Proteinuria

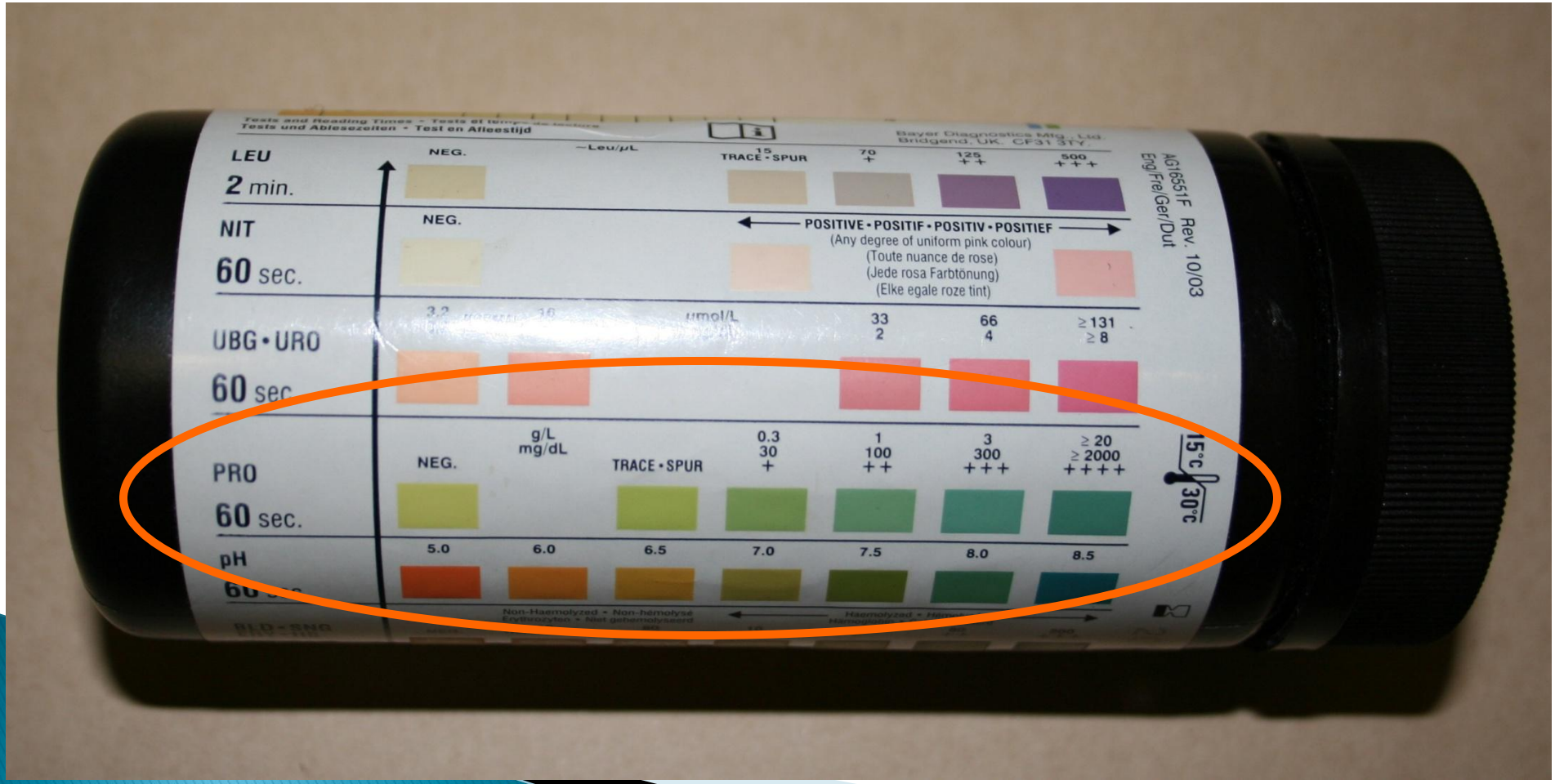
Dr P Sigwadi

Paediatric Nephrology

Introduction

- Prevalence - 5-15 % on a single urine sample
- After a series of 4 tests only 0.1% of children had persistent positive proteinuria
- Persistent proteinuria indicates the presence of glomerular lesion
- Plays a role in the progression of any form of kidney disease to end-stage renal disease

Estimate of proteinuria on dipstix



Proteinuria

- Diagnostic tool
  - for renal disease
  - assessing progress & response to treatment
- Mild transient proteinuria may occur with
  - febrile illnesses
  - after heavy exercise
  - dehydration

Proteinuria

- Postural or orthostatic proteinuria
  - No proteinuria early in morning
  - Proteinuria later in the day
- Mild to moderate proteinuria may occur in
  - Acute or chronic glomerulonephritis
  - Reflux nephropathy, other forms of CKD

Proteinuria

- Heavy proteinuria
  - Characteristic of nephrotic syndrome

Mechanisms of urine concentration

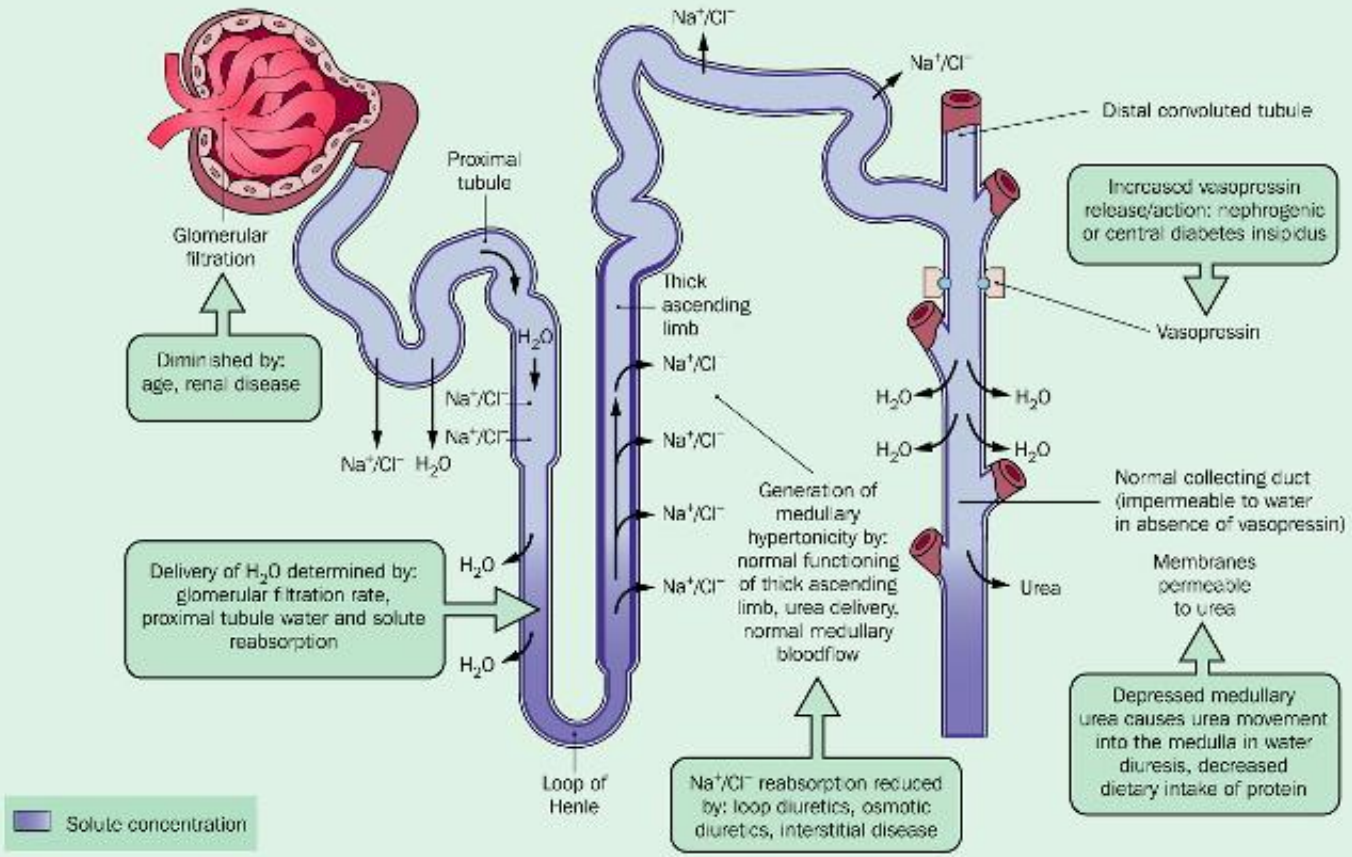
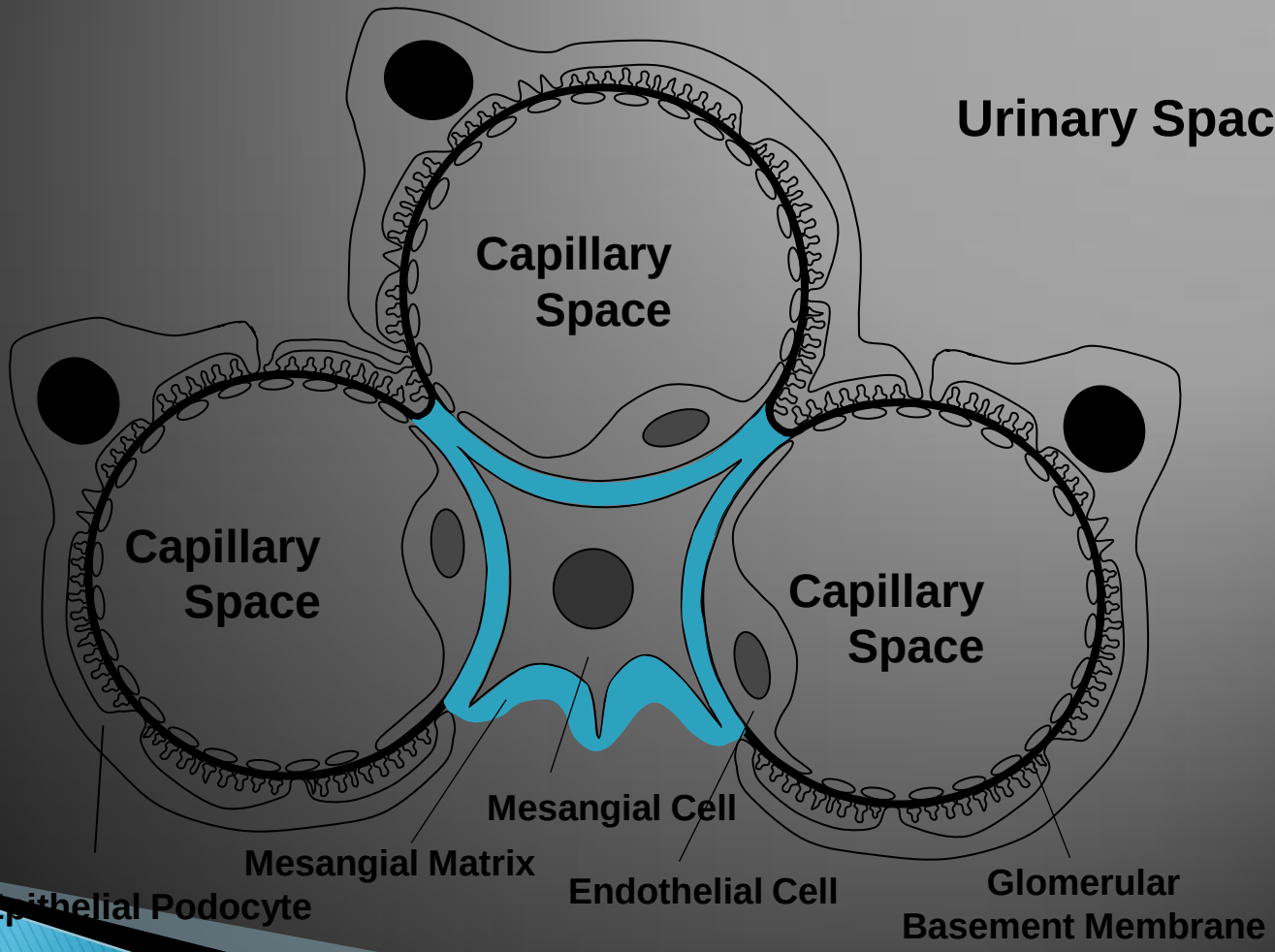


Diagram of glomerular structure



Glomerular Filtration Barrier

Composed of 3 layers:

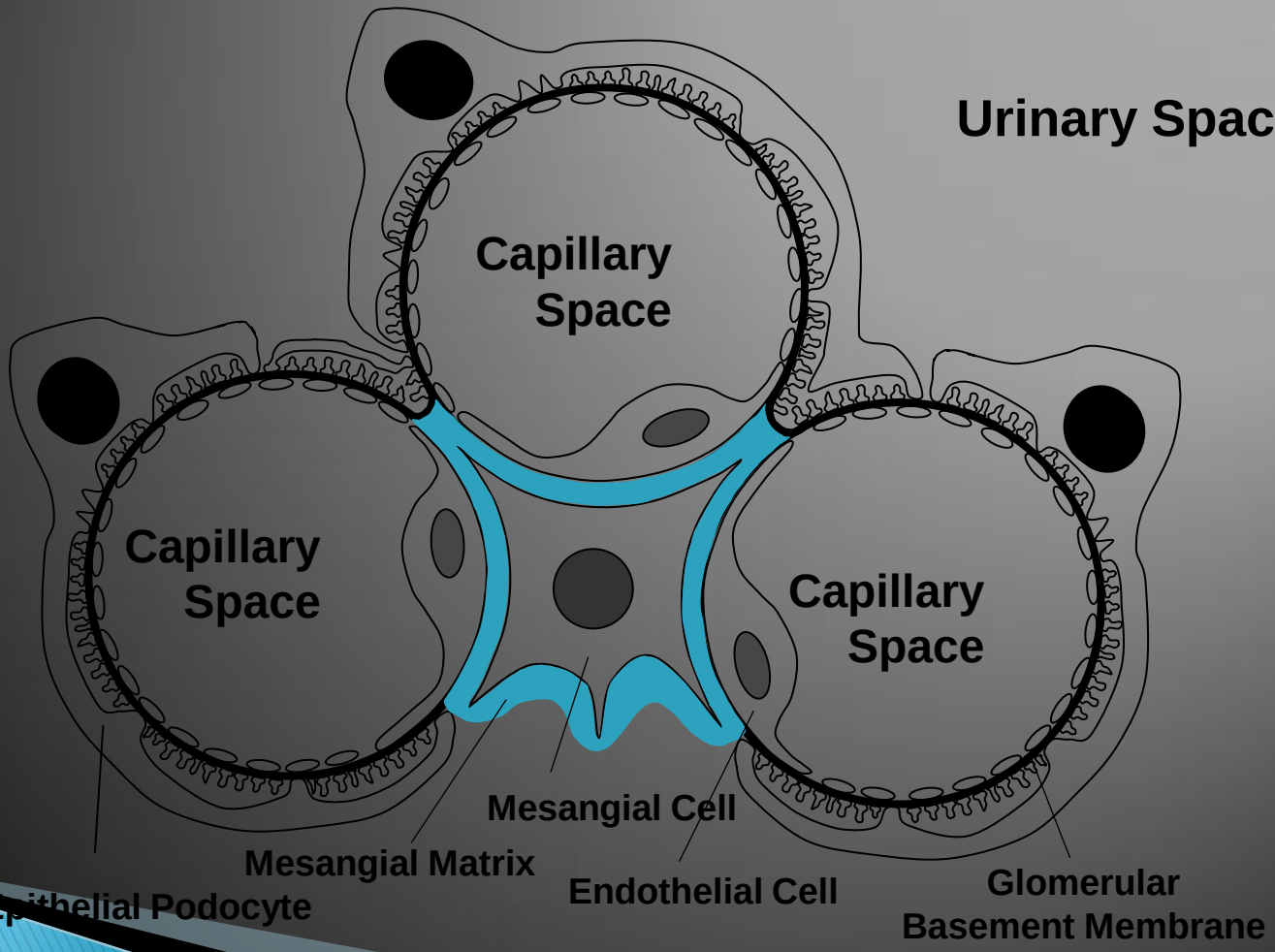
- A fenestrated endothelium
- The glomerular basement membrane (GBM)
- The epithelial cell (podocyte) layer with distal foot processes and interposed slit diagrams

Glomerular Filtration Barrier

Podocytes

- Enclose the capillaries →form an interrupted sheet
- Have a cytoskeleton (microtubules and filaments)
- Filaments anchor the podocytes to the GBM
- Openings/filtration pores between adjacent feet processes are bridged by slit diaphragms

Diagram of glomerular structure

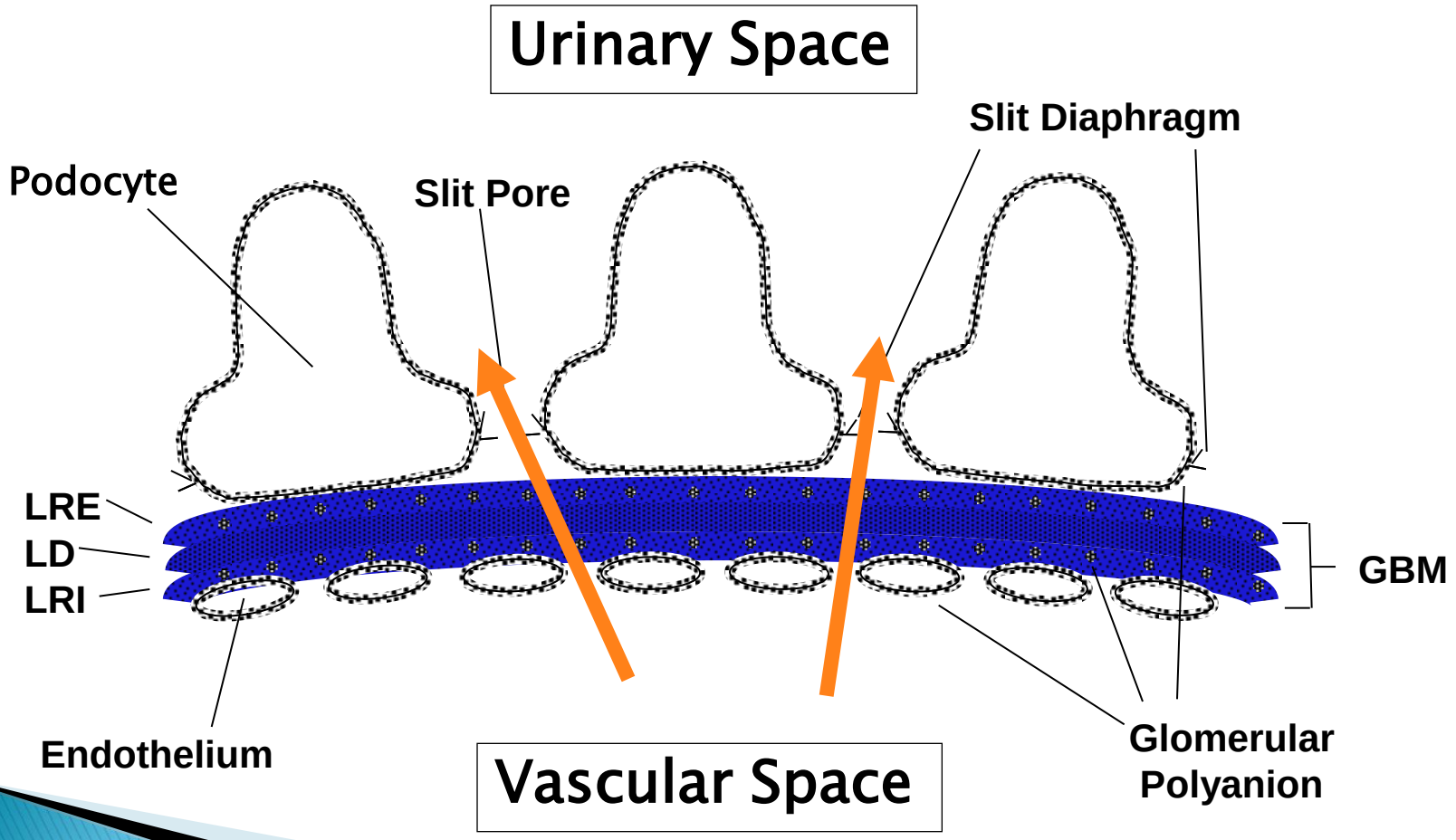


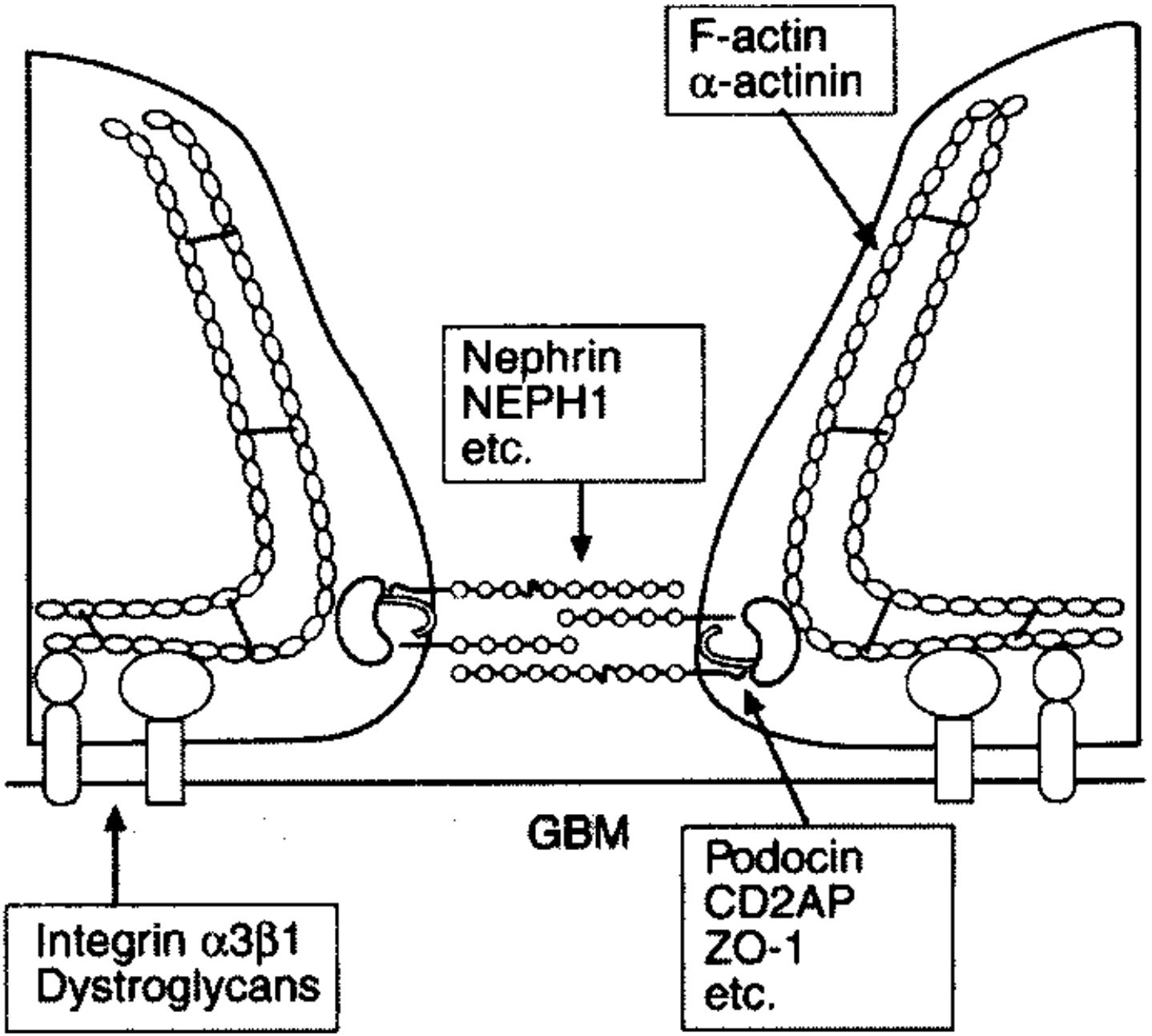
Glomerular Filtration Barrier

- GBM = network of fibrils forming a filter
- Main component =heparan sulphate proteoglycan (HSPG)

  → responsible for negative charge
- Negatively charged proteins are repelled by the negative charge on the GBM – keep them in the circulation

Glomerular Filtration Barrier




F-actin
α-actinin
Nephrin
NEPH1
etc.
GBM
Integrin α3β1
Dystroglycans
Podocin
CD2AP
ZO-1
etc.

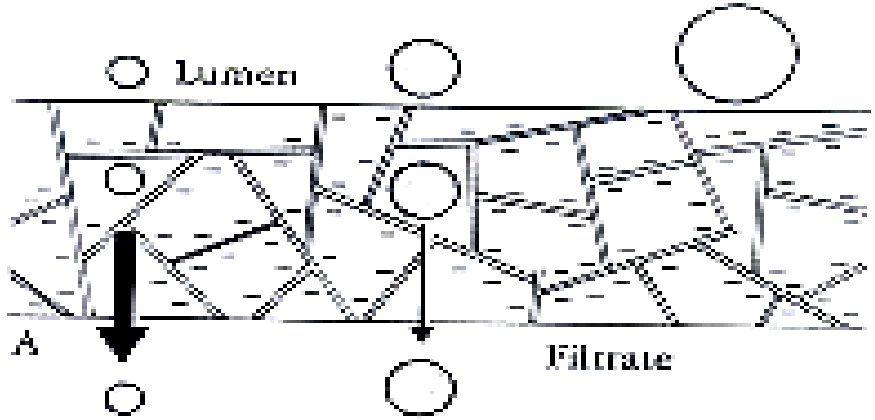
Glomerular Filtration Barrier

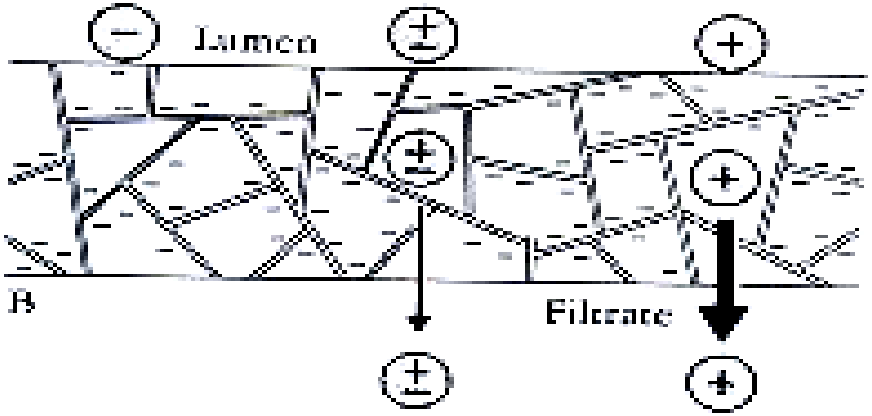
- Plasma components can pass through endothelial fenestrae
- Small molecules pass
  - across GBM
  - and through the slit pores
- Passage of albumin + larger molecules is restricted by GBM = size + charge selective barrier

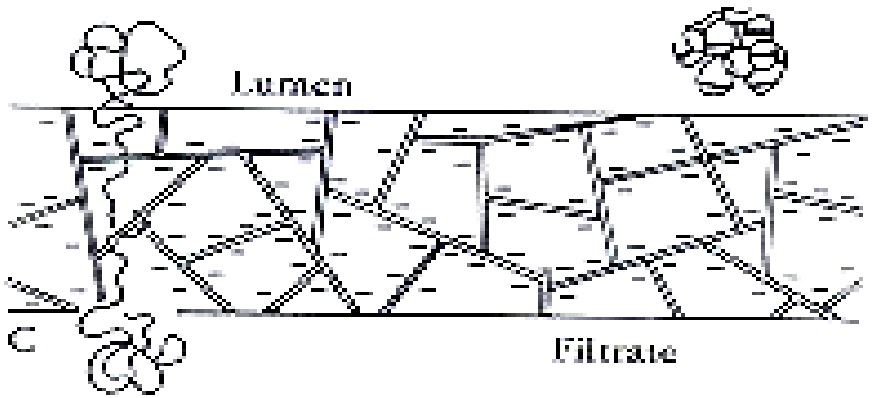
Mechanisms of proteinuria

The ability of molecules to pass through the basement membrane depends on their

- Size
- Charge
- Molecular configuration



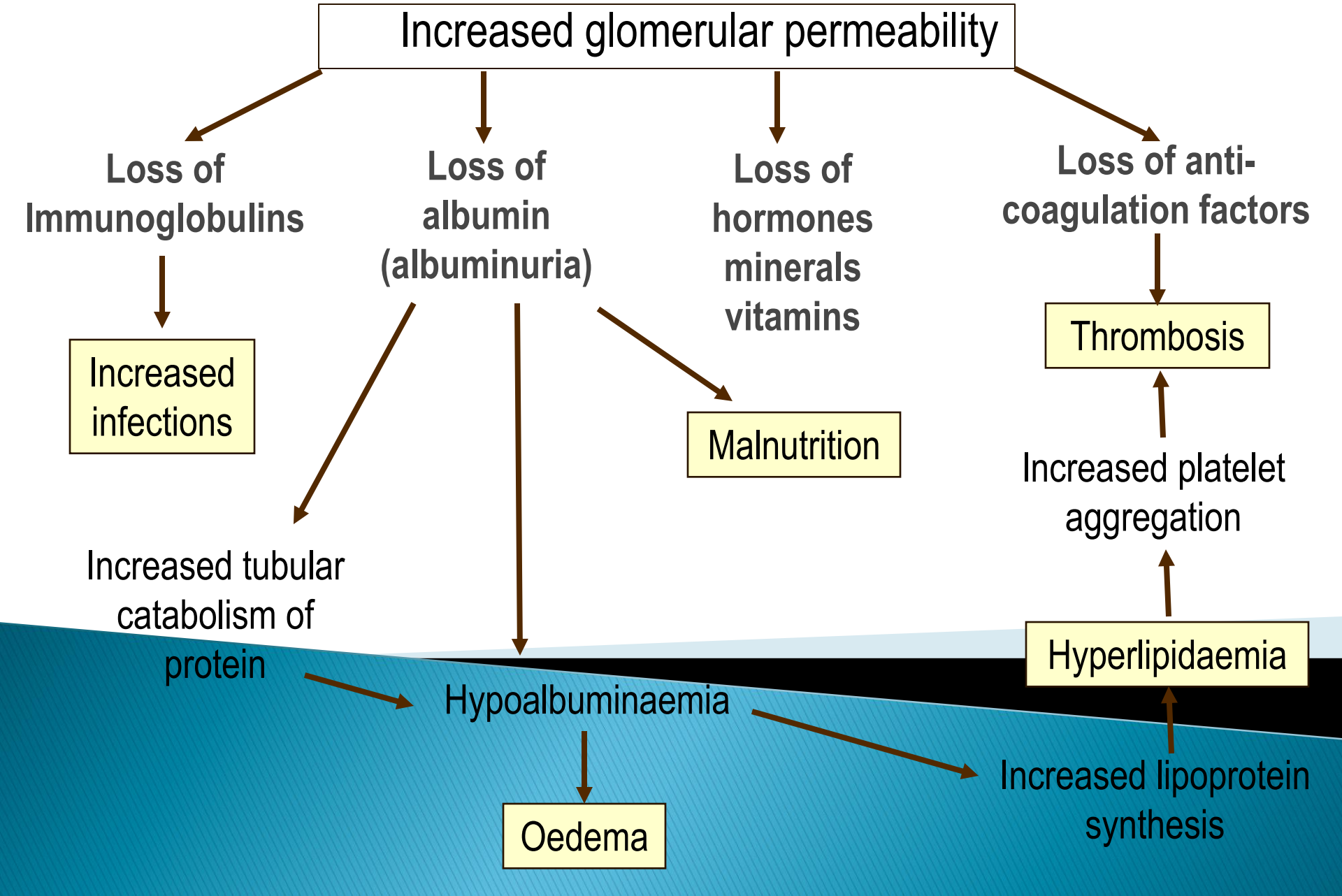




Mechanisms of Proteinuria

- Barriers to glomerular filtration
  - Mechanical
    - Endothelial cells
    - Glomerular basement membrane (GBM)
    - Epithelial cells
    - Slit-pore membrane
  - Electrostatic
    - Negative charge on GBM
- Minimal change nephrotic syndrome:
  - Decreased negative charge of the GBM

Consequences of Massive Proteinuria



Nephrotic syndrome

- Nephrotic syndrome is a disorder that is characterized by
  - Heavy proteinuria (3-4+ proteins on U-dipstick or protein:creatinine ratio>0.2 gram/mmol)
  - Oedema
  - Hyperlipidaemia
  - Hypoalbuminaemia of <25 g/L

Minimal Change Nephrotic syndrome

- Is 15x more common in children than adults
- Incidence: 2-3/100 000 per year
- M:F of 2:1
- Median age of presentation is 4 years (Range 2-6)

Features of Nephrotic syndrome

- Massive proteinuria of >40 mg/m2/hour or protein: creatinine ratio of >0.2g/mmol(1st urine sample in the morning)
- Hypoalbuminaemia of < 25 g/l
- Hyperlipidemia
- Oedema
- Haematuria- 25% of patients

Pathophysiology

- Increase in permeability of the glomerular capillary wall → massive proteinuria – ↓ S-Alb
- The cause of increased permeability is not well understood
- Induction NaK-ATPase →Na retention → edema
- Alterations capillary permeability → asymmetric volume expansion

Pathophysiology

- Postulates:

  T-cell dysfunction leads to alteration of cytokines which causes loss of negatively charged glycoproteins within the capillary wall (Minimal Change Nephrotic Syndrome MCNS)

Pathophysiology

- Focal Segmental Glomerulosclerosis (FSGS)

→Mutation in the podocyte protein or plasma factor produced by the lymphocytes may be responsible for increased capillary wall permeability

→ Genetic Susceptibility

Causes of Nephrotic syndrome

- Primary (Idiopathic)
  - Minimal change disease (commonest-80%)
  - Congenital Nephrotic syndrome (Finnish type)
  - Diffuse mesangial sclerosis
  - Focal segmental glomerulosclerosis
  - Membranous nephropathy

Causes of Nephrotic syndrome

- Secondary causes
  - Infections
    - HIV
    - Hepatitis B and C
    - Cytomegalovirus
    - Congenital syphilis
    - Congenital Rubella
    - Malaria

Causes of Nephrotic syndrome

- Others
  - SLE
  - HUS
  - Drug reaction e.g ACEI, NSAID's
  - Toxins e.g. mercury

Secondary causes cont

- Syndrome-associated e.g.
  - Denys-Drash syndrome
  - Frasier syndrome

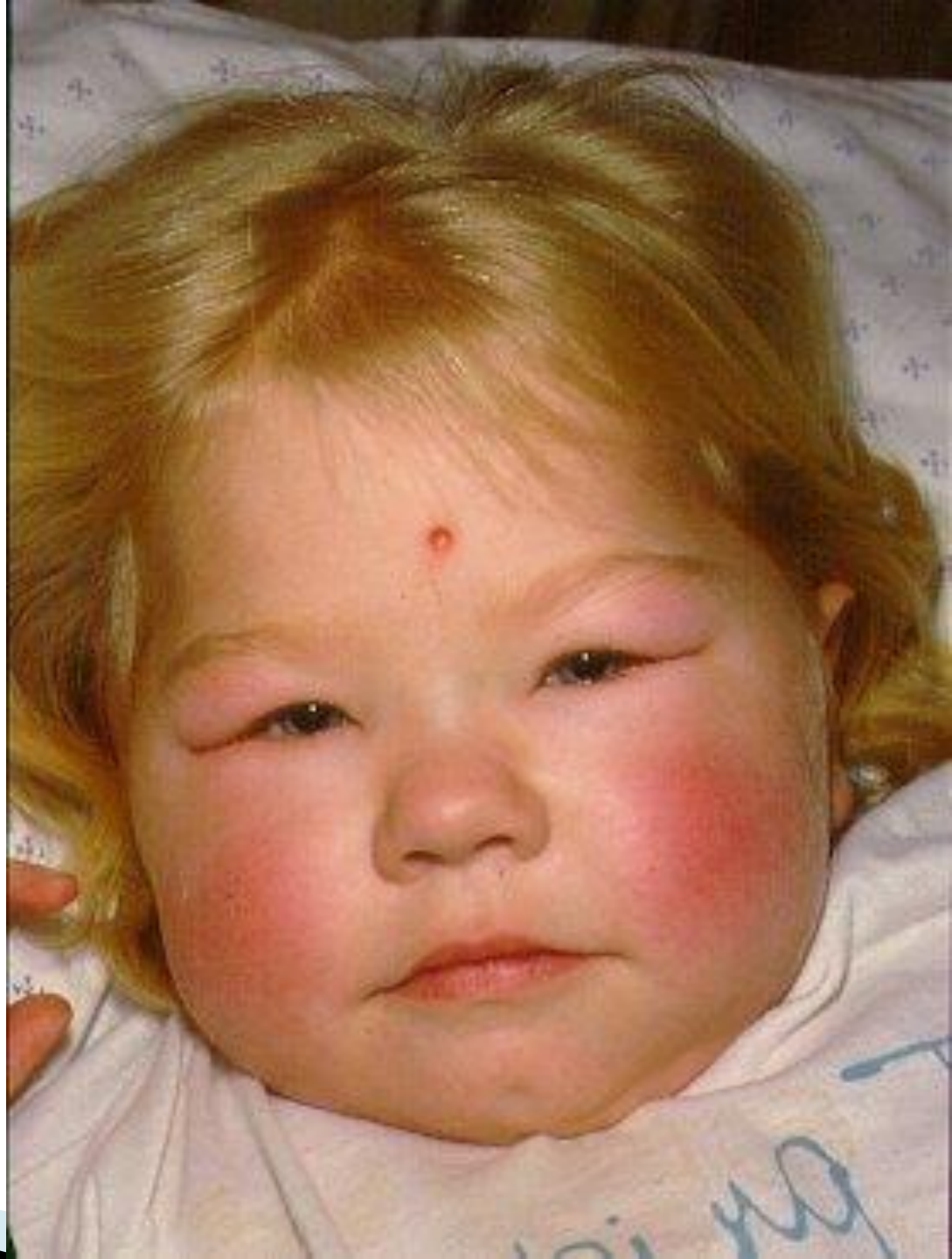
Signs and symptoms

- History
  - Presenting complaint
  - History of sore throat or scarlet fever
  - Family history of renal diseases/ nephrotic syndrome
  - Birth history
    - Birth weight, placenta size
    - Raised AFP in the amniotic fluid during pregnancy

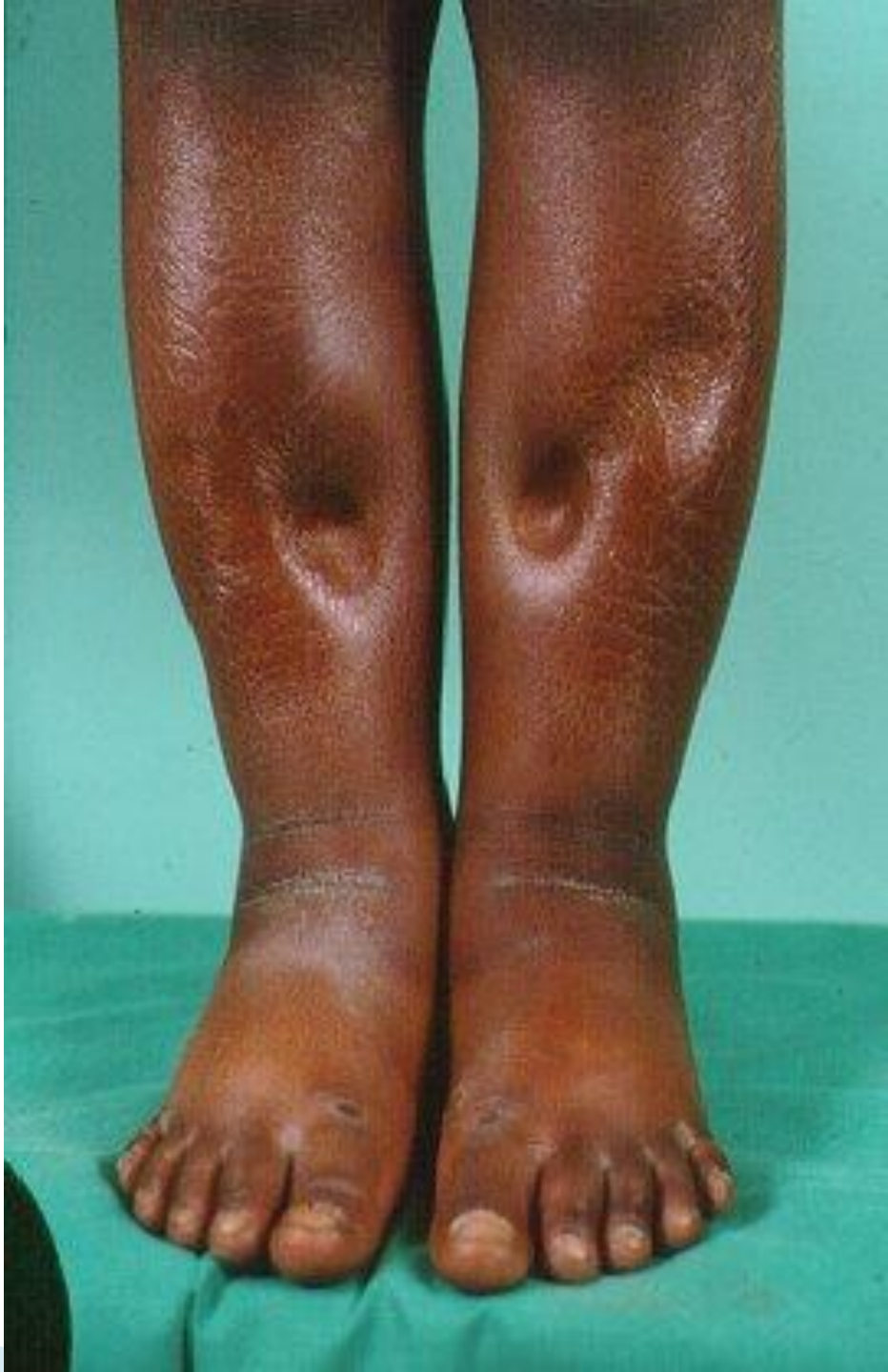
Clinical examination

- Oedema-Pedal, periorbital, scrotal
- CVS: pericardial effusion
- Respiratory
  - Pleural effusions
- Abdomen:
  - Ascites
  - +/-Hepatomegaly

Peri orbital oedema

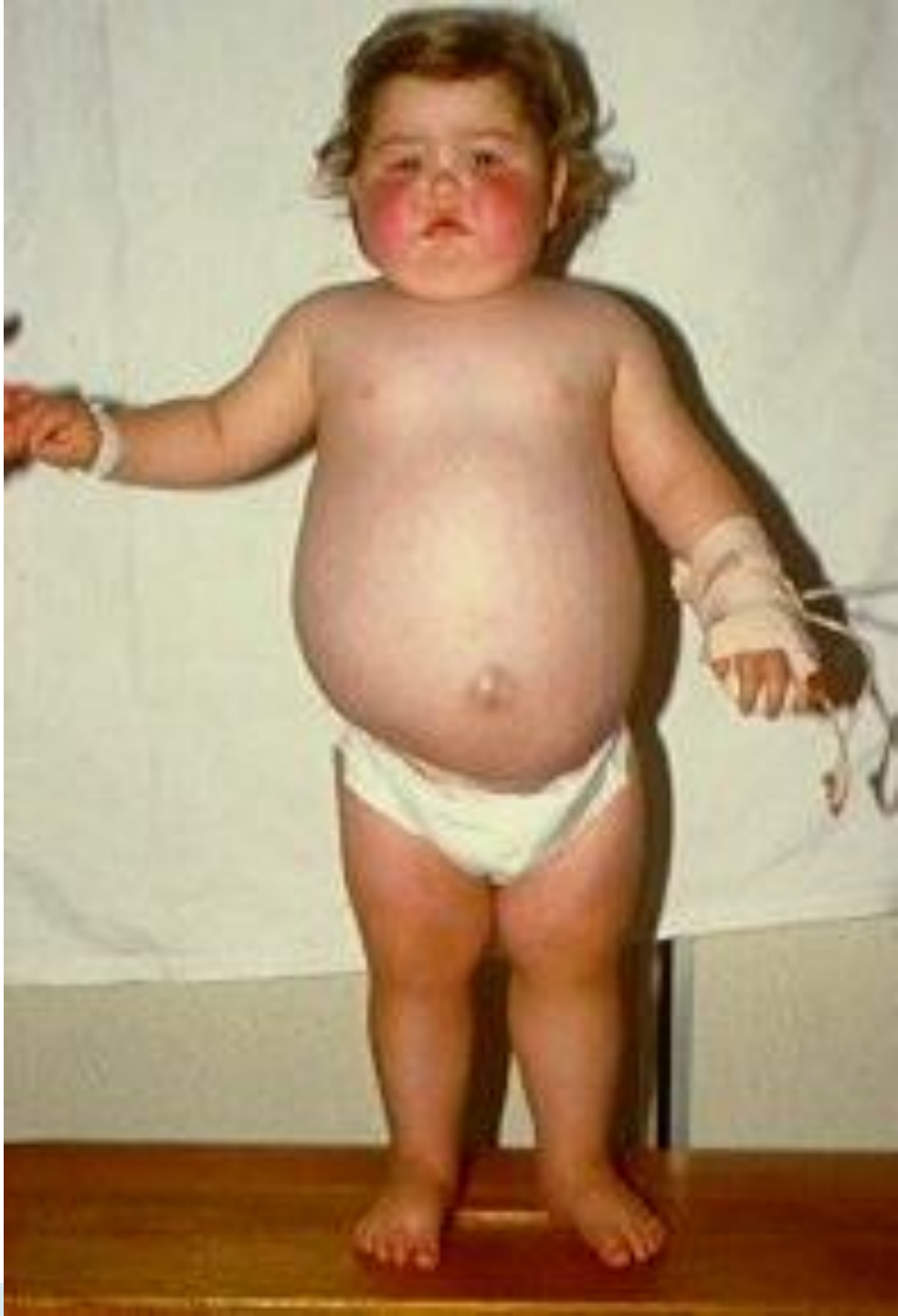


Peripheral oedema mostly in dependant parts of body



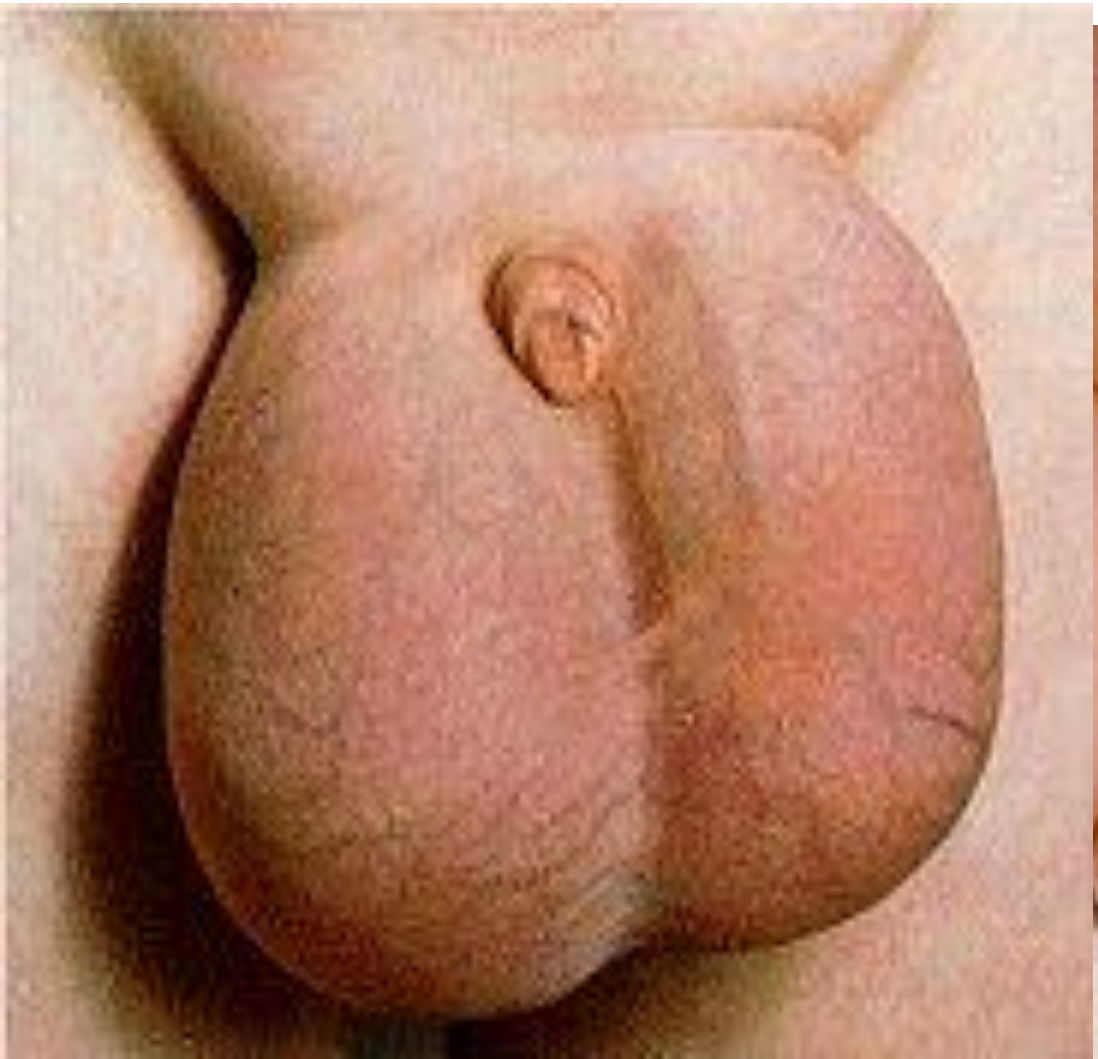
Nephrotic Syndrome

Generalised oedema (anasarca)

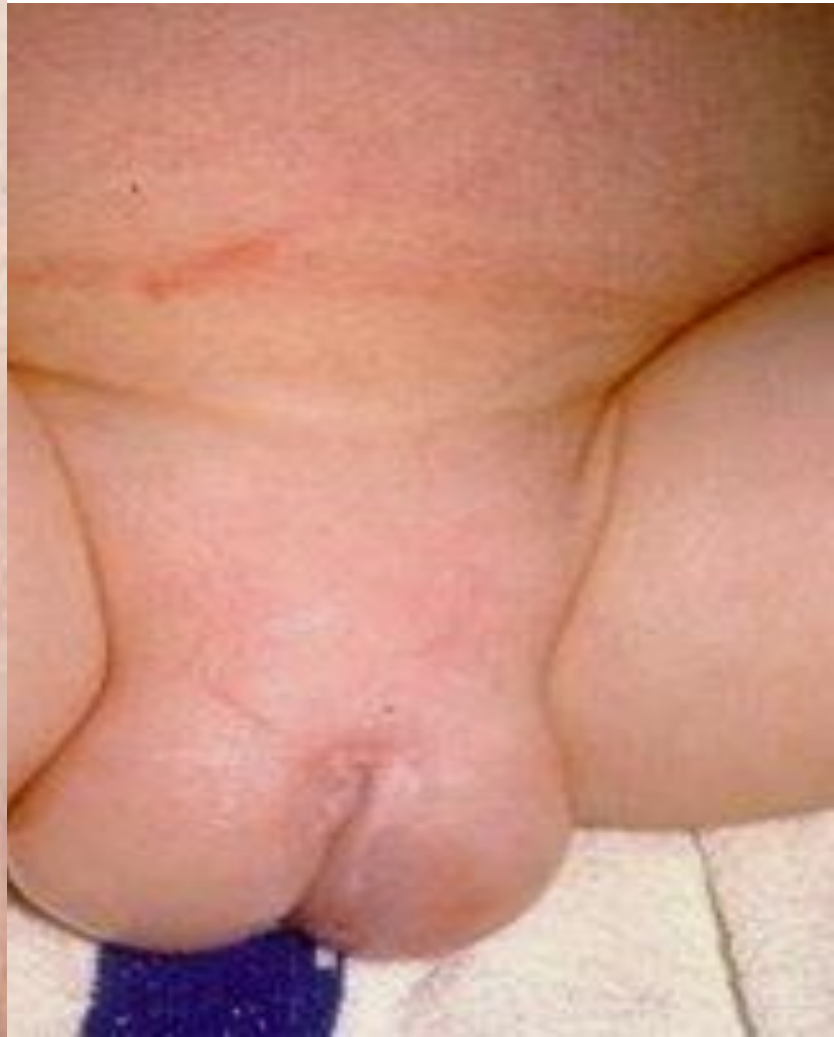


Oedma of genitalia

Scrotal oedema



Labial oedema

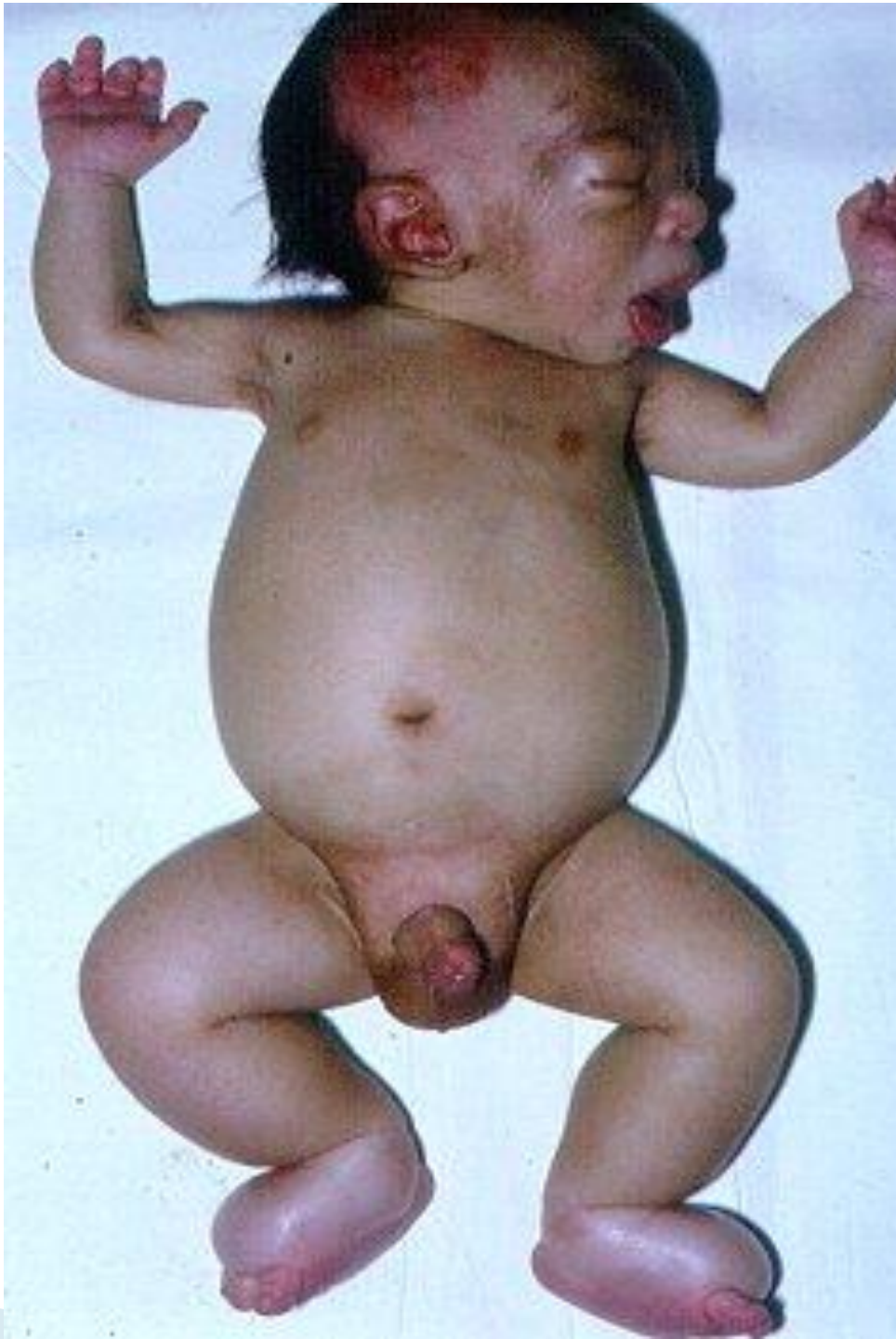


Congenital NS

= Onset in first 3 months

Baby with anasarca

= generalised oedema



Investigations

- Urine
  - Urine dipstick 3-4+ proteins,
    - May have haematuria
  - Urine microscopy- hyaline or lipid casts
  - Urine protein: creatinine ratio >0.2g/mmol
- Blood
  - Serum albumin, urea and electrolytes
  - Cholesterol
  - Complement C3 and C4

Investigations

- Blood
  - ASO Titre, Anti DNAse B
  - TPHA/RPR
  - Hepatitis B and C serology
  - CMV serology
  - HIV
  - Malaria antigen
  - Autoimmune screen

Kidney biopsy

Indications for renal biopsy

- Steroid resistant –Not responding to treatment after 4 weeks of steroid therapy
- Hypocomplementaemia
- Family history of nephrotic syndrome
- Renal impairment and persistent hypertension
- Secondary NS
- Age of presentation <2 years or >6 years

Treatment of Nephrotic Syndrome

Supportive non specific treatment

- **Infections**
  - Complete immunizations before immunosupressive treatment
  - Pneumococcal vaccine
- **Volume depletion or volume overloaded-**
  - IV fluid if volume contracted or
  - Lasix for volume overload + oliguria / to prevent acute renal failure
- **Protein malnutrition**
  - No fluid restriction; salt intake restricted
  - Protein intake not restricted, except for advanced renal failure
  - Supplemental vitamins and minerals

Supportive treatment for non-remitting NS

- **Reno-protection – ACEI**
  - Monitor proteinuria – aim to decrease proteinuria
  - Monitor K and renal function
- **Thrombotic risk**
  - Aspirin for prevention of arterial thrombosis
- **Decreased levels of carrier proteins/hormones**
  - Iron supplementation
  - Supplement Vit D + Ca
  - Treat hypothyroidism if present
- **Hyperlipidaemia**
  - Limit cholesterol, saturated fat intake (± statin)

Steroid treatment

- Prednisone start: 2 mg/kg/day for 4 weeks
- Taper over 3-4 months – steroid treatment on alternate days
- Refer if
  - No response = steroid resistant
  - Relapses within 14 days after drug is stopped = steroid dependant
  - Relapses more than 3 per year = frequently relapsing NS

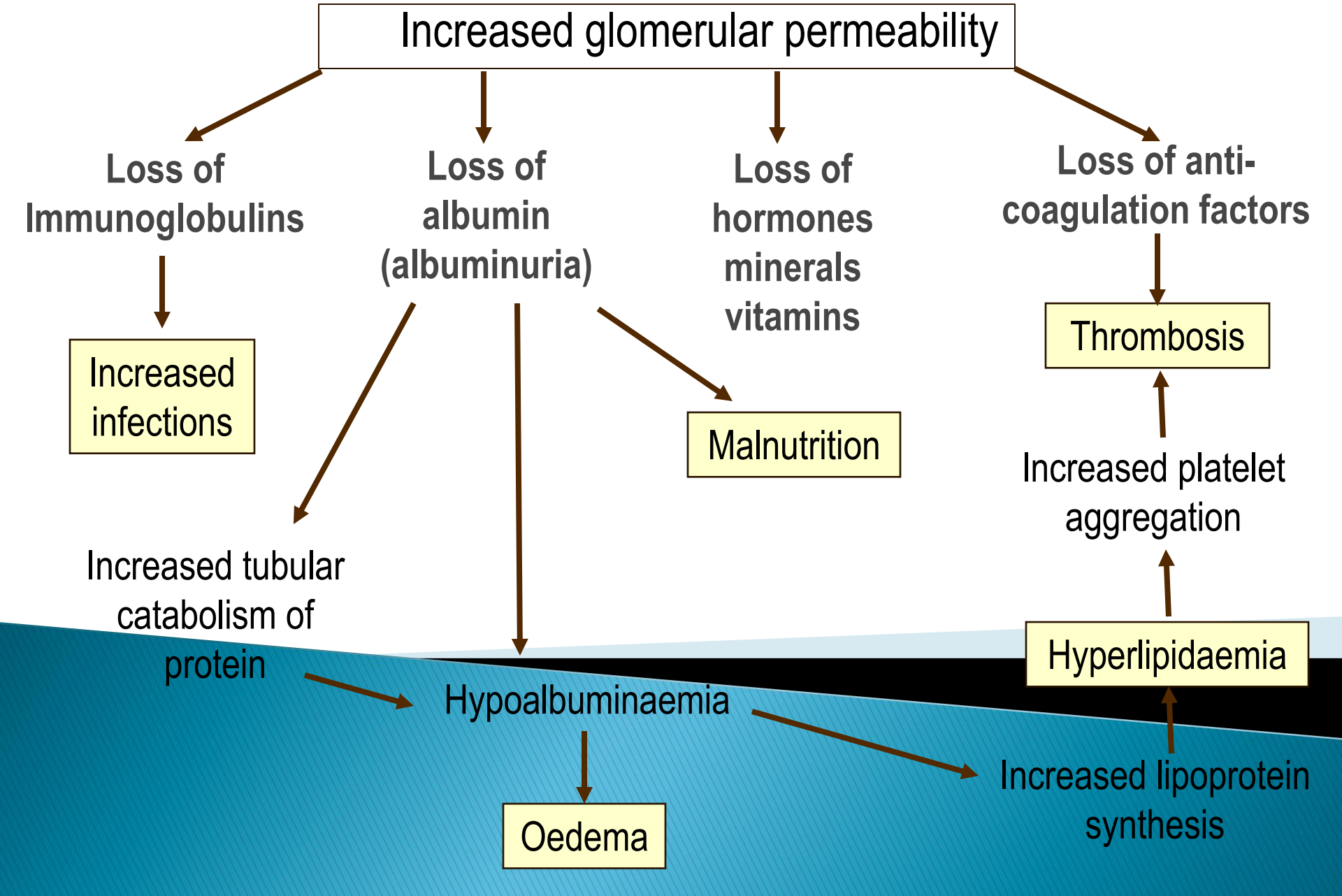
Treatment of NS

- For Secondary causes of NS e.g
  - Infections- HIV ,Hepatitis B and C,

    -Congenital syphilis, Malaria

Treat the specific cause

Consequences of Massive Proteinuria



Complications of Nephrotic Syndrome

- Infections
  - Capsulated organisms e.g. *S pneumoniae*
  - peritonitis, septicaemia & cellulitis
- Thrombosis
- Hernias

Complications of Nephrotic Syndrome

- Protein malnutrition
- Decreased levels of carrier proteins→
  - Hypothyroidism
  - Rickets
  - Iron deficiency

References

1. Johnson RJ, Feehally J. Comprehensive Clinical Nephrology. 2nd ed. London: Mosby; 2003
2. Jalanko H. Pathogenesis of Proteinuria: Lessons learned from nephrin and podocin. Pediatr Nephrol 2003; 18:487–491
3. D'Amico G, Bazzi C. Pathophysiology of Proteinuria. Kidney Int 2003; 63:809–825
4. Kliegman RM, Behrman RE, Jenson HB, Stanton BF.Nelson textbook of paediatrics. 18th ed. Saunders;2007
5. Rees L, Webb NJA, Brogan PA. Paediatric nephrology.1st ed. New york: Oxford; 2007
6. Coovadia 's paediatrics and child health