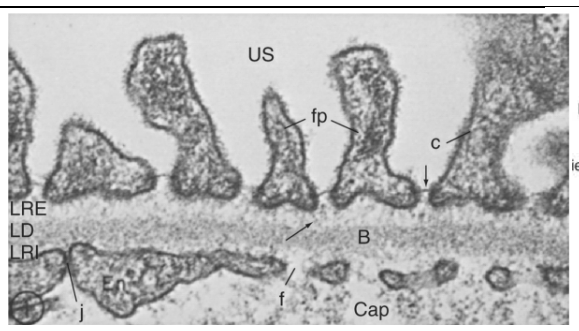
Nephrotic syndrome

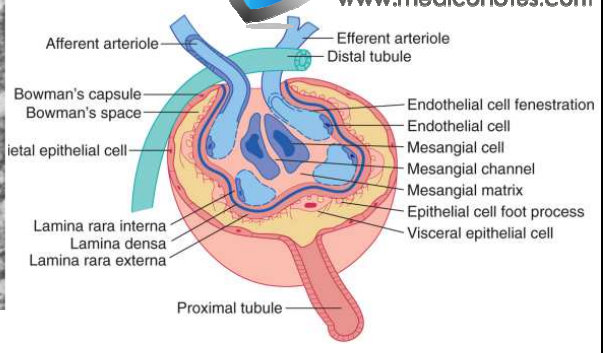
1- Glomerular capillaries are lined by **endothelial cells** , that contains **"fenestrations"**

2- Glomerular basement membrane (GBM) forms a continuous layer between :
- Endothelial and mesangial cells on one side and
- Epithelial cells on the other.

The membrane has 3 layers:
(1) Central lamina densa
(2) Lamina rara interna, which lies between the lamina densa and the endothelial cells
(3) Lamina rara externa, which lies between the lamina densa and the epithelial cells.

3- Visceral epithelial cells (Podocytes) cover the capillary and project cytoplasmic "foot processes," which attach to the lamina rara externa → between the foot processes **"filtration slits"**





- **Mesangium (mesangial cells and matrix)** lies between the glomerular capillaries on the endothelial cell side of the GBM and forms the medial part of the capillary wall.
  - The mesangium may serve as a supporting structure for the glomerular capillaries and probably has a role in :
    1- Regulation of glomerular blood flow and filtration and
    2- Removal of macromolecules (such as immune complexes) from the glomerulus, either through → a- intracellular phagocytosis or b- by transport through intercellular channels to the juxtaglomerular region.
- **Bowman's capsule**, which surrounds the glomerulus, is composed of
  (1) a basement membrane, which is continuous with the basement membranes of the glomerular capillaries and the proximal tubules
  (2) the parietal epithelial cells, which are continuous with the visceral epithelial cells.

- The endothelial cell, basement membrane, and epithelial cell of the glomerular capillary wall possess strong **negative ionic charges**.
  These charges are a consequence of two negatively charged moieties: **1- Proteoglycans (heparan sulfate) 2- Glycoproteins containing sialic acid.**
- Proteins in the blood carry a net **negative charge** → Consequently, they are repelled by the negatively charged sites in the glomerular capillary wall → thus restricting filtration.

Types of Nephrotic syndrome :

1- Primary Idiopathic nephrotic syndrome (90%) :
- **Minimal change nephrotic syndrome** (MCNS) is the most common histologic form
- More than 80% of children under 7 years of age with nephrotic syndrome have MCNS.

2- Secondry nephrotic syndrome (10%) :
- may be seen with systemic lupus erythematosus, Schönlein-Henoch purpura, infections (hepatitis B, hepatitis C, malaria), Wegener and other vasculitides, allergic reactions, diabetes, amyloidosis, malignancies, congestive heart failure, constrictive pericarditis, renal vein thrombosis.

3- Congenital Nephrotic syndrome :
- The Finnish type is an autosomal recessive disorder most common
- presents during the first 2 months of life.
- Prenatal onset is supported by ↑ of maternal alpha-fetoprotein.

Pathogenesis :

- The underlying abnormality in nephrotic syndrome is an **increase in permeability of the glomerular capillary wall**, which leads to → massive proteinuria and hypoalbuminemia.
- The cause of the increased permeability is not well understood, THYOERIS :

A. In minimal change disease :
1- It is possible that **T-cell dysfunction** leads to alteration of cytokines, which causes → **loss of negatively charged glycoproteins** within the glomerular capillary wall.
2- **Certain HLA types** (HLA-DR7, HLA-B8, and HLA-B12) are associated with an increased incidence of NS.

B. In focal segmental glomerulosclerosis :
1- **A plasma factor** (produced by lymphocytes) may be responsible for the increase in capillary wall permeability.
2- Mutations in podocyte proteins **(podocin, α-actinin 4).**

Pathophysiology:

1- Proteinuria :

- In patients with NS, the structural changes:
  (1) damage to the endothelial surface, causing loss of the -ve charge.
  (2) damage to the GBM
  (3) effacement of the foot processes.
  Leading to increased glomerular capillary wall permeability → large amounts of protein (primarily albumin) cross the barrier and are excreted

Types of proteinuria	
(Highly) selective proteinuria	**Non- selective proteinuria:**
the damage of glomeruli is mild and the permeability of GBM would be selectively altered → increasing capillary transport of anionically charged particles(albumin et al)	injuries of the glomeruli are severe, both: • Small (albumin, transferrin) & • Large proteins (α_2- macroglobulin) can pass through the GBM

2- Hypoproteinemia :

- Increased urinary loss of proteins is the main cause
- Other factors:
  - The capacity to increase hepatic synthesis appears insufficient to compensate for the large urinary losses.
  - Increased protein catabolism.

A- Edema :
- Hypoalbuminemia, which causes a **decrease in the plasma oncotic pressure** and transudation of fluid from the intravascular compartment to the interstitial space.
- **Edema is enhanced by:** (which causes massive generalized edema)
  The reduction of intravascular volume which causes:
  1- Decreases **R**enal **P**erfusion **P**ressure, → **activating renin-angiotensin-aldosterone system**→stimulates tubular reabsorption of Na .
  2- The reduction in intravascular volume → **stimulates release of ADH** → enhances the reabsorption of water in the collecting duct.
- **Recent opinions:**
  primary renal disturbance (reduced GFR) → primary renal retention of sodium and water
  - suppression of the renin- angiotensin-aldosterone system
  - Expansion of plasma → increased capillary hydrostatic pressure → extravasation of fluid into the interstitial space edema

B- Other effects :
- **Like albumin, the concertration of other plasma proteins are decreased:**
  - IgG and some components of complement → **decreased immunity**
  - Some anti-coagulant factors → **hypercoagulability state**
  - Vitamin D combining protein → **hypocalcemia**
  - Transferrin → **anemia**

3- Hyperlipidemia :

- **Serum lipid levels(cholesterol, triglycerides)** are elevated for two reasons:
  1- Hypoalbuminemia stimulates generalized hepatic protein synthesis, including **synthesis of lipoproteins.**
  2- Increased urinary losses of enzyme **"lipoprotein lipase"** → reduced plasma levels of this enzyme → Lipid catabolism is diminished.
- **Two pathologic patterns:**
  1- hypercholesterolemia alone and
  2- combined hypercholesterolemia & hypertriglyceridemia .
- **It plays a role in:**
  1- Hypercoagulable state.
  2- Progression of glomerulosclerosis.

Summary of Primary Renal Diseases That Present as Idiopathic Nephrotic Syndrome

	MINIMAL CHANGE NEPHROTIC SYNDROME	FOCAL SEGMENTAL GLOMERULOSCLEROSIS	MEMBRANOUS NEPHROPATHY	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
FREQUENCY[*]					
Children	75%	10%	<5%	10%	10%
Adults	15%	15%	50%	10%	10%
Clinical Manifestations					
Age (yr)	2–6, some adults	2–10, some adults	40–50	5–15	5–15
Sex	2 : 1 male	1.3 : 1 male	2 : 1 male	Male-female	Male-female
Nephrotic syndrome	100%	90%	80%	60%	60%
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria	10–20%	60–80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 yr	50% in 10–20 yr	10–20 yr	5–15 yr
Associated conditions	Allergy? Hodgkin disease, usually none	None	Renal vein thrombosis, cancer, SLE, hepatitis B	None	Partial lipodystrophy
Laboratory Findings	Manifestations of nephrotic syndrome	Manifestations of nephrotic syndrome	Manifestations of nephrotic		
	↑ BUN in 15–30%	↑ BUN in 20–40%	syndrome	Low C1, C4, C3–C9	Normal C1, C4, low
					C3–C9
Immunogenetics	HLA-B8, B12 (3.5)[†]	Mutations in podocin, α-actinin-4, other genes	HLA-DRw3 (12–32)[†]	Not established	C3 nephritic factor Not established
Renal Pathology					
Light microscopy	Normal	Focal sclerotic lesions	Thickened GBM, spikes	Thickened GBM, proliferation	Lobulation
Immunofluorescence	Negative	IgM, C3 in lesions	Fine granular IgG, C3	Granular IgG, C3	C3 only
Electron microscopy	Foot process fusion	Foot process fusion	Subepithelial deposits	Mesangial and subendothelial deposits	Dense deposits
Response to Steroids	90%	15–20%	May be slow progression	Not established	Not established

Clinical manifestations :

- **Age:** 75% of patients <6y at onset with peak age of onset between 2-3y.
- **Sex:** male: female = 2:1-3:2
- **Manifestations :**
  1- Eedema → the major clinical manifestation.
  2- Lethargy, poor appetite, weakness, pallor, diarrhea and occasional abdominal pain.
  3- Hematuria & hypertension are unusual but in a minority of patients.

Edema (soft and pitting in nature) :
- A presenting symptom in 95% of children with NS
- Usually begins insidiously with unexpected weight gain and early morning periorbital swelling → dependent areas (lower extremities, genitals and feet).
- It can develop into generalized and marked edema.
  - "anasarca" : inability to open the eyes.
  - ascites and pleural effusion → respiratory distress , swelling in the abdomen, scrotal or labial areas → prevents walking.
  - decreased urine output.

Classifications :

A- Clinical classification :

1- Simple nephrosis : Only has the 4 major features of NS:
- massive proteinuria,
- hypoalbuminemia,
- marked edema,
- hypercholesterolemia.

2- Nephritic nephrosis → hematuria, azotemia, hypertension, C_3↓
Besides the 4 major features of NS, also has one or more of the following features:
- **Hematuria:** Increased RBCs (>10/HP) in urine are detected for several times (at least in 3 centrifuged urine specimens within 2 weeks)
- **Repeated hypertension:** BP>130/90mmHg in shchool-aged patients, & >120/80 in preshchool-aged patients (not caused by corticosteroids)
- **Persistent azotemia:** BUN>10.7mmol/L (not caused by hypovolemia)
- Repeated or prolonged low serum levels of total complement(CH_{50})or C_3

B- Responsive to steroid therapy (prednisone 1.5~2mg/kg/d) :
1- Complete response: urinary protein negative
2- No response: + + + ~ + + + +
3- Partial response: + ~ + +

Complications :

1- Infections

- Causes:
  - decreased immunity (urinary loss of Ig and C)
  - edema fluid acting as a culture medium
  - immunosuppressive therapy
  - protein deficiency
- The common infectious complications:
  bacterial sepsis, cellulitis, pneumonia, urinary tract infections and primary peritonitis.

2- Hypovolemia

- Causes:
  - Hypoalbuminemia → the plasma oncotic pressure decreases → loss of plasma water into the interstitial space and causing a decrease in circulating blood volume.
  - Diuresis
- Symptoms & signs: restlessness, cold hands and feet, delayed capillary filling, oliguria, tachycardia and Hypotension.

3- Electrolyte disturbances

Hypoonatremia, Hypokalemia, Hypocalcemia

- Causes:
  - Limitations of diet
  - Poor intake
  - GI loss (vomiting and diarrhea)
  - Diuresis

4- Hypercoagulability states and thrombosis

- Causes:
  - Urinary loss of anti-coagulant proteins
  - Hemoconcentration and hypovolemia
  - Hyperlipidemia (increased viscosity) and increased platelet aggregation
  - Elevated coagulation factors
- Renal vein thrombosis is more common
- Pulmonary or cerebral embolism→ life-threatening
- Avoidance of bed rest, volume depletion, diuretics and deep venous or arterial punctures to prevent embolism.

5- Acute renal failure

- Is more often precipitated by hypovolemia
- Reduction in the glomerular filtration rate has also been hypothesized

Laboratory findings :

1. Urinalysis :

a- Proteinuria:

- Protein: qualitatively +++~++++
  quantitatively >0.1g/kg.d.
- The ratio of urinary protein to urinary creatinine: >2

b- Hematuria :

- RBC may be increased in nephritic-nephrotic syndrome
- Occasionally appears in simple nephrosis

2. Blood:

- **Hypoalbuminemia:** albumin < 10g~20g/L
- **Hyperlipidemia:** cholesterol > 5.7mmol/L
- ESR > 100mm/h
- **Renal functions and serum complement 3 may be reduced** → In nephritic-nephrotic syndrome,
- **Serum electrolyte determination:** to evaluate hyponatremia, hypokalemia, hypocalcemia

Criteria of diagnosis :

1- **Massive proteinuria:** Urinalysis reveals 3+ or 4+. Protein excretion exceeds 100mg/kg.d.
2- **Hypoalbuminemia:** Serum albumin level is less than 30g/L (usually 10g~20g/L)
3- **Hypercholesterolemia:** the serum concentration of cholesterol is > 5.7mmol/L
4- **Edema with various degrees**

- The first two items are the most necessary for diagnosis
- The diagnosis of different clinical types of NS

Differential Diagnosis :

Primary NS should be differentiated from :

1- Secondary NS or
2- GN with nephrotic picture, such as→ HSP nephritis, SLE nephritis, APSGN.

Treatment :

A- General measures

1- Activity :

- Do not restrict activity unless the patient is severely edematous or with severe hypertention or infections.
- To prevent thrombosis, patients restricted to bed rest should change position frequently.

2- Diet :

- The diet should provide adequate energy (calorie) intake and adequate protein (1-2 g/kg/d).
- Sodium restriction (Low sodium or no sodium diet) is indicated for patients with edema or hypertension, but should be adjusted according to the serum levels of sodium. Long-term sodium restriction is not recommended.
- Fluid restriction is required when the edema is severe with oliguria.
- Replacement of vitamins and minerals.

3- Diuretic therapy :

- Diuretic is indicated when edema is severe, esp. with ascites
- It can be used for symptomatic relief until steroid diuresis occurs
  - Hydrochlorothiazide(HCT): 2-4mg/kg.d
  - Antisterone: may be added if HCT is not effective.
  - Salt-poor albumin at 0.5~1g/kg iv, over 1 hr (when serum albumin<20g/L), followed by iv injection furosemide 1-2mg/kg.dose . Multiple use is not recommended.
  - A renal blood vessel dilator should be given (dopamine 2~4 μg/kg.min) in patients with refractory edema, combined with furosemide.
- Hypovolemic shock or postural hypotension should be monitored during diuresis.

4- Treatment of complications

- **Anti-infection:** antibiotics that cover both gram-positive and negative organisms should be given; But continuous prophylactic antibiotics are not recommended.
- **Anti-coagulation therapy:** heparin, persantin, exercise of extremities,
- **Therapy for electrolyte disturbance.**

B- Specific therapy :

1- Glucocorticoid therapy
2- Cytotoxic agent therapy
3- Pulse therapy

1- Glucocorticoid therapy

- At initial diagnosis, Prednisone or Prednisolone oral therapy is the first line:
- Before starting steroid therapy, a tuberculin skin test should be done.

A) Medium-long term prednisone therapy

- **Commonly used in China, including 3 phases:**
  1- 2mg/kg/d (maximum 60 mg/day) once daily, until the proteinuria has dissappeared for 6 weeks
    - *Remission can be achieved during this phase in most children with PNS, then entered the next phase*
    - *If remission isn't achieved, continue the initial dosage, but not over 8 weeks before entered the next phase.*
  2- 1.5- 2mg/kg, qod (single dose, every other morning, alternate-day therapy) for another 4 weeks.
  3- Reduced by 2.5~5 mg q2-4w until stopped.
- **Medium term therapy:** total course is 6m
- **Long term therapy:** total course is 9~12m

B) Short term prednisone therapy :

- Prednisone dosage at:
  1- 2mg/kg/d (maximum 60 mg/day) once daily, for 4 weeks
  Regardless of the responses, entered the next phase.
  2- 1.5mg/kg, qod for another 4 weeks, then stopped.
- The total therapy course is 8~12 weeks.
- May be associated with a higher rate of early recurrence or relapse.

NS types classified by response to steroid therapy

1- **Steroid sensitive NS:**
Complete remission is achieved within the first 8 w of the initial steroid therapy.
2- **Partialy steroid sensitive NS:**
After 8w of the initial steroid therapy, edema subsides, but urinary protein is still +~++.
3- **Steroid resistant NS:**
Failure to achieve remission (urinary protein ≥ +++) in spite of 8 weeks of standard prednisone therapy.

- **Steroid dependent NS:** Patients who has 2~3 consecutive relapses occurring during the period of steroid taper or within 14 days of its cessation is defined as…
- **Relapse or recurrence:** Patients who has urinary protein≥++ after 4w of steroid cessation or during maintenance
- **Frequent relapses or recurrences:** Patients who has 2 or more relapses or recurrences within 6 months, or ≥3 within 12 months is said to have …

Adverse effects of long term corticosteroid treatment

- Cushingoid features (obesity, round face, striae)
- Increased susceptibility to infections
- Hypertension
- Osteoporosis
- Hypokalemia
- retarded growth
- Cataracts
- Peptic ulcer disease
- Diabetes mellitus

2- Cytotoxic agent therapy :

- Cyclophosphamide, cyclosporine, chlorambucil, nitrogen mustard…
- Indication:
  - Intractable NS (steroid resistance, frequent relapses or recurrences)
  - Steroid dependent NS with signs of steroid toxicity.
- The adverse effects: sexual gland damage; bone marrow depression; hemorrhagic cystitis; nausea, vomitting, gastritis; alopecia; liver damage.

3- Pulse therapy :

1- Methylprednisolone:

- 15~30 mg/kg.d (<1.0g/d) add 10% glucose 100~250 ml in drip, for 3 days. Repeated same as above every 1~2 weeks if necessary.

2- CTX:

- 0.5~0.75g/m^2 in drip, once monthly, for 6 months if necessary.

Prognosis :

- Varies depending on the histological type
- >90% of MCNS respond to corticosteroid therapy
  - Only 30% of children never have a relapse after the initial remission
  - approximately 50% have 1-2 relapses within 5 years
  - 20% continue to relapse 10 years after diagnosis\
  - Approximately 3% of patients who initially responded to steroids become steroid resistant.
  - Only approximately 20% of patients with FSGS undergo remission of proteinuria
  - Approximately 50% of patients with MsPGN undergo complete remission of proteinuria during steroid therapy
  - MPGN has the most worse prognosis. no difference was evident in the outcome between treated and untreated patients;

Indications of renal biopsy

- Unsuccessful therapeutic trial of steroids :
  - Steroid resistance
  - Frequent relapses or steroid dependency
- A child >10y at onset
- Coexistence of significant hematuria, hypertension, azotemia and depressed serum C3 at onset.
- Secondary causes of nephrotic syndrome.

Sources : 1- Nelson
2- Lang pathophysiology
3- Dr/ Sherein Shalaby lecture