM) and complement (C3) and C1q and C4

Membranoproliferative GN

ii) type II (and III)

- circulating C3 Ab (C3 nephritic factor) → ↓ C3 (hypocomplementemia)
- characteristic "ribbon-like" zone of ↑ cellularity on thickened GBM ("dense deposit disease")

Membranoproliferative GN

c) Clinical:

i) occurs primarily in older children and young adults

ii) nephritic or nephrotic syndrome

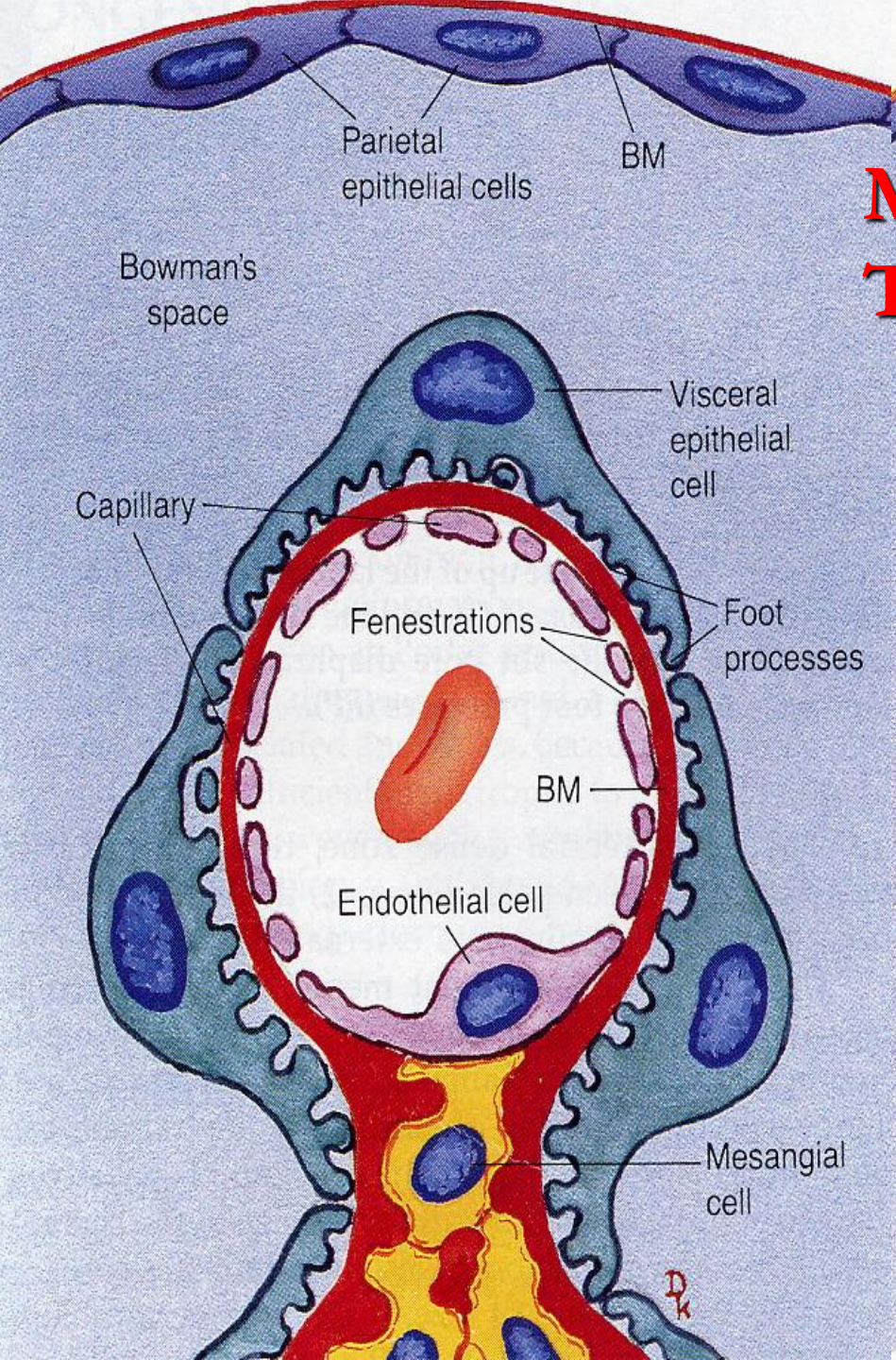
iii) low levels of C3

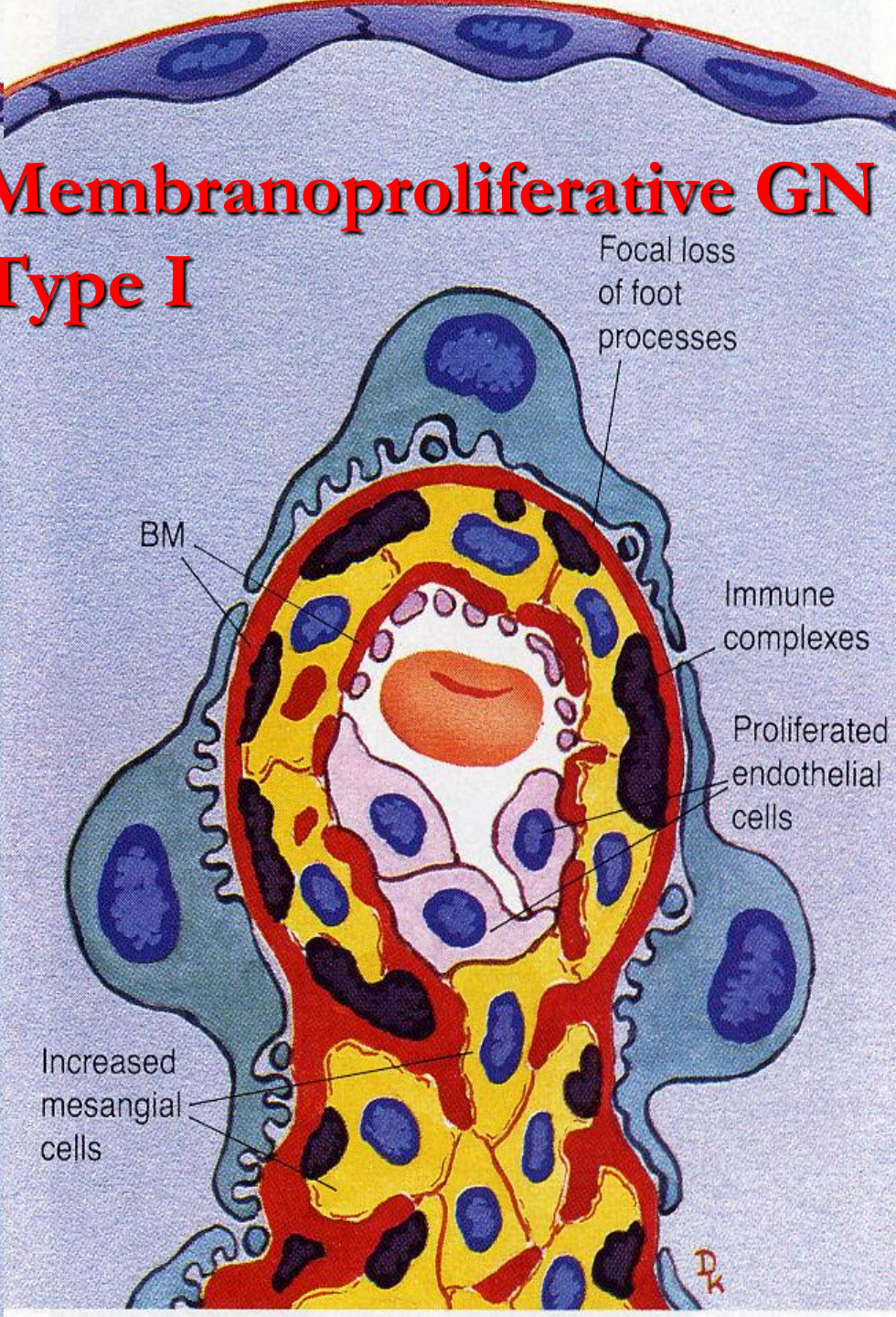
iv) do not have postinfectious GN

v) no systemic inflammatory condition

vi) most progress to end-stage renal failure, regardless of treatment !!

Membranoproliferative GN Type I





NEPHRITIC SYNDROME

- hematuria
- oliguria
- ↑ BUN and creatinine
- hypertension
- proteinuria (< 3.5 g/day); ± edema

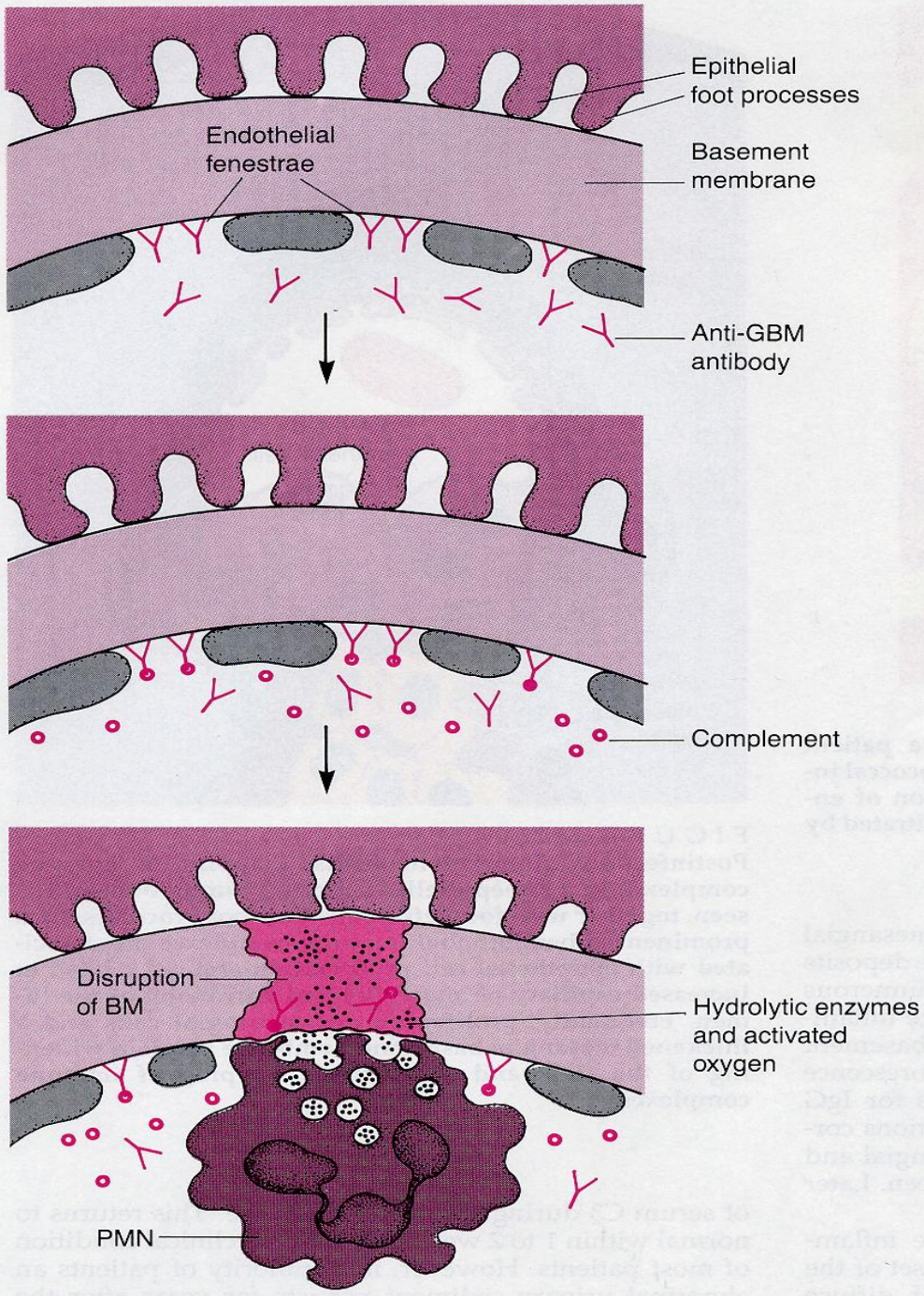


FIGURE *16-29*
Immunologic mechanisms involved in the pathogenesis of glomerular lesions. (*A*) Passive Heymann nephritis. Antibodies directed against a glycoprotein present in the epithelial cell plasma membrane bind to this protein, forming an immune complex. Complement is then activated, producing damage to the epithelial cell membrane that results in proteinuria. Aggregates of these immune complexes form a large subepithelial deposit, which later becomes intercalated into the basement membrane, as with membranous nephropathy (see Fig. 16-18). (*B*) Antiglomerular basement membrane antibody (anti-GBM) disease. Anti-GBM antibodies bind to a component of the glomerular basement membrane. Complement is activated, and chemotactic fragments of complement are liberated. Neutrophils (PMN) are attracted to the glomerulus, which then produce damage to the glomerular capillaries, resulting in glomerulonephritis.

Glomerulornephritis - INFLAMMATORY

Acute GN (post infectious GN)

a) sudden onset of nephritic syndrome

b) diffuse hypercellularity og glomeruli

c) most often associated with

- i) group A β-hemolytic streptococci
  - S. pyogenes
- ii) others less frequently
  - staph
  - spirochetes
  - viruses

d) most often affect children

- i) one of most common renal diseases

Acute GN (post infectious GN)

e) latent period of ~ 10-14 days

f) diffuse enlargement and hypercellularity of glomeruli, hypercellularity due to:

i) proliferation of endothelial and mesangial cells and infiltration of neutrophils and monocytes

g) characteristics:

i) subepithelial "humps" of GBM

ii) granular IgG and C3 along GBM in association with "humps"

Acute GN (post infectious GN)

h) Clinical:

i) most resolve but in rare occasions can progress to develop many crescents and renal failure

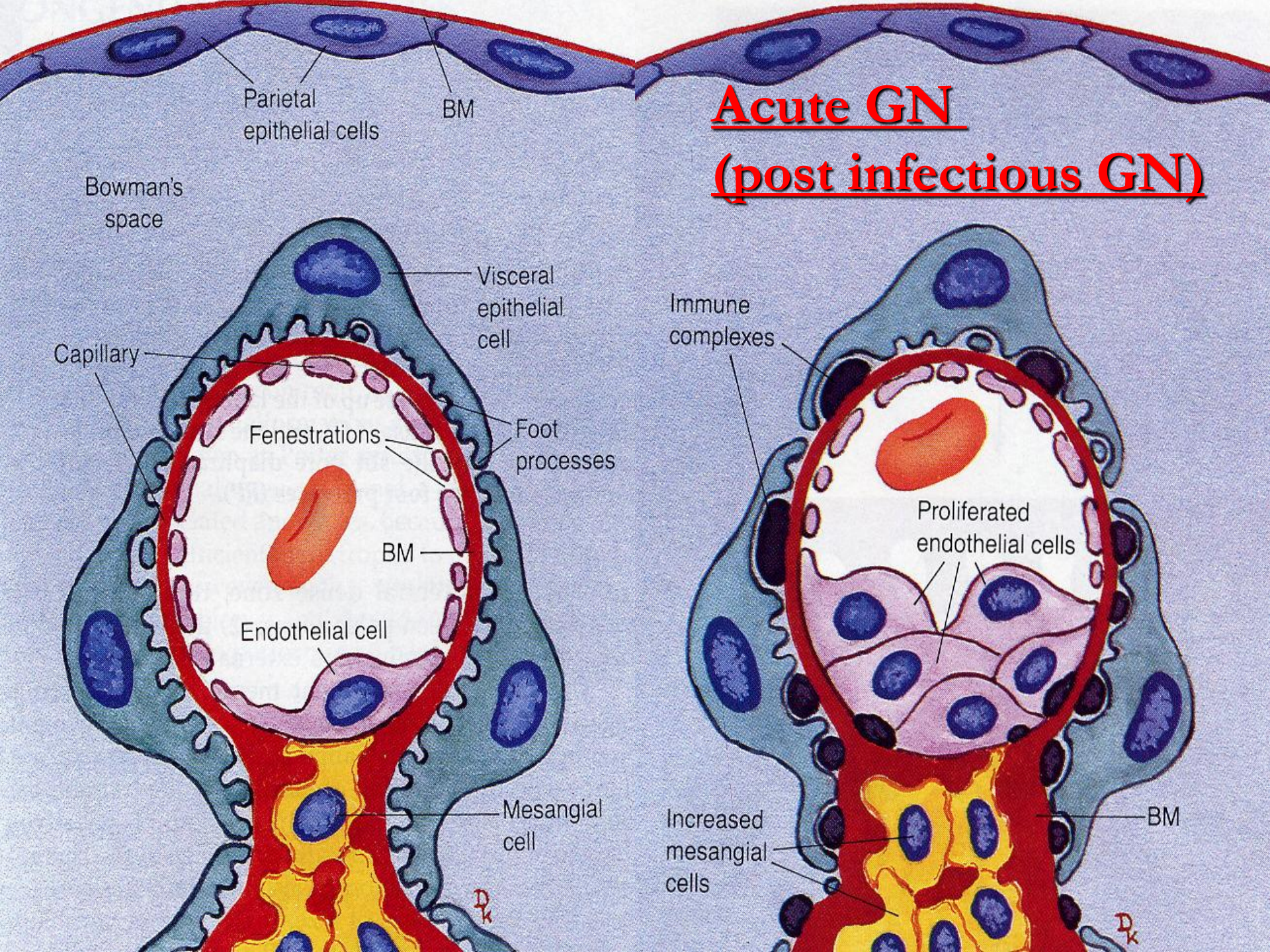
ii) primary infection in pharynx or skin

iii) nephritic syndrome (abrupt)

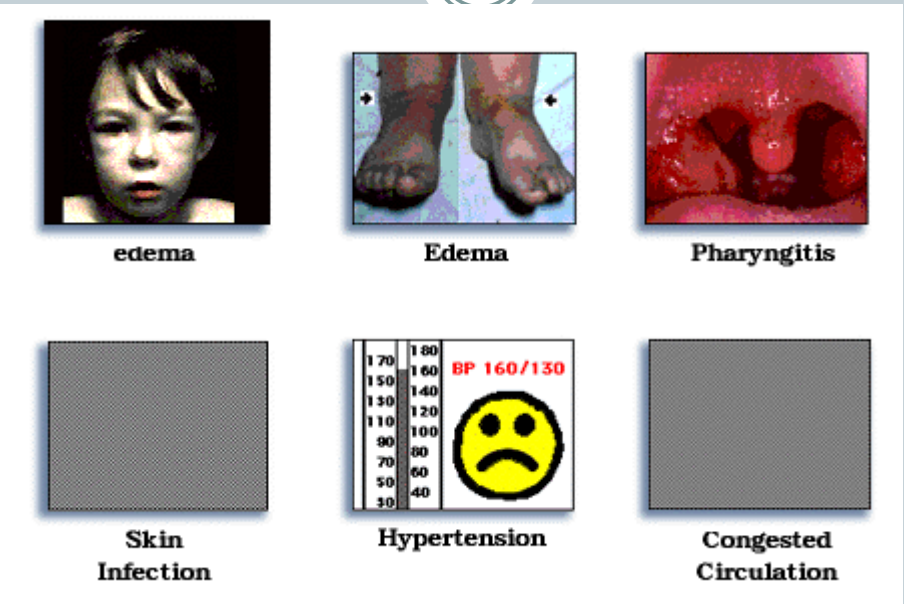
- hematuria
- oliguria
- facial edema
- hypertension

iv) ↓ serum C3

Acute GN (post infectious GN)

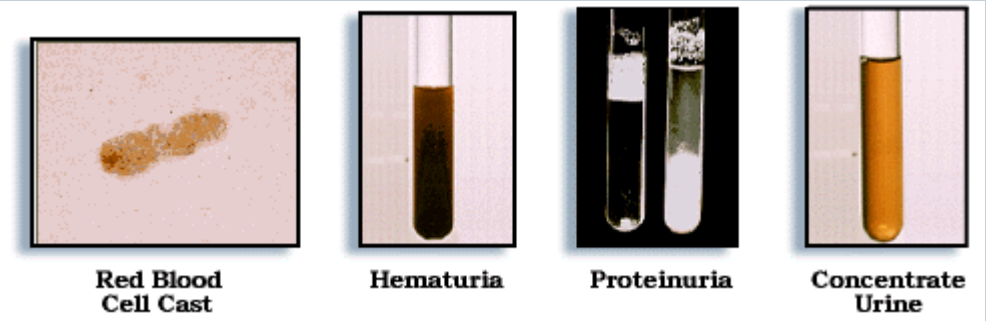


Clinical Features: G.Nephritis



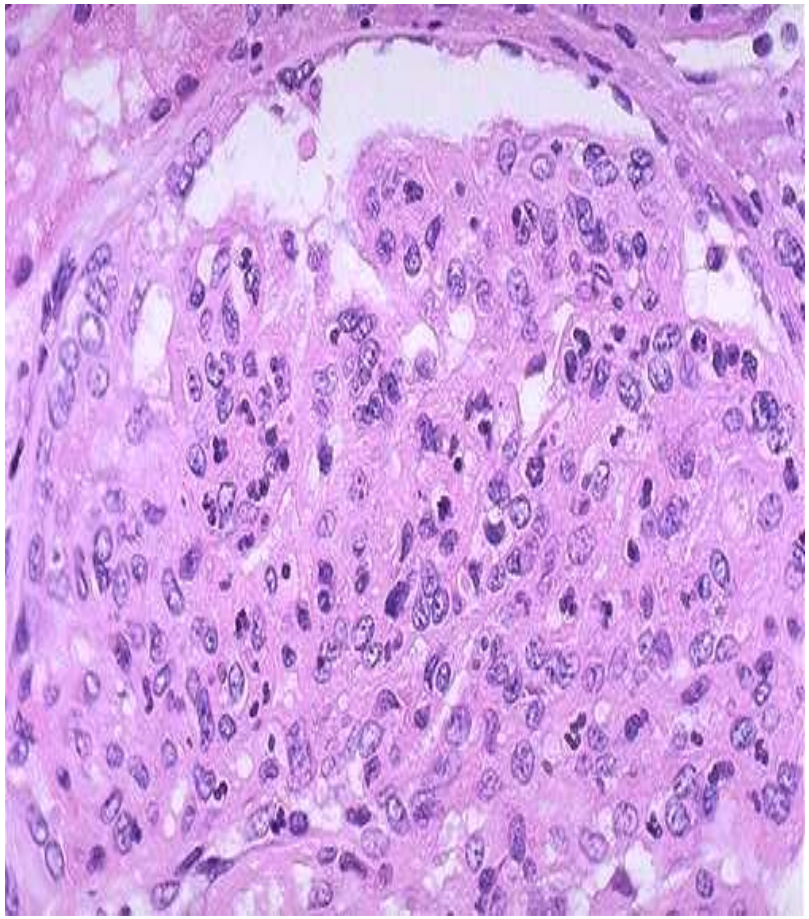
- Hypertension
- Skin Infections
- Congestive Cardiac Failure

Laboratory Features: G.Nephritis

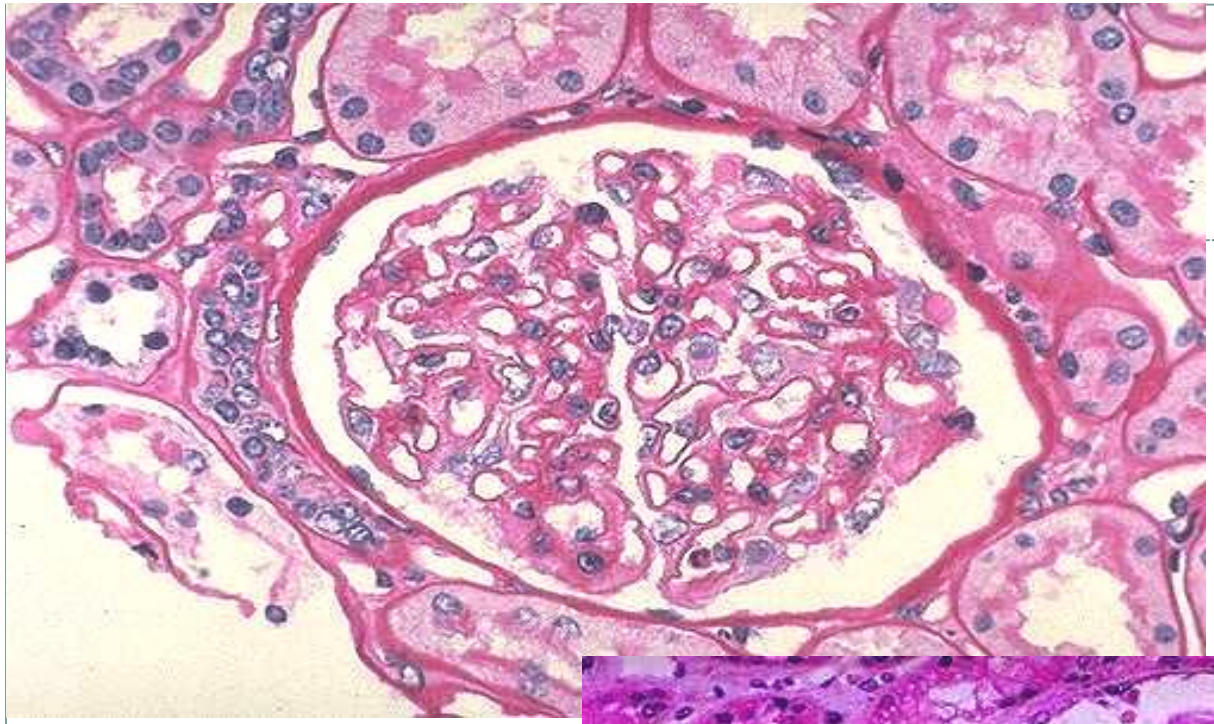


- Inflammation
- Decreased filtration
- Damage to filtration unit

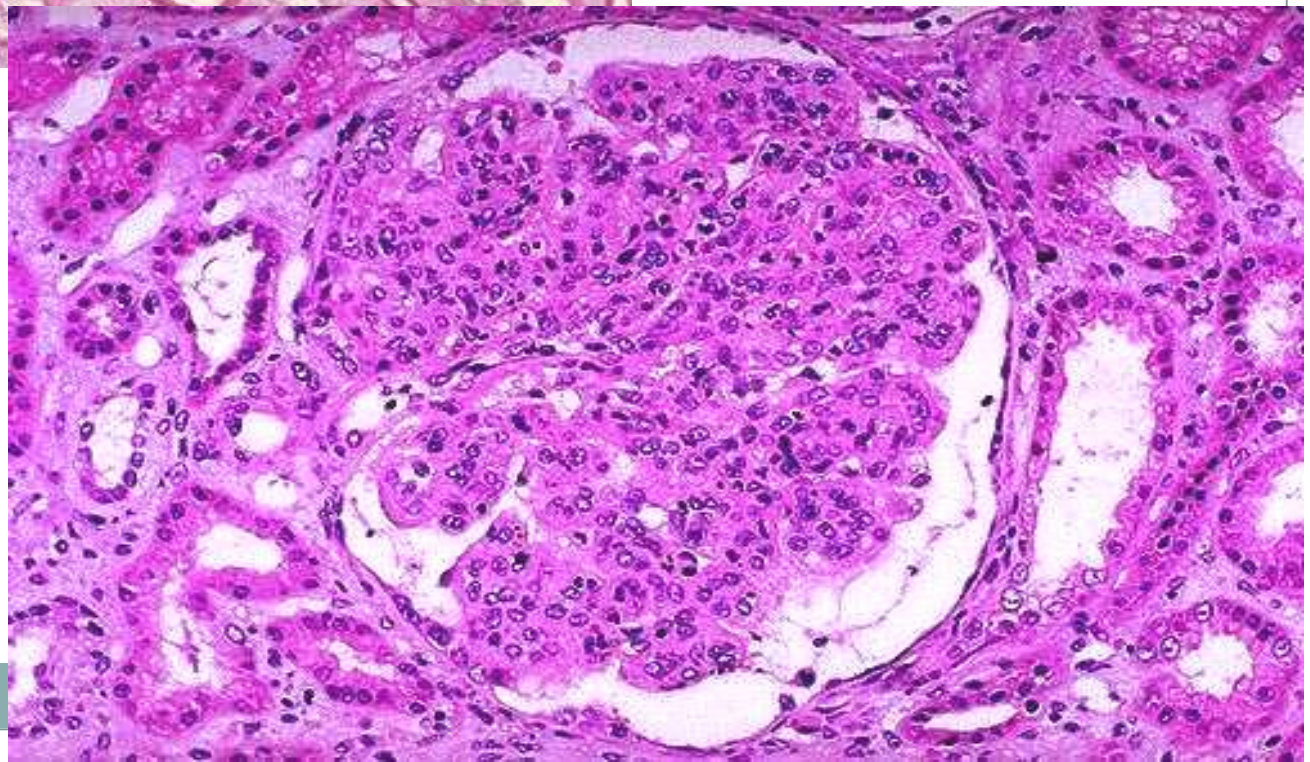
Diffuse Proliferative GN:



- Hyperplasia of epithelium & endothelium.
- Cell Swelling.
- Inflammatory cells.
- Obstruction to flow.
- Enlarged hypercellular glomeruli.



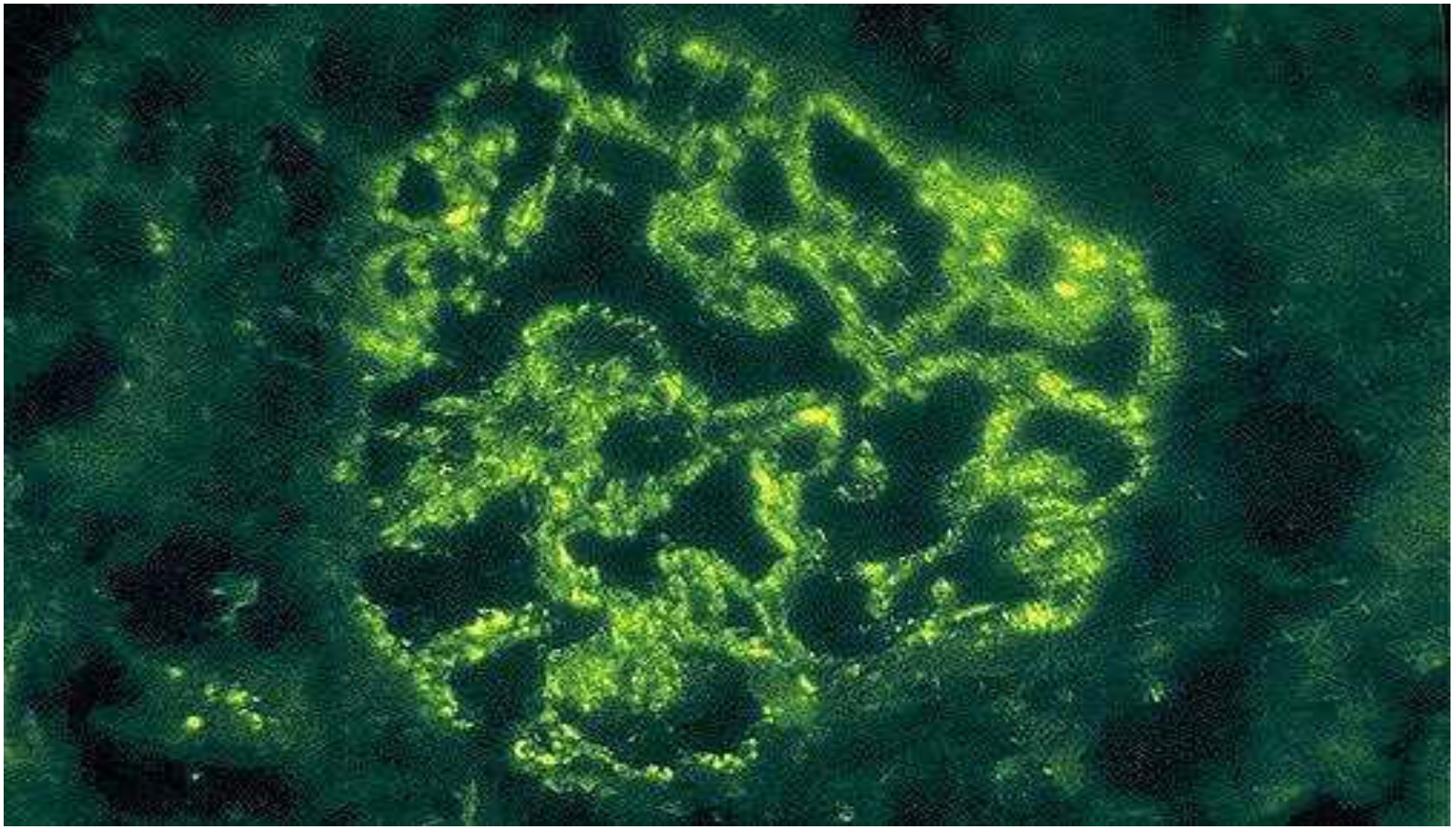
•Normal



•Proliferative

Post streptococcal

IF- Diffuse Proliferative GN



Crescentic GN

a) ominous morphological pattern

i) majority of glomeruli are surrounded by accumulation of cells in Bowman's capsule (parietal epithelial cells)

ii) indicative of fulminant glomerular damage and always leaves scarring

iii) does not denote a specific etiologic form of GN

Crescentic GN

b) most patients with substantial (~ 80%) crescents progress to renal failure

c) Fibrin in Bowman's capsule is important for the formation of glomerular crescents

i) Tx with anticoagulants

d) associated with areas of segmental necrosis within glomeruli

Crescentic GN

e) Types:

i) *Type I* – anti-GBM antibody disease (GOODPASTURE SYNDROME) or idiopathic
-plasmapheresis to remove circulating Ab ***is helpful*** in this type of RPGN (i.e., crescentic)
-- etiology unknown

Crescentic GN

e) Types:

ii) *Type II* – immune-complex mediated disease

- can be complication of any of the immune complex nephritides
  - SLE, IgA nephropathy,
  - HS Purpura
  - all these show granular pattern (characteristic of immune complex)

- ***not helped*** with plasmapheresis

Crescentic GN

e) Types:

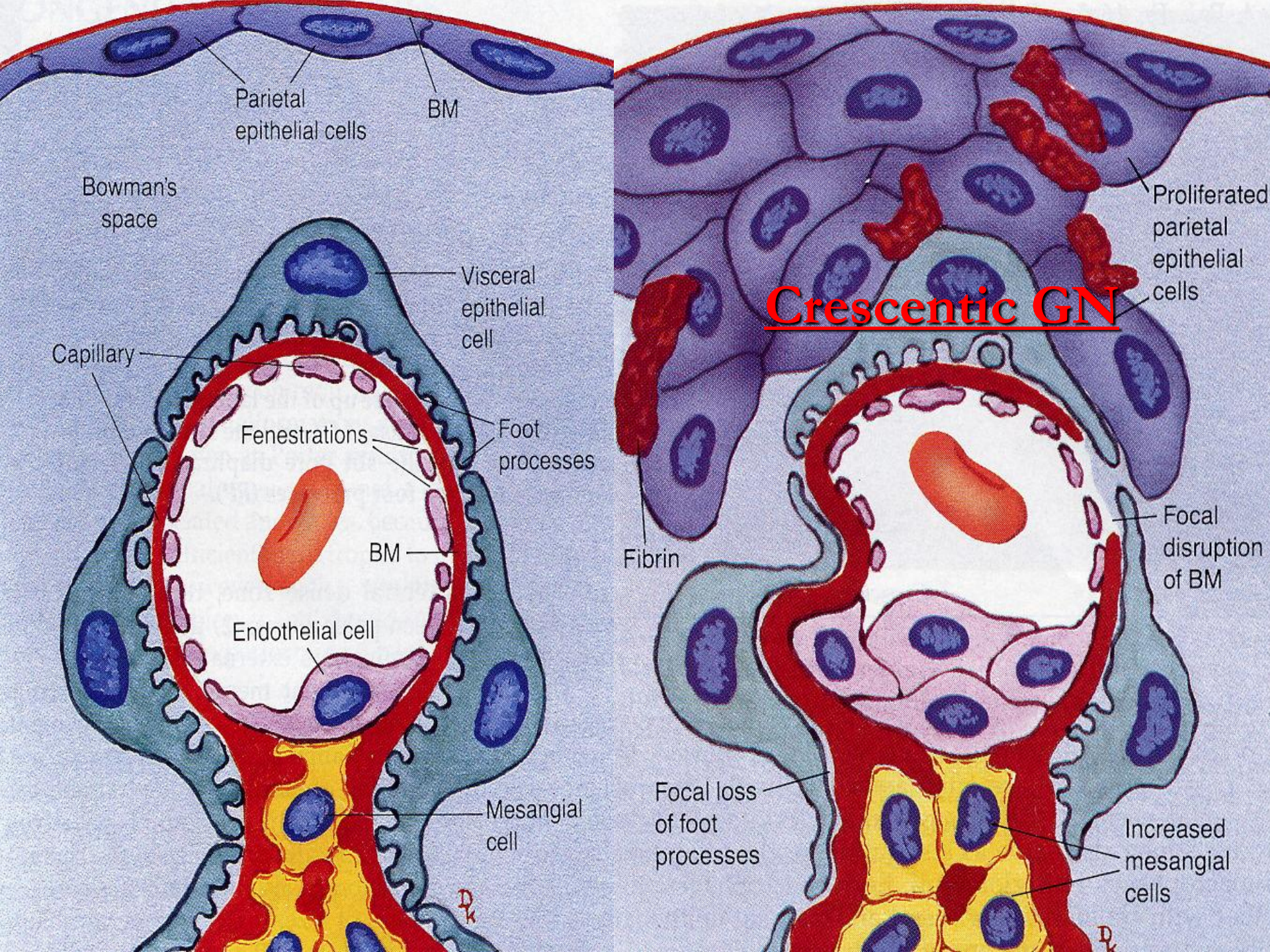
iii) *Type III* – pauci-immune type

- lack of anti-GBM Ab or immune complexes
- patients do have ANCA (~90%)
  - ▸ either c or p patterns
- in some cases, is a component of vasculitides (i.e., Wegener Granulomatosis)

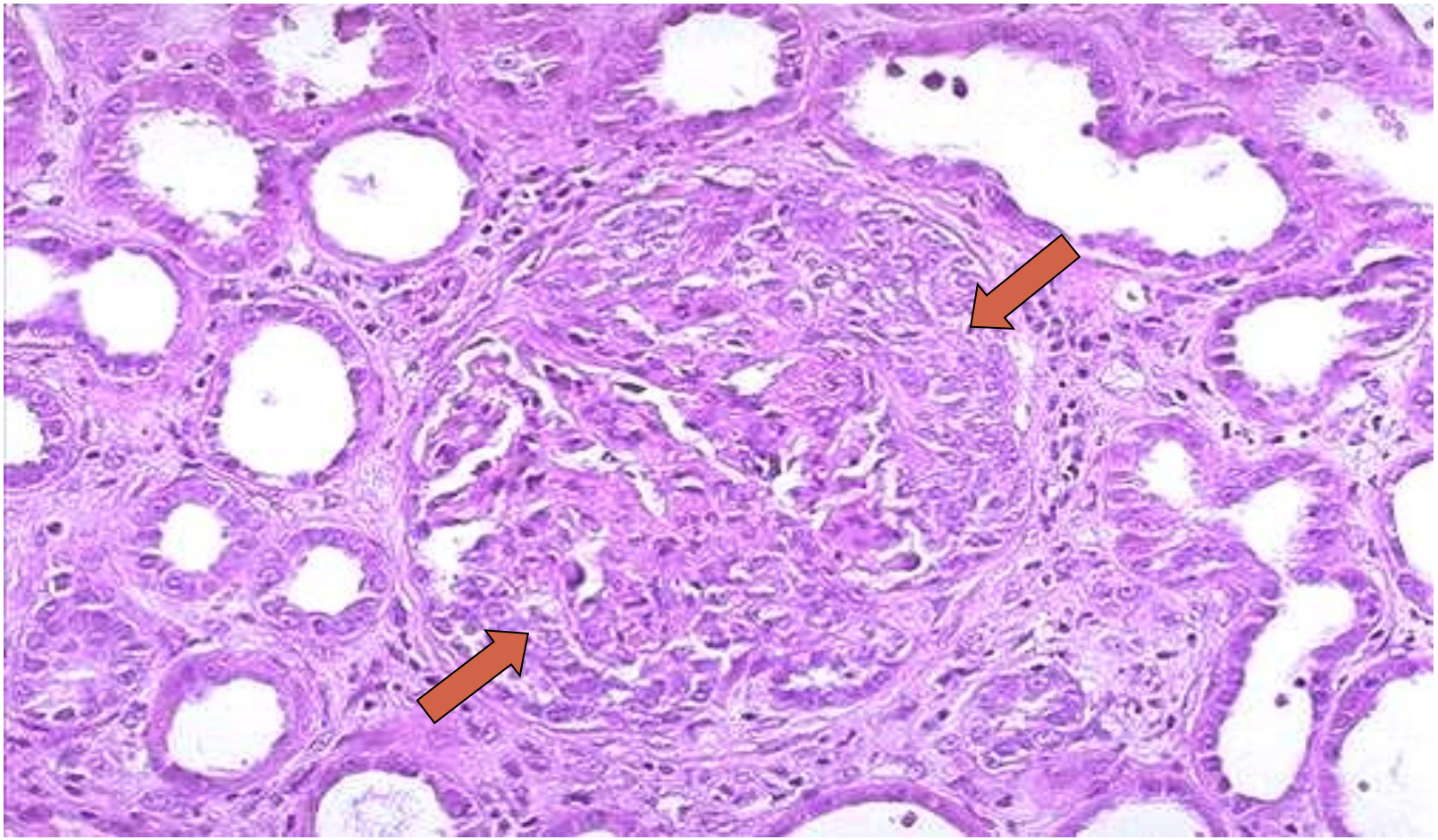
f) clinical:

i) hematuria with red cell cast in urine

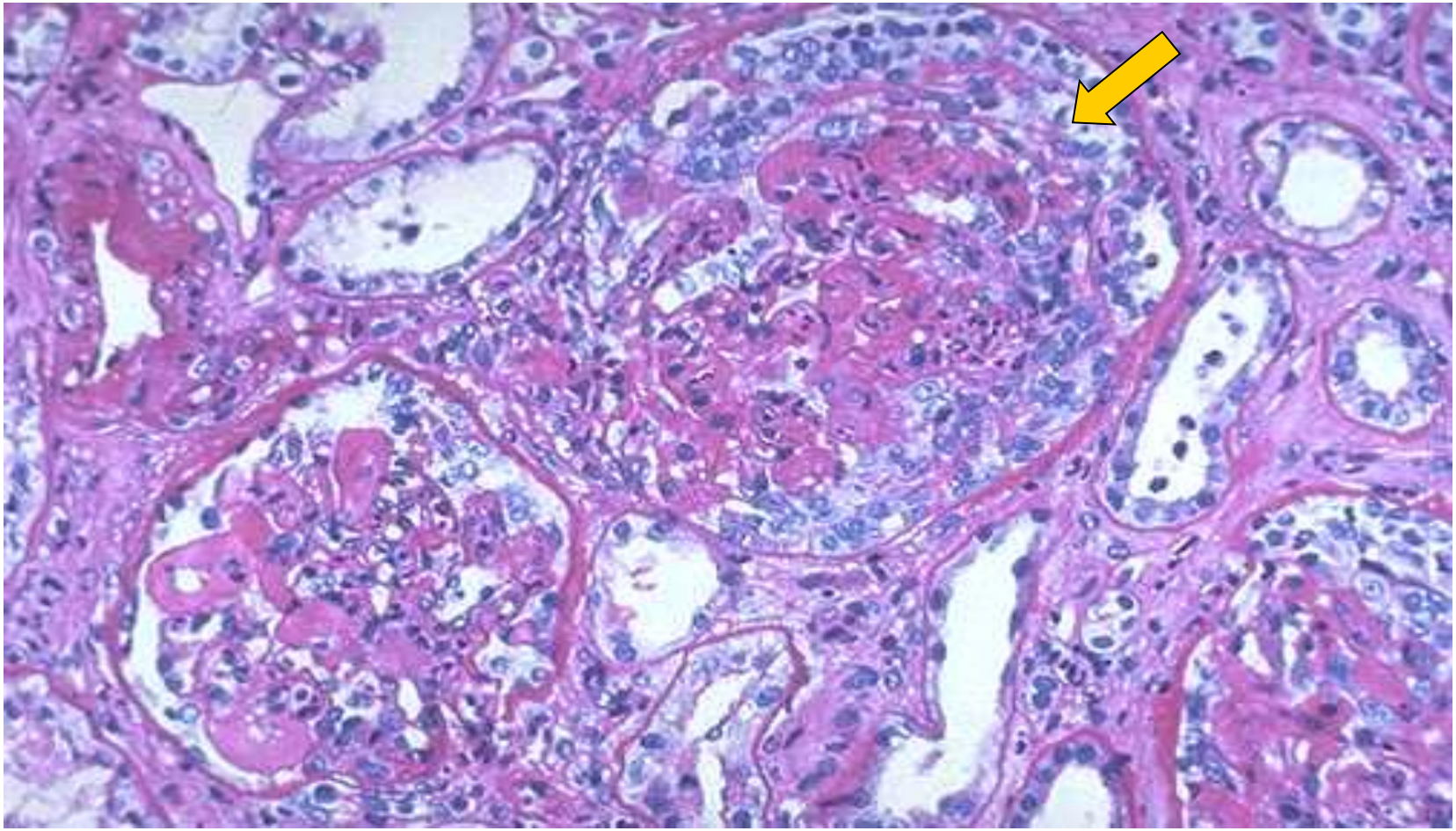
ii) transplant or chronic dialysis in most patients


Parietal epithelial cells
BM
Bowman's space
Visceral epithelial cell
Capillary
Fenestrations
Foot processes
BM
Endothelial cell
Mesangial cell
Crescentic GN
Proliferated parietal epithelial cells
Fibrin
Focal disruption of BM
Focal loss of foot processes
Increased mesangial cells

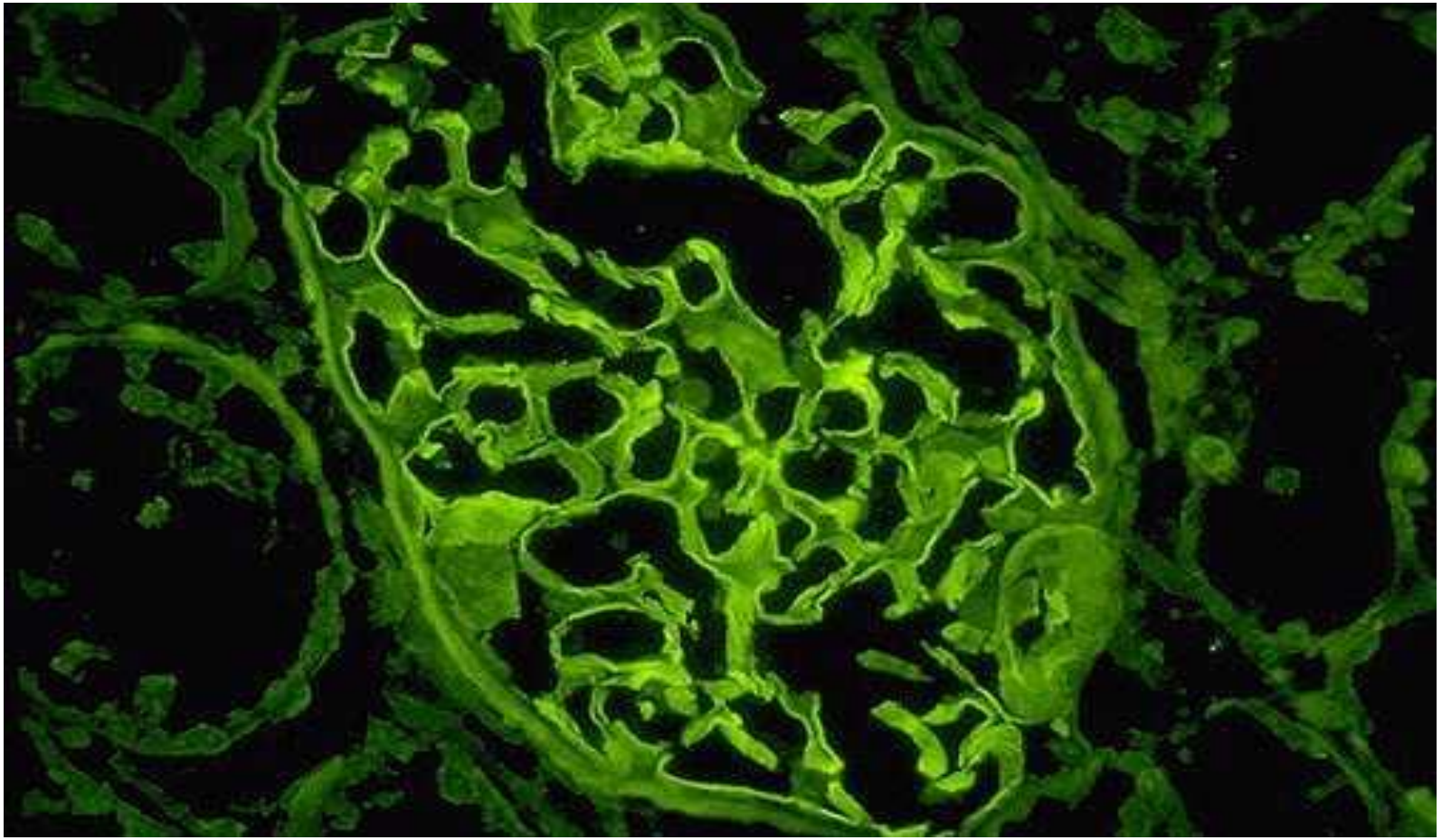
Crescentic GN - (RPGN)



Crescentic GN - (Trichrome Stain)



Goodpasture Syndrome:



Focal GN

a) only some of the glomeruli are involved
    i) or to segments of the glomerulus
b) different from focal & segmental glomerulosclerosis which is a noninflammatory disease
    i) glomeruli essentially normocellular
c) many conditions produce this defect
    i) primary renal disease or systemic diseases such as IgA nephropathy and Henoch-Schönlein GN

Focal GN

d) IgA nephropathy (Berger Disease)

i) association with chronic liver disease

- impaired capacity to remove circulating immune complexes

ii) IgA and fibronectin found in > 70 % of IgA nephropathy patients.

iii) Ag involve bacterial, viral and dietary

- infectious agents is suggested from data showing hematuria following upper respiratory or GI infection !!

- dietary agents → milk proteins in mesangium; gluten-sensitivity

Focal GN

d) IgA nephropathy (Berger Disease)

iv) C3 and properdin (via activation of alternate pathway) usually present together with IgA in mesangium

- C1q and C4 (classic pathway activation) are typically absent

v) IgA nephropathy is a mesangial proliferative lesion (granular deposits)

Focal GN

d) IgA nephropathy (Berger Disease)

vi) clinical:

- common in young men (15-30)
- presents with hematuria
- nephrotic type proteinuria is uncommon (may indicate more severe glomerular damage)
- ~ 20 % of IgA nephropathy patients progress to end-stage renal failure !!
- most common type of 1° GN in several parts of the world (France, Italy, Japan, Singapore and Austria) ~ 20 %.
- In USA is responsible for ~ 3-10 % of 1° GN

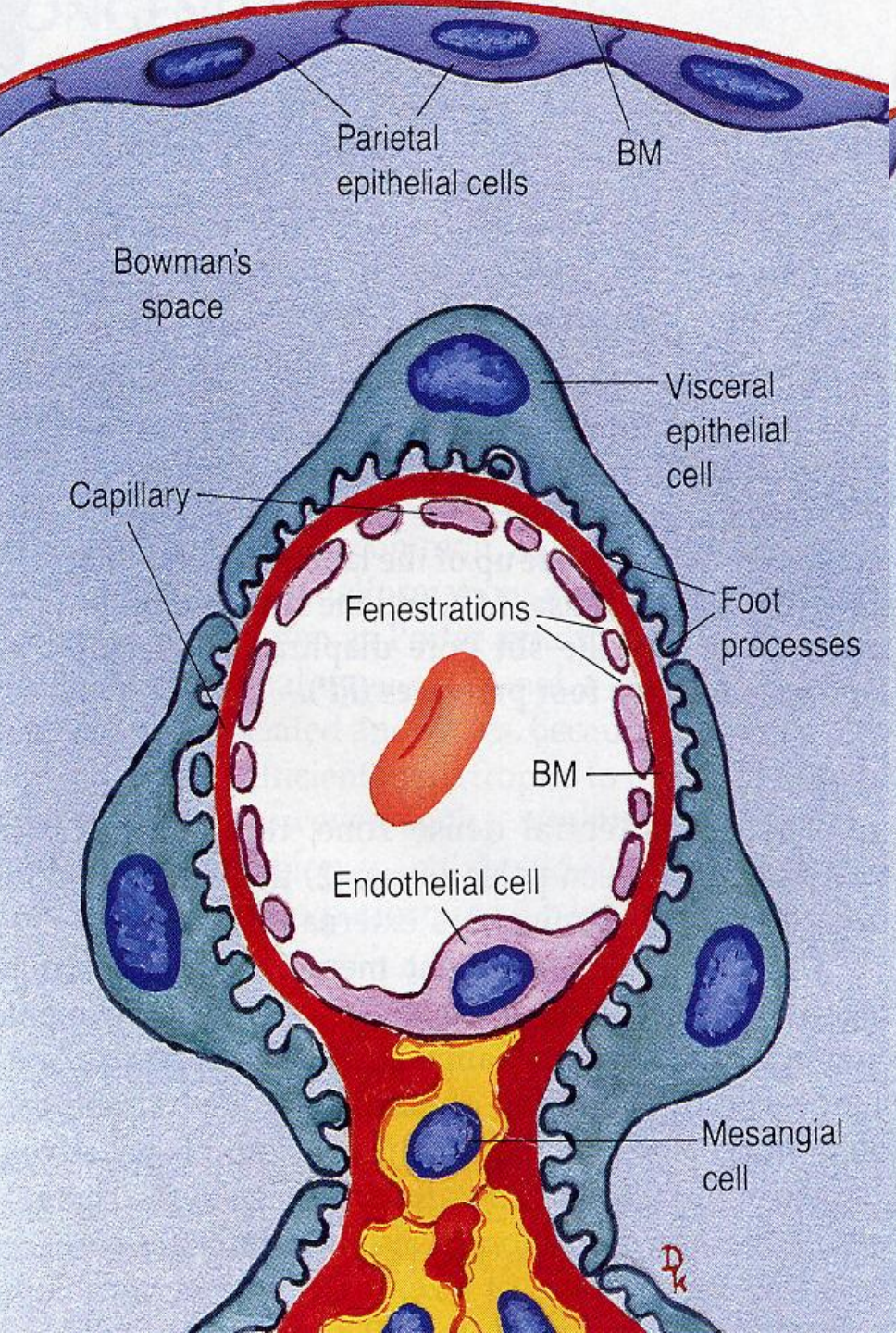
Focal GN

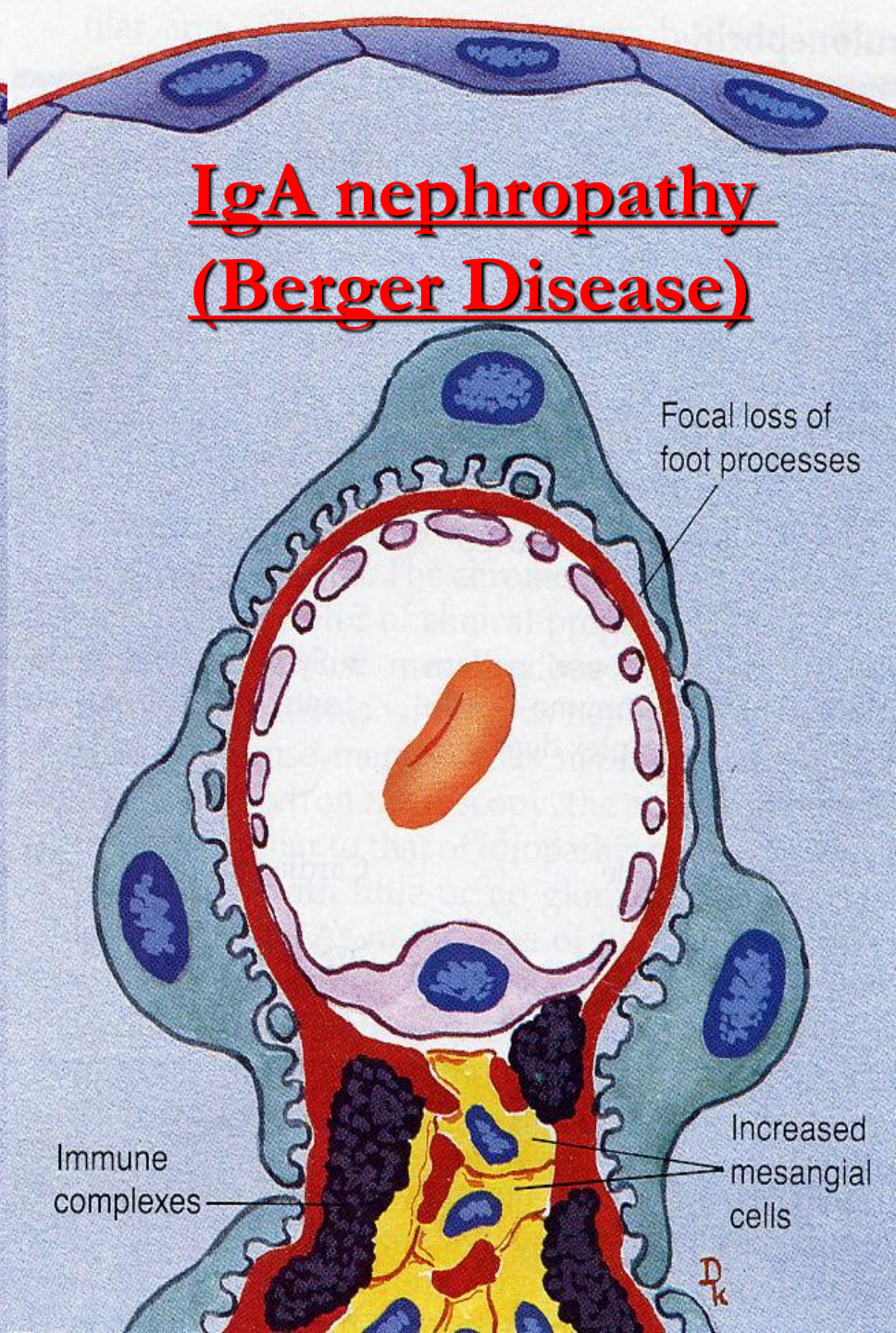
e) Henoch-Schönlein (HS) Purpura

i) close relationship with IgA nephropathy

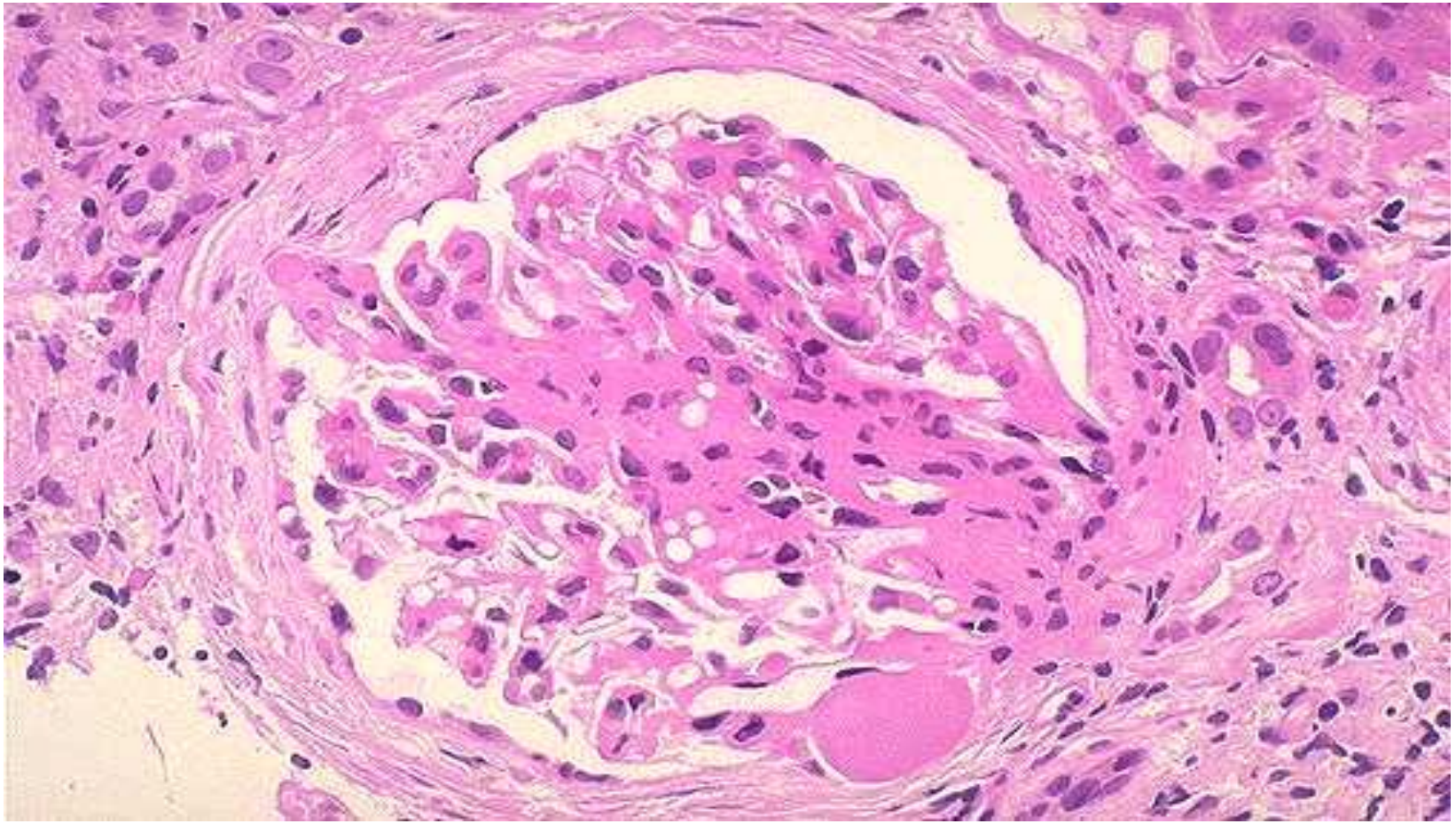
- differentiate: IgA purely renal;
  HS is a systemic disease, etc.

IgA nephropathy (Berger Disease)





Focal Segmental Gl. Sclerosis:



Hereditary nephritis (Alport syndrome)

a) most often present as recurrent hematuria

b) structural defects in GBM

    i) specific molecular defect affecting type IV collagen

c) usually does not present with nephrotic syndrome and proteinuria

d) more severe in men

        i) die by age 40

e) progressive hearing loss (high frequencies)

f) ocular defects most often $\rightarrow$ the lens

Benign familial hematuria (thin GBMdisease)

a) presents as recurrent hematuria in childhood or young adults (similar to Alport syndrome)

b) no progression to renal failure (unlike Alport syndrome)

c) reduced thickness of GBM (capillary site)

d) one of most important causes of asymptomatic hematuria

e) IgA nephropathy and this disease are two most major diagnostic considerations of asymptomatic hematuria

The only place success comes before work is in a dictionary…!