Renal Block

Lecture Four & Five

Nephrotic & Nephritic Syndromes

Objectives:

- Recognize the five major renal clinical syndromes.
- Describe the main differential pathological diagnosis for each syndrome.
- Perform a clinico-pathological correlation.
- Describe the patterns of injury of each syndrome.

Terminology: The following terms are used to describe the extent of glomerular injury:

- Diffuse – All glomeruli are affected
- Focal – Some glomeruli are affected
- Segmental – Part of the glomerulus is affected
- Global – The entity of one glomerulus is affected

Techniques used for studying of glomerular diseases:

- Light microscopy: using routine (haematoxylin and eosin) and special stains.
- Immunofluorescence: antibodies tagged (labeled) with fluorochrome are used to localize immunoreactants in the glomerulus.
- Electron microscopy: ultrastructural studies of the glomerulus are used to features like the position and location of immune complex, basement membrane reactions and epithelial changes.

Glomerular diseases:

Nephrotic syndrome:

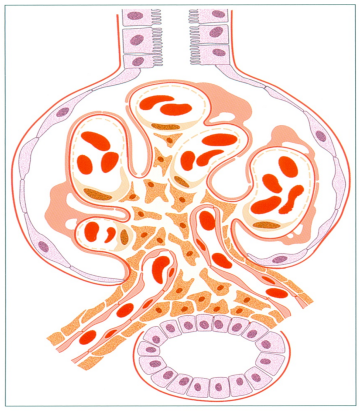
Includes a group of conditions characterized by increased basement membrane permeability, permitting the urinary loss of plasma proteins, particularly low-weight proteins such as albumin.

Classical manifestations:

In all diverse causes of the nephrotic syndrome there is a derangement in the capillary walls of the glomeruli that results in increased permeability to plasma proteins → allows protein to escape from the plasma into the glomerular filtrate →extremely heavy proteinuria, serum albumin is decreased→ hypoalbuminemia and a drop in plasma colloid osmotic pressure. → Increased release of renin from renal juxtaglomerular cells → Renin in turn stimulates the angiotensin-aldosterone axis→ promotes the retention of salt and water by the kidney. At the onset, there is little or no azotemia, hematuria, or hypertension.

- Heavy proteinuria = proteins in urine = loss of 3,5 g/day
- Not accompanied by increased urinary red cells or white cells. (No increased cells or no cells)
- Hypoalbuminemia is often marked by Serum concentration of less than 3g/100 ML
- Generalized edema results from decreased plasma colloid or oncotic pressure
- Hyperlipidemia and hypercholesterolemia are caused by increased hepatic lipoprotein synthesis.

1. Minimal change disease (lipoid nephrosis):



Diffuse Epithelial Cell Disease

Seen most often in young children but can also occur in older children and adults. It is the prototype of the nephrotic syndrome.

- Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells) particularly in cells of proximal convoluted tubules.
- Light microscopy → normal-appearing glomeruli.
- Electron microscopy → normal except for the diffuse **effacement of epithelial foot processes.**
- Most often this condition responds well to corticosteroid therapy. *More than 90% of children*
- Benign disorder, the most frequent cause of the nephrotic syndrome in children (most commonly between the ages of 1 – 7 yrs.
- The protein loss usually is confined to the smaller plasma proteins, chiefly albumin (selective proteinuria).

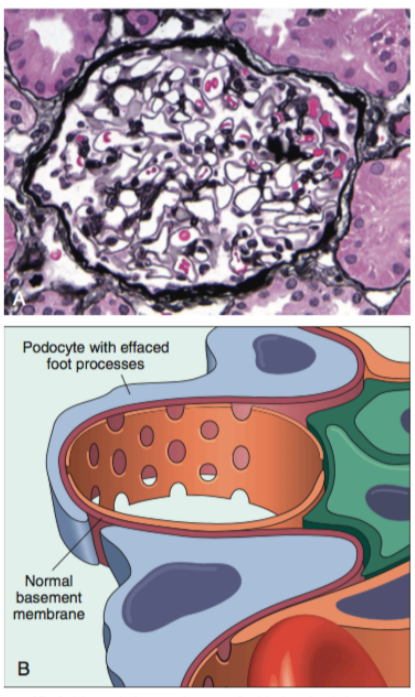
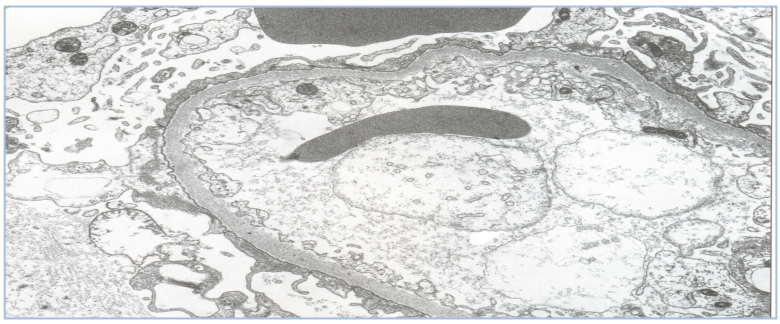
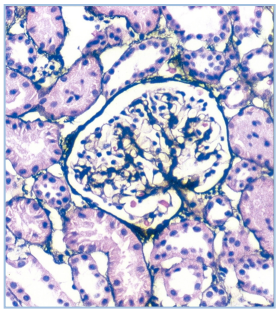


Figure 13–6 Minimal-change disease. **A,** Under the light microscope the silver methenamine–stained glomerulus appears normal, with a delicate basement membrane. **B,** Schematic diagram illustrating diffuse effacement of foot processes of podocytes with no immune deposits.

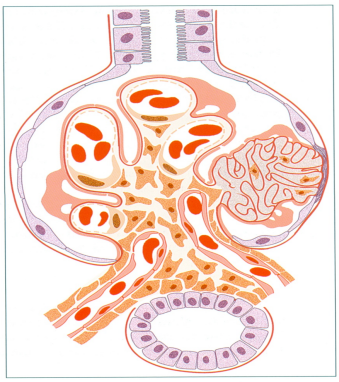


Minimal change disease. Extensive foot process effacement and microvillous transformation of visceral epithelial cells in MCD

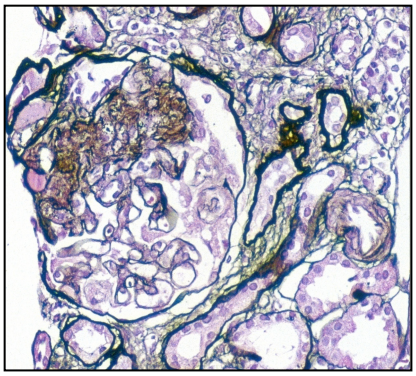


Minimal change disease. Glomeruli appear unremarkable by light microscopy, and in young patients there is no tubulionterstial fibrosis, as in this patient.

2. Focal segmental glomerulosclerosis:



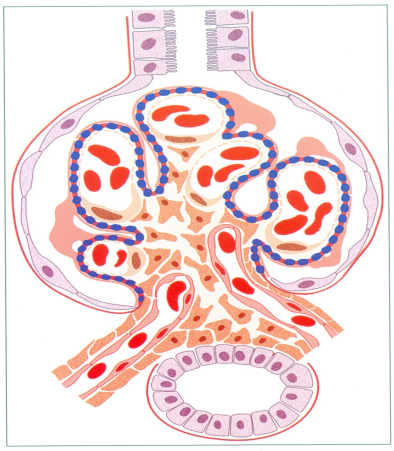
Clinically similar to minimal change disease but occurs in somewhat older patients. It is characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution. Defined as obliteration of capillary loops and increased matrix, without deposits and with diffuse foot process effacement by EM. Adhesions can also be present.



FSGS. The typical segmental sclerotic lesion in FSGS is characterized by increased matrix and obliteration of capillary lumina, frequently with hyalinosis and adhesions, as illustrated here.

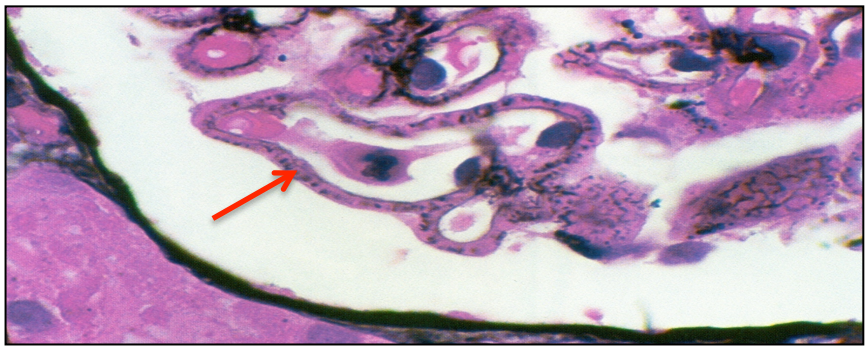
- **Injury to the podocytes is thought to represent the initiating event of primary FSGS.**
- The incidence of hematuria and hypertension is higher in persons with FSGS than in those with minimal-change disease.
- Proteinuria is nonselective; and in general the response to corticosteroid therapy is poor.
- **FSGS may be primary (idiopathic) or secondary to one of the following conditions:**
    - In association with other conditions, such as HIV nephropathy or heroin nephropathy.
    - As a secondary event in other forms of GN (e.g., IgA nephropathy).
    - As a maladaptation to nephron loss.
    - In inherited or congenital forms. Autosomal dominant forms are associated with mutations in cytoskeletal proteins and podocin, both of which are required for the integrity of podocytes. In addition, a sequence variant in the apolipoprotein L1 gene (*APOL1*) on chromosome 22 appears to be strongly associated with an increased risk of FSGS and renal failure in individuals of African descent.

3. Membranous glomerulonephritis:



An immune complex disease of an unknown etiology.

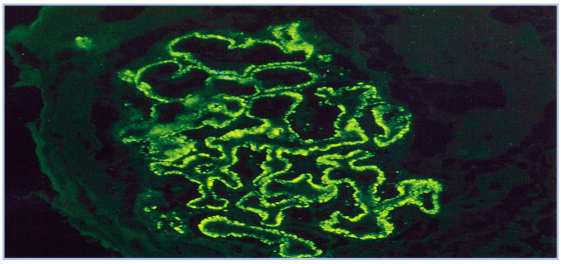
- This disease is a major primary cause of the nephrotic syndrome. Incidence is highest in teenagers and young adults
- The diagnosis should be suspected when the nephrotic syndrome is accompanied by **azotemia** (increased concentrations of serum urea nitrogen and creatinine).
- **Morphologic characteristics:**
    - There is no evident proliferation by light microscopy, with global subepithelial deposits, which may be visualized by light microscopy by the glomerular basement membrane spike reaction on silver stain.
        - With special stains, "spike and dome" appearance resulting from the extension of basement membrane between and around the immune deposits is seen; the spikes are basement membrane material and the dome are immune complex deposits.
        - Granular deposits of immunoglobulin G (IgG) or C3 are apparent on immunofluorescence. Granular immunofluorescence is a general characteristic of immune complex disease.
    - Greatly thickened capillary walls, which are visible by light microscopy and visible by electron microscopy as a 5- to 10- fold thickening of the basement membrane.

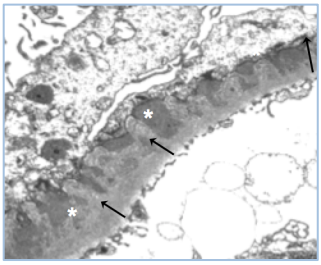


Membranous glomerulopathy. There are well-developed spikes and holes in tangential sections in stage-2 membranous glomerulopathy.

- **Ultrastructural findings:**

  Include numerous electron-dense immune complexes in intramembranous and epimembranous (epithelia) locations within and on the basement membrane.





There is an evenly distributed granular capillary loop pattern of positively in membranous glomerulopathy

- Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.
- The disorder sometimes causes renal vein thrombosis.
- Induced by antibodies reacting in situ to endogenous or planted glomerular antigens.

In about 85% of cases, membranous nephropathy is caused by autoantibodies that cross-react with antigens expressed by podocytes. In the remainder (secondary membranous nephropathy), it occurs secondary to other disorders, including:

- Infections (chronic hepatitis B, syphilis, schistosomiasis, malaria)
- Malignant tumors, particularly carcinoma of the lung and colon and melanoma
- Systemic lupus erythematosus and other autoimmune conditions
- Exposure to inorganic salts (gold, mercury)
- Drugs (penicillamine, captopril, nonsteroidal anti- inflammatory agents)

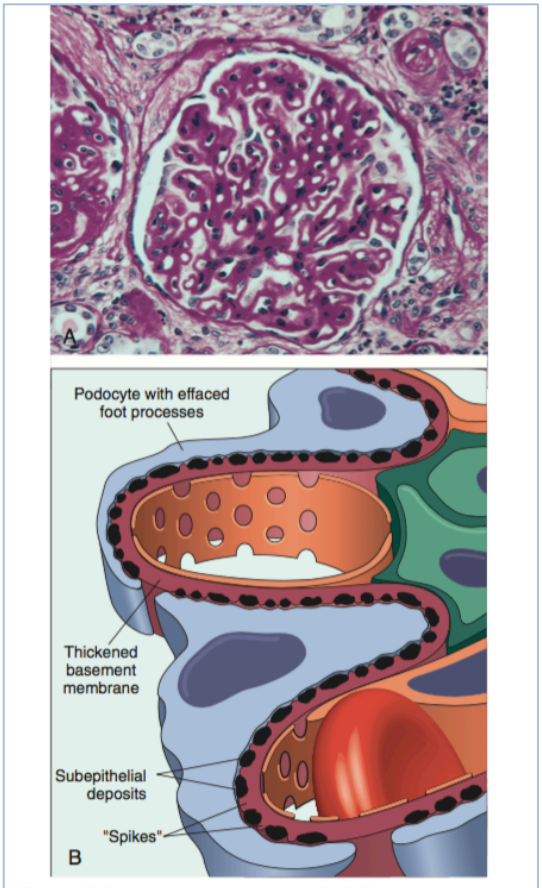
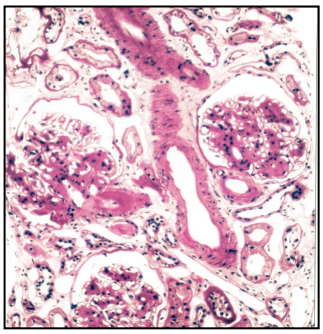


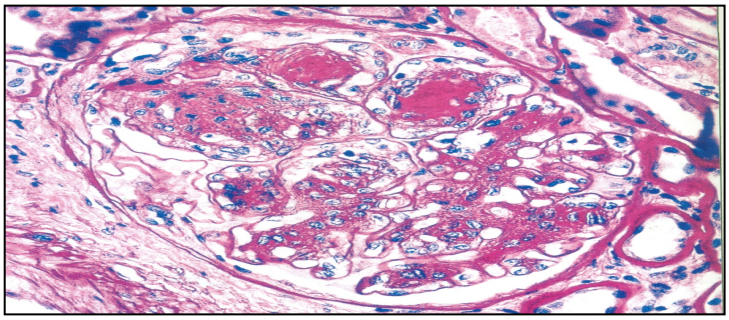
Figure 13–8 Membranous nephropathy. **A,** Diffuse thickening of the glomerular basement membrane (periodic acid–Schiff stain). **B,** Schematic diagram illustrating subepithelial deposits, effacement of foot processes, and the presence of *spikes* of basement membrane material between the immune deposits.

Diabetic nephropathy:

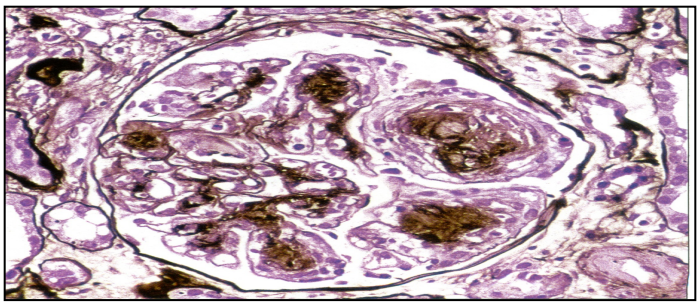
- Often, this is disease is clinically manifested by the nephrotic syndrome.
- Electron microscopy demonstrates striking increase in thickness of the glomerular basement membrane. Thickening of vascular basement membrane is one of the earliest morphologic changes in diabetes mellitus.
- An increase in mesangial matrix results in two characteristic morphologic patterns:
    1) Diffuse glomerulosclerosis is marked by a diffusely distributed increase in mesangial matrix.
    2) Nodular glomerulosclerosis is marked by nodular accumulations of mesangial matrix material (Kimmelstiel-Wilson nodules).



The lesions in diabetic nephropathy are characterized by arteriolar hyalinization, mesangial matrix expansion and glomerular basement thickening.



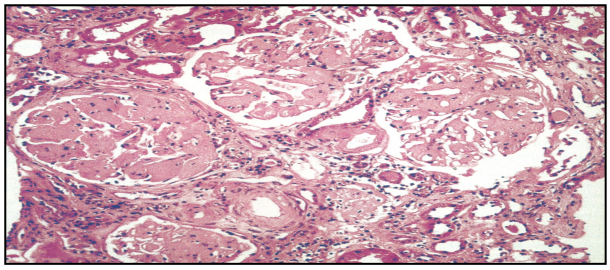
Diabetic nephropathy. Diabetic nephropathy may manifest either as diffuse mesangial increase, or with nodular glomerulosclerosis as in this case.



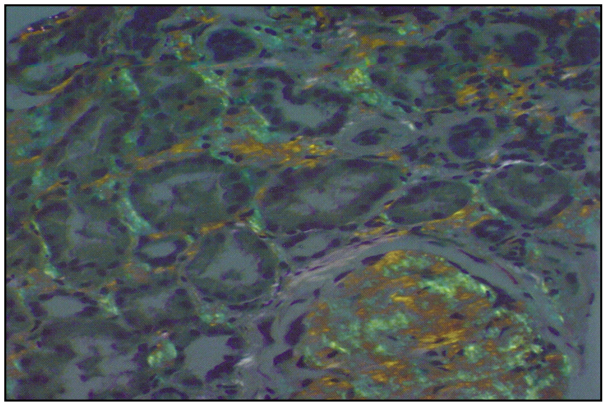
Diabetic nephropathy. The lamellated appearance of the Kimmelstiel-Wilson nodule characteristic of the nodular sclerosis form of diabetic nephropathy is shown, along with arteriolar hyalinization and surrounding tubulointerstitial fibrosis.

Renal amyloidosis:

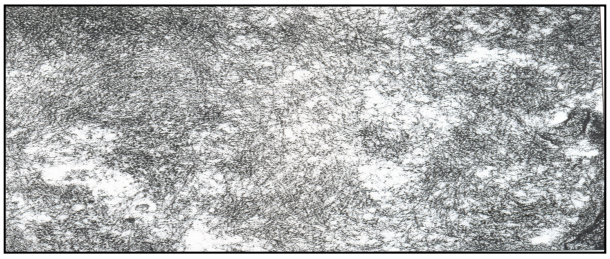
- This condition is another cause of nephrotic syndrome.
- Predominantly subendothelial and mesangial amyloid deposits are characteristic.
- The amyloidosis can be identified by reactivity of amyloid with special stains (e,g, Congo Red, crystal violet, thioflavin T) and by birefringence under polarized light. It is also demonstrated by a characteristic crisscross fibrillary pattern of amyloid by electron microscopy.
- Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumors such as multiple myeloma.



Massive amyloid deposits are present in glomeruli and arterioles



. Tubular involvement with amyloid is verified by apple-green birefringence under polarized light.

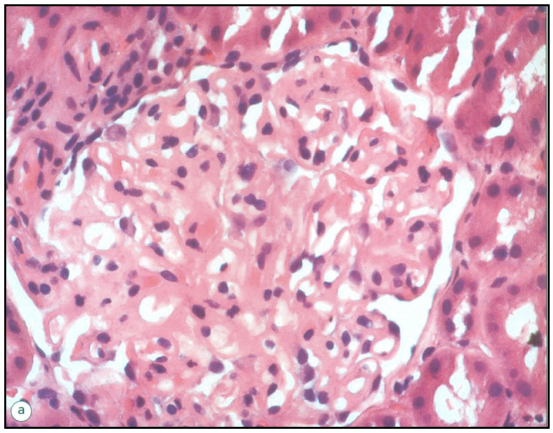


Randomly oriented, 8-10nm fibrils, typical of amyloid within the mesangium.

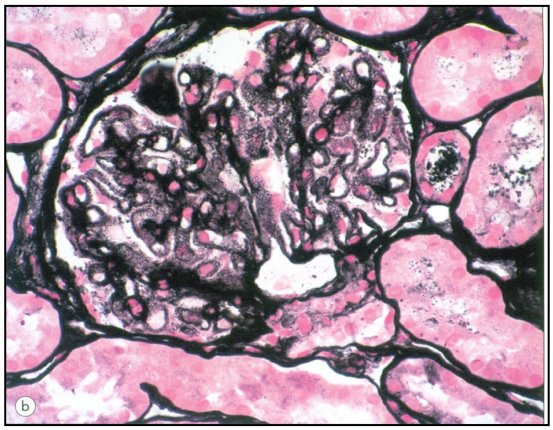
Lupus nephropathy:

- This is the renal component of SLE, the severity of the renal lesion often determines the overall prognosis in patients with SLE. It is often manifest as the nephrotic syndrome but many cases also have major nephritic features.

- The pathogenesis of all forms of glomerulonephritis in SLE involves deposition of DNA and anti DNA complexes within the glomeruli. This causes an inflammatory response that may cause proliferation of the endothelial, mesangial and/or epithelial glomerular cells and in severe cases necrosis of the glomeruli.



a) Class V lesion or lupus membranous glomerulopathy. There is diffuse thickening of the peripheral capillary walls associated with an increase in mesangial matrix.



(b) Silver methenamine (jones) stains reveal a spike and dome pattern to be present along the peripheral capillary loops where the wall of the capillaries cut tangentially; there is a moth-eaten appearance of the capillary wall.

The world health organization has divided SLE glomerular disease into five classes:

Class one: (seen less than 5% of SLE patients).

Normal by light, electron and immunofluorescence microscopy.

Class two: (seen in 10 to 25% of cases)

Mesangial lupus glomerulonephritis and it's associated with mild clinical symptoms and immune complex deposits in the mesangium.

Class three: (seen in 20 to 35% of patients)

Focal proliferative lupus glomerulonephritis. Here one or two foci within an otherwise normal glomerulus show swelling and proliferation of endothelial and mesangial cells with neutrophilic infiltration or fibrinoid deposits and capillary thrombi.

Class four: (seen in 35% to 60% of SLE patients)

In diffuse proliferative lupus glomerulonephritis. The histological features are similar to the one described in class 3 but are more diffuse. In this condition, immune complexes depositions create an overall thickening of the capillary walls, which resembles rigid "wire loops" on light microscopy.

Class five: (occurs in 10 to 15% of cases)

Membranous lupus glomerulonephritis. In class 5, the patients have severe nephrotic syndrome and there is thickening of the capillary walls due to deposition of basement membrane like material as well as immune complexes.

Table 13–2 Causes of Nephrotic Syndrome

Cause	Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	5	30
Minimal-change disease	65	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis	10	10
IgA nephropathy and others	10	15
Systemic Diseases with Renal Manifestations		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Ingestion of drugs (gold, penicillamine, "street heroin")		
Infections (malaria, syphilis, hepatitis B, HIV infection)		
Malignancy (carcinoma, melanoma)		
Miscellaneous (bee sting allergy, hereditary nephritis)		

*Approximate prevalence of primary disease is 95% of the cases in children, 60% in adults. Approximate prevalence of systemic disease is 5% of the cases in children, 40% in adults.
HIV, human immunodeficiency virus.

Nephritic syndrome:

Characterized by inflammatory rupture of the glomerular capillaries, with resultant bleeding into the urinary space; proteinuria and edema may be present but usually are mild.

The lesions that cause the nephritic syndrome have in common **proliferation of the cells** within the glomeruli, often accompanied by an inflammatory leukocytic infiltrate. This inflammatory reaction severely injures the capillary walls, permitting blood to pass into the urine and inducing hemodynamic changes that lead to a reduction in the GFR. The reduced GFR is manifested clinically by oliguria, fluid retention, and azotemia.

Clinical findings:

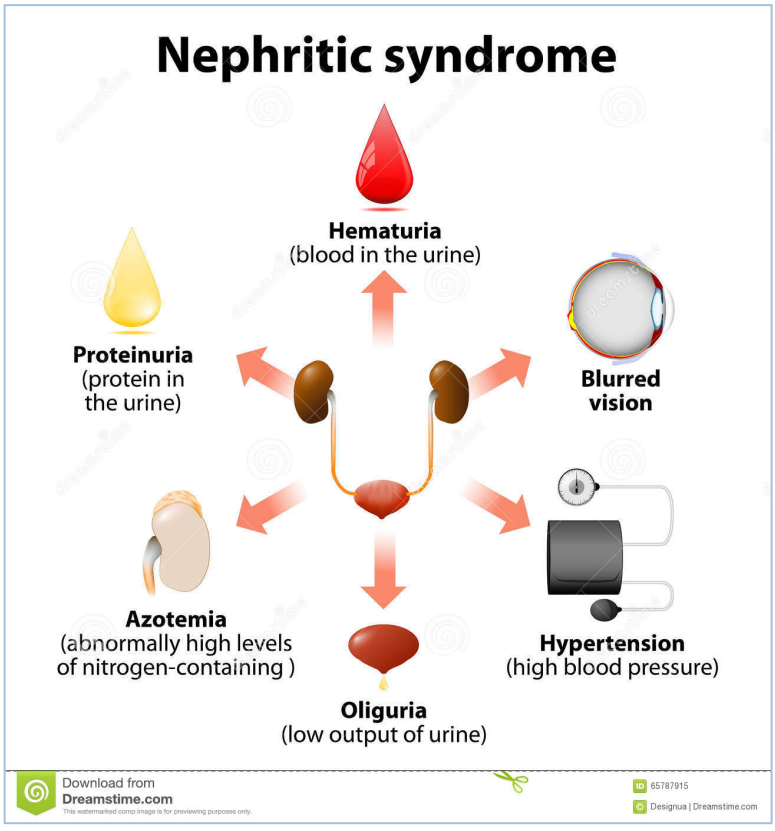
(a) Oliguria

(b) Azotemia (which is elevation of blood urea nitrogen and creatinine levels due to decreased GFR)

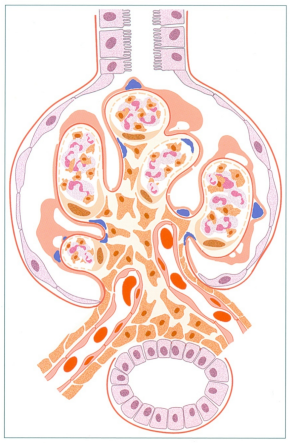
(c) Hypertension (A result of both the fluid retention and some augmented renin release from the ischemic kidneys.)

(d) Hematuria (results from leakage of red cells directly from glomerular capillaries into the Bowman space. Many of the red cells are aggregated into the shape of the renal tubules and embedded in a proteinaceous matrix forming red cells casts that can be observed in the urine).

(e) The patient often reports having "smoky brown urine". Red cell casts can degenerate and become pigmented granular casts.



1- Poststreptococcal glomerulonephritis (acute proliferative glomerulonephritis):



It is the prototype of the nephritic syndrome. It is immune complex disease with the antigen being of streptococcal origin.

How? It is caused by glomerular deposition of immune complexes resulting in proliferation of and damage to glomerular cells and infiltration of leukocytes, especially neutrophils.

This disorder most often follows or accompanies infection (tonsillitis, streptococcal impetigo, infected insect bites) with **nephritogenic strains of group A B-hemolytic streptococci.**

Pathogenesis:

The classic case of poststreptococcal GN develops in a child 1 to 4 weeks after they recover from a group A streptococcal infection. Only certain "nephritogenic" strains of β-hemolytic streptococci evoke glomerular disease. In most cases, the initial infection is localized to the pharynx or skin.

A) Complete recovery in almost all children and many adults follow. A very minority develops rapidly progressive glomerulonephritis.

B) Several laboratory abnormalities are characteristic, including urinary red cells and red cell casts, azotemia, decreased serum C3 and increased titers of anticationic proteinase (ASO) as an evidence of recent streptococcal infection.

C) An intense inflammatory reaction involving almost all glomeruli in both kidneys result in:

1. Innumerable punctuate hemorrhages on the surface of both kidneys.
2. Enlarged, hypercellular, swollen, bloodless glomeruli
3. Glomerular basement membrane of normal thickness and uniformity despite the extensive inflammatory changes. + Same morphologic changes mentioned below.

Morphology:

Light microscopy:

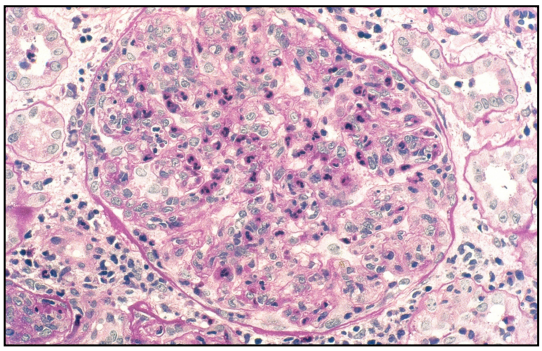
The most characteristic change in postinfectious GN is **increased cellularity** of the glomerular tufts that affects nearly all glomeruli. Caused both by proliferation and swelling of endothelial and mesangial cells and by infiltrating neutrophils and monocytes.

Electron microscopy:

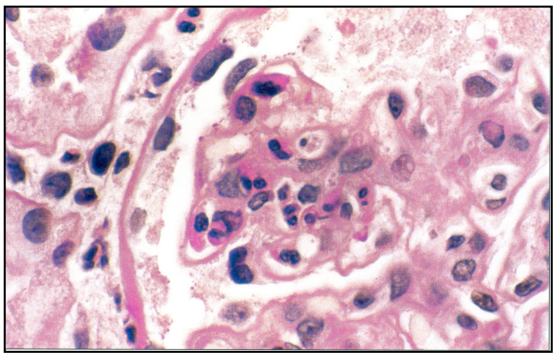
Characteristic electron- dense "humps" on the epithelial side of basement membrane with subepithelial localization.

Immunofluorescence:

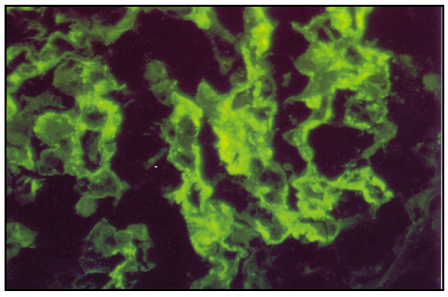
"Lumpy bumpy" immunofluorescence (extremely coarse granular immunofluorescence for IgG or C3).



Acute post-infectious glomerulonephritis. There is diffuse, global exudative proliferation with prominent endocapillary proliferation and numerous neutrophils.



Acute post-infectious glomerulonephritis. Endocapillary proliferation and numerous PMNs both within capillary loops and within the mesangial area are present.



Acute post-infectious glomerulonephritis. A more extensive garland pattern with elongated peripheral loop deposits is illustrated, along with occasional small mesangial deposits.

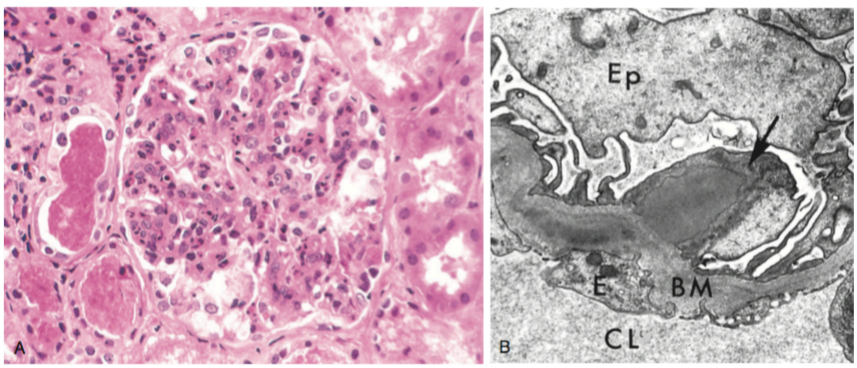


Figure 13–10 Poststreptococcal glomerulonephritis. **A,** Glomerular hypercellularity is caused by intracapillary leukocytes and proliferation of intrinsic glomerular cells. Note the red cell casts in the tubules. **B,** Typical electron-dense subepithelial "hump" (*arrow*) and intramembranous deposits. BM, basement membrane; CL, capillary lumen; E, endothelial cell; Ep, visceral epithelial cells (podocytes).

Rapidly progressive (crescentic) glomerulonephritis (RPGN):

It progresses rapidly to renal failure within weeks or months, laboratory findings typical of the nephritic syndrome, and often-severe oliguria.

Pathogenesis:

Crescentic GN may be caused by diseases restricted to the kidney or systemic. In most cases the glomerular injury is immunologically mediated. It may be idiopathic.

1. 12% of the patients have anti-GBM antibody–mediated crescentic GN with or without lung involvement
2. 44% have immune complex GN with crescents;
3. The remaining 44% have pauci- immune crescentic GN.

All have severe glomerular injury.

- Antiglomerular basement membrane antibodies (non streptococcal) are characteristic in approximately 10% of cases; these cases often present clinically as Goodpasture syndrome.

  How can it present as Goodpasture syndrome?

  In some patients, the anti- GBM antibodies also bind to pulmonary alveolar capillary basement membranes to produce the clinical picture of pulmonary hemorrhages associated with renal failure. These patients are said to have *Goodpasture syndrome,* to distinguish their condition from so-called idiopathic cases, in which renal involvement occurs in the absence of pulmonary disease.

- It's poststreptococcal in approximately of 50% of cases with immune Complex deposition; other forms or RPGN include, among others, lupus nephropathy and IgA nephropathy.

Morphology:

The kidneys are enlarged and pale, often with **petechial hemorrhages** on the cortical surfaces, Glomeruli show segmental necrosis and GBM breaks Defined by the formation of crescents between the Bowman capsule and the glomerular tuft which result from deposition of fibrin in the bowman space and from proliferation of parietal epithelial cells in response to the exudation of plasma proteins. In addition to migration of monocytes/macrophages into Bowman's space

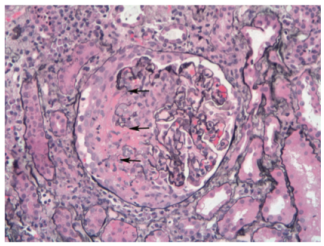
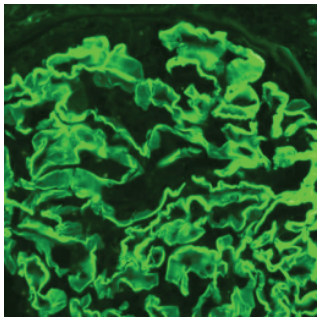


Figure 13–12 Crescentic glomerulonephritis (GN) (Jones silver methenamine stain). Note the areas of necrosis with rupture of capillary loops (*arrows*) and destruction of normal glomerular structures, and the adjacent crescent-shaped mass of proliferating cells and leukocytes filling the urinary space. The segmental distribution of the necrotizing and crescentic GN is typical of ANCA (antineutrophil cytoplasmic antibody)-associated crescentic GN.

Immunofluorescence:

Characteristically show strong staining of linear IgG and C3 deposits along the GBM (deposition of immune complexes)



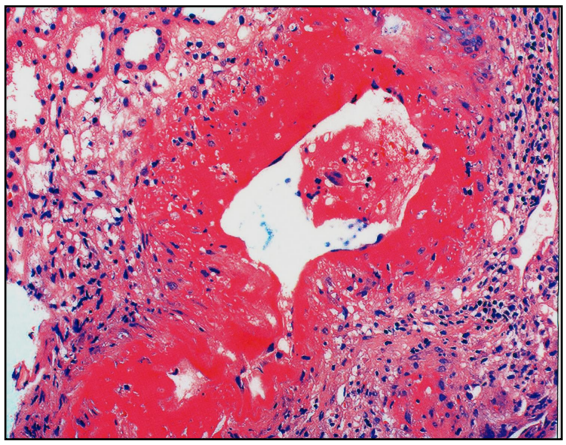
Electron microscopy:

Show distinct ruptures in the GBM. The crescents eventually obliterate Bowman's space and compress the glomeruli. In time, crescents may undergo scarring, and glomerulosclerosis develops.

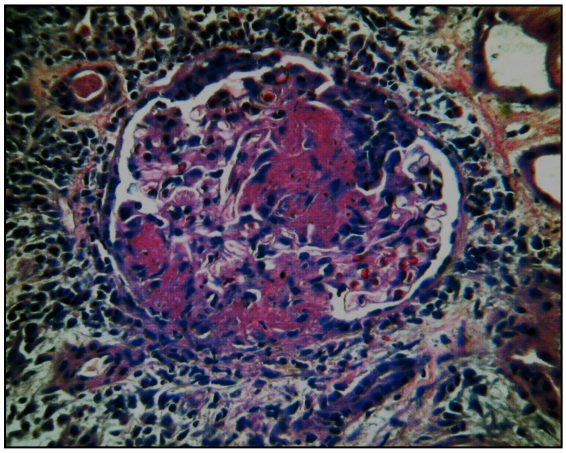
Diseases that cause crescentic glomerulonephritis:

- **Idiopathic or primary crescentic glomerulonephritis:**
  - **Type I, anti-GBM disease:**
  - **Type II, immune complex-mediated**
  - **Type III, pauci immune (ANCA-associated)**
    - **Vasculitides (ANCA-associated):**
    - **Microscopic form of polyarteritis nodosa,**
    - **Wegener's granulomatosis/ microscopic polyangiitis**
    - **Churg-Strauss syndrome**
    - **Drug-induced vasculitides**
- **Other primary glomerulonephritides:**
  - **Post-infectious GN, IgA nephropathy, MPGN, etc.**
  - **Systemic diseases (SLE, RA, H-S purpura)**

Wegener's granulomatosis/ microscopic polyangiitis:

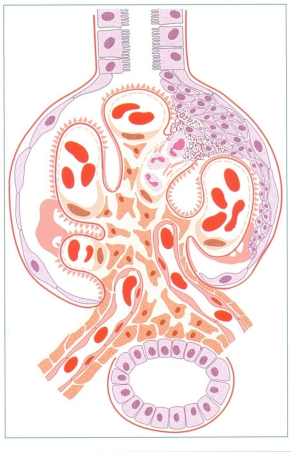


Vessel with transmural necrosis involving the vessels circumferentially with a significant inflammatory infiltrate with mixed polymorphonuclear leukocytes and mononuclear cells.



Glomerulus demonstrating focal and segmental necrosis with adhesion to Bowman's capsule and proliferation of parietal epithelium.

Good pasture syndrome (antiglomerular basement membrane disease):



This disease is a hereditary nephritis associated with nerve deaflines and ocular disorders, such as lens dislocation and cataracts.

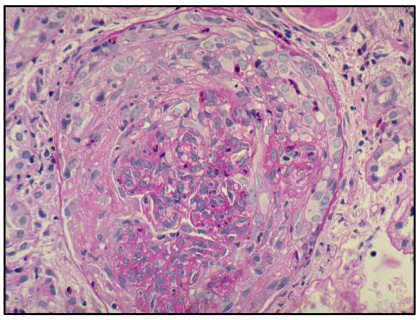
There is segmental necrosis with a break of the glomerular basement membrane, and fibrinoid necrosis and PMNs in the area, with a cellular crescent developing in response to this GBM break.

Clinical manifestations include:

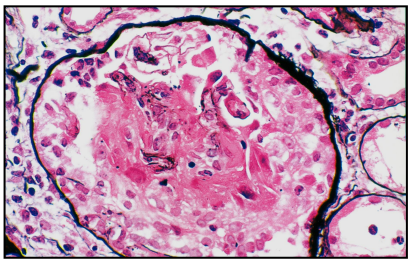
1. Nephritic syndrome, often progressing to end stage renal disease by 30 years of age.
2. Pneumonitis with hemoptysis (hemorrhagic pneumonitis).
3. Peak incidence in men in their mid-20s.
4. RPGN crescentic morphology with linear immunofluorescence.
5. Alport syndrome.

Pathogenesis:

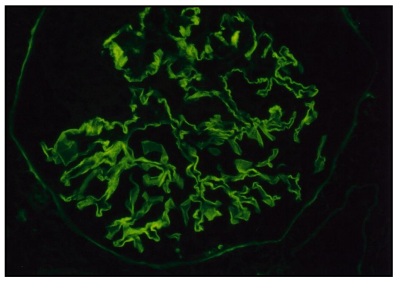
- The cause **is mutation in the gene for the 5-chain type IV collagen.** Which leads to formation of antibodies (antiglomerular basement membrane antibodies), which are directed against antigen in the glomerular and pulmonary alveolar basement membranes.
- Irregular glomerular basement membrane thickening with foci of splitting of the lamina densa are seen by electron microscopy.



Crescentic glomerulonephritis: this image shows details of the cellular composition of the crescent. Notice mostly mononuclear cells (monocytes, epithelioid cells, proliferated parietal epithelial cells from Bowman's capsule, some polymorphonuclear neutrophils) in the crescent and the collapsed, fragmented capillary tuft, as highlighted by the PAS positive basement membranes (center and right). (PAS)



Anti-GBM antibody-mediated glomerulonephritis with karyorrhexis and ruptured fragments of GBM, with a small remaining intact portion of the glomerulus at the top.



Anti-GBM antibody-mediated glomerulonephritis. Linear glomerular basement membrane staining with lgG is diagnostic of this disease in this setting.

Immune Complex-Mediated Crescentic Glomerulonephritis:

Characteristic granular ("lumpy bumpy") pattern of staining of the GBM and/or mesangium for immunoglobulin and/or complement on immunofluorescence studies. This disorder usually does not respond to plasmapheresis.

Morphology:

There is severe injury in the form of **segmental necrosis** and GBM breaks with resultant crescent formation. Segments of glomeruli without necrosis show evidence of the underlying immune complex GN (e.g., diffuse proliferation and leukocyte exudation in postinfectious GN or systemic lupus erythematosus; mesangial proliferation in IgA nephropathy or Henoch-Schönlein purpura). Immunofluorescence shows the characteristic **granular pattern** of immune complex disease, and electron microscopy demonstrates discrete deposits.

Pauci-Immune Crescentic Glomerulonephritis

This means that in these cases RPGN is without immune complex deposition or antiglomerular basement membrane antibodies. Associated with antineutrophilic cytoplasmic antibodies (ANCAs) typically are found in the serum, in contrast to the immune complex or antiglomerular basement membrane forms of RPGN, which are ANCA-negative. The ANCA-negative forms of RPGN:

- Type I when RPGN is of the antiglomerular basement membrane antibody type.
- Type II when it is of the immune complex type.
- The ANCA- positive pauci-immune form of RPGN is designated type III.

In some instances, therefore, crescentic GN is a component of a systemic vasculitis such as microscopic polyangiitis or Wegener granulomatosis. In many cases, however, pauci-immune crescentic GN is limited to the kidney and is thus called idiopathic.

Morphology:

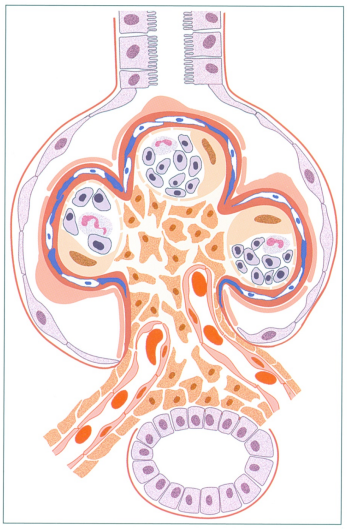
Glomeruli show **segmental necrosis** and GBM breaks with resulting crescent formation. However, results of immunofluorescence studies for immunoglobulin and complement are negative, and no deposits are detectable by electron microscopy.

Clinical Course

Oliguria and azotemia are more pronounced. Some affected persons become anuric and require long-term dialysis or transplantation.

The prognosis is roughly related to the fraction of involved glomeruli Plasma exchange is of benefit in those with anti-GBM antibody GN and Goodpasture disease, as well as in some patients with ANCA-related pauci-immune crescentic GN.

Membranoproliferative glomerulonephritis:

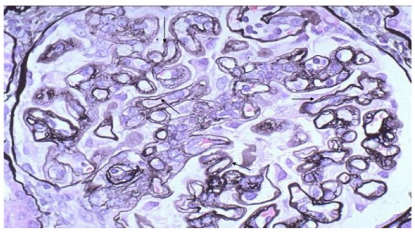


Membranoproliferative GN (MPGN) is manifested histologically by alterations in the GBM and mesangium and by proliferation of glomerular cells. Some patients present only with hematuria or proteinuria in the non-nephrotic range; others exhibit a combined nephrotic–nephritic picture. Two major types of MPGN (I and II) have traditionally been recognized on the basis of distinct ultrastructural, immunofluorescence, microscopic, and pathogenic findings, but these are now recognized to be separate entities, termed MPGN type I and dense deposit disease (formerly MPGN type II). Of the two types of disease, MPGN type I is far more common.

There is endocapillary proliferation and glomerular basement membrane splitting, due to mesangial and subendothelial deposits, with resultant interposition and new basement membrane being laid down, causing the split appearance.

Pathogenesis:

This silver stain demonstrates a double contour of the basement membranes("**tram-tracking**")that is characteristic of (MPGN)(arrows).

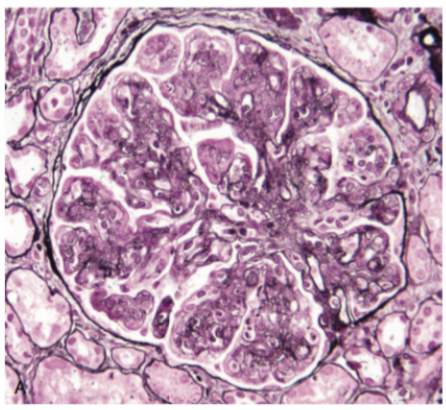


- **Type I MPGN may be caused by circulating immune complexes.**
  - Occurs in association with **hepatitis B and C antigenemia**, systemic lupus erythematosus, infected atrioventricular shunts, and extrarenal infections with persistent or episodic antigenemia.
- **Dense deposit disease:**
  - The fundamental abnormality in dense deposit disease appears to be **excessive complement activation.**
  - Some patients have an autoantibody against C3 convertase, called **C3 nephritic factor.**
  - Mutations in the gene encoding the complement regulatory protein **factor H** or autoantibodies to factor H result in excessive complement activation.
  - Hypocomplementemia: produced in part by excessive consumption of C3 and in part by reduced synthesis of C3 by the liver.

Morphology:

By LM, type I MPGN and many cases of DDD are similar.

1. The glomeruli are large, with an accentuated **lobular appearance**
2. **Proliferation of mesangial and endothelial cells**
3. Infiltrating leukocytes
4. **GBM is thickened**
5. Glomerular capillary wall often shows a double contour, or "tram track," appearance.



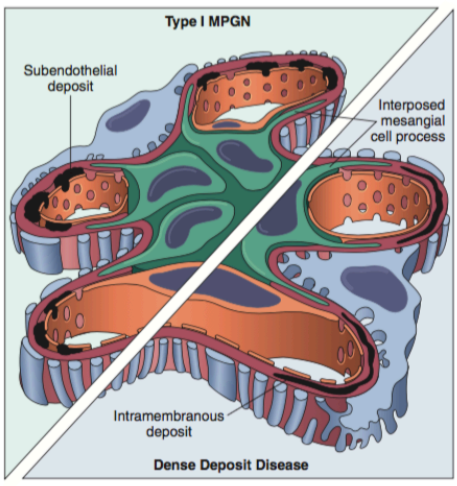
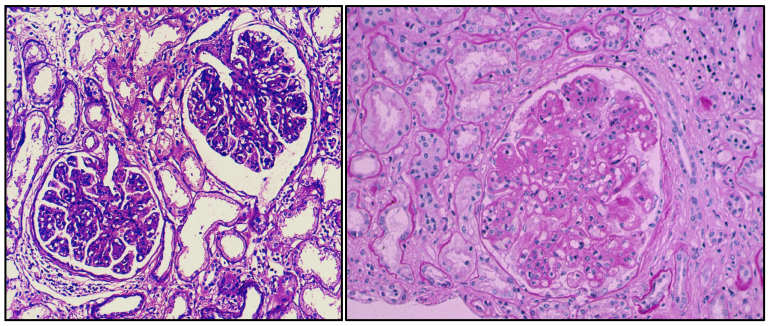
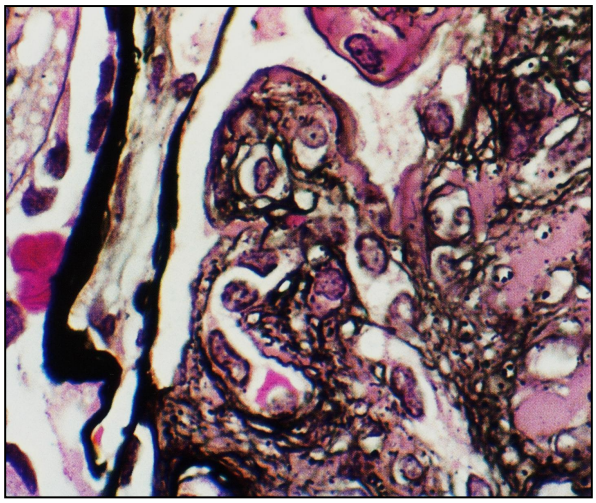


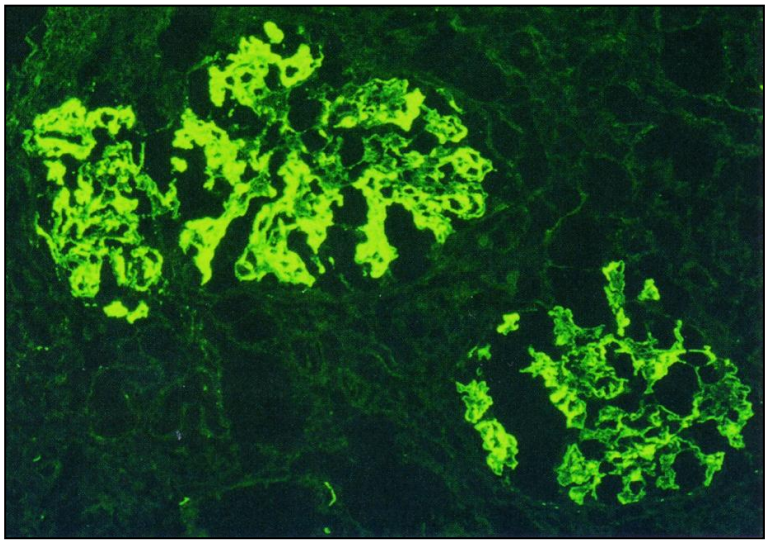
Figure 13–9 A, Membranoproliferative glomerulonephritis (MPGN), showing mesangial cell proliferation, basement membrane thickening, leukocyte infiltration, and accentuation of lobular architecture. **B,** Schematic representation of patterns in the two types of MPGN. In type I there are subendothelial deposits; in type II, now called dense deposit disease, intramembranous characteristically dense deposits are seen. In both types, mesangial interposition gives the appearance of split basement membranes when viewed by light microscopy.



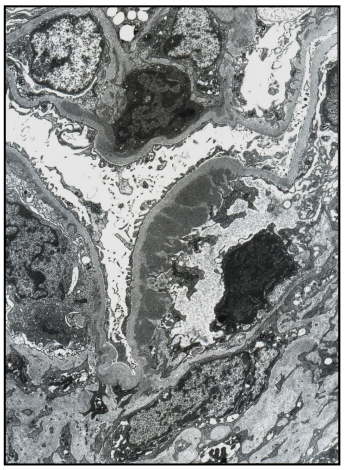
MPGN type I.
There is segmental interposition of cells which splitting of peripheral capillary GBM along with subendothelial deposits.



MPGN type I.
MPGN is characterized by diffuse endocapillary proliferation, which results in a lobular, uniform appearance of glomeruli.



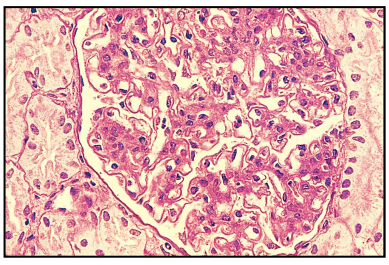
MPGN type I.
in addition to IgG, there is often very prominent complement deposition in MPGN with prominent mesangial and coarse, chunky peripheral loop deposits, corresponding to the subendothelial deposits.



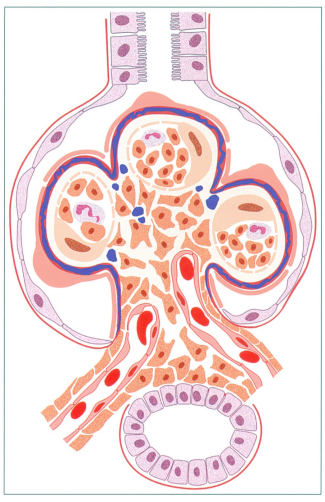
MPGN type I
There are massive subendothelial deposits in the right loop, with minimal endocapillary proliferation, and small, silver-like deposits on the left and top loops, with associated proliferation.

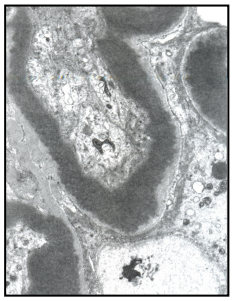
Dense deposit disease (DDD):

The glomerulus shows a membranoproliferative pattern, with endocapillary proliferation and GBM splitting



DDD
Dense deposit disease has membranoproliferative features by light microscopy, with diffuse, global mesangial and often endocapillary proliferation, and frequent glomerular basement membrane splitting.





DDD.
There is dense transformation of nearly the entire thickness of the glomerular basement membrane, with associated endocapillary proliferation.

Clinical Course

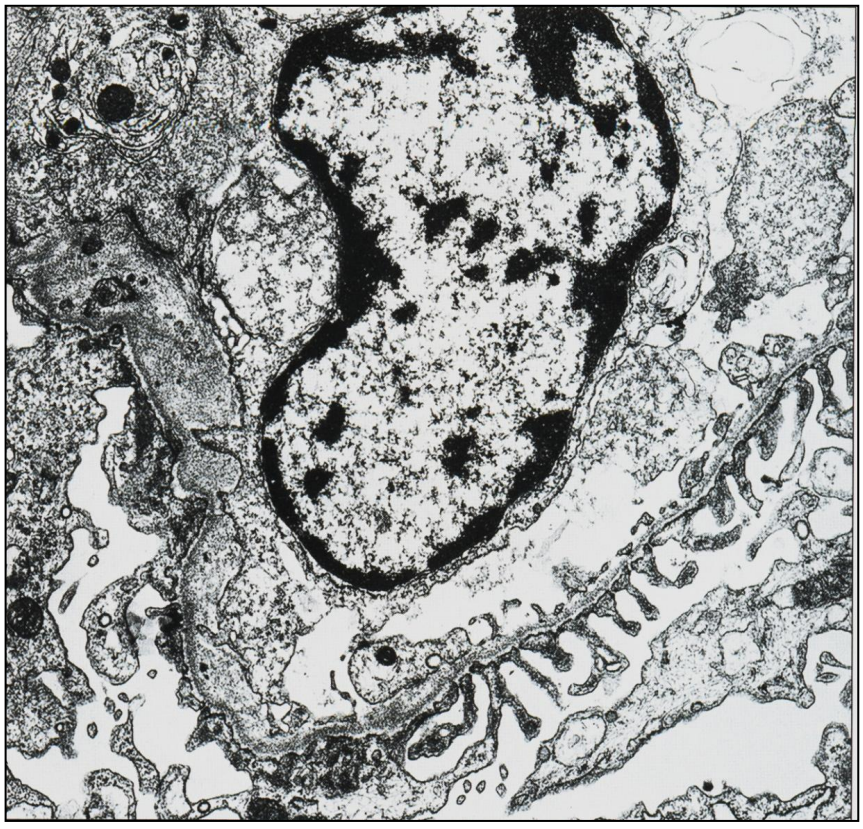
- The principal mode of presentation is the nephrotic syndrome, although MPGN or dense deposit disease may begin as acute nephritis or mild proteinuria.
- The prognosis of MPGN type I generally is poor:
    - Some will progress to end-stage renal failure
    - Some will have variable degrees of renal insufficiency
    - Some will have persistent nephrotic syndrome without renal failure.
- Dense deposit disease carries an even worse prognosis, and it tends to recur more frequently in renal transplant recipients.

Asymptomatic hematuria/proteinuria:

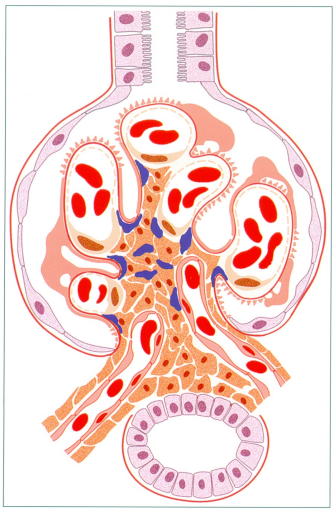
Microscopic hematuria with red cell casts; proteinuria usually <1 gram/24 hours; normal renal function.

Alport syndrome:

Alternating areas of extreme thinning of the glomerular basement membrane (~120 nm) with thick, irregular areas with basket weaving are shown.



IgA nephropathy (Berger disease):



It's an extreme common entity defined by deposition of IgA in the magnesium. Most frequently, the disease is characterized by benign recurrent hematuria (gross or microscopic) in children, usually following an infection, lasting 12 days, and usually of minimal clinical significance.

The hallmark of the disease is **the deposition of IgA in the mesangium.**

Pathogenesis:

- IgA nephropathy is associated with an abnormality in IgA1 production "abnormally glycosylated" and clearance, (reduces plasma clearance and favors deposition in the mesangium.)
- Increased production of the IgA1 subtype by plasma cells in the bone marrow.
- IgA is the main immunoglobulin in mucosal secretions.
- In genetically susceptible individuals, exposure to some antigens may lead to increased IgA synthesis, which of some is abnormal; this causes the deposition of IgA and IgA-containing immune complexes in the mesangium, where they activate the alternative complement pathway and initiate glomerular injury. And also cause proliferation of mesangial cells.
- In support of this scenario, IgA nephropathy occurs with increased frequency in individuals with celiac disease, in whom intestinal mucosal defects are seen, and in liver disease, in which there is defective hepatobiliary clearance of IgA complexes (secondary IgA nephropathy).

IgA nephropathy can be a component of the Henoch- Schonlein vasculitis disease.

Henoch-Schönlein purpura is a systemic syndrome involving the skin (purpuric rash), gastrointestinal tract (abdominal pain), joints (arthritis), and kidneys.

Clinical Course:

The disease often affects children and young adults. More than half of those with IgA nephropathy present with gross hematuria after an infection of the respiratory or, less commonly, gastrointestinal or urinary tract. The hematuria typically lasts for several days and then subsides, only to return every few months.

Morphology:

Characterized morphologically either by focal necrotizing and/or inflammatory lesions of the glomeruli or by basement membrane anomalies that result in greater capillary fragility.

Focal glomerulonephritis may be the presenting feature.

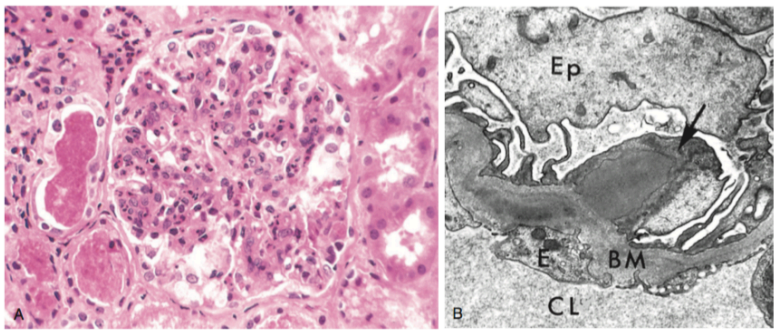


Figure 13–10 Poststreptococcal glomerulonephritis. **A,** Glomerular hypercellularity is caused by intracapillary leukocytes and proliferation of intrinsic glomerular cells. Note the red cell casts in the tubules. **B,** Typical electron-dense subepithelial "hump" (*arrow*) and intramembranous deposits. BM, basement membrane; CL, capillary lumen; E, endothelial cell; Ep, visceral epithelial cells (podocytes).

The glomeruli may be normal or may show mesangial widening and segmental inflammation confined to some glomeruli (focal proliferative GN); diffuse mesangial proliferation (mesangioproliferative GN); or (rarely) overt crescentic GN.

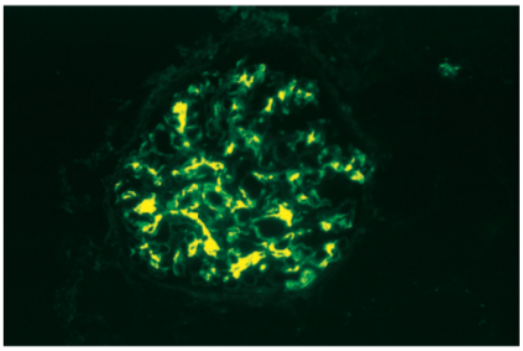
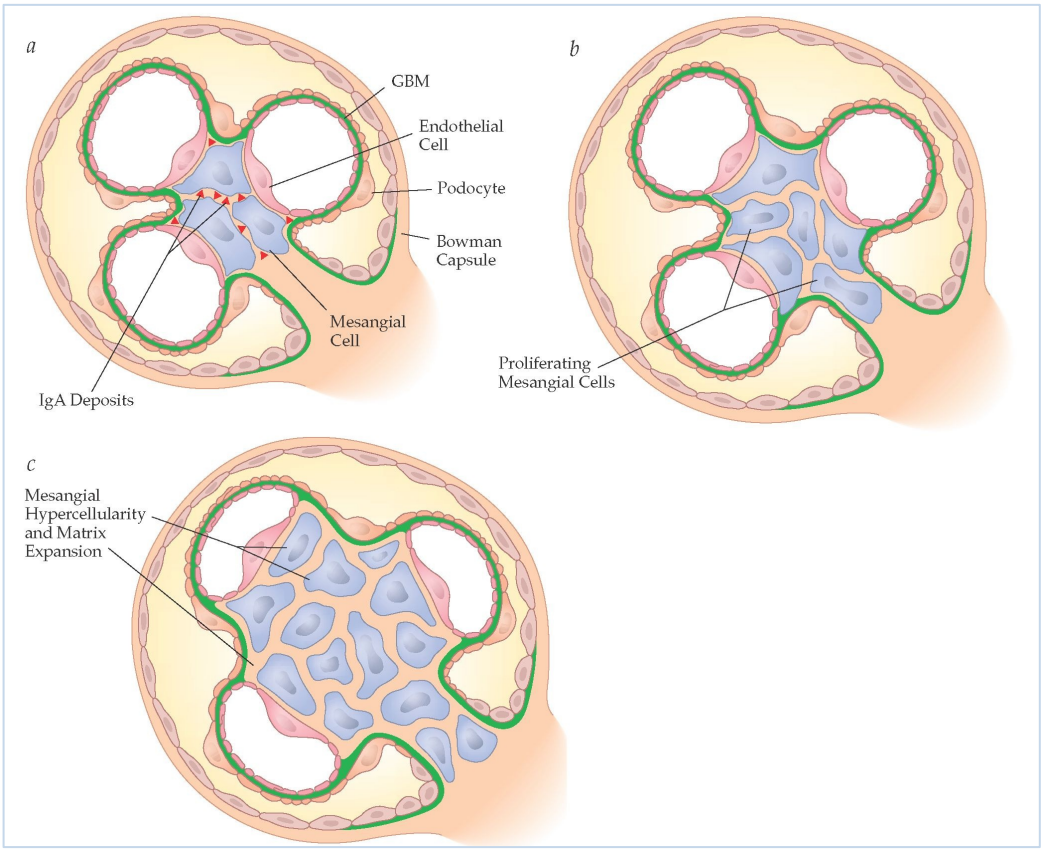


Figure 13–11 IgA nephropathy. Characteristic immunofluorescence deposition of IgA, principally in mesangial regions, is evident. IgA, immunoglobulin A.

You notice a mesangial deposition of IgA, often with C3 and other immune complexes (properdin + small amounts of IgG & IgM). The deposits may extend to the subendothelial area of adjacent capillary walls in a minority of cases, usually those with focal proliferation.

Electron microscopy confirms the presence of electron-dense deposits in the mesangium.



Chronic Kidney Disease:

(Chronic renal failure = chronic uremia = end of all renal diseases = end stage renal disease (uremia))

Renal failure can be acute or chronic and can result from any of the glomerular or tubulointerstitial lesions diseased in the preceding sections.

(1) Azotemia (elevated urea and creatinine) of renal origin is always an associated feature.

(2) In advanced stages, renal failure results in uremia; the term uremia denotes the biochemical and clinical syndrome characteristic of symptomatic renal disease.

A. Uremic syndrome clinical features due to increase urea and creatinine

1. Skin manifestations → pruritus, uremic "frost", skin
2. Cardiac manifestations → uremic pericarditis
3. Neurological manifestations → peripheral neuropathy
4. Pulmonary complications → pneumonitis and hemorrhage
5. Hematopoietic manifestations → anemia, bleeding diathesis
6. Skeletal abnormalities → renal osteodystrophy (secondary hyperparathyroidism)
7. Other → metabolic imbalances

B. Pathogenesis of uremic syndrome

1. Uremic "Toxins"
2. Middle molecules
3. The "Trade off" hypothesis

It's the result of **progressive scarring** resulting from any type of kidney disease. This eventually results in an end-stage kidney where glomeruli, tubules, interstitium and vessels are sclerosed. Unless the disorder is treated with **dialysis** or **transplantation**, death from uremia results.

Morphology:

- **Advanced scarring** of the glomeruli, sometimes to the point of complete sclerosis
- There is also marked interstitial fibrosis, associated with atrophy and dropout of many of the tubules in the cortex, and diminution and loss of portions of the peritubular capillary network.
- The small and medium-sized arteries frequently are thick-walled, with narrowed lumina, secondary to hypertension.

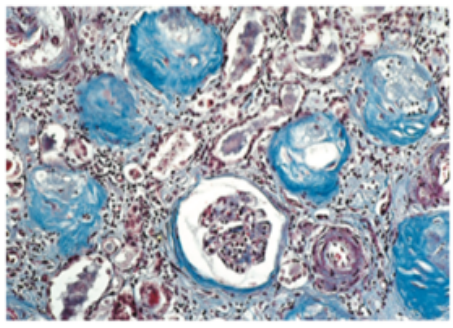


Figure 13–20 Chronic glomerulonephritis. A Masson trichrome preparation shows complete replacement of virtually all glomeruli by blue-staining collagen.
(Courtesy of Dr. M.A. Venkatachalam, Department of Pathology, University of Texas Health Sciences Center, San Antonio, Texas.)

- Lymphocytic (and, rarely, plasma cell) infiltrates are present in the fibrotic interstitial tissue.
- As damage to all structures progresses, it may become difficult to ascertain whether the primary lesion was glomerular, vascular, tubular, or interstitial. Such markedly damaged kidneys have been designated end- stage kidneys

Clinical Course:

- May develop insidiously and be discovered after the onset of renal insufficiency.
- Renal disease is first detected with the discovery of proteinuria, hypertension, or azotemia on routine medical examination.
- In patients with glomerular disease resulting in nephrotic syndrome, as the glomeruli undergo sclerotic changes, the avenue for protein loss is progressively closed, and the nephrotic syndrome thus becomes less severe with more advanced disease. Some degree of proteinuria, however, is present in almost all cases. Hypertension is very common, and its effects may dominate the clinical picture. Although microscopic hematuria is usually present, grossly bloody urine is infrequent at this late stage.

Treatment of End Stage Renal Disease

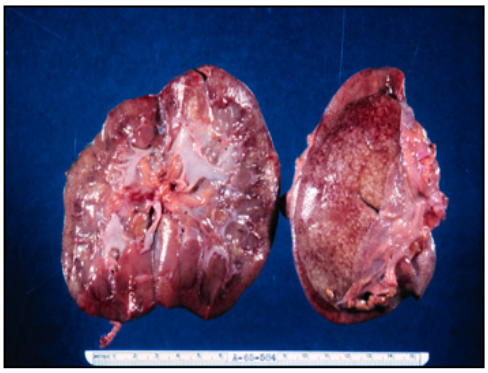
A. Supportive therapy
B. Dialysis
C. Renal transplantation

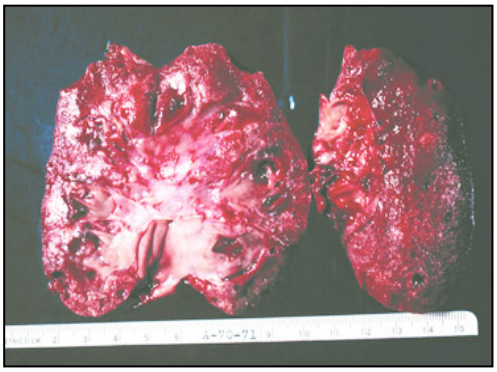
Chronic Nephritic Syndrome:

- Azotemia
- Active urine sediment (variable)
- Proteinuria (variable)
- Past history of RPGN, nephrotic syndrome, or nephritic syndrome
- Hypertension

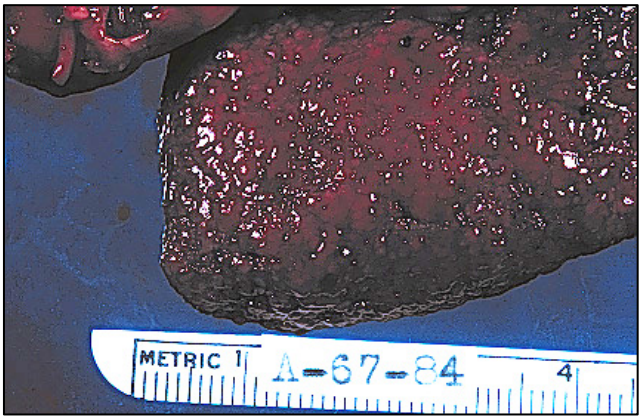
Chronic Nephritic Syndrome:

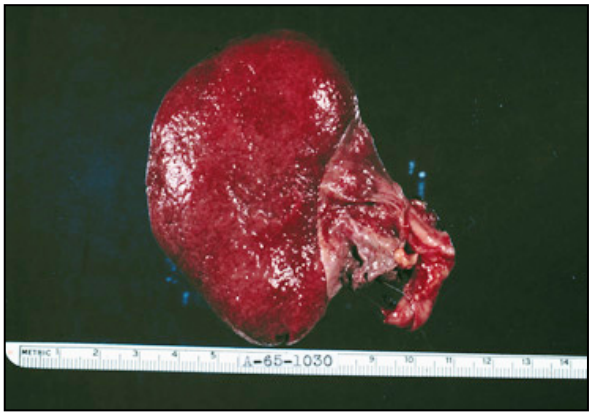
The structural equivalent of this syndrome is end-stage renal disease, with widespread global glomerular obsolescence (sclerosis), tubular atrophy, interstitial fibrosis, and variable degree of arterial and arteriolar sclerosis. A more precise diagnosis can often be established by immunohistochemical and ultrastructural studies.



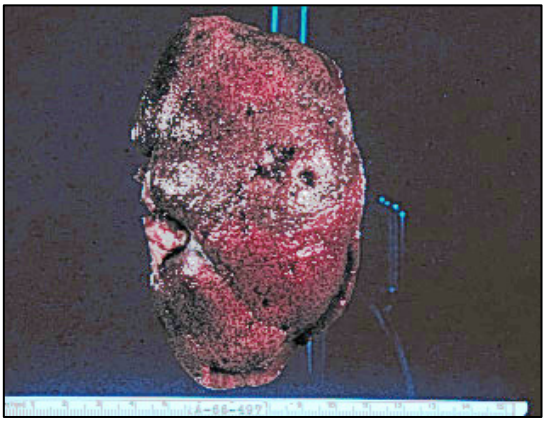


"End stage kidney" of chronic glomerulonephritis. These are severely contracted kidneys each measure about 2 x 3".. Notice the cortices small amount of parenchyma and the finely granular surfaces. Such kidneys are incompatible with life.

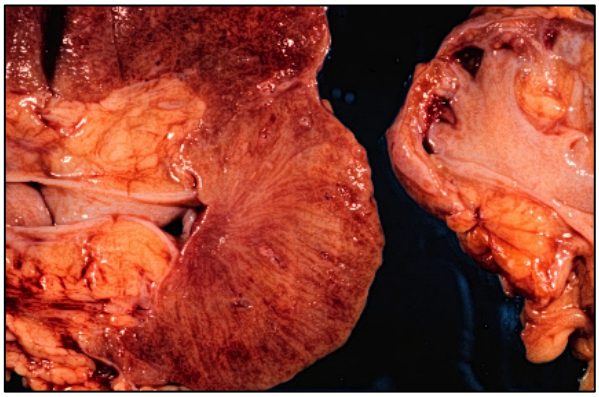




"End stage kidney" of chronic glomerulonephritis. This is the kidney of a 38-year-old man who presented with an insidious onset of the three signs of uremia, that is loss of appetite, lethargy, and the laboratory finding of an increased BUN. He had no antecedent history of acute glomerulonephritis.



Contracted kidney with a finely granular surface representing another glomerular disease, Kimmelstiel-Wilson disease or diabetic glomerulosclerosis. Grossly is indistinguishable from chronic glomerulonephritis. Notice larger scars rather shallow pits on the surface: these represent chronic pyelonephritis another disease that diabetics are apt to develop.



This is a close-up photograph of a cross-section of a kidney with chronic glomerulonephritis. The cortex has largely turned to scar tissue and there is a poor demarcation between cortex and medulla due to the glomerular scarring.

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Qusai Abdulbaqi Ajlan

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Zeyad Abdulaziz Alsalem

قال صلى الله عليه وسلم: (من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة).

دعواتنا لكم بالتوفيق.