# Pathophysiology

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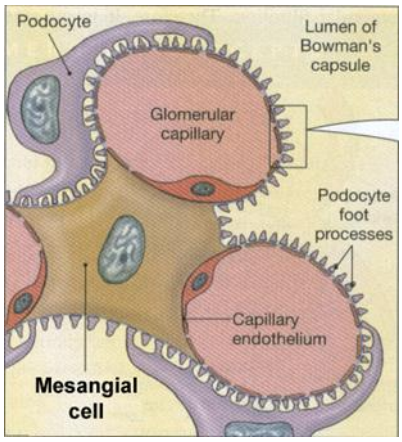
Lecture 13

# I. Disorders of the Renal system

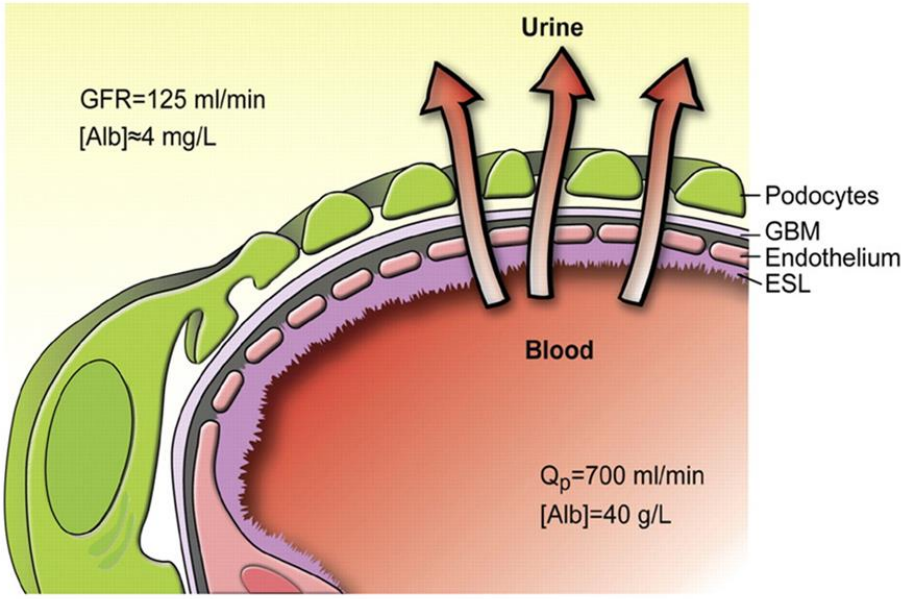
## I. Glomerular injuries

The causative agents or the triggering events that lead to glomerular injuries could be:

1. Immunological,
2. non-immunological or
3. hereditary mechanisms.



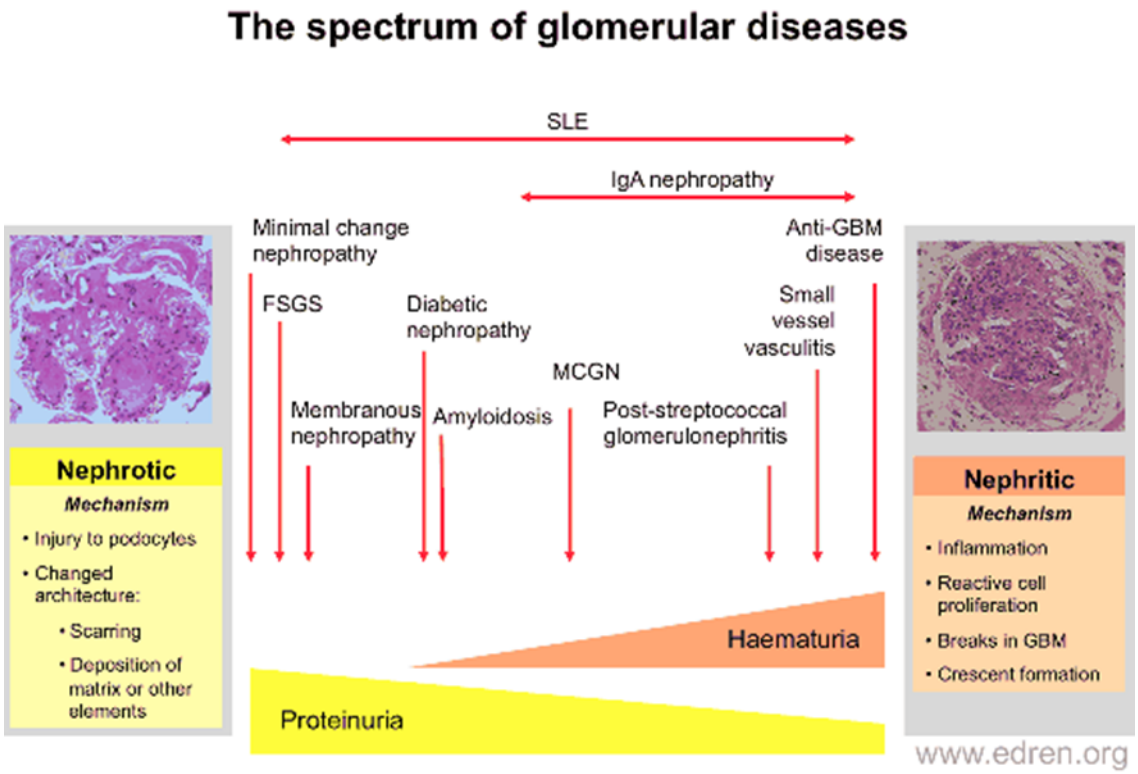

Although **most cases of primary and secondary glomerular diseases have an immunological origin**, many non-immunological causes lead to glomerular diseases like metabolic (e.g. Diabetes) hemodynamic (e.g. hypertension) and toxic (e.g. drugs, chemicals), stress either alone or in combination with immunological mechanisms.




**Schematic drawing of the glomerular barrier. Podo = podocytes; GBM = glomerular basement membrane; Endo = fenestrated endothelial cells; ESL = endothelial cell surface layer (often referred to as the glycocalyx). Primary urine is formed through the filtration of plasma fluid across the glomerular barrier (arrows); in humans, the glomerular filtration rate (GFR) is 125 mL/min. The plasma flow rate (Qp) is close to 700 mL/min, with the filtration fraction being 20%. The concentration of albumin in serum is 40 g/L, while the estimated concentration of albumin in primary urine is 4 mg/L, or 0.1% of its concentration in plasma. Reproduced from Haraldsson et al, Physiology Rev 88: 451-487, 2008, and by permission of the American Physiological Society (www.the-aps.org).**

## Glomerular Disorders

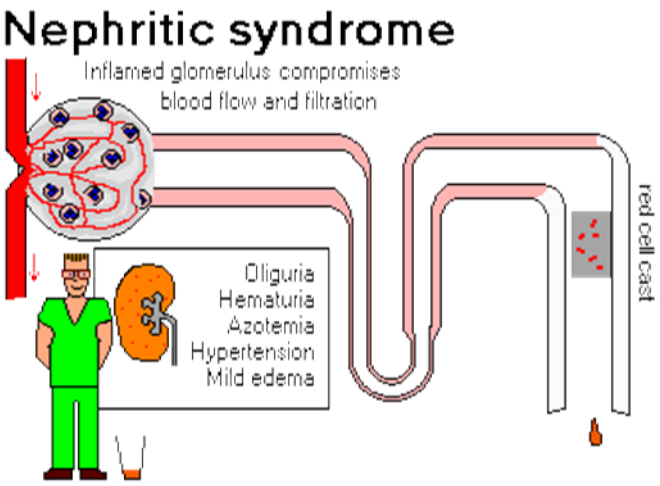
i. **Acute nephritic syndrome** (e.g Post-streptococcus glomerulonephritis)
ii. **Rapid progressive glomerulonephritis** (e.g Good posture syndrome)
iii. **Nephrotic syndrome**
iv. **Asymptomatic disorders of urinary sedimentation** (hematuria, proteinuria).
v. **Chronic glomerulonephritis.**




## i. Acute nephritic syndromes

**Classically present with**:

1. hypertension,
2. hematuria,
3. red blood cell casts,
4. pyuria, and
5. mild to moderate proteinuria.
6. Extensive inflammatory damage to glomeruli causes a fall in GFR and
7. eventually produces **uremic symptoms** with salt and water retention,
8. leading to edema and hypertension.




***Post-streptococcal glomerulonephritis***

This disease is a classic example of the **acute nephritic syndrome** characterized by

1. the sudden onset of gross hematuria,
2. edema,
3. hypertension, &
4. renal insufficiency.

Acute post-streptococcal glomerulonephritis (APSGN) is an inflammatory disease of the kidneys which occurs **2 to 3 weeks after skin or throat infection** with a particular type of bacteria called group A streptococcus (GAS), Post-streptococcal glomerulonephritis **is an immune-mediated disease** involving **putative** streptococcal antigens,

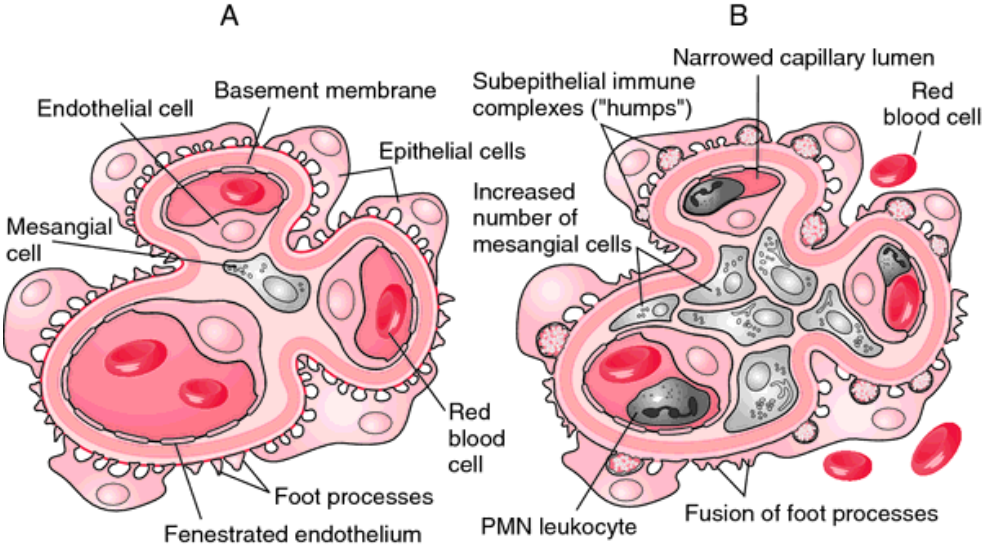
- circulating immune complexes, and activation of complement in association with cell-mediated injury.

**ii. Rapid progressive glomerulonephritis**

Rapidly progressive glomerulonephritis (RPGN) is a kidney disease **characterized clinically** by a **rapid decrease in the glomerular filtration rate (GFR) of at least 50% over a short period, from a few days to 3 months**. The main pathologic finding is **extensive glomerular crescent formation**. The ubiquitous pathological feature of crescentic glomerulonephritis is **a focal rupture of glomerular capillary walls** that can be seen by light microscopy and electron microscopy. If left untreated, it rapidly progresses into acute renal failure and death within months.

## Etiology

In 50% of cases, RPGN is associated with an **underlying disease** such as **Goodpasture syndrome, systemic lupus erythematosus, or Wegener granulomatosis**; the remaining cases **are idiopathic**. Regardless of the underlying cause, RPGN involves severe injury to the kidneys' glomeruli, with many of the glomeruli containing characteristic glomerular crescents (crescent-shaped scars).




Rapidly progressive glomerulonephritis is classified pathologically into 3 categories, as follows:

(1) **Anti-GBM antibody disease** (approximately 3% of cases).

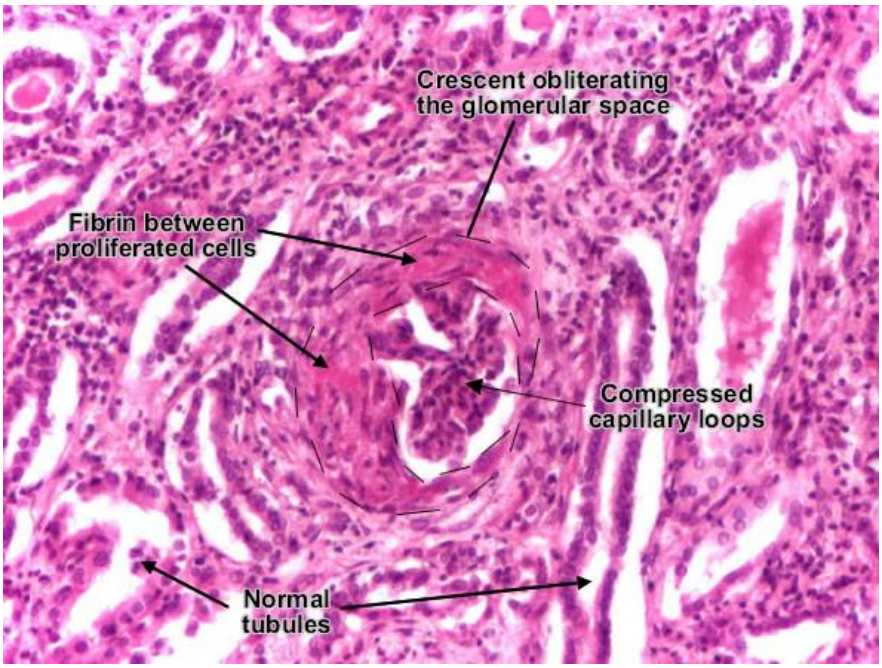
(2) **Immune complex disease** (45% of cases).

(3) **Pauci-immune disease** (50% of cases). Immunologic classification is based on the presence or absence **of Anti-neutrophil cytoplasmic antibodies (ANCAs)**. The disorders are also classified based on their clinical presentation.

## Pathophysiology of Pauci-immune glomerulonephritis

1. The Anti-neutrophil cytoplasmic antibodies (ANCAs) induces
2. a premature degranulation and activation of neutrophils at the time of their margination,
3. leading to the release of lytic enzymes and toxic oxygen metabolites at the site of injury.
4. ANCAs are directly involved in the pathogenesis of pauci-immune small vessel vasculitis or glomerulonephritis. these autoantibodies activate normal human polymorphonuclear (PMN) leukocytes.

There is fibrous proliferation in a crescent shape causing compression on the glomeruli and thickening in the glomerular basement membrane progressively ending in renal failure.




**Clinical manifestations** RPGN

**Severe and rapid loss of kidney function featuring**

1- **Severe hematuria** (blood in the urine), red blood cell casts in the urine.

2- **Proteinuria** (protein in the urine), sometimes exceeding 3 g protein/24 h, a range associated with nephrotic syndrome.

3- **Hypertension** (high blood pressure) and edema.

Severe disease is characterized by

4- **Oliguria or anuria**, which portends a poor prognosis.

The clinical picture is consistent with nephritic/nephrotic syndrome. Untreated disease may progress to decreased urinary volume (oliguria), which is associated with poor kidney function.

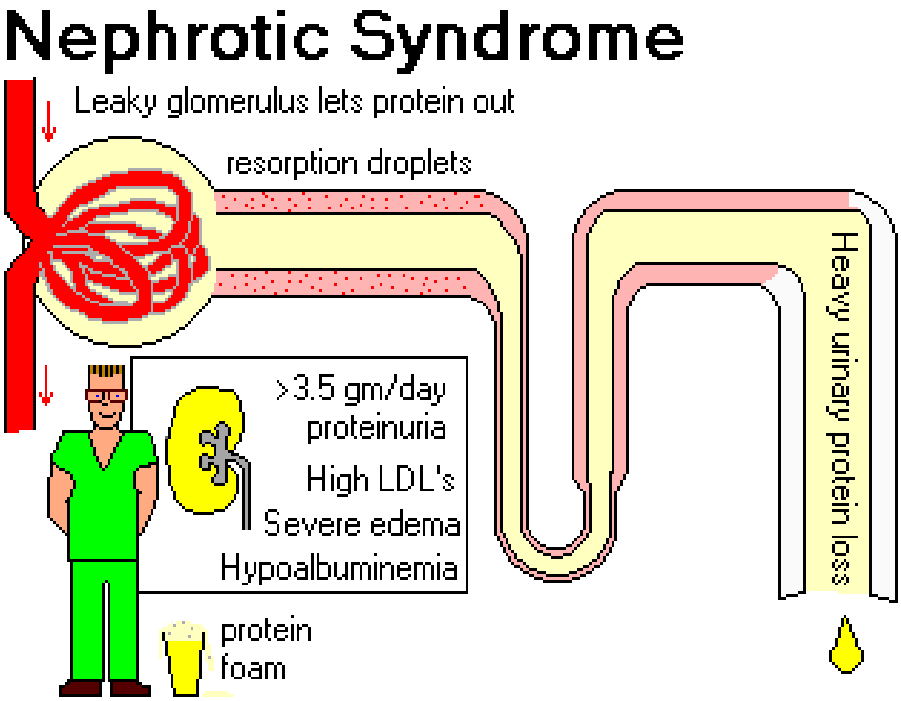
### iii. Nephrotic syndrome

*A collection of Penta symptoms:*

1. *a **massive proteinuria** (≥3.5 g/day in adult),*
2. ***lipidurea** (free fat, oval bodies & fatty cast),*
3. *associated with **hypoalbuminemia** (>3g/dL),*
4. ***generalized** **edema** and*
5. ***hyperlipidemia**.*

***Clinically*** *The nephrotic syndrome is defined by albuminuria in amounts of more than 3 to 3.5 g/day accompanied by hypoalbuminemia, edema, and hyperlipidemia.*

In practice, many clinicians refer to "**nephrotic range**" proteinuria regardless of whether their patients have the other manifestations of the full syndrome, which is a consequence of the proteinuria.



## Etiology

**Primary (idiopathic):**

- **Minimal change disease**

Most common cause in children

- **Membranous Nephropathy**

Most common cause in Adults

- **Focal Segmental Glomerulosclerosis**
- **MembranoProliferative Glomerulonephritis**

**Secondary to:**

- **DM** (the leading cause of secondary nephrotic syndrome)
- **SLE**
- **Amyloidosis**
- **Infections**: Hepatitis B and C, HIV, syphilis, post-streptococcal
- **Malignancy:** multiple myeloma , Hodgkin lymphoma, solid tumor
- **Drugs** (NSAIDs, gold, penicillamine ,heavy metals etc).

## Pathophysiology

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

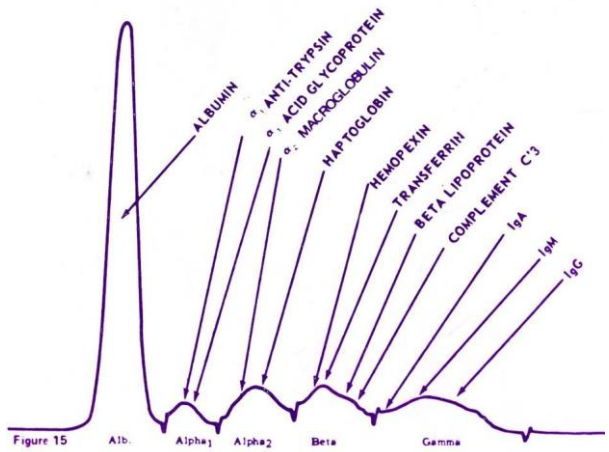
In nephrotic syndrome there is ongoing albumin passage into the urine, in many grams per day, with equivalent substantial tubular uptake of albumin, the result being that the urine has 80 mg per day or less of daily albumin.

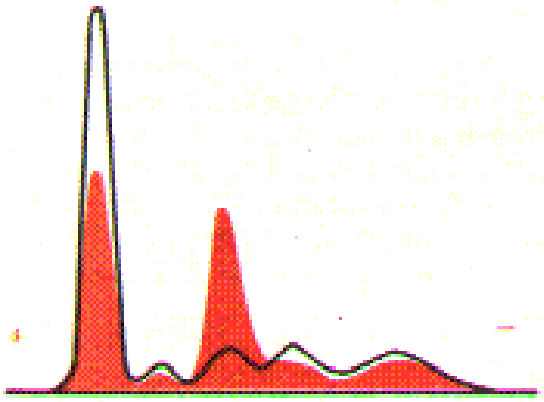
However, humans with tubular transport defects and a normal glomerular system with a urinary space albumin concentration is 3.5 mg/L. With this concentration, and a normal daily glomerular filtration rate (GFR) of 150 liters, one would expect no more than 525 mg per day of albumin in the final urine. Amounts above that level point to glomerular disease.

The 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—the fenestrated endothelium, glomerular basement membrane, and glomerular epithelium—**are the glomerular filtration barrier.**

1. The glomerular structural changes that may cause proteinuria are damage to the endothelial surface, the glomerular basement membrane, or the podocytes.
2. One or more of these mechanisms may be seen in any one type of nephrotic syndrome. Albuminuria alone may occur, or,
3. with greater injury, leakage of all plasma proteins, (proteinuria) may take place.
4. Proteinuria that is more than 85% albumin is selective proteinuria.
5. Albumin has a net negative charge, and **it is proposed that loss of glomerular membrane negative charges could be important in causing albuminuria.**
6. Nonselective proteinuria, being a glomerular leakage of all plasma proteins, would not involve **changes in glomerular net charge but rather a generalized defect in permeability.**
7. This construct does not permit clear-cut separation of causes of proteinuria, except in minimal-change nephropathy, in which proteinuria is selective.



NEPHROTIC SYNDROME

8. An increase in glomerular permeability leads to **albuminuria** and eventually to **hypoalbuminemia**.
9. In turn, hypoalbuminemia lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water throughout the body and thus the development of **edema.**

Capillary hydrostatic pressure and the gradient of plasma to interstitial fluid oncotic pressure determine the movement of fluid from the vascular compartment to the interstitium. The oncotic pressure is mainly determined by the protein content.
With a high enough capillary hydrostatic pressure or a low enough intravascular oncotic pressure, the amount of fluid filtered exceeds the maximal lymphatic flow, and edema occurs. In patients with nephrotic syndrome, this causes a reduction in plasma volume, with a **secondary increase of sodium and water retention by the kidneys.**

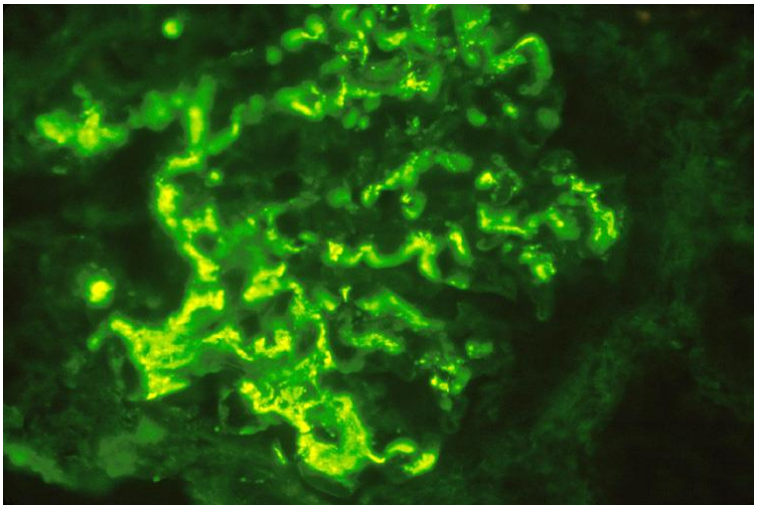
**Metabolic consequences of the nephrotic syndrome include the following:**

1. Infection: due to **Loss of complement components and possibly immunoglobulins.**
2. Hyperlipidemia and atherosclerosis: due to **increase liver synthesis of triglyceride and LDL.**
3. Hypocalcemia and bone abnormalities
4. Hypercoagulability: due to loss of proteins such as **anti-thrombin III.**?
5. Hypovolemia

## iv. Asymptomatic disorders of urinary sedimentation

Many cases of glomerulonephritis result in mild asymptomatic illnesses that are discovered only by routine checkups by physicians or health care professionals or screening tests.

***IgA Nephropathy***



The pathogenesis of IgA nephropathy remains incompletely understood. The characteristic pathologic findings by immunofluorescence microscopy of granular deposits of IgA and complement 3 (C3) in the **glomerular mesangium** suggest that this disease is the result of the

deposition of circulating immune complexes leading to the activation of the complement cascade.

Clinical features range from **asymptomatic hematuria** to rapidly progressive glomerulonephritis (RPGN). IgA nephropathy is most often associated with microscopic hematuria or recurrent macroscopic hematuria, and spontaneously resolving acute renal failure can occur. The condition can sometimes lead to chronic kidney disease as well. Pathologically, a spectrum of glomerular lesions can be seen, but mesangial proliferation with prominent IgA deposition is observed in almost all biopsies.

## v. Chronic glomerulonephritis.

**Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis.**

The condition is characterized by

1. **irreversible and**
2. **progressive glomerular** and
3. **tubulointerstitial fibrosis**,
4. ultimately leading to a **reduction in the glomerular filtration rate** (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, the net results are chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular disease.
5.

**Pathophysiology of Chronic renal failure**

1. Reduction in nephron mass from the initial injury reduces the GFR.
2. This reduction leads to hypertrophy and hyperfiltration of the remaining nephrons and to the initiation of intraglomerular hypertension.
3. These changes occur in order to increase the GFR of the remaining nephrons, thus minimizing the functional consequences of nephron loss. The changes, however, are ultimately detrimental because they lead to glomerulosclerosis and further nephron loss.

In early renal disease (stages 1-3), a substantial decline in the GFR may lead to only slight increases in serum creatinine levels. Azotemia (i.e., a rise in blood urea nitrogen [BUN] and serum creatinine levels) is apparent when the GFR decreases

to less than 60-70 mL/min. In addition to a rise in BUN and creatinine levels, the substantial reduction in the GFR results in the following:

1. **Decreased production of erythropoietin**, thus resulting in **anemia.**
2. *Decreased production of vitamin D*, resulting in **hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy**
3. Reduction in acid, potassium, salt, and water excretion, resulting in acidosis, hyperkalemia, hypertension, and edema
4. Platelet dysfunction, leading to increased **bleeding tendencies**
5. **Accumulation of toxic waste products** (uremic toxins) affects virtually all organ systems. Azotemia occurring with the signs and symptoms listed above is known as uremia. Uremia occurs at a GFR of approximately 10 mL/min.