DEFINITION

- According to ISKDC (International Study of Kidney Disease in Children) it is defined as

1. Massive proteinuria - 40 mg/m^2/hr (50 mg / kg / d or 3.5 gm/day)
2. Hypoalbuminemia (< 2.5g/dl)
3. Hypercholesterolemia (>220 mg/dL)

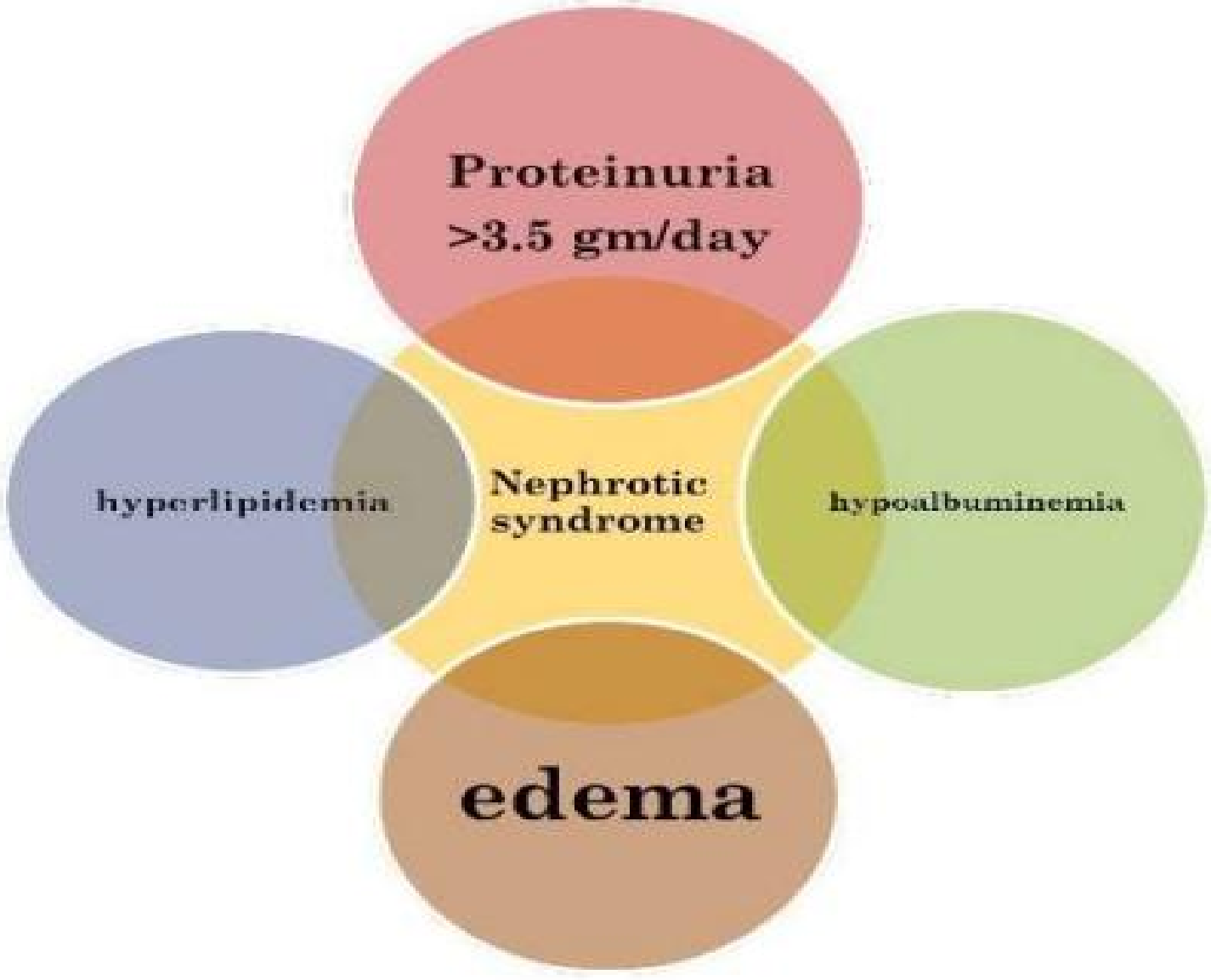
With or without

4. Edema

Nephrotic syndrome is a clinical complex characterized by a number of renal and extra renal features, most prominent of which are

- Proteinuria (in practice > 3.0 to 3.5gm/24hrs),
- Hypoalbuminemia,
- Edema,
- Hypertension
- Hyperlipidemia,
- Lipiduria and
- Hypercoagulabilty.

NEPHROTIC SYNDROME IS NOT A DISEASE



Classification

Nephrotic syndrome can be

- Primary, being a disease specific to the kidneys,
- Secondary, being a renal manifestation of a systemic general illness

Primary causes

Primary causes include-

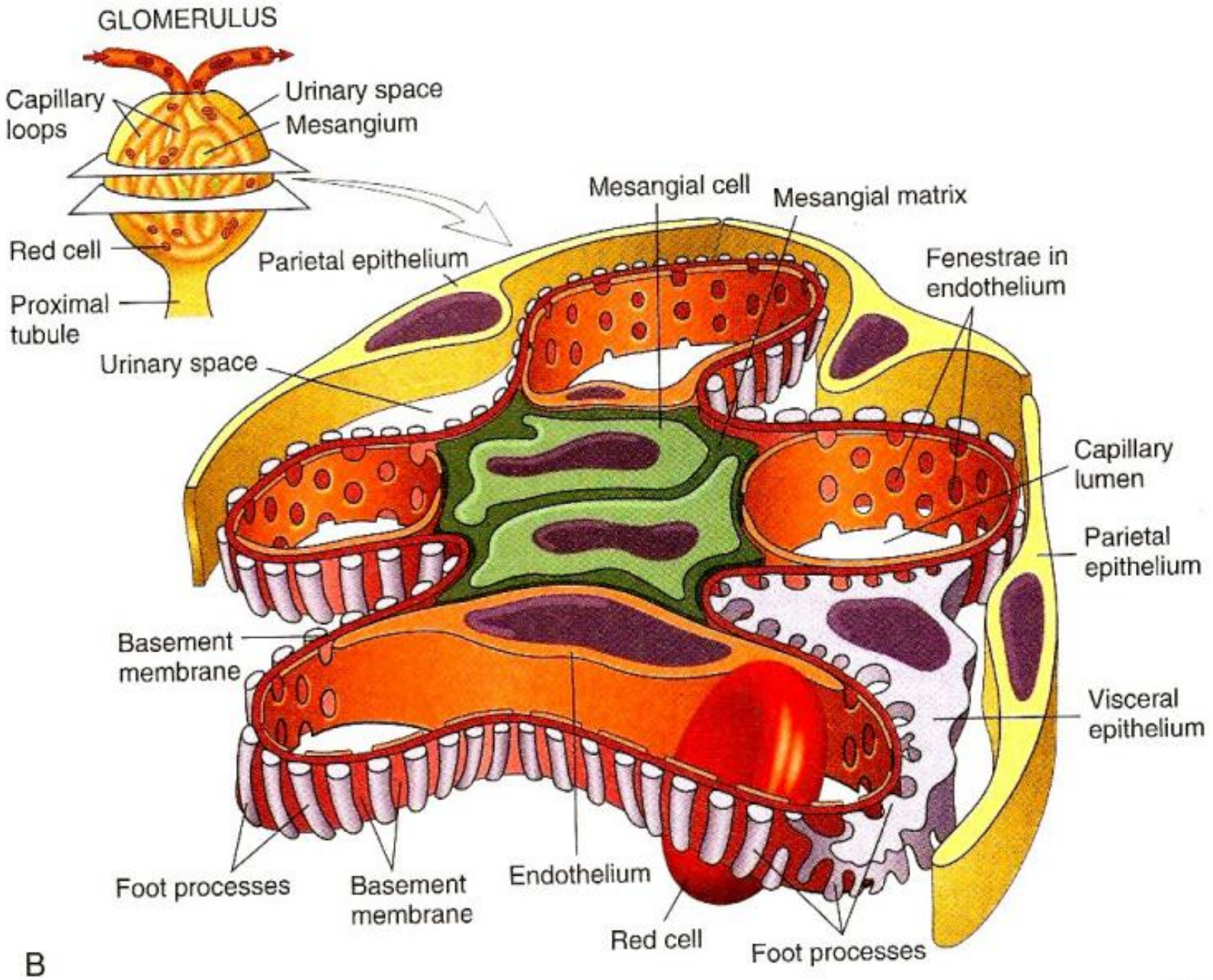
- Minimal-change nephropathy (70-90% children and 10- 15% in adult)
- Focal segmental glomerulosclerosis (FSGS)(15% in adult)
- Membranous nephropathy (30% in adult)
- Mesangial proliferative glomerulonephritis .
- Rapidly progressive glomerulonephritis

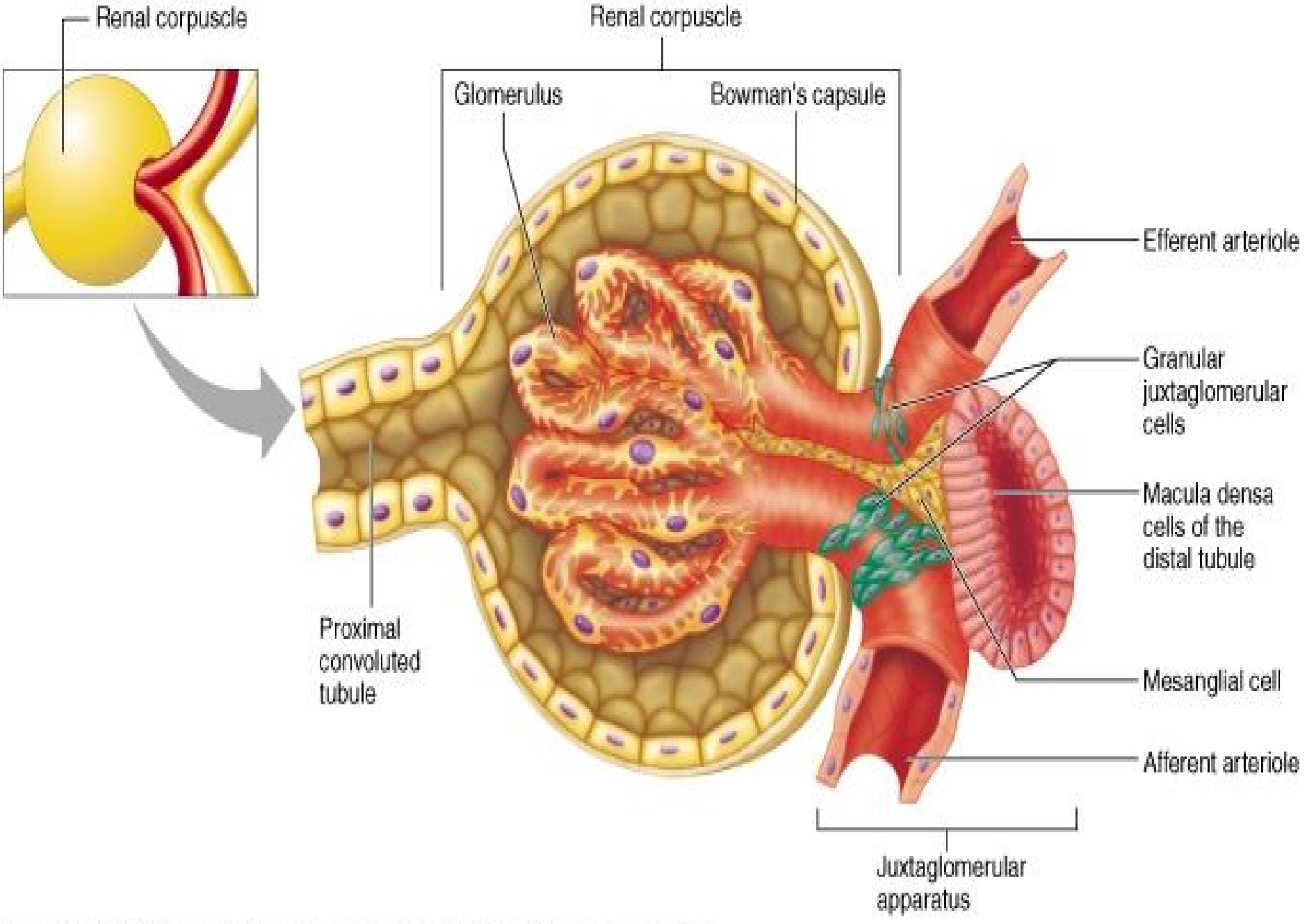
Secondary causes

Secondary causes include-

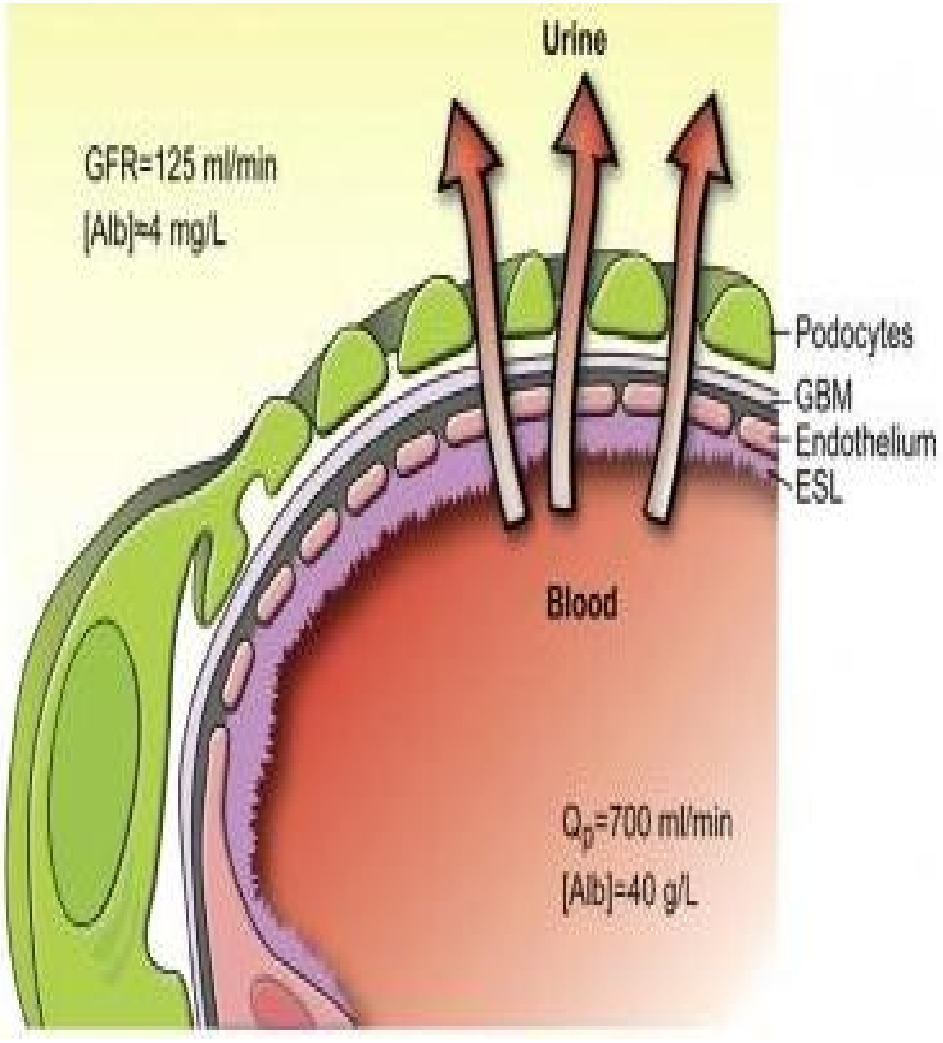
- Diabetes mellitus
- Lupus erythematosus
- Amyloidosis and paraproteinemias
- Viral infections (eg, hepatitis B, hepatitis C, HIV)
- Preeclampsia

- Nephrotic syndrome is 15 times more common in children
- Most cases in children are due to minimal-change disease.
- In adults, the most common form is membranous glomerulonephritis, followed by FSGS.
- Diabetic nephropathy is emerging as a major cause of nephrotic syndrome





• In a healthy individual, less than 0.1% of pl. albumin may traverse the glomerular filtration barrier.



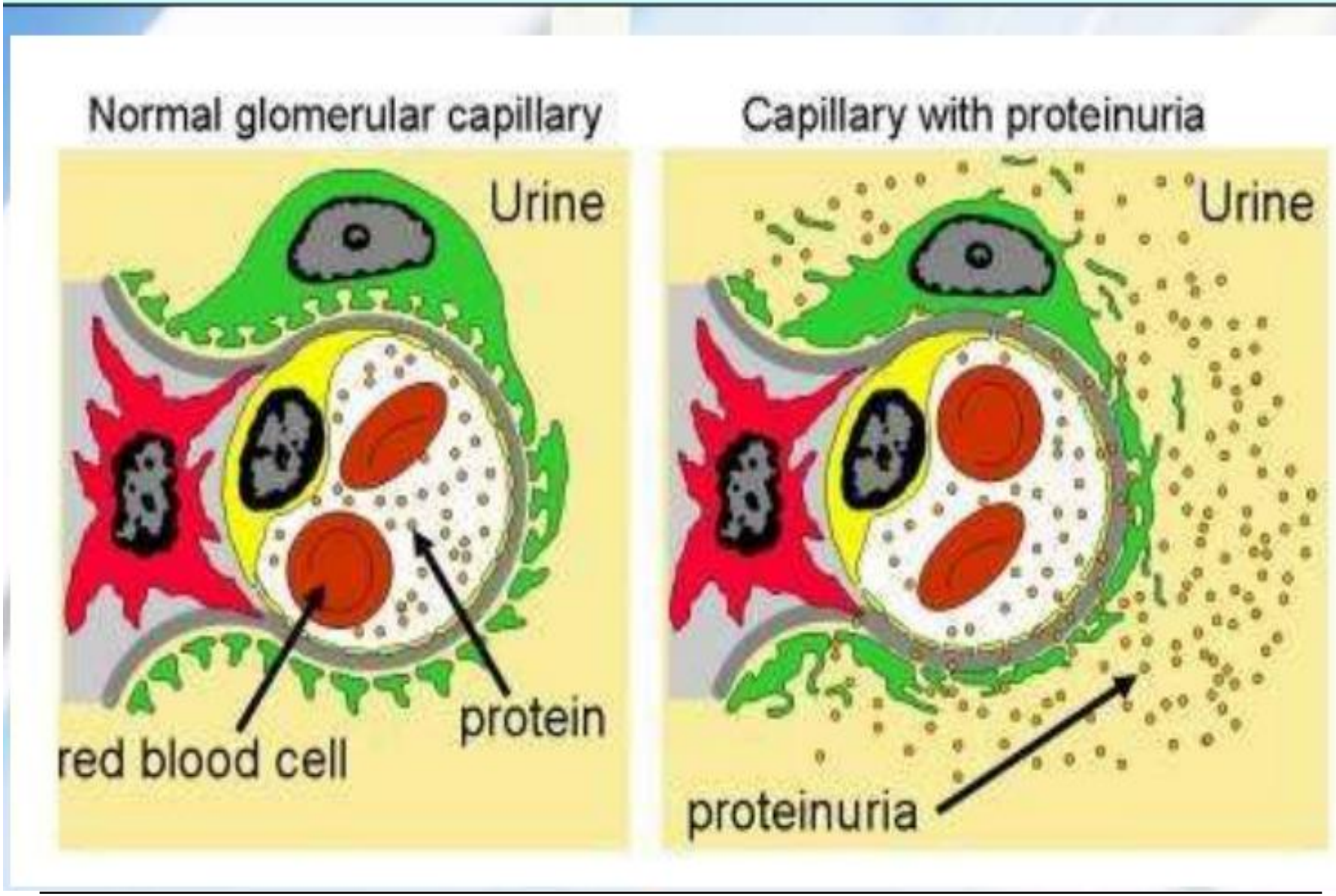
•Glomerular capillaries are lined by a fenestrated endothelium that sits on the glomerular basement membrane

•Which in turn is covered by glomerular epithelium, or podocytes, which envelops the capillaries with cellular extensions called foot processes.

•In between the foot processes are the filtration slits.

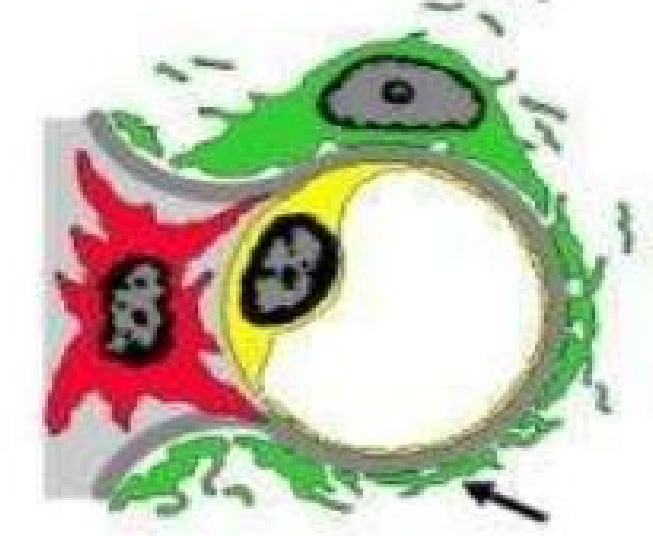
•These 3 structures are the glomerular filtration barrier

1. Minimal Change Disease (85%)

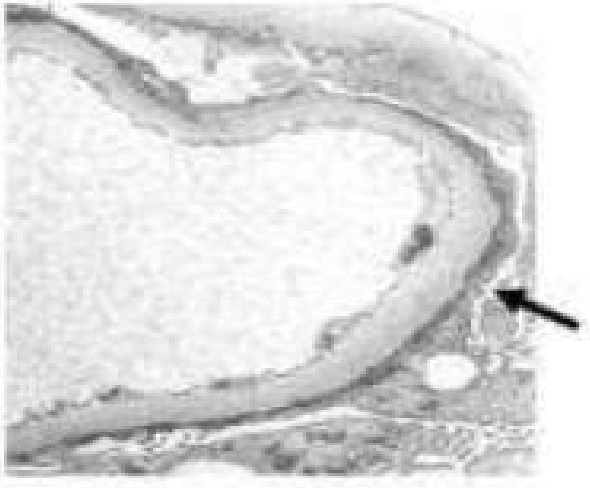


1. Minimal Change Disease (85%)

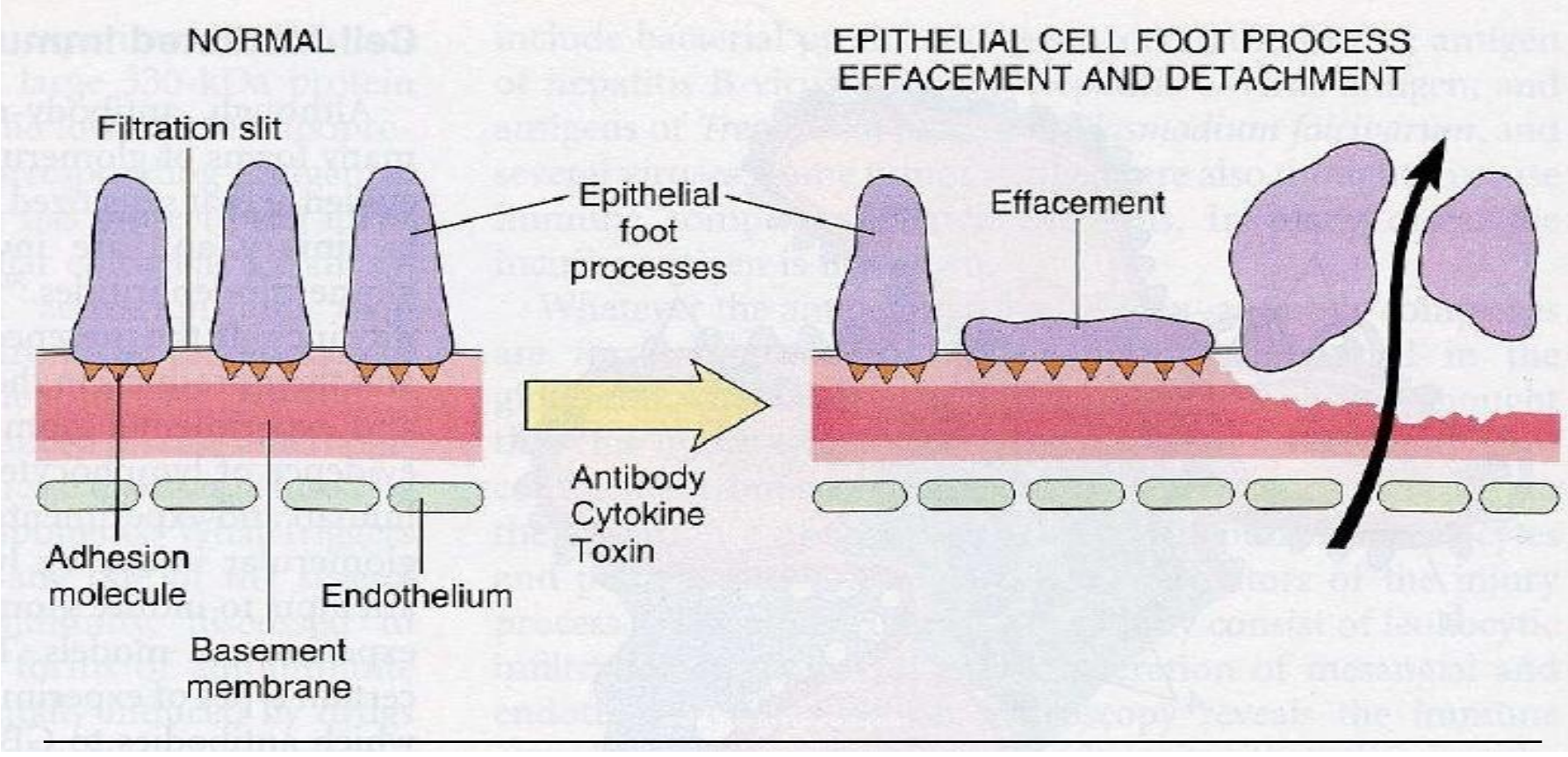
By electron microscopy, a normal glomerular capillary has separate foot processes (arrows).



A minimal change disease glomerular capillary has fused foot processes (arrow).



- Idiopathic, Drugs, Malignancy, especially Hodgkin's lymphoma,
- Hepatitis C, autoimmune disease (SLE), and diseases of intraglomerular coagulation



Pathophysiology of NS

Increased permeability of glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia.

In MCNS :

T Cell dysfunction leads to alteration of cytokines which causes a loss of negatively charged glycoproteins within capillary wall

In FSGS:

A plasma factor produced by lymphocytes responsible
Mutations in podocyte proteins (podocin, a – actinin 4)

In Steroid resistant NS:

Mutations in NPHS 1(nephrin) & 2(podocin) and WT1 or ACTN4 (α-actinin) genes

Pathophysiology of proteinuria

- The glomerular structural changes that may cause proteinuria are damage to the endothelial surface, the glomerular basement membrane, or the podocytes.

- Glomerular haemodynamics (Intraglomerular hypertension and hyperfiltration) can alter Glomerular permeabiality.

- **Selectivity of proteinuria-** Excretion of relatively low M.W. protein (Albumin or transferrin) is known as selective proteinuria while if excretion is predominately high M.W. protein (IgG, IgM or α2 macroglobulin) it is nonselective proteinuria

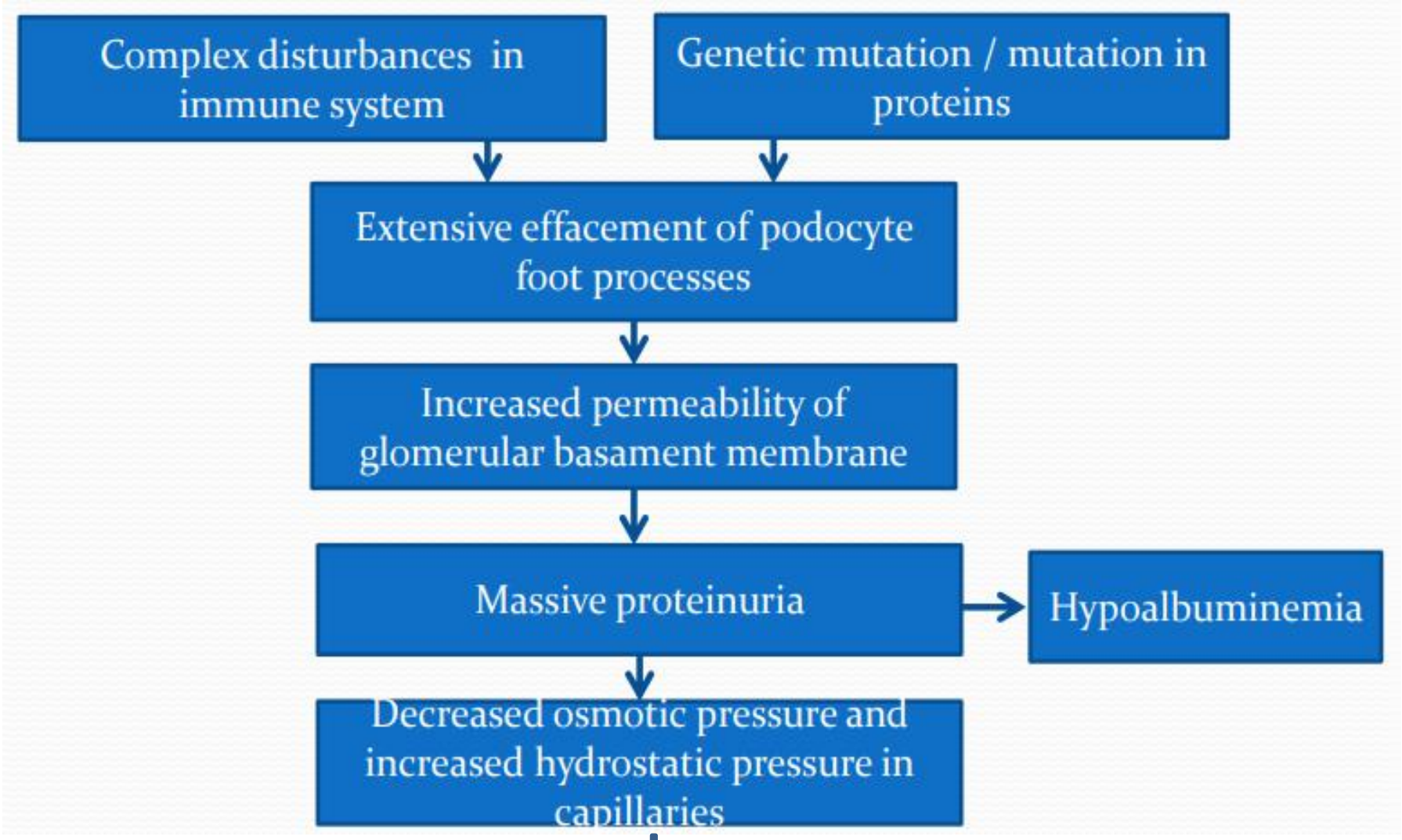
- It is also related to relative damage of Glomerular filter.
- If there is predominantly loss of charge selectivity → selective proteinuria.
- If there is predominantly loss of size selectivity → nonselective proteinuria
- A clearance of IgG > 20% of transferrin or albumin represents nonselective proteinuria and < 10% is selective proteinuria.
- Proteinuira leaking through damaged glomeruli are toxic to renal tubules.
- So every attempts should be made to prevent and reduce proteinuria irrespective of serum protein level or basic disease

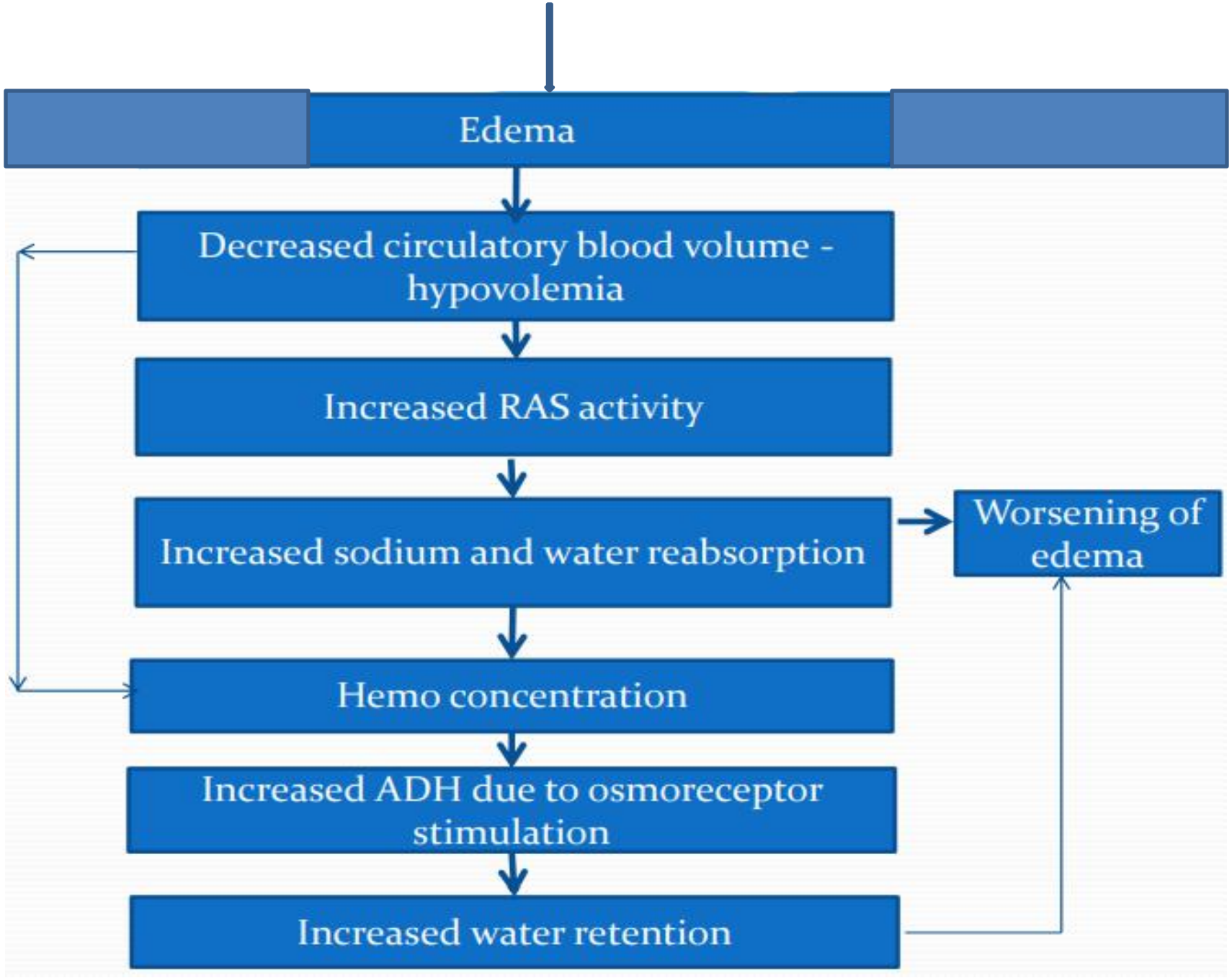
Hypoalbunemia

- It is due to both the proteinuria and due to the increase renal catabolism (in tubules).

- In fact hepatic albumin synthesis is increased from 145±9mg/kg/day to 213±17mg/kg/day in nephrotic patients.

Pathogenesis of edema





Metabolic consequences of proteinuria

- Metabolic consequences of the nephrotic syndrome include the following:

  Infection

  Hyperlipidemia and atherosclerosis

  Hypocalcemia and bone abnormalities

  Hypercoagulability

  Hypovolemia

Infection in Nephrotic Syndrome

Proposed explanations include the following:

- Urinary immunoglobulin losses
- Edema fluid acting as a culture medium
- Protein deficiency
- Decreased bactericidal activity of the leukocytes
- Immunosuppressive therapy
- Urinary loss of a complement factor (properdin factor B) that opsonizes certain bacteria

Hyperlipedemia

- Due to increase hepatic lipoprotein synthesis that is triggered by reduced oncotic pressure.
- Defective lipid catabolism has also important role.
- LDL and cholesterol are increased in majority of patients whereas VLDL and triglyceride tends to rise in patients with severe disease.
- It increases the relative risk for MI 5.5 fold and coronary death 2.8 fold.
- It also increases progression of renal disease

Hypercoagulability

- Multifactorial in origin
- Increase urinary loss of antithrombin III.
- Altered levels and/or activity of protein C & S.
- Hyperfibronogenemia due to increase hepatic synthesis.
- Impaired fibrinolysis due to decrease plasminogen.
- Increase platelet aggregability – relative immobility - haemoconcentragtion from hypovolemia. – hyperlipidemia
- Alteration in endothelial function

Hypocalcemia

- Hypocalcemia is common in the nephrotic syndrome, but rather than being a true hypocalcemia, it is usually caused by a low serum albumin level.

- Nonetheless, low bone density and abnormal bone histology are reported in association with nephrotic syndrome.

- This could be caused by urinary losses of vitamin D–binding proteins, with consequent hypovitaminosis D and, as a result, reduced intestinal calcium absorption

Hypovolemia

- Hypovolemia occurs when hypoalbuminemia decreases the plasma oncotic pressure
- Resulting in a loss of plasma water into the interstitium and causing a decrease in circulating blood volume.
- Hypovolemia is generally observed only when the patient's serum albumin level is less than 1.5 g/dL.
- Hypotension is a late feature

FUNCTIONAL CONSEQUENCE OF URINARY LOSS OF PLASMA PROTEIN

- Thyroid binding globulins and thyroxin – may lead to hypothyroidism.
- Vit D binding protein – osteomalacia, but rare
- Total calcium is also low due to low albumin level.
- Transferrin and erythropoietin and – microcytic hypochromic anaemia.
- ARF – is rare in nephrotic syndrome. In whom it occur patient are elderly of minimal changes disease / FGSS

Clinical Features

COMMON:

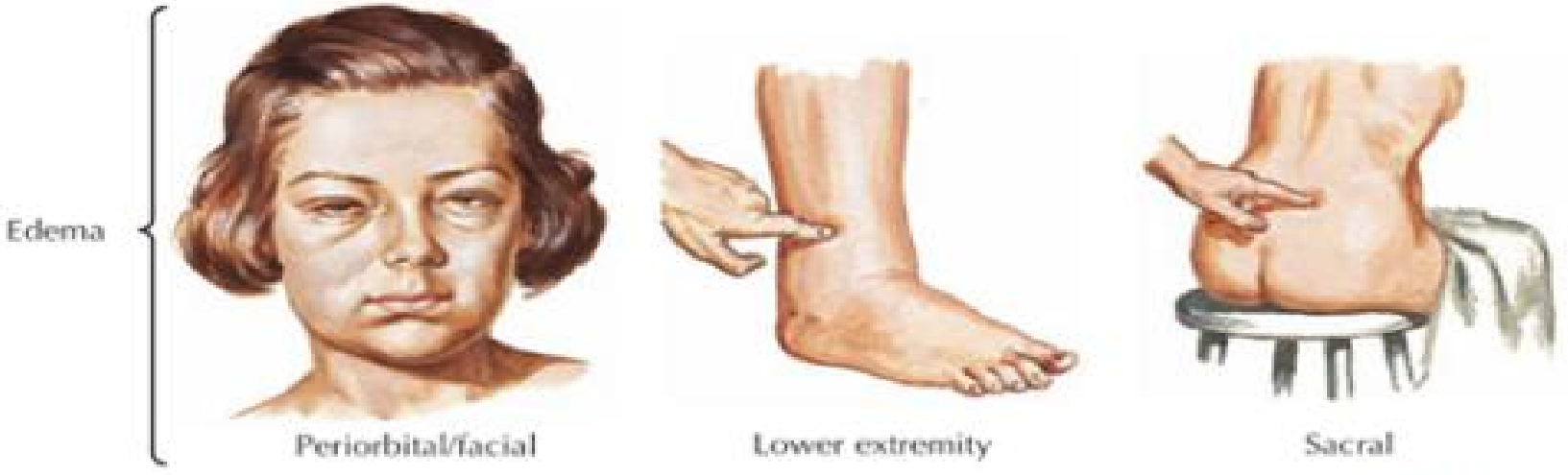
- Anorexia, irritability, abdominal pain, diarrhoea and genital edema
- Frothy urine (high concentrations of protein)
- Edema may cause dyspnea (pleural effusion or laryngeal edema),
- Chest discomfort (pericardial effusion), arthralgia (hydrarthrosis), or abdominal pain (ascites or, in children, mesenteric edema).
- Edema may obscure signs of muscle wasting and cause parallel white lines in fingernail beds (Muehrcke's lines).

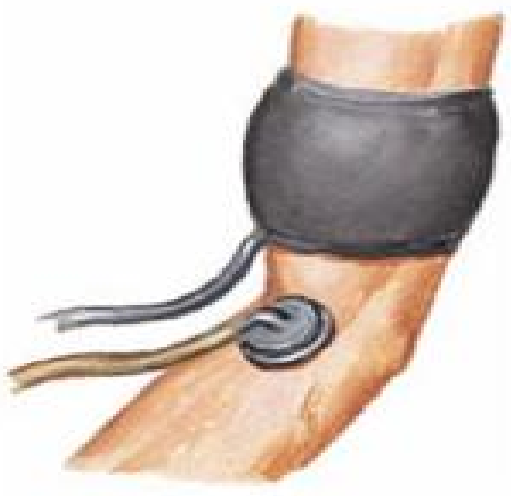
UNCOMMON:

- Hypertension, Gross hematuria

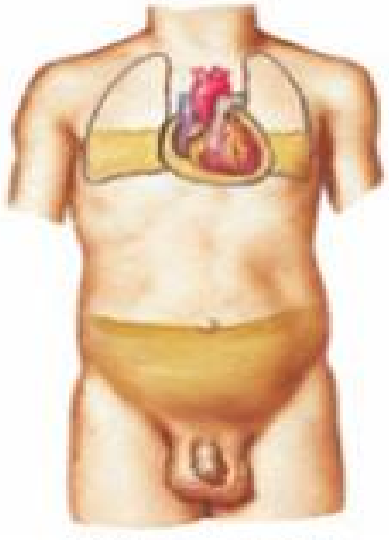
Presentation and Diagnosis of Nephrotic Syndrome

Signs and symptoms



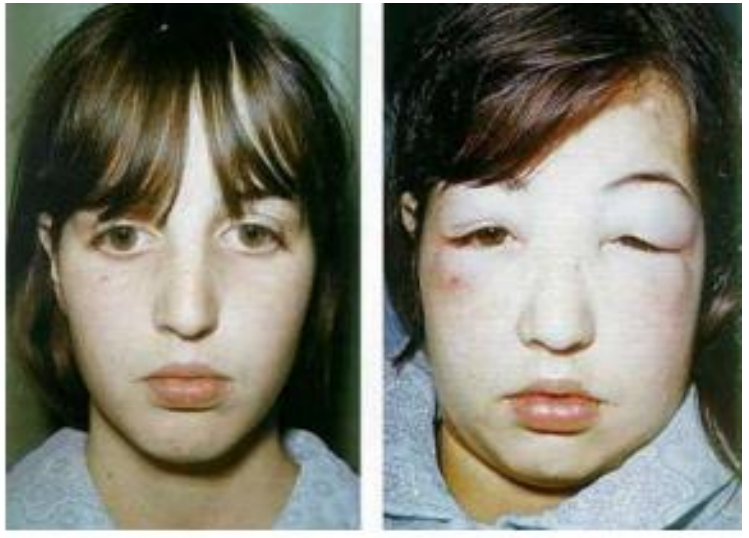


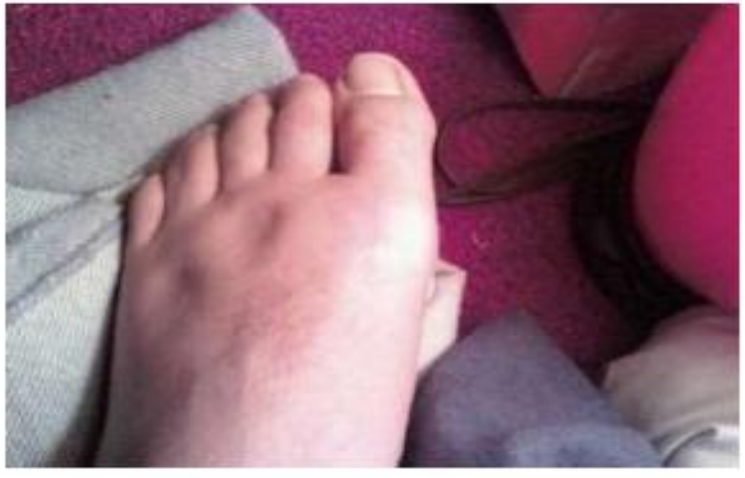
Hypertension
(minority of patients)



Pulmonary edema, pleural effusion, ascites, anasarca in severe cases

- Prolonged NS may result in nutritional deficiencies, including protein malnutrition
- Myopathy
- Decreased total Ca^{+2}, tetany
- Spontaneous peritonitis and opportunistic infections
- Coagulation disorders, with decreased fibrinolytic activity





Differential Diagnosis

- Heart failure
- Cirrhosis
- Glomerulonephritis
- Protein losing enteropathy
- PEM

INVESTIGATIONS

Urine Analysis

- Routine exam. : 3+ or 4 + proteinuria
- 24 hour urine protein >3.0 gm or 40 mg/m²/hr
- Spot Urine protein/creatinine ratio : > 2.0
- Urine protein selectivity
- Hyaline casts
- Microscopic hematuria in 20%

Proteinuria - Parameters

Urine routine:

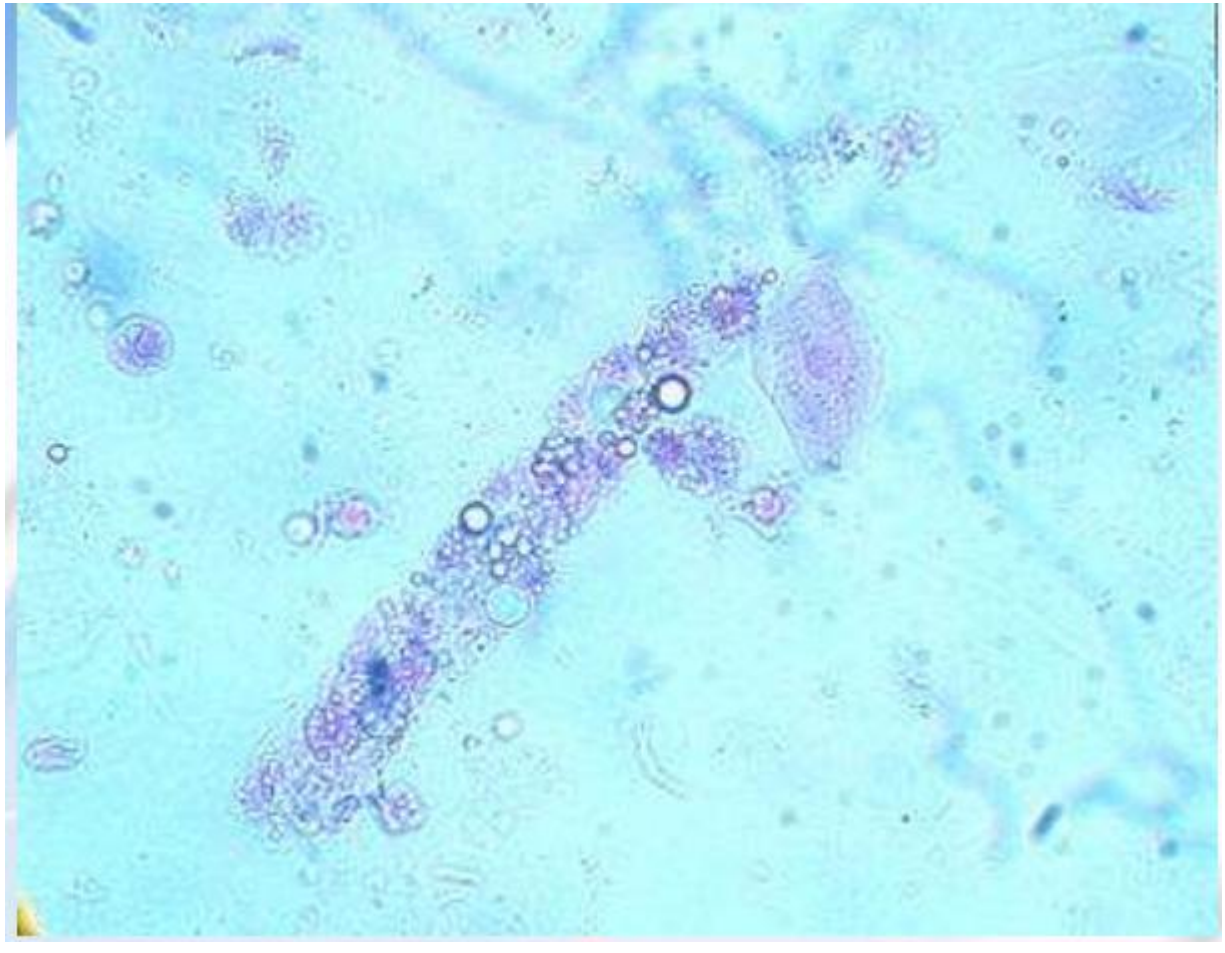
1 + = 30 mg / dL
2 + = 100 mg / dL
3 + = 300 mg / dL
4 + = > 2 g / dL

24 hour Urine Protein Estimation:

Mild : < 500 mg / m^2 / d
Moderate : 500 – 1000 mg / m^2 / d
Massive : > 1000 mg / m^2 / d

40 mg / m^2 / hr
(Normal = 4 mg / m^2 / hr)
[> 3 g / d]

Hyaline Cast in urine



Blood

- S.Cholesterol (> 250 mg/dL)
- S.Albumin (< 2.5 gm/dl)
- S. A/G ratio – reversal
- S.Creatinine
- Bl. Urea
- S . C3 and C4 levels
- CBC : Increased Hb, Platelets, Hct

BLOOD

- Serum proteins -Total proteins decreased
- Serologic studies for infection and immune abnormalities

OTHER INVESTIGATIONS:

- Renal ultrasonography
- Renal biopsy
- CXR: – Pleural effusion
  – Pulm edema - rare

MANAGEMENT

Specific treatment

- In minimal-change nephropathy, glucocorticosteroids, such as prednisone, are used. Children who relapse may be treated with rituximab
- In some lupus nephritis, prednisone and cyclophosphamide are useful
- Secondary amyloidosis with nephrotic syndrome may respond to antiinflammatory treatment of the primary disease.
- In membranous nephropathy, expectant management without immunosuppression can be used for the first 6 months, in patients at low risk for progression (ie, those with serum creatinine level < 1.5 mg/dL).
- Patients with renal insufficiency (serum creatinine level > 1.5 mg/dL) are at greatest risk for the development of end-stage renal disease and should receive immunosuppressive therapy. [3

DIET AND ACTIVITY

- The diet in patients with nephrotic syndrome should provide adequate energy (caloric) intake and adequate protein (1-2 g/kg/d).
- A diet with no added salt will help to limit fluid overload.
- Management of hyperlipidemia could be of some importance if the nephrotic state is prolonged.
- Fluid restriction per se is not required.
- Ongoing activity, rather than bed rest, will reduce the risk of blood clots

Acute Nephrotic Syndrome in Adults

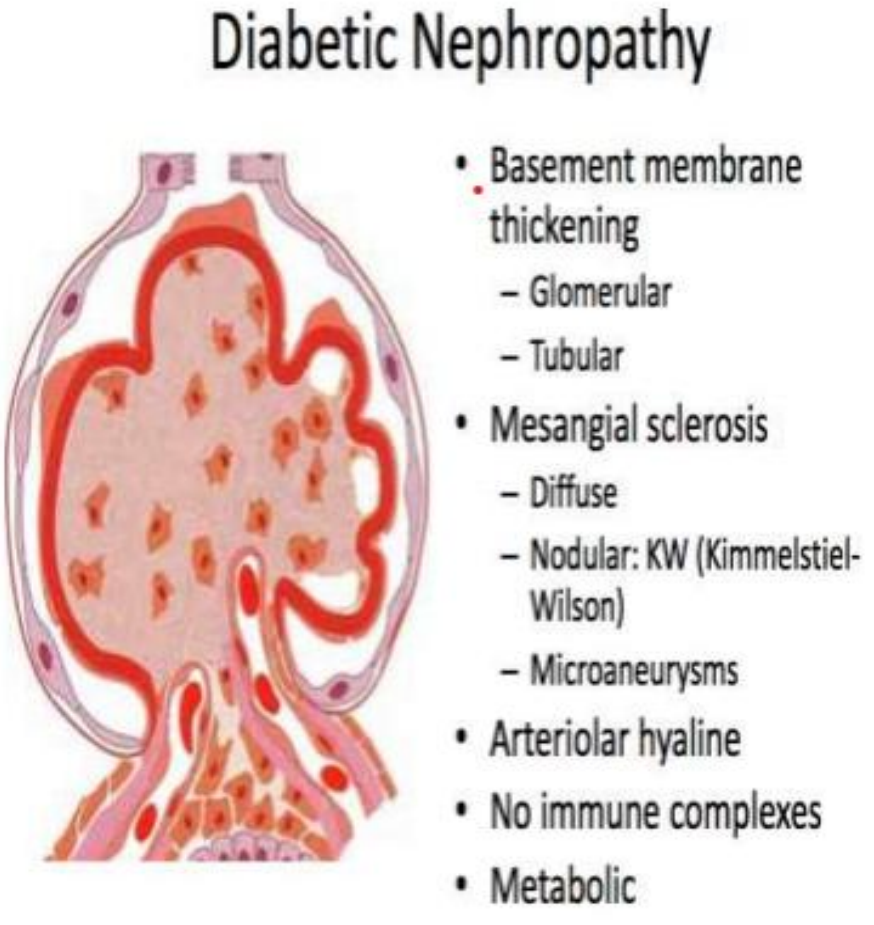
- Diuretics will be needed; furosemide, spironolactone, and even metolazone may be used. Volume depletion may occur with diuretic use, which should be monitored.
- Anticoagulation has been advocated by some for use in preventing thromboembolic complications,
- Hypolipidemic agents may be used, but if the nephrotic syndrome cannot be controlled, the patient will have persistent hyperlipidemia.
- ACE inhibitors and/or ARB are widely used. These may reduce proteinuria by reducing the systemic blood pressure, by reducing intraglomerular pressure, and also by direct action on podocytes

Management

- Long-Term Monitoring- Follow-up care in patients with nephrotic syndrome includes
- Immunization
- Treatment of relapses of steroid-responsive nephrotic syndromes,
- Monitoring for steroid toxicity, and
- Monitoring of diuretic and angiotensin antagonist regimens.

DIABETIC NEPHROPATHY

- The earliest morphologic abnormalities in nephropathy are thickening of the GBM and expansion of mesangium.
- Composition of GBM is altered with loss of heparan sulfate moities.
- Prominent nodular matrix expansion (classical Kimmelsteil-Wilsonlesion) are often found.



Case Scenario 1

A 5yrs old boy came with c/o generalized swelling for 7 days along with oliguria for same duration. On examination, patient **was grossly edematous, mildly pale, BP-100/50 mm of Hg (both SBP &DBP on 50th centile), BSUA(+++).** Anthropometrically he is well thriving, **signs of ascites present**, other systemic examination revealed no abnormality