Nephrotic Syndrome in Children

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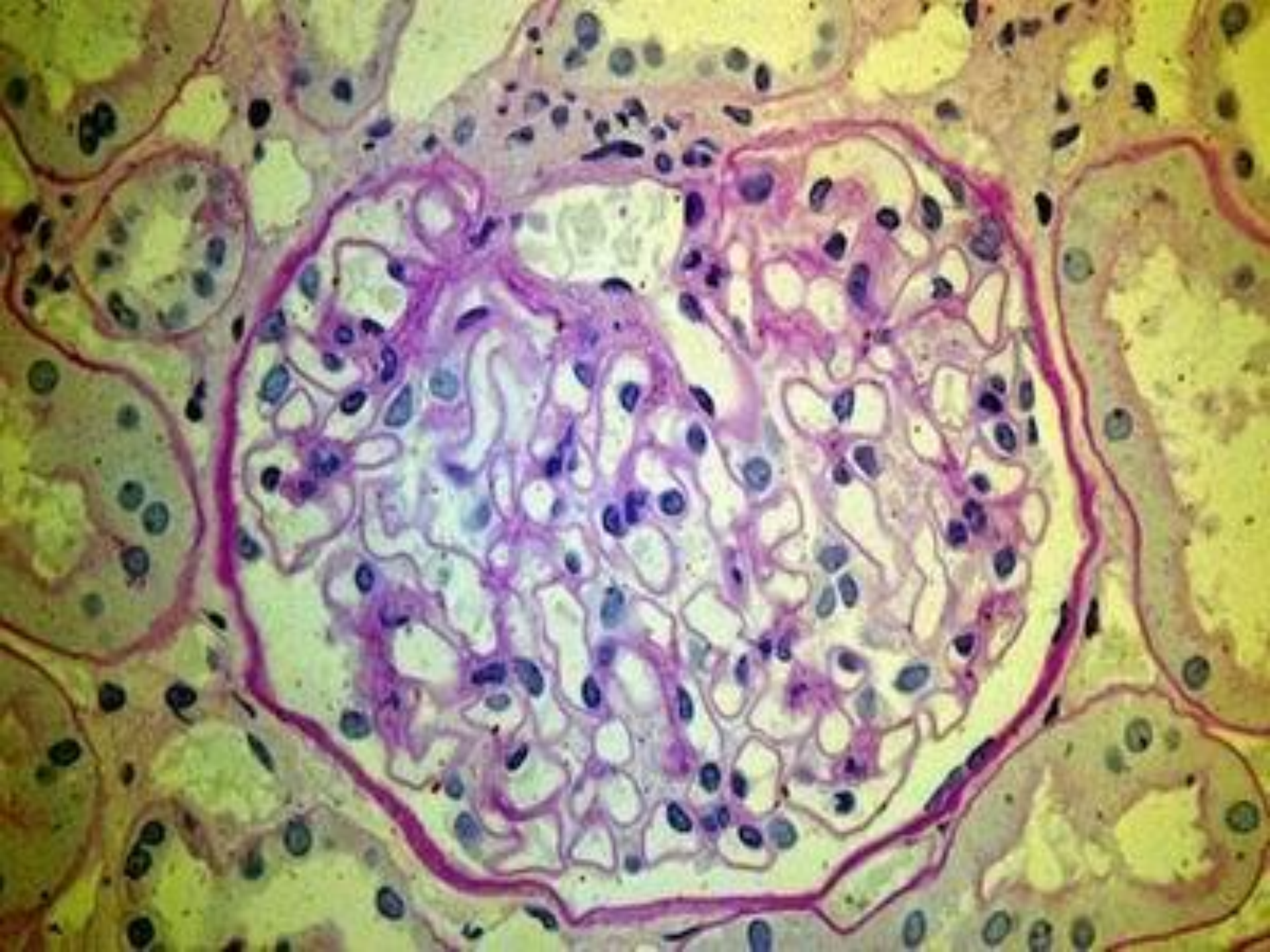
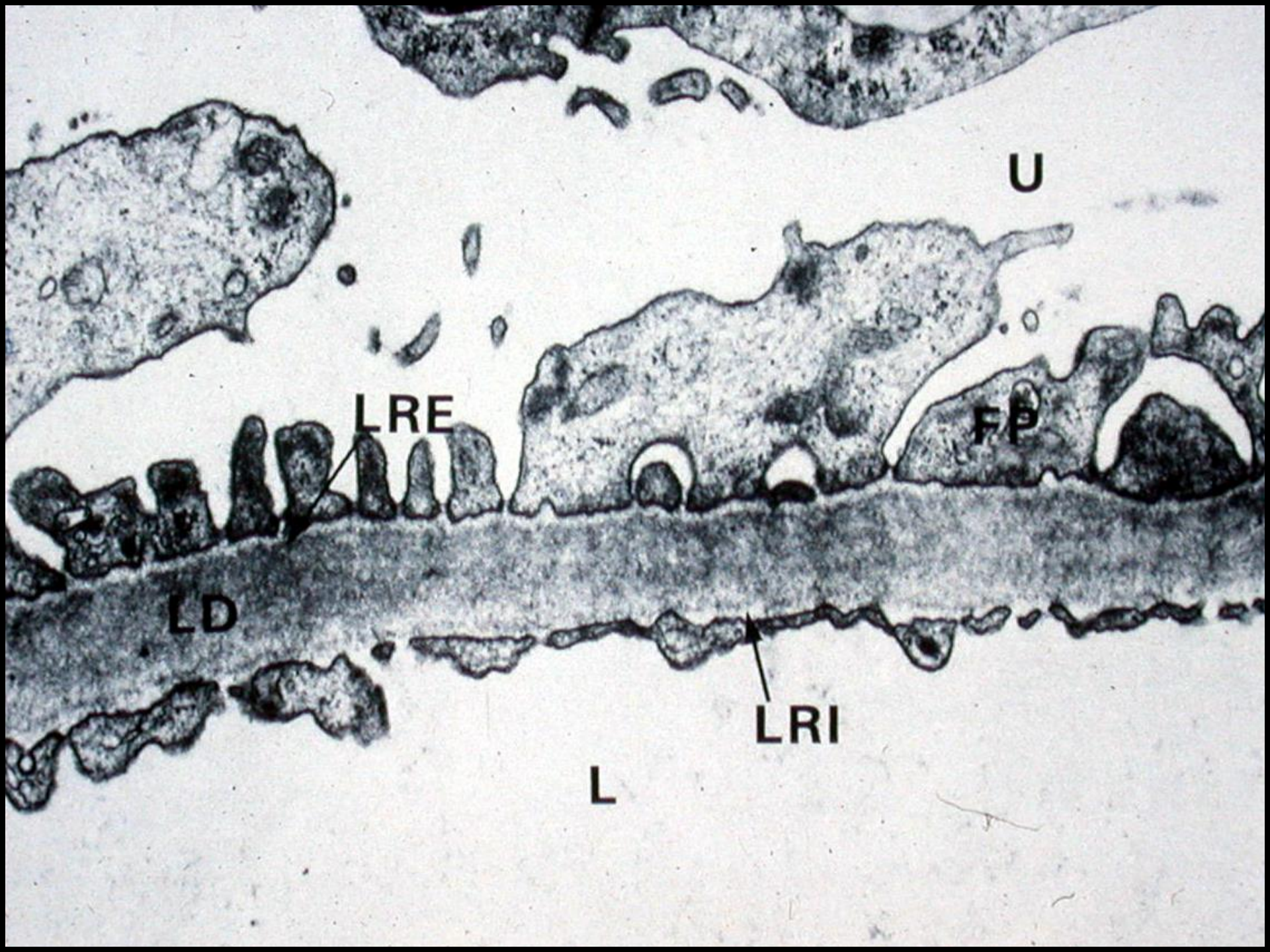


Glomerular capillary wall

A three-layer structure:

1. Endothelial cell layer.
2. Glomerular basement membrane (GBM).
    - Lamina rara interna
    - Lamina densa
    - Lamina rara externa
3. Epithelial cells (podocytes).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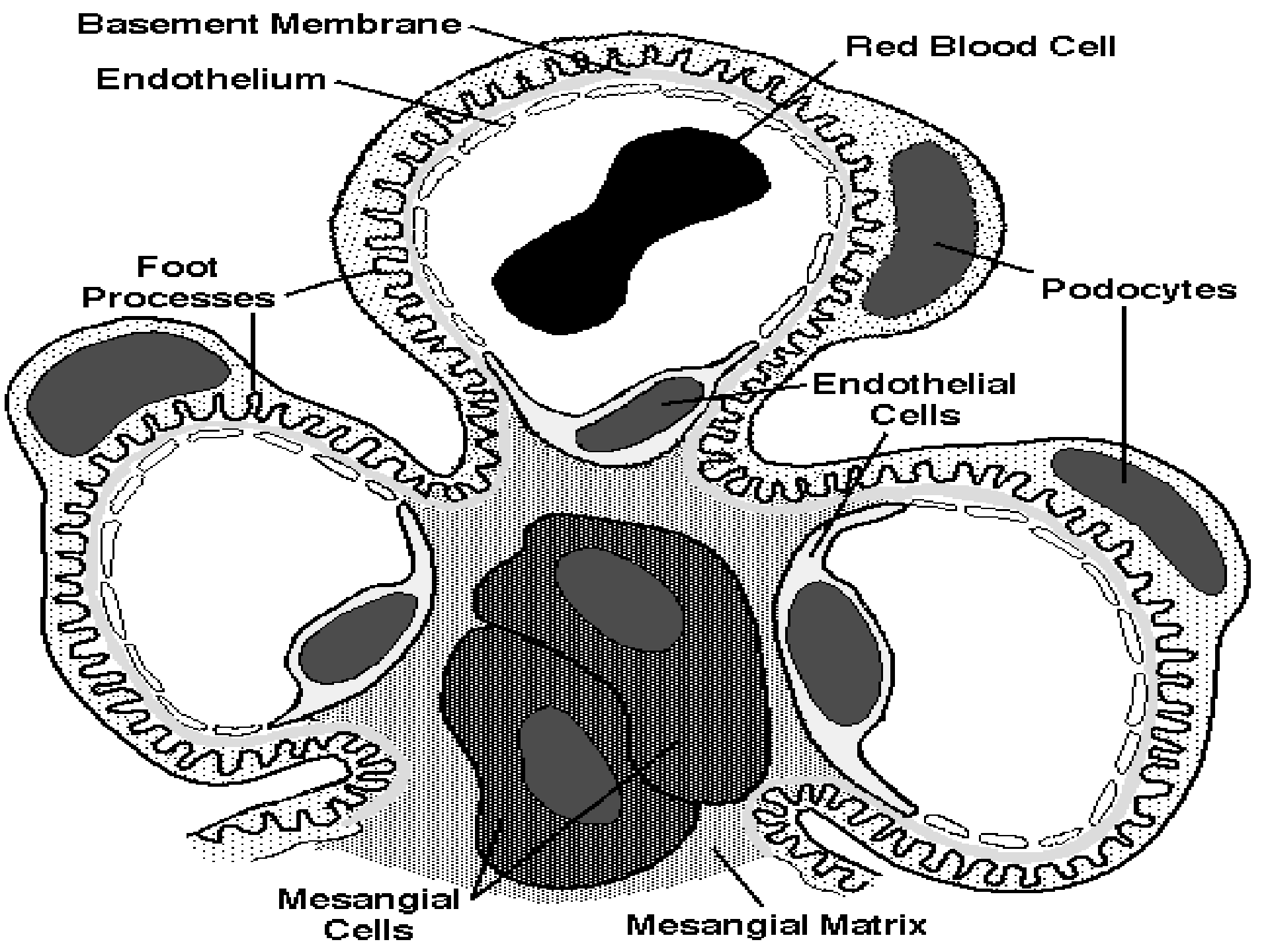

Basement Membrane
Endothelium
Red Blood Cell
Foot Processes
Podocytes
Endothelial Cells
Mesangial Cells
Mesangial Matrix

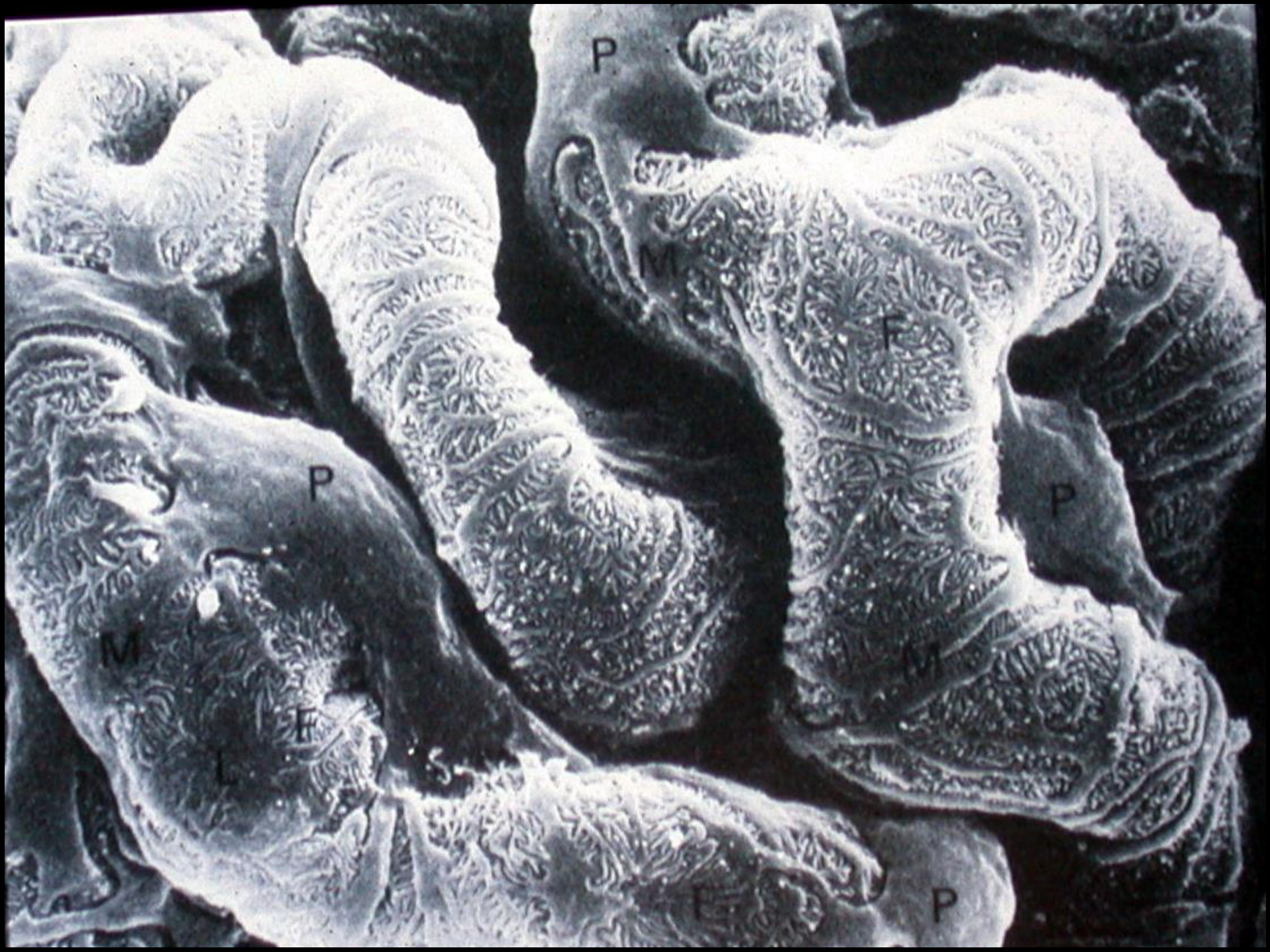
Glomerular capillary wall (GCW)

GCW is a barrier to the passage of plasma proteins from the capillary lumen to the urinary space.

Podocytes

Slit diaphragm (pivotal role)

Basement membrane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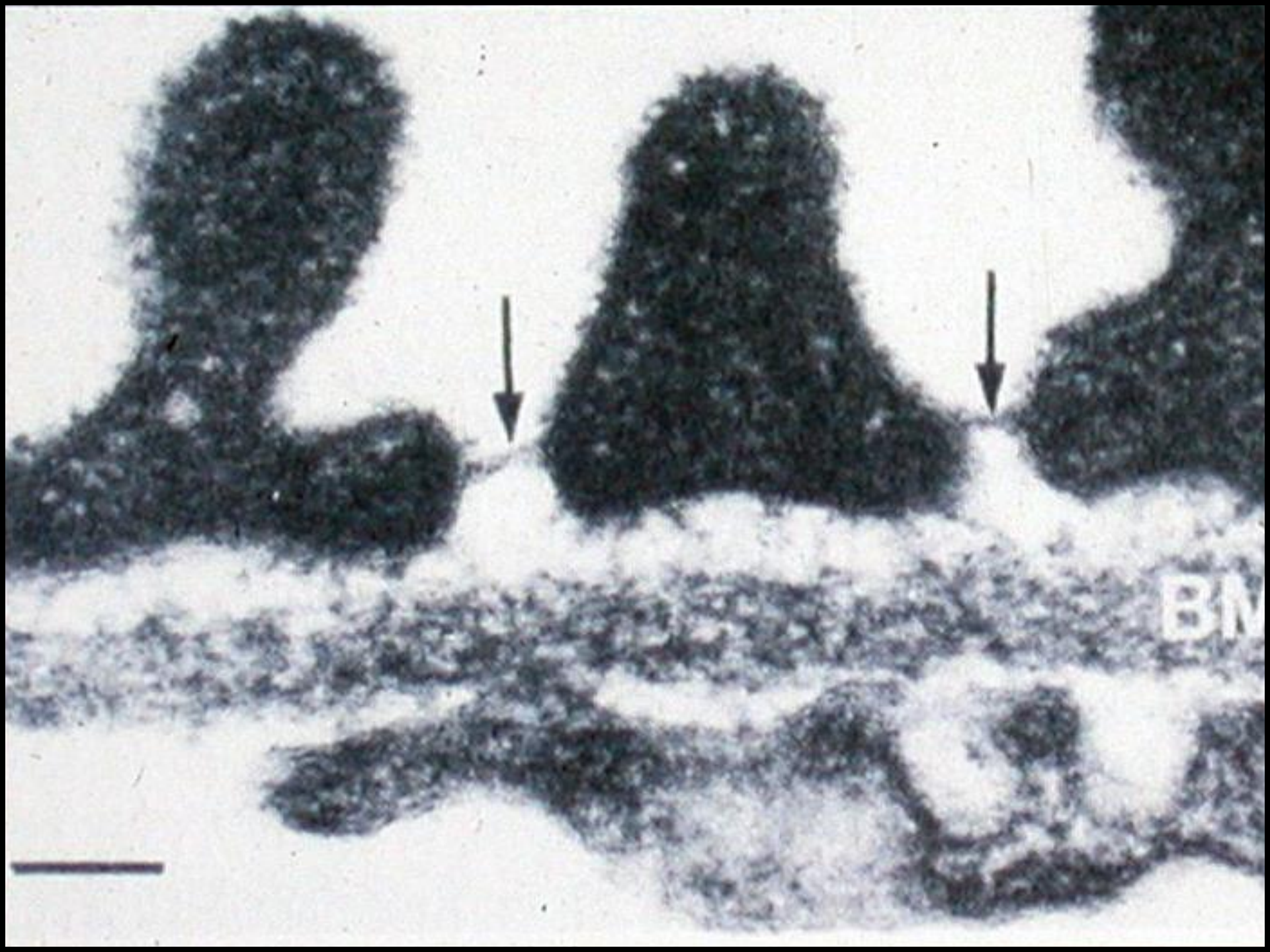
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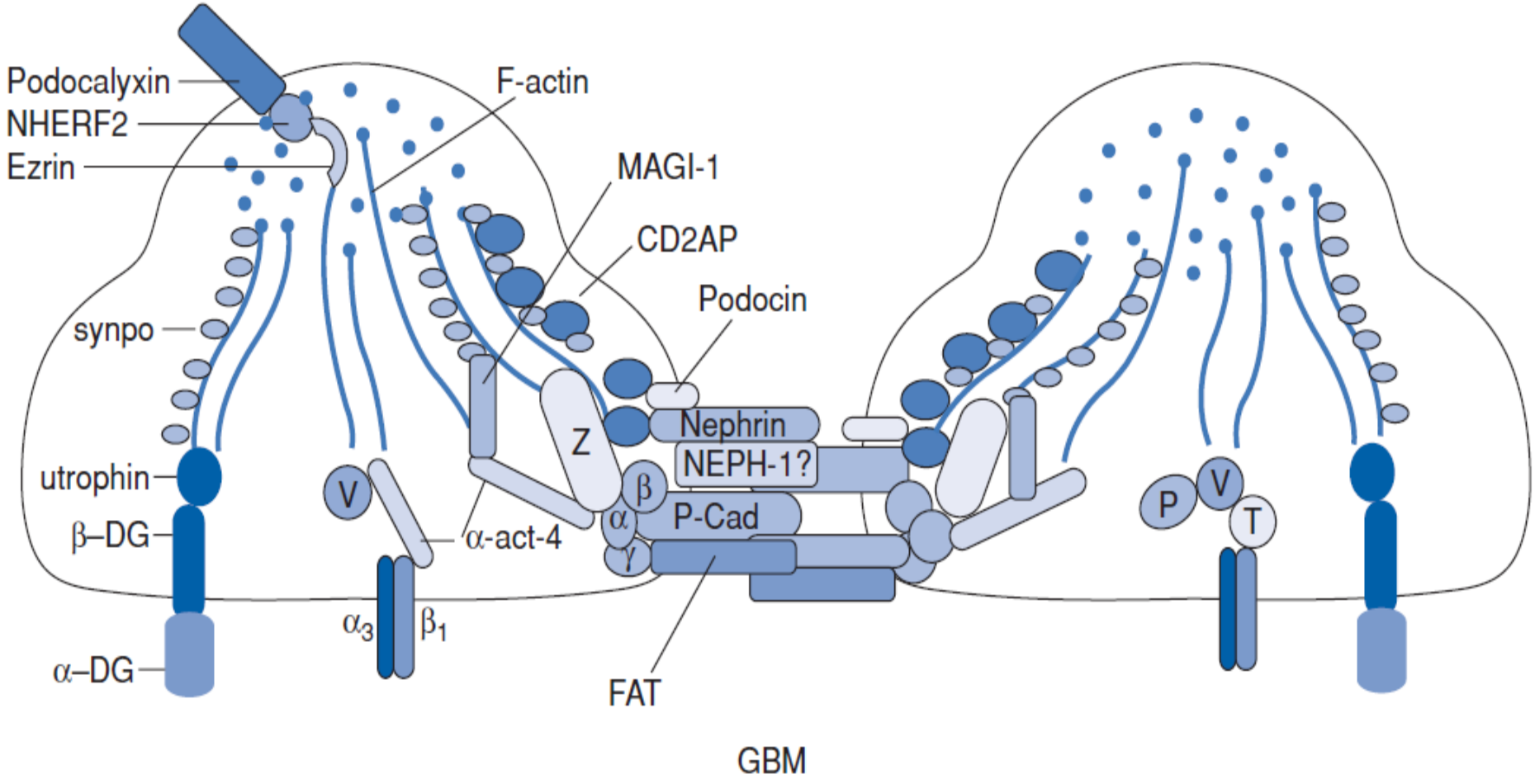
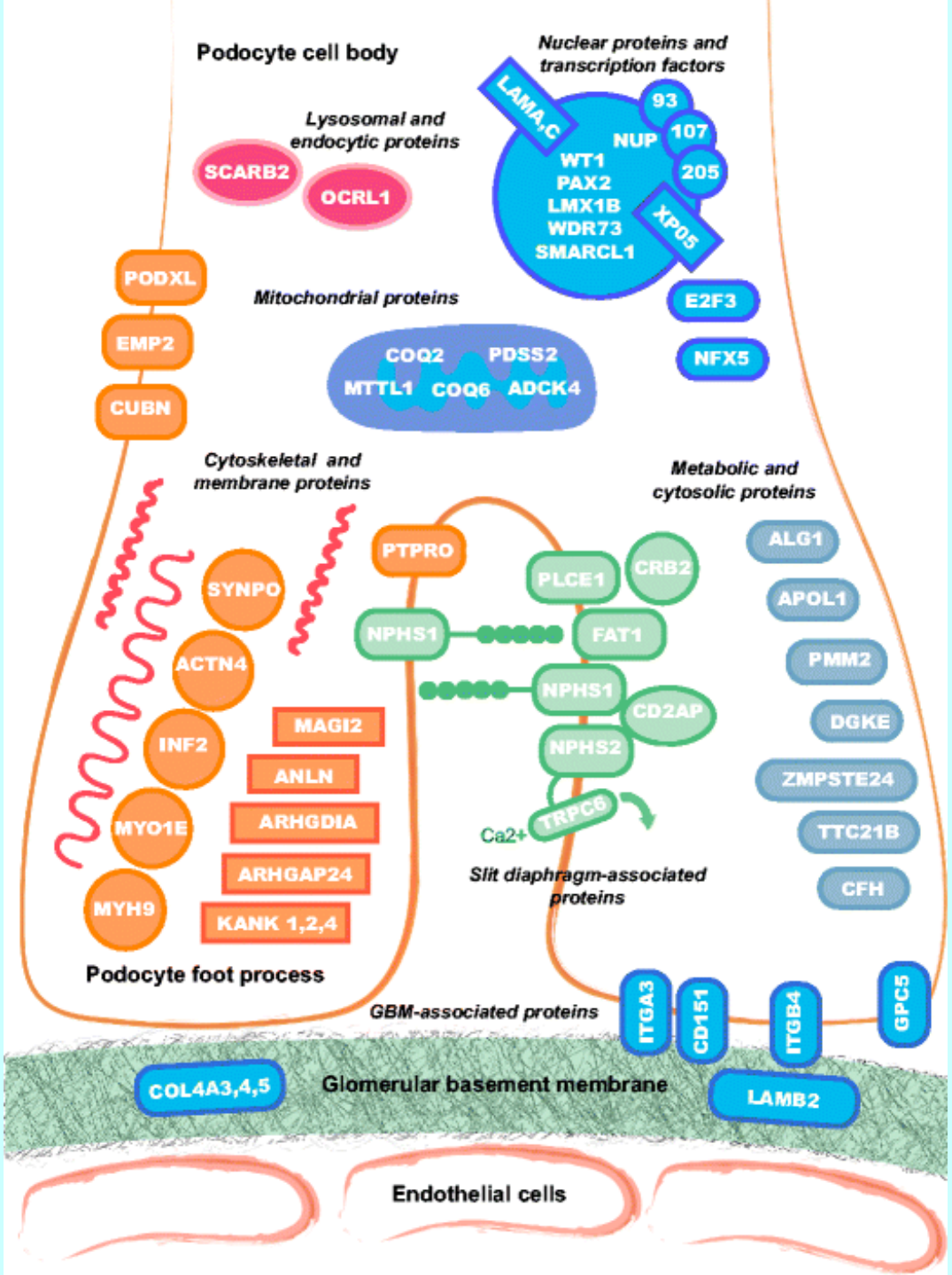


▲ **Figure 25–2.** Podocyte architecture.
GBM, glomerular basement membrane; synpo, synaptopodin; DG, dystroglycan; α-act-4, α-actinin-4; P-Cad, P-cadherin; P, paxillin; V, vinculin; T, talin. (Reproduced with permission from Mundel P, Shankland SJ: Podocyte biology and response to injury. J Am Soc Nephrol 2002;13:3005.)

Genetic mutations associated with steroid-resistant NS (SRNS)



Nephrotic Syndrome (NS)

Nephrotic syndrome is a clinical entity of multiple causes characterized by a change in the GCW permeability and thereby:

Massive proteinuria;

Edema (variable tendancy).

Hypoalbuminemia.

Hyperlipidemia.

Nephrotic Syndrome (NS)

Edema

Salt and water retention.

secondary hyperaldosteronism

Excess total body sodium.

(Hypervolemic-hyponatremia)

Onset of Presentation

- Any age (Peak 2-6 years).
- MCNS is present in 85-90% of NS patients <6 yr of age.
- Congenital NS usually in the first 3 months (genetic mutations).
- Infantile presentation – usually serious / familial – genetic mutations / tendency for steroid resistance.

- Heritable disorders:

  Common:

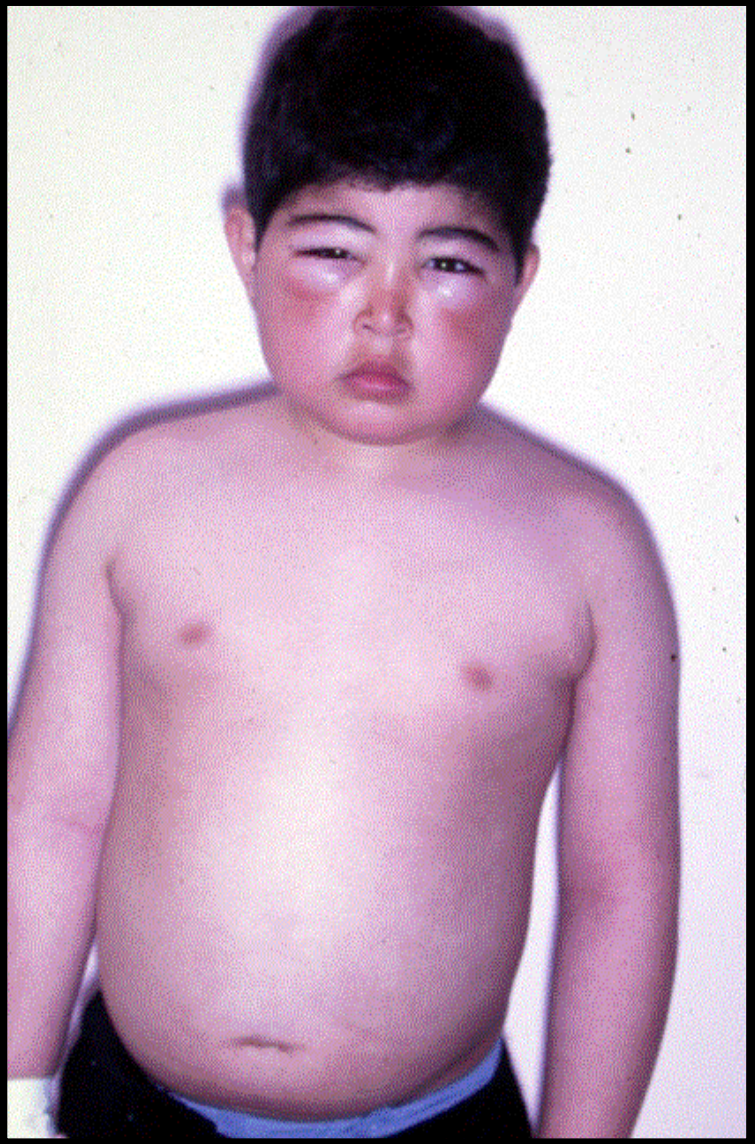
  ACTN4

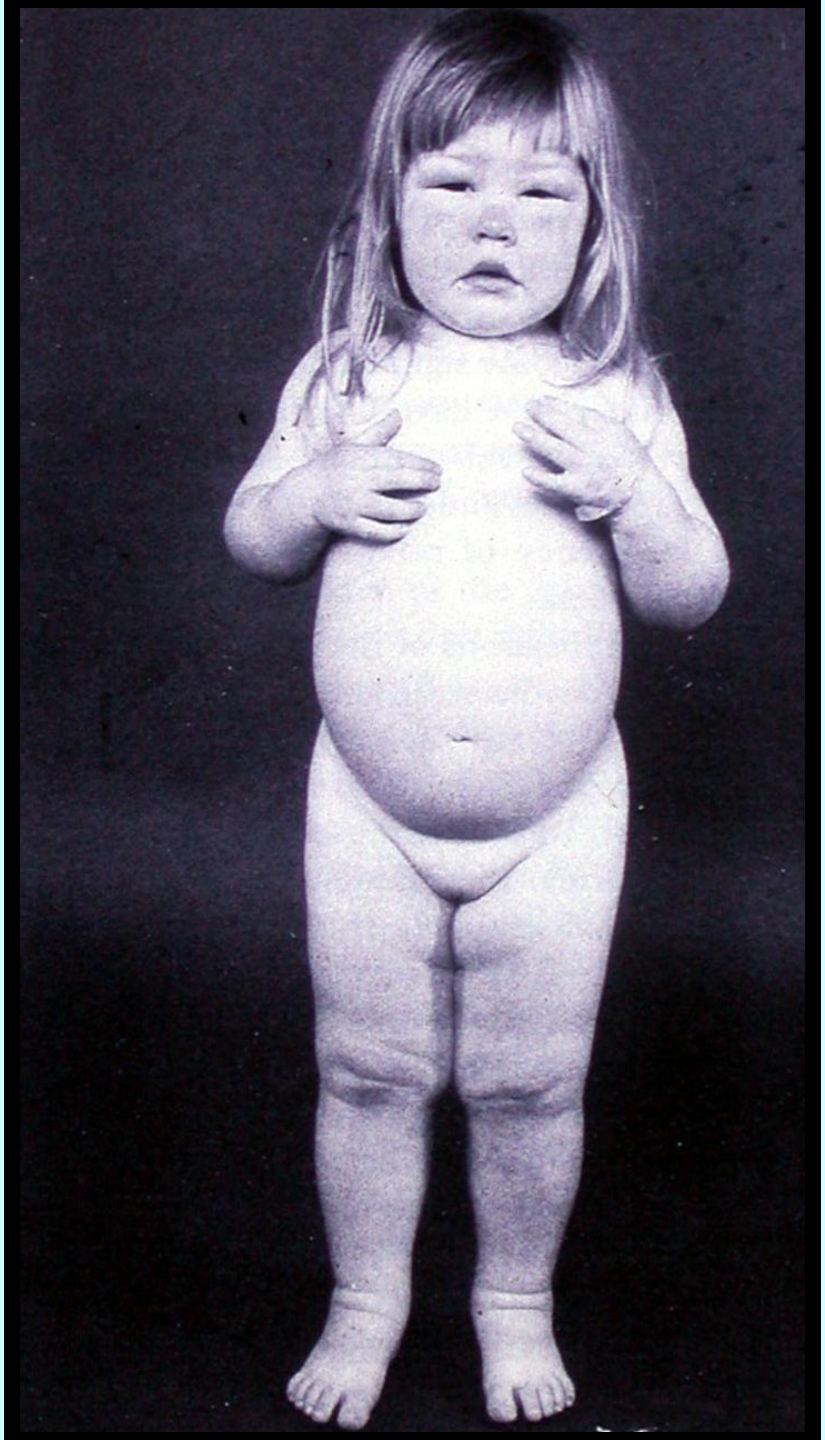
  NPHS2 / NPHS1

  PLCE1

  TRPC6

  WT1





Nephrotic Range Proteinuria

40 mg/m^2/hour

50 mg/kg body weight/day

Urine protein/creatinine ratio > 2

(normal < 0.2)

Albumin

Accounts for 75-80% of plasma oncotic pressure

Systemic Biochemical Disturbance

Defect	Consequence
Factor B & D loss in urine	Deficiency of opsonic anti-capsular antibody
Disturbance in cell-mediated immunity	Susceptibility for infection
Hypo-gammaglobulinemia	Susceptibility for infection
hypercoagulability	Susceptibility for thrombosis
Hyperlipidemia	Infection, atherosclerosis
Transferrin loss in urine	Iron deficiency anemia
Cholicalciferol binding protein loss	Vitamin-D deficiency
Trace element binding-protein loss	Zinc & Copper deficiency

Nephrotic Syndrome

Complications

1. Infections: Gammaglobulin loss in urine (& hypercatabolism).
   - Factor-B loss.
   - Abnormal macrophage function (hyperlipidemia).
   - T-Cell abnormalities.
   - Edema & skin abrasions.

   microrganisms: encapsulated (Pneumococci, H. influenzae), gram negative (e.g E.coli).

2. Hypercoagulability (Thrombosis).

2. Contracted Intravascular Compartment → → →
   - Thrombosis.
   - Postural hypotension.
   - Metabolic alkalosis.
   - Acute kidney injury.

Nephrotic Syndrome
Causes

Primary "Idiopathic" (95%)

- Minimal lesion NS (minimal change disease, lipoid nephrosis)
- Focal segmental glomerulosclerosis (FSGS)
- Mesangiocapillary glomerulonephritis (MCGN, MPGN)
- Membranous nephropathy

Secondary (5%)

- Complication / part of
  - Systemic disease (Vasculitic/SLE/HSP etc.)
  - Drugs
  - Infections etc.

Idiopathic Nephrotic Syndrome

Genetic Predisposition

- Variations in racial incidence.
- Familial cases of MLNS.
- Linkage to HLA DR7.
- Familial FSGS (various gene defects)

Minimal Change Nephrotic Syndrome
MCNS

Features:

- More frequent in boys.
- Tendency for frequent relapses in early onset disease (<6 years).
- Usually less relapses & disappears towards puberty.
- 10-15% continue to have relapses as adults.

MCNS
Associated conditions

- Atopy
- Asthma
- Eczema
- Hay fever
- Hodgkin's disease
- Thymoma ± Myasthenia

MCNS

Pathology

- Light microscopy – Normal.
- Immunofluorescence – Normal.
- Electron microscopy:

  Adherence of the foot processes of podocytes.

Nephrotic Syndrome
Investigations

- Urine analysis:

  RBCs, Casts,

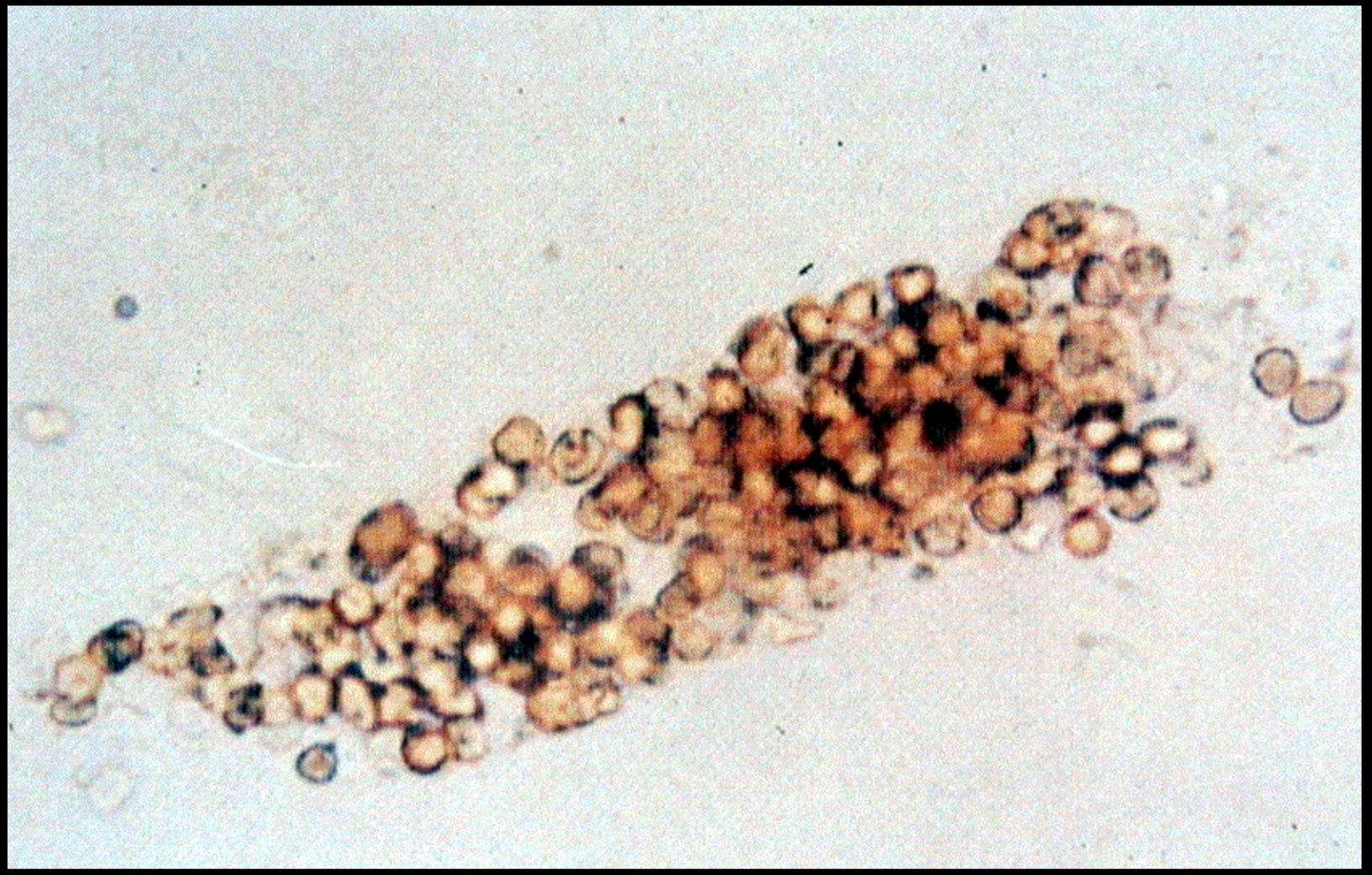
  Protein: 1 + = 0.3 gm/L

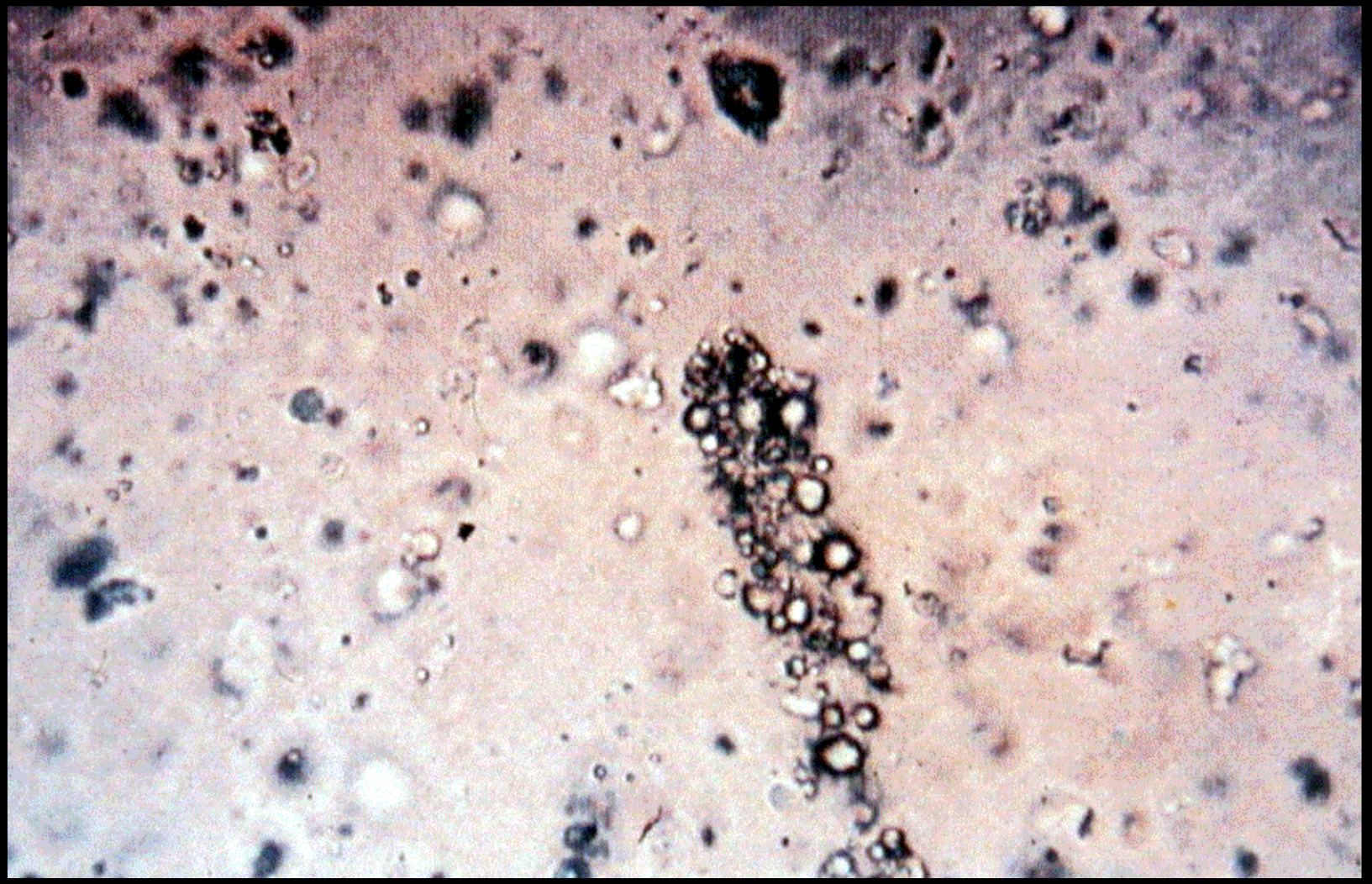
  2 + = 1 gm/L

  3 + = 3 gm/l

  4 + $\geq$ 4 gm/L

- Kidney function tests (urea, creatinine, HCO^-_3 ,Na^+, K^+).
- 24-hour protein: type, amount.
- Spot-random urine Prot./Creat. Ratio.
- CBC.
- C_3 , C_4.
- Serum lipids (Cholesterole, TG, LDL, HDL).





Nephrotic Syndrome
Investigations

- Total protein, Albumin
- HBsAg
- ANA
- Anti-dDNA

Nephrotic Syndrome
Investigations

Kidney Biopsy

Required for:

- diagnosis / therapy guide
- staging of disease

Considered in:

- Secondary N.S (Hematuria/significant proteinuria)
- Frequent relapsing N.S
- Steroid resistant N.S
- Hypertension.
- Low GFR / RPGN

Nephrotic Syndrome

Definitions

- Remission: no edema, urine is protein free for 5 consecutive days.

- Relapse: edema, or first morning urine sample contains > 2 + protein for 7 consecutive days.

- Frequent relapsing: > 2 relapses within 6 months (> 4/year).

- Steroid resistant: failure to achieve remission with prednisolone given daily for 1 month.

Idiopathic Nephrotic Syndrome
Management

Admission to Hospital:

- "A new case"
- Biopsy
- Extensive edema (anasarca)
- Complications (infections/thrombosis, etc.)

Nephrotic Syndrome

Management

Family Education

- Factors precipitating relapses:
  Vaccination, infections
- Diet:
  regular protein intake, low salt intake
- Steroids protocols, side effects.
- Flow sheets.

Nephrotic Syndrome
Management / supportive

- Albumin + Lasix (20 % salt poor)
  - Severe edema
  - Ascites
  - Pleural effusion
  - Genital edema
  - "Low" serum albumin
- ± Gentle diuresis (e.g Thiazides).
- Vaccination : PCV-13
- Anticoagulation therapy in children with thrombotic events.

Nephrotic Syndrome

Management

Medications

- Steroids (oral, IV bolus)
- Immunosuppressive agents:
  - Alkylating agents (Cyclophosphamide / Chlorambucil)
  - Calcineurin inhibitors (Cyclosporin A / Tacrolimus)
  - Mycophenolate mofetil
  - Monoclonal antibodies (Rituximab / anti-CD20)
- T- cell stimulants:
  Levamisole
- Anti-platelet agents:
  Aspirin, Dipyridamole
- ACEi / ARBs.
- Special therapeutic protocols (secondary NS).

Prednisolone

- Induction of Remission

  Until urine is protein free for 5 days.

  2 mg/kg/day (divided)

  (max. 60-80 mg/day)

- Maintain Remission :

  Same dose, given as a single dose every 48 hours.

  Gradual tapering over about 2 months.

- Steroid Dependent and Frequent Relapsing Patients :

Maintain at a low dose (every 48 hours)

Side effects with high/long term steroids
"Steroid toxicity"

- Stunted growth.
- Cataracts.
- Pseudotumor cerebri, Psycosis.
- Osteoporosis.
- Cushingoid features.
- Adrenal gland suppression.
- High B.P

Remission in MCNS Following Induction with Steroids

%	weeks
35	1
55	2
75	3
95-98	4

Natural History
Steroid Responsive MCNS

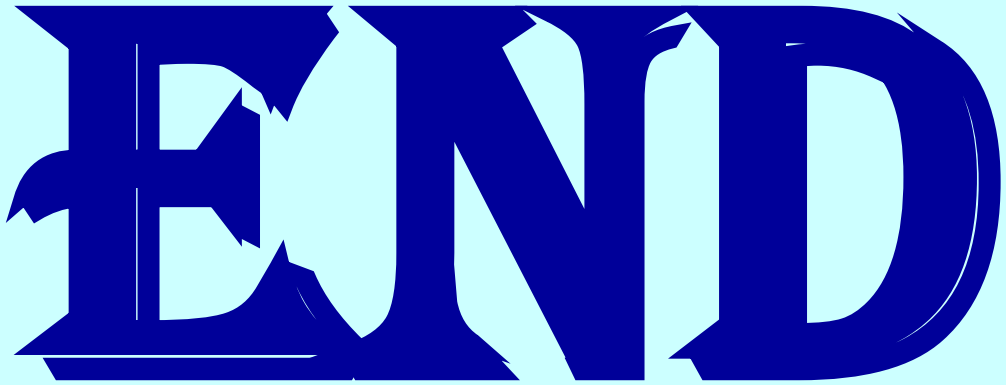
%	History
40	No relapse after an initial response to therapy
30	Infrequent relapses
30	Frequent relapsing

Idiopathic Nephrotic Syndrome

Alkylating Agents.
Calcineurin inhibitors.
Mycophenolate mofetil.
Monoclonal antibodies.
Levamisole.

Considered in the following situations:

- Steroid resistance (no Levamisole).
- Steroid dependence.
- Frequent relapses.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