The Kidney

Acute glomerulonephritis
Chronic glomerulonephritis
Chronic pyelonephritis
Diabetic glomerulopathy
Urothelial cell carcinoma
Renal cell carcinoma

Glomerular Diseases

I. Primary Glomerular Diseases
- Minimal-change disease
- Focal and segmental glomerulosclerosis
- Membranous nephropathy
- Acute postinfectious GN
- Membranoproliferative GN
- IgA nephropathy
- Chronic GN

II. Glomerulopathies Secondary to Systemic Diseases
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- GN secondary to lymphoplasmacytic disorders
- Goodpasture syndrome
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III. Hereditary Disorders
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- Podocyte/alpha-diaphanous protein mutations

The major clinical glomerular syndromes:

Nephrotic syndrome
and
Nephritic syndrome

The nephrotic syndrome refers to a clinical complex that includes the following:
1. massive proteinuria, with daily protein loss in the urine of 3.5 g/day or more;
2. hypalbuminemia, with plasma albumin levels less than 3 gm/dL;
3. generalized edema, the most obvious clinical manifestation; and
4. hyperlipidemia and lipiduria.

The relative frequencies of the several causes of the nephrotic syndrome vary according to age. In children, for example, the nephrotic syndrome is almost always caused by a lesion primary to the kidney, whereas among adults it is often due to renal manifestations of a systemic disease.

ADULTS
- Systemic disease (40%) - diabetes, amyloidosis, and SLE.
- Primary disease (60%) - the most frequent - focal and segmental glomerulosclerosis (FSGS).

CHILDREN
- Systemic disease (5%)
- Primary disease (95%) - the most frequent - Minimal-change disease (MCD).

Azotemia - Uremia

Azotemia refers to an elevation of blood urea nitrogen and creatinine levels and is largely related to a decreased glomerular filtration rate (GFR).

Azotemia is produced by many renal disorders (Renal azotemia), but it also arises from extrarenal disorders.

Prerenal azotemia is encountered when there is hypoperfusion of the kidneys, which decreases GFR in the absence of parenchymal damage.

Postrenal azotemia can result when urine flow is obstructed below the level of the kidney.

When azotemia progresses to clinical manifestations and systemic biochemical abnormalities, it is termed uremia.

Uremia is characterized not only by failure of renal excretory function but also by a host of metabolic and endocrine alterations incident to renal damage. There is, in addition, secondary gastrointestinal (e.g., uremic gastroenteritis), neuromuscular (e.g., peripheral neuropathy), and cardiovascular (e.g., uremic fibrinous pericarditis) involvement.

Minimal-Change Disease-MCD (Lipoid Nephrosis)

This relatively benign disorder is the most frequent cause of the nephrotic syndrome in children.

It is characterized by glomeruli that have a normal appearance by light microscopy but show diffuse effacement of podocyte foot processes when viewed with the electron microscope.

Although it may develop at any age, this condition is most common between ages 1 and 7 years.

The pathogenesis of proteinuria in minimal change disease remains to be clearly elucidated.

Based on some experimental studies, the proteinuria has been attributed to a T-cell derived factor that causes podocyte damage and effacement of foot processes. However, neither the nature of such a putative factor nor a causal role of T cells is established in the human disease, and there is no good experimental model of minimal change disease.
Minimal-Change Disease - Morphology

With the light microscope, the glomeruli in minimal change disease appear normal. The cells of the proximal convoluted tubules are often heavily laden with protein droplets and lipids, but this is secondary to tubular reabsorption of the lipoproteins passing through the diseased glomeruli. This appearance of the proximal convoluted tubules is the basis for the older term for this disorder, lipid nephrosis.

![Glomerulus stained with PAS. Note normal basement membranes and absence of proliferation.](image)

Minimal-Change Disease - Morphology

With the electron microscope the only obvious glomerular abnormality is the uniform and diffuse effacement of the foot processes of the podocytes. The GBM appears normal. The cytoplasm of the podocytes thus appears flattened over the external aspect of the GBM, obliterating the network of arcades between the podocytes and the GBM. There are also epithelial cell vacuolization, microvillus formation, and occasional focal detachments. When the changes in the podocytes reverse (e.g., in response to corticosteroids), the proteinuria remits.

![Ultrastructural characteristics of minimal-change disease include effacement of foot processes (arrows) and absence of deposits. CL, capillary lumen; M, mesangium; P, podocyte cell body.](image)

Minimal-Change Disease – Clinical course

- The disease manifests itself by development of the nephrotic syndrome in an otherwise healthy child. There is no hypertension, and renal function is preserved in most individuals.
- The prognosis in children with this disorder is good. More than 90% of cases respond to a short course of corticosteroid therapy; however, proteinuria recurs in more than two-thirds of the initial responders, some of whom become steroid dependent.
- Less than 5% develop chronic renal failure after 25 years, and it is likely that most persons in this subgroup had nephrotic syndrome caused by focal and segmental glomerulosclerosis not detected by biopsy.
- Adults with MCD also respond to steroid therapy, but the response is slower and relapses are more common.

Focal and Segmental Glomerulosclerosis (FSGS)

Focal segmental glomerulosclerosis (FSGS) is a lesion characterized histologically by sclerosis affecting some but not all glomeruli (focal involvement) and involving only segments of each affected glomerulus. This histologic picture is often associated with the nephrotic syndrome and can occur:
- as a primary disease
- in association with other known conditions, such as HIV infection or heroin abuse (human immunodeficiency virus nephropathy, heroin nephropathy);
- as a secondary event in other forms of GN (e.g., immunoglobulin A- IgA nephropathy);
- in inherited or congenital forms resulting from mutations affecting cytoskeletal or related proteins expressed in podocytes (e.g., nephrin).

FSGS- MORPHOLOGY

The affected glomeruli exhibit increased mesangial matrix, obliteration of capillary lumens, and deposition of hyaline masses (hyalinosis) and lipid droplets. Occasionally, glomeruli are completely sclerosed (global sclerosis).

![Focal segmental glomerulosclerosis, PAS stain. A, Low-power view showing segmental sclerosis in one of three glomeruli (at 3 o'clock). B, High-power view showing hyaline insudation and lipid (small vacuoles) in sclerotic area.](image)

Focal and Segmental Glomerulosclerosis (FSGS)

- It is becoming an increasingly common cause of nephrotic syndrome in adults and remains a frequent cause in children.
- In children it is important to distinguish this cause of the nephrotic syndrome from MCD, because the clinical courses are markedly different.
- Unlike MCD, there is a higher incidence of hematuria and hypertension in persons with this lesion; their proteinuria is nonselective, and in general their response to corticosteroid therapy is poor.
- At least 50% of individuals with FSGS develop end-stage renal failure within 10 years of diagnosis. Adults in general fare even less well than children.
THE NEPHRITIC SYNDROME

The nephritic syndrome is a clinical complex, usually of acute onset, characterized by:
1. hematuria with dysmorphic red cells and red blood cell casts in the urine,
2. some degree of oliguria and azotemia, and
3. hypertension.

Although there may also be some proteinuria and even edema, these are usually not as severe as in the nephrotic syndrome.

The acute nephritic syndrome may be produced by systemic disorders such as SLE, or it may be the result of primary glomerular disease. The latter is exemplified by acute postinfectious GN.

Acute glomerulonephritis
Syn. postinfectious, poststreptococcal GN

Pathogenesis

It is generally agreed that immune complex deposition is involved in the pathogenesis of acute poststreptococcal GN.

Typical features of immune complex disease, such as hypocomplementemia and granular deposits of IgG and complement on the GBM, are seen.

The relevant antigens are probably streptococcal proteins, but their identity is not established.

It is also not clear if immune complexes are formed mainly in the circulation or in situ (the latter by binding of antibodies to bacterial antigens “planted” in the GBM).

Acute glomerulonephritis
Syn. postinfectious, poststreptococcal GN

MORPHOLOGY - electron microscopy:

Electron microscopy shows deposited immune complexes arrayed as subendothelial, intramembranous, or, most often, subepithelial "humps" nestled against the GBM. Mesangial deposits are also occasionally present. Immunofluorescence studies reveal scattered granular deposits of IgG and complement within the capillary walls and some mesangial areas, corresponding to the deposits visualized by electron microscopy. These deposits are usually cleared over a period of about 2 months.
Chronic glomerulonephritis (ch.g)

Ch.g. represents the end-stage of various types of glomerulopathies (prominent among which are the crescentic GN, FSGS, MG and MPGN). It is an important cause of end-stage renal disease presenting as chronic renal failure. Among all individuals who require chronic hemodialysis or renal transplantation, 30% to 50% have the diagnosis of chronic GN. By the time chronic GN is discovered, the glomerular changes are so far advanced that it is difficult to discern the nature of the original lesion. It probably represents the end stage of a variety of entities. It has been estimated that 20% of cases arise with no history of symptomatic renal disease.

Although chronic GN may develop at any age, it is usually first noted in young and middle-aged adults.

Primary glomerular diseases leading to chronic glomerulonephritis (GN).
The thickness of the arrows reflects the approximate proportion of patients in each group who progress to chronic GN: poststreptococcal (1% to 2%); rapidly progressive (crescentic) (90%), membranous (30% to 50%), focal segmental glomerulosclerosis (50% to 80%), membranoproliferative GN (50%), IgA nephropathy (IgAN, 30% to 50%).

Chronic glomerulonephritis (ch.g)- morphology

MA: Classically, the kidneys are symmetrically contracted and their surfaces are red-brown and diffusely granular.

MI: The feature common to all cases is advanced scarring of the glomeruli (complete or partial). This obliteration of the glomeruli is the end point of many diseases, and it is impossible to ascertain from such kidneys the nature of the earlier lesion. There is also marked interstitial fibrosis, associated with atrophy of many of the tubules in the cortex. The small and medium-sized arteries are frequently thick walled, with narrowed lumina, secondary to hypertension. 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 are designated "end-stage kidneys."

Acute pyelonephritis (a.p)

A.p. is an acute disorder of kidney caused by direct bacterial contamination. Bacteria may reach the kidney by: ➢ ascending route (by migration through urinary tract)– much more common or by ➢ descending one (by bloodstream).

Factors predisposing to the urinary tract infection (UTI) and kidney infection include:
- increased urine content in the bladder after micturition (BPH, pregnancy)
- glycosuria in diabetics
- vesicoureteral reflux (VUR)
- urolithasis
- instrumentation of the urinary tract

Pathogenesis.
The principal causative organisms are the enteric gram-negative rods. *Escherichia coli* is by far the most common one. Other important organisms are species of *Proteus*, *Klebsiella*, *Enterobacter*, and *Pseudomonas*; *Staphylococci* and *Streptococcus faecalis* may also cause pyelonephritis, but they are uncommon.

Renal calculi

Materials making up renal stones:
- calcium: 75% of stones (calcium oxalate or phosphate) radiodense
- *Proteus mirabilis* induce alkaline urine: precipitation of magnesium ammonium phosphate, 15%, (a catlike formation of the renal pelvis — “staghorn calculi”) — infections, pain, bleeding, urosepsis
- uric acid: less than 10% of stones; in patients with gout and hyperuricemia
- cystine: 1% of stones, in childhood, hereditary cystinuria

Staghorn calculi
**Acute pyelonephritis (a.p.) - morphology**

One or both kidneys may be involved. The affected kidney may be normal in size or enlarged.

**MA:** Kidney shows yellowish areas of suppuration in the medullae or small abscesses in the subcapsular region.

**MC:** Diffuse infiltration of the stroma with neutrophils and formation of multiple abscesses are characteristic histological features. The tubules are filled with pus. Typically, the glomeruli are not affected.

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**Chronic pyelonephritis (ch.p)**

Chronic pyelonephritis is a chronic primarily interstitial inflammation of the kidney, associated with destruction of the glomeruli and tubules.

It occurs in patients at any age, especially those with chronic impairment of urine outflow, vesicoureteric reflux and diabetes mellitus.

Frequently, the condition is insidious, clinically silent until renal insufficiency or arterial hypertension develops.

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**Diabetic glomerulopathy**

*Diabetes mellitus* alters the renal structure and function affecting not only glomeruli but also causing arterio- and arteriolosclerosis, necrotizing renal papillitis or facilitating the development of acute and chronic pyelonephritis.

The morphologic manifestations of diabetic nephropathy are identical in type 1 and type 2 diabetes.

The morphologic changes in the glomeruli include:

1. capillary basement membrane thickening.
2. diffuse mesangial sclerosis, and
3. nodular glomerulosclerosis.

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**Capillary Basement Membrane Thickening.**

The glomerular capillary basement membranes are thickened throughout their entire length. This change can be detected by electron microscopy within a few years of the onset of diabetes, sometimes without any associated change in renal function.
Diabetic glomerulopathy

Diffuse mesangial sclerosis consists of a diffuse increase in mesangial matrix along with mesangial cell proliferation and is always associated with basement membrane thickening. It is found in most individuals with disease of more than 10 years duration. When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome.

Diabetic glomerulopathy

Nodular glomerulosclerosis describes a glomerular lesion made distinctive by ball-like deposits of a laminated matrix situated in the periphery of the glomerulus. These nodules are PAS positive and usually contain trapped mesangial cells. This distinctive change has been called the Kimmelstiel-Wilson lesion. N.g, is encountered in approximately 15% to 30% of long-term diabetics and is a major cause of morbidity and mortality. Diffuse mesangial sclerosis may also be seen in association with old age and hypertension; on the contrary, the nodular form of glomerulosclerosis is essentially pathognomonic of diabetes.

Diffuse and nodular diabetic glomerulosclerosis (PAS stain). Note the diffuse increase in mesangial matrix and characteristic acellular PAS-positive nodules.

Nodular glomerulosclerosis in a person with long-standing diabetes

Urothelial cell carcinoma

The entire urinary collecting system from renal pelvis to urethra is lined with transitional epithelium, so its epithelial tumors assume similar morphologic patterns. Tumors in the collecting system above the bladder are relatively uncommon; those in the bladder, however, are an even more frequent cause of death than are kidney tumors.

Morphology:

Tumors arising in the urinary bladder range from small benign papillomas to large invasive cancers.

These tumors are classified into:

- a rare benign papilloma,
- a group of papillary urothelial neoplasms of low malignant potential, and
- two grades of urothelial carcinoma (low and high grade).

Urothelial cell carcinoma

Urothelial (transitional) cell carcinomas range from papillary to flat, noninvasive to invasive, and low grade to high grade.

Papilloma—papillary carcinoma

Invasive papillary carcinoma

Flat noninvasive carcinoma

Flat invasive carcinoma

Four morphologic patterns of bladder tumor.

Low-grade papillary urothelial carcinoma of the bladder. The delicate papilla is covered by orderly transitional epithelium.

Renal cell carcinoma (RCC)

RCCs are derived from the renal tubular epithelium, and hence they are located predominantly in the cortex.

Renal carcinomas represent 80% to 85% of all primary malignant tumors of the kidney, and 2% to 3% of all cancers in adults. Carcinomas of the kidney are most common from the sixth to seventh decades, and men are affected about twice as commonly as women. The risk of developing these tumors is higher in:

- smokers,
- hypertensive or obese patients, and
- those who have had occupational exposure to cadmium.

Smokers who are exposed to cadmium have a particularly high incidence of renal cell carcinomas.

The risk of developing renal cell cancer is increased 30-fold in individuals who develop acquired polycystic disease as a complication of chronic dialysis.
Renal cell carcinoma (RCC)

The three most common forms of RCCs are as follows:

- **Clear Cell Carcinomas (70-80%)**
- **Papillary Renal Cell Carcinomas (10-15%)**
- **Chromophobe Renal Carcinomas (5%)**

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Clear Cell Renal Carcinomas - morphology

- CCCs are usually solitary and large when symptomatic (spherical masses 3-15 cm in diameter)
- They may arise anywhere in the cortex.
- The cut surface of clear cell renal cell carcinomas is yellow to orange to gray-white, with prominent areas of cystic softening or of hemorrhage.
- The margins of the tumor are well defined. However, at times small processes project into the surrounding parenchyma and small satellite nodules are found in the surrounding substance.
- As the tumor enlarges, it may fungate through the walls of the collecting system, extending through the calyces and pelvis as far as the ureter.
- Even more frequently, the tumor invades the renal vein and grows as a solid column within this vessel, sometimes extending in serpentine fashion as far as the inferior vena cava and even into the right side of the heart.
- Occasionally, there is direct invasion into the perinephric fat and adrenal gland.

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Clear Cell Renal Carcinomas - morphology

**HISTOLOGICALLY** the tumor consists of large pale cells with abundant foamy cytoplasm due to cytoplasmic lipids and glycogen. The classic vaculated (lipid-laden), or clear cells are demarcated only by their cell membranes. Vesicular nuclei are situated centrally and may show atypia of various degree. The cells may form abortive tubules or may cluster in cords or disorganized masses. The stroma is usually scant but highly vascularized.

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RCC - Clinical Course

The symptoms vary, but the most frequent presenting manifestation is **hematuria**, occurring in more than 50% of cases.

Less commonly the tumor may declare itself simply by virtue of its size, when it has grown large enough to produce **flank pain** and a palpable mass.

- Extra-renal effects are fever and polycythemia, both of which may be associated with a RCC (they are nonspecific).
- Uncommonly, these tumors produce a variety of hormone-like substances, resulting in hypercalcemia, hypertension, Cushing syndrome, or feminization or masculinization.

In many individuals the primary tumor remains silent and is discovered only after its metastases have produced symptoms. The prevalent locations for metastases are the lungs and the bones.

It must be apparent that renal cell carcinoma presents in many fashions, some quite devious, but the triad of painless hematuria, a palpable abdominal mass, and dull flank pain is characteristic.
Wilms’ Tumor = Nephroblastoma

WT is the most common primary tumor of the kidney in children. Most cases occur in children between 2 and 5 years of age.

Three groups of congenital malformations are associated with an increased risk of developing Wilms’ tumor.

1. Patients with the WAGR syndrome, characterized by aniridia, genital abnormalities, and mental retardation, have a 33% chance of developing Wilms’ tumor.

2. Another group of patients, those with the so-called Denys-Drash syndrome (DDS) also have an extremely high risk (~90%) of developing Wilms’ tumor. This syndrome is characterized by gonadal dysgenesis and renal abnormalities.

Both of these conditions are associated with abnormalities of the Wilms’ tumor 1 (WT1) gene, located on chromosome 11p13.

3. A third group of patients, those with the Beckwith-Wiedemann syndrome (BWS), also have an increased risk of developing Wilms’ tumor.

These patients have enlargement of individual body organs (e.g., tongue, kidneys, or liver) or entire body segments (hemihypertrophy); enlargement of adrenal cortical cells (adrenal cytomegaly) is a characteristic microscopic feature.

The genetic locus that is involved in these patients is in band p15.5 of chromosome 11 distal to the WT1 locus.

Although this locus is called “WT2” for the second Wilms’ tumor locus, the gene involved has not been identified.

In addition to Wilms’ tumors, patients with BWS are also at increased risk for developing hepatoblastoma, adrenocortical tumors, rhabdomyosarcomas, and pancreatic tumors.

Wilms’ Tumor- MORPHOLOGY

Grossly, Wilms’ tumor tends to present as a large, solitary, well-circumscribed mass, although 10% are either bilateral or multicentric at the time of diagnosis. On cut section, the tumor is soft, homogeneous, and tan to gray, with occasional foci of hemorrhage, cystic degeneration, and necrosis.

Approximately 5% of tumors contain foci of anaplasia (cells with large, hyperchromatic, pleomorphic nuclei and abnormal mitoses).

The classic triphasic combination of blastemal, stromal, and epithelial cell types is observed in most lesions, although the percentage of each component is variable.

- Blastemal component - Sheets of small blue cells
- Epithelial “differentiation” usually takes the form of abortive tubules or glomeruli.
- Stromal cells are usually fibrocytic or myxoid in nature, although skeletal muscle “differentiation” is not uncommon.

Trichiasis histology of Wilms’ tumor: the stromal component is comprised of spindle-shaped cells in the less cellular area on the left; the immature tubule in the center is an example of the epithelial component and the tightly packed blue cells, of the blastemal elements.