THE PATHOLOGY OF THE KIDNEY

INTRODUCTION

Diseases of the kidney are divided into four categories depending on which component of the kidney is primarily affected; these are


This division is useful because

a. The early manifestations of each group of diseases tend to be distinctive.

b. These groups differ in their pathogenesis, for e.g., glomerular diseases are often immunologically mediated, whereas tubular and interstitial disorders are more likely to be caused by toxic or infectious agents. However, it should be noted that

1. The interdependence of renal components translated into that damage to one component is almost always affects secondarily the others.

2. All forms of chronic renal disease tend ultimately to damage all four components of the kidney thus, eventuates in chronic renal failure (end-stage kidney disease).

Clinical Manifestations of Renal Diseases

These can be grouped into well-defined syndromes, each of which is distinctive to the component that is primarily affected. At this point certain terms need to be clarified

Azotemia is an "elevation of blood urea, nitrogen and creatinine levels". It is largely related to a decreased glomerular filtration rate (GFR). Azotemia is divided into

1. Prerenal azotemia, encountered with hypoperfusion of the kidneys, which decreases GFR as in shock states

2. Renal, which is due to renal parenchymal damage

3. Postrenal that results from urine out flow obstruction below the level of the kidney.

Uremia signifies "azotemia associated with biochemical and systemic clinicopathological alterations" such as metabolic and endocrine changes, uremic gastroenteritis, peripheral neuropathy and fibrinous pericarditis.

The major renal syndromes are

Acute nephritic syndrome is characterized by acute onset of usually gross hematuria, mild to moderate proteinuria, azotemia, edema, and hypertension; it is the classic presentation of acute poststreptococcal glomerulonephritis.

The nephrotic syndrome is characterized by heavy proteinuria (excretion of >3.5 gm of protein/day in adults), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria.

Asymptomatic (microscopic) hematuria or proteinuria, or a combination thereof, is usually a manifestation of mild glomerular abnormalities.

Acute renal failure refers to recent onset of oliguria or anuria, with azotemia.

Chronic renal failure refers to prolonged symptoms and signs of uremia; it is the end result of all chronic renal diseases.

Urinary tract infection (UTI) is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine. The infection may be symptomatic or asymptomatic, and may affect the kidney (pyelonephritis) or the bladder (cystitis) only.

Nephrolithiasis (renal stones) is manifested by renal colic, hematuria, and recurrent stone formation.

GLOMERULAR DISEASES

The glomerulus consists of an anastomosing network of capillaries invested by two layers of epithelium; visceral & parietal. The visceral epithelium (podocytes) is an intrinsic part of the capillary wall, whereas the parietal epithelium lines Bowman
space (urinary space), the cavity in which plasma ultrafiltrate first collects. The glomerular capillary wall is the filtration unit and consists of the following structures:
1. A thin layer of fenestrated endothelial cells (each hole is about 100 nm in diameter).
2. Glomerular basement membrane (GBM), ultrastructurally made up of a thick, dense central layer (lamina densa), and thinner, lucent peripheral layers, (lamina rara interna & externa).
3. The visceral epithelial cells (podocytes) that possess foot processes adherent to the lamina rara externa of the basement membrane. Adjacent foot processes are separated by 25-nm-wide filtration slits bridged by a thin slit diaphragm composed in largely of nephrin.
4. The entire glomerular tuft is supported by mesangial cells lying between the capillaries. Basement membrane-like mechanical matrix forms a meshwork through which the mesangial cells are scattered.

The glomerular basement membrane shows selective permeability, which is size-dependent and charge-dependent. The major characteristics of glomerular filtration are
1. A high permeability to water and small solutes
2. Almost complete impermeability to molecules of the size and molecular charge of albumin.
3. More permeability to cations than anions.

The podocyte is decisive to the glomerular barrier function by providing a distal resistance to the flow of water and a barrier to the filtration of proteins. It is also largely responsible for synthesis of GBM components.

PATHOGENESIS OF GLOMERULAR DISEASES

Immune mechanisms (antibody-associated & cellular) underlie most primary and many secondary glomerular diseases.

Circulating Immune Complex-mediated Nephritis (type III hypersensitivity reactions)

With circulating immune complex-mediated disease, the glomerulus is an “innocent bystander” because it is not responsible for their formation. The antigen in these complexes may be
1. Endogenous, as in SLE or
2. Exogenous, as in bacterial (streptococcal), viral (hepatitis B), parasitic (Plasmodium falciparum malaria), and spirochetal (Treponema pallidum) infections.
3. Unknown as often the case in membranous nephropathy.

The antigen-antibody complexes are trapped in the glomeruli, where they produce injury, mainly through the activation of complement and the recruitment of leukocytes. Electron microscopy reveals the immune complexes as electron-dense deposits or clumps that are:
1. Mesangial
2. Subendothelial i.e. between the endothelial cells and the GBM
3. Subepithelial i.e. at the outer surface of the GBM and the podocytes

The presence of immunoglobulins and complement in these deposits can be demonstrated by immunofluorescence microscopy. When fluoresceinated anti-immunoglobulin or anti-complement antibodies are used, the immune complexes are seen as granular deposits in the glomerulus.

Cell-Mediated Immune Glomerulonephritis
T cell-mediated injury may account for some cases of glomerulonephritis (GN) in which either there are no deposits of antibodies or immune complexes, or the deposits do not correlate with the severity of damage.

**Mediators of Immune Injury**

A major pathway of antibody-initiated injury is activation of the complement that leads to the generation of chemotactic agents (mainly C5a) and thus recruitment of neutrophils and monocytes. Neutrophils in turn release

1. Proteases, which cause GBM degradation;
2. Oxygen-derived free radicals, which cause cell damage; and
3. Arachidonic acid metabolites, which contribute to reduction in GFR.

In some cases, however, complement-dependent (but not neutrophil-dependent) injury occurs through the effect of the C5-C9 lytic component (membrane attack complex) of complement, which causes

1. Epithelial cell detachment and
2. Stimulation of mesangial and epithelial cells to secrete various mediators of cell injury.
3. Up-regulation of transforming growth factor-β (TGF-β) receptors on podocytes; TGF-β stimulates synthesis of extracellular matrix, thus giving rise to altered GBM composition and thickening.

**Nephritis Caused by In Situ Immune Complexes**

Antibodies in this form of injury react directly with planted antigens in the glomerulus. The best-characterized disease in this group is anti-GBM antibody GN, where antibodies are directed against fixed antigens in the GBM. It results from the formation of autoantibodies directed against the GBM. Deposition of these antibodies creates a linear pattern of staining when visualized with immunofluorescence microscopy, this is in contrast to the granular pattern described for other forms of immune complex-mediated nephritis. Sometimes, the anti-GBM antibodies cross-react with basement membranes of lung alveoli, resulting in combined lung and kidney lesions (Goodpasture syndrome). Planted antigens also include DNA, bacterial products, aggregated IgG, which deposit in the mesangium because of their size. Most of these planted antigens induce a granular pattern of immunoglobulin deposition as seen by immunofluorescence microscopy.

**Other Mechanisms of Glomerular Injury**

1. **Podocyte injury:** this can be induced by antibodies to visceral epithelial cell antigens as in some cases of focal and segmental glomerulosclerosis. Such injury is reflected by effacement of podocyte's foot processes associated with proteinuria. In most forms loss of normal slit diaphragms is a key feature in the development of proteinuria.
2. **Nephron Loss:** any renal disease destroying sufficient nephrons to the extent of reducing the GFR to 30%-50% of normal shows relentless progression to end-stage renal failure. Such individuals develop proteinuria, and their kidneys show widespread glomerulosclerosis. The latter is initiated by the adaptive hypertrophy of the remaining unaffected glomeruli to maintain renal function. These adaptations ultimately lead to further endothelial and epithelial cell injury, which is followed by capillary collapse and obliteration, increased deposition of mesangial matrix, and eventually by segmental or global sclerosis of glomeruli. This results in further reductions in the nephron mass and a vicious cycle of continuing glomerulosclerosis.

**THE NEPHROTIC SYNDROME**

This refers to a clinical complex that includes
1. Massive proteinuria i.e. daily urine protein loss of 3.5 gm or more in adults
2. Hypoalbuminemia i.e. plasma albumin levels less than 3 gm/dl
3. Generalized edema
4. Hyperlipidemia and lipiduria

The initial event is a derangement in the glomerular capillary walls that leads to increased permeability to plasma proteins allowing their escape from the plasma into the glomerular filtrate. With long-standing or extremely heavy proteinuria, serum albumin is decreased, resulting in hypoalbuminemia. The generalized edema is, in turn, a consequence of the drop in plasma colloid osmotic pressure as a result of hypoalbuminemia, and retention of salt and water by the kidney. As fluid escapes from the vascular tree into the tissues, there is a concomitant drop in plasma volume, with diminished glomerular filtration. Compensatory secretion of aldosterone, along with the reduced GFR and reduction of secretion of natriuretic peptides, promotes retention of salt and water by the kidneys, thus further aggravating the edema. By repetition of this chain of events, generalized edema (anasarca) may develop. It is possible that hypoalbuminemia triggers increased synthesis of lipoproteins in the liver & thus hyperlipidemia. The lipiduria reflects the increased permeability of the GBM to lipoproteins.

The relative frequencies of the several causes of the nephrotic syndrome vary according to age. In children 1 to 7 years of age, the nephrotic syndrome is almost always caused by a primary kidney disease, whereas among adults it is often due to renal manifestations of a systemic disease. The most frequent systemic causes of the nephrotic syndrome in adults are
1. Diabetes
2. Amyloidosis
3. SLE

The most important primary glomerular lesions that lead to the nephrotic syndrome are
1. Focal and segmental glomerulosclerosis (FSGS), which is more important in adults.
2. Minimal-change disease (MCD), which is more important in children
3. Membranous nephropathy
4. Membranoproliferative GN

Minimal-Change Disease (MCD) (Lipoid Nephrosis)
This is the most frequent cause of the nephrotic syndrome in children, mostly between ages 1 and 7 years (65%). The glomeruli have a normal appearance under light microscopy; however, electron microscopy shows diffuse effacement of podocyte foot processes. This is presumably due to a T-cell derived factor that causes podocyte damage. The cells of the proximal convoluted tubules are often heavily loaded with protein droplets and lipids secondary to tubular reabsorption of the leaking lipoproteins. The renal function is preserved in most individuals. The protein loss is confined to the smaller serum proteins, chiefly albumin (selective proteinuria). The prognosis in children with this disorder is generally good; more than 90% of cases respond to a short course of corticosteroid therapy.

Focal and Segmental Glomerulosclerosis (FSGS) is characterized histologically by sclerosis (fibrosis) affecting some but not all glomeruli (focal) and involving only segments of each affected glomerulus (segmental). FSGS is either primary
(idiopathic) or secondary. The former is a common cause of nephrotic syndrome in adults (30%) & frequent cause in children (10%). The secondary form is seen with
1. HIV immunodeficiency or heroin abuse (HIV nephropathy, heroin nephropathy)
2. IgA nephropathy
3. Maladaptation after nephron loss (see above)
4. Mutations affecting cytoskeletal proteins of podocytes (e.g., nephrin) (inherited form)

Unlike MCD, there is a higher incidence of hematuria and hypertension; the proteinuria is nonselective, and the response to corticosteroid therapy is poor. At least 50% of individuals with FSGS develop end-stage renal failure within 10 years of diagnosis. The pathogenesis of primary FSGS is unknown. As with MCD, permeability-increasing factors produced by lymphocytes have been proposed. The entrapment of plasma proteins and lipids occurs in foci of injury where sclerosis develops. FSGS initially affects focally the juxtamedullary glomeruli. With progression, eventually all levels of the cortex are affected. The affected segment of the glomerulus shows increased mesangial matrix, obliterated capillary lumens, and deposition of hyaline masses. In time, progression of the disease leads to global sclerosis of the glomeruli with secondary tubular atrophy and interstitial fibrosis. About 50% of individuals suffer renal failure after 10 years.

Membranous Nephropathy (Membranous Glomerulonephritis, MGN)
This is a slowly progressive disease, most common in adults 30 to 50 years of age. The disease is idiopathic (primary) in about 85% of cases. In the remainder it may be secondary to other disorders, including:
1. Infections (chronic hepatitis B, syphilis, schistosomiasis, malaria)
2. Malignancy, particularly lung and colonic carcinomas and melanoma
3. Autoimmune diseases e.g. SLE
4. Exposure to inorganic salts (gold, mercury)
5. Drugs (penicillamin, captoril, NSIAD)

MGN is a chronic immune complex nephritis. Most idiopathic forms are considered autoimmune disease caused by antibodies to renal GBM autoantigen. There seems to be a direct action of C5b-C9 (the membrane attack complex) on the podocyte and mesangial cells, inducing them to liberate proteases and oxidants that can cause the damage. The basic change microscopically is diffuse thickening of the GBM. By electron microscopy, this thickening is caused by subepithelial deposits that are separated from each other by small, spike-like protrusions of GBM matrix ("spike and dome" pattern); these can be highlighted by silver stains. With progression, these spikes close over the deposits, to incorporate them into the GBM. Podocytes show effacement of foot processes. Eventually the glomeruli become gradually sclerosed. Immunofluorescence microscopy shows typical granular deposits of immunoglobulins and complement along the GBM. The proteinuria is nonselective, involving globulins and albumin molecules. Overall, only 40% suffer progressive disease terminating in renal failure after 2 to 20 years.

Membranoproliferative Glomerulonephritis (MPGN)
This is manifested histologically not only by GBM thickening but also by proliferation of glomerular cells. It accounts for up to 10% of cases of primary nephrotic syndrome in children and adults. Some individuals present only with hematuria or subnephotic proteinuria; others have a combined nephrotic-nephritic picture. Two major types of MPGN (I and II) are recognized; type I is far more
common (80% of cases). Different pathogenic mechanisms are involved in the development of type I and type II disease. Most cases of type I MPGN seem to be caused by circulating immune complexes, but the inciting antigen is not known (primary); it also occurs as a secondary form in association with hepatitis B and C antigenemia, SLE, & extra-renal infections. The fundamental abnormality in type II appears to be excessive complement activation. By light microscopy, both types of MPGN are similar. The glomeruli are large, with an accentuated lobular appearance, and proliferation of mesangial and endothelial cells as well as leukocytic infiltration. The GBM is thickened, and the glomerular capillary wall often shows a double contour, or "tram track," appearance, especially evident in silver or periodic acid-Schiff (PAS) stains. This is caused by "splitting" of the GBM due to the inclusion within it of processes of mesangial and inflammatory cells. Types I and II have different ultrastructural and immunofluorescence microscopic features. The prognosis of MPGN is generally poor in that 40% of the cases progressed to end-stage renal failure. Type II MPGN (also called dense-deposit disease) has a worse prognosis.

THE NEPHRITIC SYNDROME
This is a clinical complex, usually of acute onset, characterized by
1. Hematuria
2. Oliguria with azotemia
3. Hypertension
The lesions that cause the nephritic syndrome have in common proliferation of the cells within the glomeruli, accompanied by leukocytic infiltrate. This inflammatory reaction injures the capillary walls, permitting escape of red cells into the urine, and induces hemodynamic changes that lead to a reduction in the GFR. The reduced GFR is manifested clinically by oliguria, fluid retention, and azotemia. Hypertension is the result of both the fluid retention and excessive renin release. The acute nephritic syndrome may be secondary to a systemic disorders such as SLE, or it may be the result of primary glomerular disease e.g. acute postinfectious GN.

Acute postinfectious (Poststreptococcal) GN is typically associated with streptococcal infection, but other infectious agents may be responsible. The latter include certain pneumococcal and staphylococcal infections, as well as some common viral diseases such as mumps, measles, chickenpox, and hepatitis B and C. The classic case of poststreptococcal GN develops in a child 1 to 4 weeks after recovery from "nephritogenic" strains of β-hemolytic, group A streptococcal infection, usually of the pharynx or skin. Immune complex deposition is involved in the pathogenesis. The relevant antigens are probably streptococcal proteins. Serum complement levels are low and serum anti-streptolysin O antibody titers are elevated. Characteristically the histology shows a uniformly increased cellularity of the glomerular tufts that affects nearly all glomeruli. This increased cellularity is caused both by proliferation and swelling of both endothelial and mesangial cells as well as by a neutrophilic and monocytic infiltrate. Electron microscopy shows subepithelial "humps". Immunofluorescence displays these immune complexes as scattered granular deposits of IgG and complement within the capillary walls. Recovery occurs in most children. Conversely up to 50% of adults develop end-stage renal disease.

IgA Nephropathy (Berger Disease) usually affects children and young adults as an episode of gross hematuria occurring within 1 or 2 days of a nonspecific upper respiratory tract infection, to lasts several days and then subsides, only to recur every few months. IgA nephropathy is one of the most common causes of recurrent microscopic or gross hematuria and is the most common glomerular disease revealed
by renal biopsies worldwide. The pathogenic hallmark is the deposition of IgA in the mesangium. IgA nephropathy may be viewed as a localized (renal) variant of Henoch-Schönlein purpura, which is also characterized by IgA deposition in the mesangium but it is a systemic syndrome characterized by purpuric rash, abdominal pain and arthritis. Microscopically, the glomeruli may be normal or show one of the following:

1. Focal proliferative GN
2. Diffuse mesangiproliferative GN
3. Crescentic GN (rare).

The characteristic immunofluorescence picture is of mesangial deposition of IgA. Electron microscopy shows mesangial electron-dense deposits. Serum IgA is increased in 50% of patients due to its increased production in the marrow presumably in response to respiratory or GIT exposure to viruses, bacteria, or food proteins. The deposition of IgA and IgA-immune complexes in the mesangium activate the alternative complement pathway and initiate glomerular injury. Slow progression to chronic renal failure occurs in up to 50% of cases.

**Rapidly Progressive (Crescentic) Glomerulonephritis (RPGN; CrGN)**

This is a clinical syndrome associated, irrespective of the etiology, with glomerular crescents; these are produced by proliferation of the parietal epithelial cells associated with infiltration by monocytes and macrophages. CrGN is characterized clinically by

1. Rapidly progressive loss of renal function
2. Nephritic syndrome
3. Severe oliguria (often)
4. Death from renal failure within weeks to months (if untreated).

A practical classification divides CrGN into three groups on the basis of immunologic findings. In each group, the disease may be associated with a known disorder or it may be idiopathic.

**Type I (Anti-GBM Antibody)**

a. Idiopathic
b. Goodpasture syndrome

This group is characterized by linear IgG deposits along the GBM. In some of these individuals the anti-GBM antibodies also bind to pulmonary alveolar capillary basement membranes to produce the clinical picture of pulmonary hemorrhages associated with renal failure (Goodpasture syndrome). In idiopathic cases the renal involvement occurs in the absence of pulmonary disease. Anti-GBM antibodies are present in the serum and are helpful in diagnosis. Immunofluorescence is characteristic with strong linear staining of deposited IgG and C3 along the GBM; these deposits are not visualized by electron microscopy.

**Type II (Immune Complex)**

a. Idiopathic
b. Postinfectious/infection related
c. SLE
d. Henoch-Schönlein purpura/IgA nephropathy

In all of these cases, immunofluorescence shows the characteristic granular pattern of staining of the GBM and/or mesangium for immunoglobulin and/or complement. In addition to the crescents, segments of glomeruli show evidence of the underlying GN.

**Type III (Pauci-Immune) ANCA Associated**

a. Idiopathic
b. Wegener granulomatosis
c. Microscopic angiitis
This group is defined by the lack morphologically of both anti-GBM antibodies and immune complex deposition. Most of these individuals have antineutrophil cytoplasmic antibodies (ANCA) in the serum. The latter have a role in some vasculitides. Therefore, in some cases type there is a component of a systemic vasculitis. In the idiopathic form the disease is limited to the kidney. The uninvolved segments of glomeruli appear normal. Immunofluorescence studies for immunoglobulin and complement are negative (cf. type I and II), and there are no ultrastructural deposits.

The onset of RPGN is much like that of the nephritic syndrom. Proteinuria sometimes approaching nephrotic range may occur. The prognosis can be related to the number of crescents; those with crescents in less than 80% of the glomeruli have a better prognosis than those with higher percentages of crescents.

**CHRONIC GLOMERULONEPHRITIS** is one of the outcomes of the various glomerular diseases already discussed. It is an important cause of end-stage renal disease. 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 advanced that it is difficult to detect the nature of the original lesion. Classically, the kidneys are symmetrically contracted with red-brown surface. Microscopically, the feature common to all cases is advanced scarring of the glomeruli, sometimes to in the point of complete sclerosis. There is relentless progression to uremia and death. The rate of progression is extremely variable. Renal dialysis and kidney transplantation alter this course and allow long-term survival.

**TUBULO-INTERSTITIAL DISEASES**

Most forms of tubular injury also involve the interstitium, so the two are discussed together. Under this heading are two categories

1. Inflammatory involvement of the tubules and interstitium (tubulo-interstitial nephritis)
2. Ischemic or toxic tubular necrosis leading to acute renal failure

**TUBULOINTERSTITIAL NEPHRITIS (TIN)** is a group of inflammatory diseases of the kidneys primarily involving the interstitium and tubules. The glomeruli are spared or affected late in the course. TIN is subdivided into

1. **Bacterial TIN**, the renal pelvis is prominently involved (pyelonephritis)
2. **Nonbacterial TIN**; these include tubular injury resulting from
   a. drugs
   b. metabolic disorders (e.g. hypokalemia)
   c. physical injury (e.g. irradiation)
   d. viral infections
   e. immune reactions

**Pyelonephritis**

This is divided into acute and chronic forms

**Acute pyelonephritis** is a common bacterial suppurative inflammation of the kidney (nephritis) and renal pelvis (pyelitis); hence the term pyelonephritis. The great majority of cases of pyelonephritis are associated with lower UTI (cystitis, prostatitis, and urethritis). E. coli is by far the most common offender. Other important organisms
are Proteus, Klebsiella, Enterobacter, and Pseudomonas; these are usually associated with recurrent infections, especially due to urinary tract instrumentations (e.g. cystoscopy, catheterization) or congenital or acquired anomalies of the lower urinary tract (e.g. vesicoureteral reflux or polycystic kidney disease, presence of stones, prostatic hyperplasia in the elderly).

**Pathogenesis**

Bacteria can reach the kidneys either through the bloodstream (hematogenous) or from the lower urinary tract (ascending infection). The former is exemplified by acute pyelonephritis complicating septicemia or infective endocarditis. Ascending infection from the lower urinary tract is the most common & is an important route by which bacteria reach the kidney. The evolution of acute pyelonephritis occurs through the following steps

1. **Bacterial adhesion to the urethral urothelium** is influenced by genetically determined properties of both the urothelium and the offending bacteria.
2. **Gaining access to the bladder** is by growth expansion of the colonies and by moving against urine flow; the latter is overcome by urethral instrumentation, including catheterization and cystoscopy. In the absence of instrumentation, UTI most commonly affects females because of factors that facilitate entry of bacteria to the bladder; these are
   a. Close proximity of the urethra to the enteric bacteria-loaded rectum favoring colonization
   b. Short urethra
   c. Trauma to the urethra during sexual intercourse (honeymoon cystitis)
3. **Outflow obstruction**: normally, bladder urine is sterile as a result of the antimicrobial properties of the bladder mucosa and the flushing action of periodic voiding of urine. With outflow obstruction or bladder dysfunction, these natural defenses are overwhelmed, setting the stage for UTI. Obstruction at the level of the urinary bladder (e.g. by prostatic hyperplasia) results in incomplete bladder emptying and hence increased residual volume of urine (urine stasis). In the presence of stasis, bacteria introduced into the bladder can multiply freely, without being flushed out or destroyed by the bladder mucosa. From the contaminated bladder urine, the bacteria ascend along the ureters to infect the renal pelvis and parenchyma. Thus, UTI is particularly frequent in association with benign prostatic hyperplasia in male and uterine prolapse in females. UTI is also frequent in diabetics because of the increased susceptibility to infection and neurogenic bladder, which in turn predisposes to urine stasis.
4. **Vesicoureteral reflux** (VUR): incompetence of the vesicoureteral orifice allows bacterial ascent along the ureter & then into the pelvis. The normal ureteral insertion into the bladder is a competent one-way valve that prevents retrograde flow of urine, especially during micturition, when the intra-vesical pressure rises. An incompetent vesicoureteral orifice allows the reflux of bladder urine into the ureters; this is termed **vesicoureteral reflux (VUR)**. Up to 40% of young children with UTI have this anomaly, which is usually a congenital defect. VUR can also be acquired in individuals with a flaccid bladder resulting from spinal cord injury and with neurogenic bladder dysfunction secondary to diabetes. The effect of VUR is similar to that of an obstruction in that after voiding there is residual urine in the urinary tract, which favors bacterial growth. Furthermore, VUR affords a ready mechanism by which the infected bladder urine can be pushed up to the renal pelvis and further into the renal parenchyma through open ducts at the tips of the papillae (**intrarenal reflux**).

**Gross features of acute pyelonephritis**
• One or both kidneys may be involved. The affected kidney may be normal in size or enlarged.
• Characteristically, discrete, yellowish, raised abscesses are grossly apparent on the renal surface. They are variably scattered and may coalesce to form a single large abscess.
• When obstruction is prominent, the pus may fill the renal pelvis, calyces, and ureter, producing pyonephrosis.

**Microscopic features**

• The characteristic feature of acute pyelonephritis is suppurative inflammation within the renal parenchyma. Both the tubules & interstitium are involved. Large numbers of intratubular neutrophils frequently extend into the collecting ducts, giving rise to the characteristic white cell casts found in the urine.
• Typically, the glomeruli are not affected.

**Papillary necrosis (necrotizing papillitis)**

This is an infrequent form of pyelonephritis, which may be encountered

1. In diabetics
2. With significant urinary tract obstruction
3. Chronic interstitial nephritis associated with analgesic abuse

This lesion consists of ischemic and suppurative necrosis of the renal papillae (tips of the renal pyramids). The pathognomonic gross feature is sharply defined gray-white to yellow necrosis of the apical two-thirds of the pyramids. The involvement ranges from one to all papillae. Microscopically, the papillae show characteristic coagulative necrosis, with surrounding neutrophilic infiltrate.

**Chronic Pyelonephritis (CPN) and Reflux Nephropathy**

For the pathological diagnosis of CPN two criteria must be met

1. Grossly visible scarring deformity of the pelvicalyceal system
2. Microscopic predominance of interstitial inflammation & fibrosis

CPN is an important cause of chronic renal failure. It can be divided into two forms:

1. **Chronic obstructive pyelonephritis**: recurrent infections superimposed on obstructive lesions lead to recurrent bouts of renal inflammation and scarring, which eventually cause chronic pyelonephritis. The disease can be bilateral, as with congenital anomalies of the urethra (posterior urethral valves), or unilateral, such as occurs with calculi and unilateral obstructive lesions of the ureter.

2. **Chronic reflux-associated pyelonephritis** is the more common form and results from superimposition of a UTI on congenital vesicoureteral reflux and intrarenal reflux. Reflux may be unilateral or bilateral; thus, the resultant renal damage is either unilateral or bilateral.

**Gross features**

• One or both kidneys may be involved, either diffusely or in patches. Even when involvement is bilateral, the kidneys are not equally damaged and therefore are not equally contracted. This uneven involvement is useful in differentiating CPN from the more symmetrically contracted kidneys of benign nephrosclerosis and chronic GN.
• The hallmark of CPN is scarring involving the pelvis &/or calyces leading to papillary blunting and marked calyceal deformities

**Microscopic features**

• These are largely non-diagnostic since similar alterations may be seen with other tubulo-interstitial disorders such as analgesic nephropathy.
• The parenchyma shows the following features:
  
  - Interstitial fibrosis with infiltration by lymphocytes, plasma cells, and sometimes neutrophils
- Dilation or contraction of tubules, with atrophic lining epithelium. Many of the dilated tubules contain pink to blue colloid-like casts; the overall appearance is reminiscent of thyroid tissue, hence the descriptive term thyroidization.

- **Chronic inflammation with fibrosis involving the pelvi-calyceal mucosa and wall.** This is an important feature that is used in the differentiation from other conditions that give otherwise similar parenchymal changes.

- Vascular changes of benign arteriolosclerosis caused by the frequently associated hypertension.

- Although glomeruli may be normal, some are sclerosed (glomerulosclerosis). Such changes represent maladaptive changes secondary to nephron loss.

Absence of significant bacteriuria should not rule out CPN. If the disease is bilateral and progressive, tubular dysfunction occurs with loss of concentrating ability, manifested by polyuria and nocturia. Some persons with CPN or reflux nephropathy ultimately develop glomerular lesions of global sclerosis and secondary FSGS. These are associated with proteinuria and eventually contribute to progressive chronic renal failure.

### Drug-Induced Interstitial Nephritis (DIN)

Drugs are important causes of renal injury. There are two forms of DIN:

1. **Acute DIN**: this is most frequently occurs with such drugs as methicillin, ampicillin, rifampin, thiazide diuretics, NSAID, phenindione, and cimetidine. Most likely, the drugs act as haptens that bind to a cytoplasmic or extracellular component of the secreting tubular cells and become immunogenic. The resultant tubulointerstitial injury is either caused by IgE (type I) or cell-mediated (type IV) immune reactions to tubular cells. The interstitium shows infiltration by principally lymphocytes and macrophages but eosinophils and neutrophils may be present. With some drugs (e.g., methicillin, thiazides, rifampin), interstitial non-necrotizing granulomas with giant cells may be seen. The glomeruli are normal. NSAID may cause membranous GN-like reaction associated with nephrotic syndrome. It is important to recognize drug-induced renal damage, because withdrawal of the offending drug is followed by recovery.

2. **Analgesic Nephropathy**: with the intake of large quantities of analgesics, patients may develop chronic interstitial nephritis, often associated with renal papillary necrosis. Most people who develop this nephropathy consume mixtures containing some combination of aspirin, paracetamol, caffeine, and codeine for long periods. Papillary necrosis is the initial event, and the interstitial nephritis in the overlying renal parenchyma is a secondary phenomenon. Cessation of analgesic intake may stabilize or even improve renal function. A complication of analgesic abuse is the increased incidence of transitional-cell carcinoma of the renal pelvis or bladder in persons who survive the renal failure.

### Acute Tubular Necrosis (ATN)

This is a clinicopathologic entity characterized acute renal failure due to necrosis of tubular epithelial cells. It is the most common cause of acute renal failure. ATN is a reversible renal lesion that arises in clinical settings that have in common a period of inadequate blood flow to the peripheral organs, often in the setting of marked hypotension and shock. The pattern of ATN associated with shock is called ischemic
ATN. Hemolytic crises including mismatched blood transfusions, and myoglobinuria, also produce a picture resembling ischemic ATN. A second pattern, called nephrotoxic ATN, is caused by a variety of poisons, including heavy metals (e.g., mercury); organic solvents (e.g., carbon tetrachloride); and drugs such as gentamicin and other antibiotics, and radiographic contrast agents.

Pathogenesis
The decisive events in both ischemic and nephrotoxic ATN are believed to be
1. Tubular injury and
2. Severe disturbances in blood flow to tubular cells.

- Tubular epithelial cells are sensitive to both anoxia & toxins.
- Toxic injury eventuates in decreased Na\(^+\) reabsorption by proximal tubules and hence increased sodium delivery to distal tubules. The latter, through a tubulo-glomerular feedback system, contributes to vasoconstriction and thus ischemia.
- The debris resulting from shedding of tubular cells results can block urine outflow, and eventually increases intratubular pressure, thereby decreasing GFR.
- Additionally, fluid from the damaged tubules could leak into the interstitium, resulting in increased interstitial pressure and collapse of the tubules.
- Ischemic tubular cells also express chemokines, cytokines, and adhesion molecules that recruit and immobilize leukocytes that can participate in tissue injury.
- Ischemic renal injury is also characterized by severe hemodynamic alterations that cause reduced GFR. The major one is intrarenal vasoconstriction, which results in both reduced glomerular plasma flow and reduced oxygen delivery to the functionally important tubules in the outer medulla.
- Vasoconstriction is mediated by sublethal endothelial injury, leading to increased release of the endothelial vasoconstrictor endothelin and decreased production of vasodilatory nitric oxide and prostaglandins.

Pathological features
Ischemic ATN is characterized by
- Necrosis of short segments mostly of the proximal tubule; thus necrosis may be missed in biopsy samples.
- Frequently a variety of tubular injuries are noted in the epithelial cells of proximal convoluted tubules e.g. brush borders attenuation, blebbing and sloughing, vacuolization and detachment of tubular cells into the urine.
- Presence of proteinaceous casts in the distal tubules and collecting ducts. They consist of Tamm-Horsfall protein (secreted normally by tubular epithelium) along with hemoglobin and other plasma proteins.
- When crush injuries have produced ATN, the casts are composed of myoglobin.
- The interstitium usually shows generalized edema along with a mild inflammatory infiltrate consisting of polymorphonuclear leukocytes, lymphocytes, and plasma cells.
- Toxic ATN The microscopic picture is basically similar, with some differences. Necrosis is more diffuse but again most prominent in the proximal tubule, and the tubular basement membranes are generally spared.
- If the patient survives for a week, epithelial regeneration becomes apparent in the form of a low cuboidal epithelial covering and mitotic activity in the persisting tubular epithelial cells.
- Except where the basement membrane is destroyed, regeneration is total and complete.

DISEASES OF RENAL BLOOD VESSELS
Changes affecting renal blood vessels are both frequent & important for the following reasons
1. The renal vasculature is secondarily involved in almost all diseases of the kidney.
2. Various forms of systemic arteritis also involve renal vessels & such involvement is clinically important.
3. The kidney is intimately involved in the pathogenesis of both essential and secondary hypertension.

**Benign Nephrosclerosis (BNS)**
Some degree of BNS is present in many of those older than 60 years of age. The frequency and severity of the lesions are increased at any age when hypertension or diabetes mellitus are present. It is not clear whether BNS is the cause of hypertension or conversely, hypertension just accelerates an age-related vascular sclerosis. However, many renal diseases cause hypertension, which in turn is associated with BNS. Thus, this renal lesion is often seen superimposed on other primary kidney diseases.

**Gross features:** The kidneys are symmetrically shrunken, with diffuse fine granularity of the surface.

**Microscopical features**
- The basic change is hyaline thickening of the walls of the small arteries and arterioles (hyaline arteriolosclerosis). This appears as a homogeneous, pink, hyaline thickening that reduces the lumen.
- The narrowing of the lumen results in markedly decreased blood flow through the affected vessels and thus producing ischemic atrophy of all structures of the kidney. In advanced cases the glomeruli become globally sclerosed. Diffuse tubular atrophy and interstitial fibrosis are often present.

BNS rarely causes severe damage to the kidney. However, all persons with this lesion usually show some functional impairment.

**Malignant Nephrosclerosis**
Malignant hypertension occurs in only about 5% of hypertensive patients. It may occur de novo, or suddenly complicates mild hypertension.

**Pathogenesis**
The following sequence of events is suggested.
1. Initially, there is renal arteriolar vascular damage, mostly from long-standing benign hypertension. The result is increased permeability of the small vessels to fibrinogen and other plasma proteins, endothelial cell injury, and platelet deposition.
2. This leads to occurrence of fibrinoid necrosis of arterioles and small arteries with thrombosis.
3. Platelet-derived and other growth factors cause intimal smooth muscle hyperplasia that results in hyperplastic arteriolosclerosis (typical of malignant hypertension) associated with further narrowing of the vascular lumina. The kidneys become markedly ischemic.
4. With severe involvement of the renal afferent arterioles, the renin-angiotensin system is stimulated. A self-perpetuating cycle is thus created in which angiotensin II causes intrarenal vasoconstriction, and the resultant renal ischemia stimulates renin secretion.
5. Aldosterone levels are elevated; the salt retention contributes to the elevation of blood pressure.

The consequences of the markedly elevated blood pressure on the blood vessels throughout the body are known as malignant arteriolosclerosis, and the renal disorder is referred to as malignant nephrosclerosis.
Gross feature:
- The kidneys, which may be normal in size or slightly shrunken display small, pinpoint petechial hemorrhages on the cortical surface due to rupture of arterioles or glomerular capillaries. These give the kidney a peculiar, flea-bitten appearance.
- **Microscopic:** There is fibrinoid necrosis of the arterioles. The vessel walls show a homogeneous, granular eosinophilic appearance.
- In the small arteries and large arterioles, proliferation of intimal smooth muscle cells produces hyperplastic arteriolosclerosis in which the intimal smooth muscle cells show concentric arrangement (*onion-skin appearance*). This lesion causes marked narrowing of arterioles and small arteries, to the point of total obliteration.
- Necrosis may also involve glomeruli, with microthrombi within the glomeruli & necrotic arterioles.

The full-blown syndrome of malignant hypertension is characterized by diastolic pressures greater than 120 mm Hg, papilledema, encephalopathy, cardiovascular abnormalities, and renal failure. At the onset of rapidly rising blood pressure there is marked proteinuria and microscopic, or sometimes macroscopic, hematuria followed soon by renal failure. The syndrome is a true medical emergency. About 50% of patients survive at least 5 years. Ninety percent of deaths are caused by uremia and the other 10% by cerebral hemorrhage or cardiac failure.

**CYSTIC DISEASES OF THE KIDNEY**

These are a heterogeneous group comprising
a. hereditary  
b. developmental but nonhereditary  
c. acquired disorders.

They are important for several reasons:
1. They are practically common and often present diagnostic problems
2. Some are major causes of chronic renal failure (adult polycystic disease)
3. They can occasionally be confused clinically with malignant tumors.

**Simple Cysts** are a common but have no clinical significance. They can be multiple or single, commonly up to 5 cm in diameter. They are translucent; filled with clear fluid; lined by a single layer of cuboidal or flattened epithelium.

**Dialysis-associated acquired cysts** occur with prolonged dialysis in those with end-stage renal disease. They may bleed, causing hematuria. Occasionally, renal adenomas or carcinomas arise in the walls of these cysts.

**Autosomal Dominant (Adult) Polycystic Kidney Disease (ADPKD)** is characterized by multiple expanding cysts of both kidneys that ultimately destroy the intervening parenchyma. *ADPKD is responsible for 10% of all chronic renal failures.* It is caused by inheritance of one of two autosomal dominant genes of very high penetrance. The kidneys may be very large (up to 4 kg for each), and thus are readily palpable abdominally. **Grossly** the kidney is composed of a mass of cysts of varying sizes (up to 4 cm). The cysts are filled with fluid (clear, turbid, or hemorrhagic)

**Microscopically**, the cysts have often atrophic, lining. The pressure of the expanding cysts leads to ischemic atrophy of the intervening renal substance. Evidence of superimposed hypertension or infection is common. *ADPKD in adults usually does not produce symptoms until the fourth decade,* by which time the kidneys are quite large. Intermittent gross hematuria commonly occurs. The most important complications are hypertension and urinary infection. Saccular aneurysms of the circle of Willis are present in up to 30% of patients, and these individuals have a high incidence of subarachnoid hemorrhage. Asymptomatic liver cysts occur in one-third of patients.
AUTOSOMAL RECESSIVE (CHILDHOOD) POLYCYSTIC KIDNEY DISEASE (ARPKD) is a rare developmental anomaly that is genetically distinct from ADPKD. Perinatal, neonatal, infantile, and juvenile subcategories have been defined, depending on time of presentation and the presence of associated hepatic lesions. Both kidneys are invariably involved with numerous small cysts that give them a sponge-like appearance. The cysts are lined by cuboidal cells. ARPKD is associated with multiple epithelium-lined cysts in the liver. Young infants may die quickly from hepatic or renal failure.

MEDULLARY CYSTIC DISEASE (MCD)

This is of two major types of
1. Medullary sponge kidney a relatively common and usually harmless condition and
2. Nephronophthisis-medullary cystic disease complex, which is associated with renal dysfunction. On the basis of the time of onset they are divided into, infantile, juvenile (the most common), adolescent, and adult types. They may be associated with other extra-renal abnormalities including cerebellar malformations, and liver fibrosis. Pathologic features of medullary cystic disease include small contracted kidneys with numerous small cysts lined by flattened or cuboidal epithelium, typically at the cortico-medullary junction. Progression to end-stage renal disease occurs within a 5- to 10-year period. The disease is difficult to diagnose, since the cysts may be too small to be seen with imaging techniques and may not be apparent on renal biopsy if the cortico-medullary junction is not well sampled.

URINARY OUTFLOW OBSTRUCTION

RENAL STONES (UROLITHIASIS) these are frequent (1% of all autopsies) and mostly form in the kidney. The majority (80%) are composed of either calcium oxalate or calcium oxalate mixed with calcium phosphate; 10% are of magnesium ammonium phosphate, and the remainder 10% are either uric acid or cystine stones. The most important cause is increased urine concentration of the stone's constituents (supersaturation). Those who develop calcium stones have
1. Hypercalciuria not associated with hypercalcemia due to either
   a. Absorption of calcium from the gut in excessive amounts (i.e. absorptive hypercalciuria)
   b. Primary renal defect of calcium reabsorption (renal hypercalciuria).
Hypercalciemia is present in only 5% to 10% (due to hyperparathyroidism, vitamin D intoxication, or sarcoidosis) and consequent hypercalciuria. In 20% of this subgroup, there is excessive excretion of uric acid in the urine, which favors calcium stone formation; the urates provide a nidus for calcium deposition. A high urine pH favors crystallization of calcium phosphate and stone formation. Magnesium ammonium phosphate stones almost always occur in persistently alkaline urine due to UTIs, particularly with urea-splitting bacteria (as Proteus vulgaris and the Staphylococci). Gout and diseases involving rapid cell turnover (as the leukemias), lead to high uric acid levels in the urine and uric acid stones. About half of the individuals with uric acid stones, however, have no hyperuricemia but unexplained tendency to excrete persistently acid urine (under pH 5.5), which favors uric acid stone formation (cf. stones containing calcium phosphate).

Common sites of formation are renal pelvis and calyces as well as the bladder. Stone may be small with smooth or jagged surface. Occasionally, progressive accumulation
of salts leads to the development of branching structures known as *staghorn calculi*, which create a cast of the renal pelvis and calyceal system. These massive stones are usually composed of magnesium ammonium phosphate; these do not produce symptoms or significant renal damage. Smaller stones may pass into the ureter, producing a typical intense pain known as renal colic. Often at this time there is gross hematuria. The clinical significance of stones lies in their capacity to obstruct urine flow or to produce sufficient trauma to cause ulceration and bleeding. In either case, they predispose the sufferer to bacterial infection.

**Hydronephrosis** refers to dilation of the renal pelvis and calyces, with accompanying atrophy of the renal parenchyma, caused by obstruction to the outflow of urine. The obstruction may be sudden or insidious, and it may occur at any level of the urinary tract, from the urethra to the renal pelvis. The most common causes are

1. **Congenital**: e.g. urethral atresia, ureteric or urethral valves, aberrant renal artery
2. **Acquired**:
   a. **Foreign bodies**: calculi
   b. **Tumors of the prostate or bladder** *(benign or malignant)*
   c. **Contiguous malignant disease**: (retroperitoneal lymphoma, carcinoma of the cervix or uterus)
   d. **Inflammation**: prostatitis, ureteritis, urethritis
   e. **Neurogenic**: Spinal cord damage with paralysis of the bladder
   f. **Normal pregnancy**: mild and reversible

**Bilateral hydronephrosis** occurs only when the obstruction is below the level of the ureters. If blockage is at the ureters or above, the lesion is unilateral. Sometimes obstruction is complete, allowing no urine to pass; usually it is only partial.

**Pathogenesis**

Even with complete obstruction, glomerular filtration persists for some time, and the filtrate subsequently diffuses back into the lymphatic and venous systems. Because of the continued filtration, the affected calyces and pelvis become dilated, often markedly so. The unusually high pressure thus generated in the renal pelvis, as well as that transmitted back through the collecting ducts, causes compression of the renal blood vessels. Both arterial insufficiency and venous stasis result. The most severe effects are seen in the papillae, because they are subjected to the greatest increases in pressure. Accordingly, the initial functional disturbances are largely tubular, manifested primarily by impaired concentrating ability. Thereafter the glomerular filtration begins to diminish. **Serious irreversible damage occurs in about 3 weeks with complete obstruction, and in 3 months with incomplete obstruction.**

**Gross features**

- The changes vary with the degree and speed of obstruction
  - With subtotal or intermittent obstruction, the kidney is massively enlarged consisting almost entirely of the greatly distended pelvicalyceal system. The renal parenchyma shows compression atrophy, with obliteration of the papillae and flattening of the pyramids.
  - With sudden complete obstruction, glomerular filtration is reduced relatively early, and as a consequence, renal function may cease while dilation is still slight.

- Depending on the level of the obstruction, one or both ureters may also be dilated (hydroureter).

**Microscopic features**
• Early lesions show tubular dilation, followed by atrophy and fibrous replacement with relative sparing of the glomeruli. Eventually, in severe cases the glomeruli also become atrophic and disappear, converting the entire kidney into a thin shell of fibrous tissue.
• With sudden and complete obstruction, there may be coagulative necrosis of the renal papillae.
• In uncomplicated cases the accompanying inflammatory reaction is minimal. Complicating pyelonephritis, however, is common.

Course & prognosis
Bilateral complete obstruction produces anuria. When the obstruction is below the bladder, there is bladder distention. Incomplete bilateral obstruction causes polyuria rather than oliguria, as a result of defects in tubular concentrating mechanisms. Unilateral hydronephrosis may remain completely silent. Removal of obstruction within a few weeks usually permits full return of function; however, with time the changes become irreversible.

TUMORS
The kidney is the site of benign and malignant tumors. In general, benign tumors (such as small cortical adenomas or medullary fibromas) have no clinical significance. The most common malignant tumors of the kidney in descending order of frequency are
1. Renal cell carcinoma
2. Nephroblastoma (Wilms tumor)
3. Transitional cell carcinoma of the calyces and pelvis

Renal Cell Carcinoma (RCC)
This is derived from the renal tubular epithelium and represents the most common primary malignant tumor of the kidney (80%). The mean age of incidence is 50 to 70 years. Risk factors include smoking, hypertension, obesity, occupational exposure to cadmium, and acquired polycystic disease complicating chronic dialysis (30-fold). RCC are currently classified according to the molecular origins of these tumors. The three most common forms are
1. Clear Cell Carcinomas (80% of RCCs): these are made up of cells with clear or granular cytoplasm. The majority are sporadic, but may occur in familial forms or in association with von Hippel-Lindau disease (VHLD). The latter is autosomal dominant and characterized by predisposition to a variety of neoplasms including bilateral & often multiple RCC of clear cell type. Patients with VHLD inherit a germline mutation of the VHL gene on chromosome 3 and lose the second allele by somatic mutation. Thus, the loss of the normal copies of both these tumor suppressor genes gives rise to clear cell carcinoma. It has been also confirmed that homozygous loss of the VHL gene seems to be the common underlying molecular abnormality in both sporadic and familial forms of clear cell carcinomas.
2. Papillary Renal Cell Carcinomas (10%). These tumors are frequently multifocal and bilateral and like clear cell carcinomas, they occur in familial and sporadic forms. However, they have no abnormality of chromosome 3. The cause is the MET proto-oncogene. It is the increased dosage of the MET gene (due to duplications of chromosome 7) seems to encourage neoplastic growth abnormal growth in the proximal tubular epithelial cell precursors. In support of this, trisomy of chromosome 7 is seen commonly in the familial cases. In the sporadic cases, although there is duplication of chromosome 7, there is no mutation of the MET gene.
3. Chromophobe RCCs: these are the least common; they arise from intercalated cells of collecting ducts. Their name indicates that the tumor cells stain more darkly than
cells in clear cell carcinomas. These tumors are unique in having multiple losses of entire chromosomes, including chromosomes 1 and 2. In general, they have a good prognosis.

**Pathologic features**

**Clear cell carcinoma**

**Gross features:**
- There is usually solitary spherical mass; large when symptomatic.
- The cut surface is variegated; yellow-orange to gray-white with red areas of hemorrhage. There are prominent areas of cystic degeneration.
- Although the margins of the tumor are well defined, with enlargement extension may occur in two directions
  1. Into the pelvicalyceal system & as far down as the ureter.
  2. Into the renal vein, then the inferior vena cava & even into the right side of the heart.

**Microscopic features**
- The classic lipid- & glycogen-laden clear cells have well defined cell membranes. The nuclei are usually small and round.
- These cells are mixed to varying extent with cells having granular pink cytoplasm.
- Some tumors exhibit marked degrees of anaplasia, with numerous mitotic figures and markedly enlarged, hyperchromatic, pleomorphic nuclei (*sarcomatoid RCC*).
- The stroma is usually scant but highly vascularized.

**Papillary renal cell carcinomas**
- Exhibit papilla formation with fibrovascular cores.
- They tend to be bilateral and multiple.
- The cells can have clear or, more commonly, pink cytoplasm.

The classical triad of painless hematuria (the most frequent), a palpable abdominal mass, and dull flank pain is characteristic. RCCs are well-known for their association with several paraneoplastic syndromes. Polycythemia may occur; it results from excessive secretion of erythropoietin by the tumor. Uncommonly, these tumors also produce a variety of hormone-like substances, resulting in hypercalcemia, hypertension, Cushing syndrome, etc. In many individuals the primary tumor remains silent and is discovered only after its metastases have produced symptoms. Common locations for metastases are the lungs and the bones. Forty percent of patients die of the disease.

**Wilms Tumor (WT) (nephroblastoma)**

This is not only the most common primary renal tumor of children (mostly between the ages of 2 and 5 years) but also the third most common organ cancer in those younger than 10 years. WT may arise sporadically or be familial. Some congenital malformations are associated with an increased risk of developing Wilms’ tumor such as aniridia, mental retardation, gonadal dysgenesis and renal abnormalities. These conditions are associated with inactivation of the Wilms’ tumor 1 (*WT1*) gene, located on chromosome11. This gene is critical to normal renal and gonadal development. Patients with the Beckwith syndrome (BWS); characterized by enlargement of individual body organs (e.g., tongue, kidneys, or liver) or hemihypertrophy of the entire body segments. In addition to Wilms’ tumors, patients with BWS are also at increased risk for developing other cancers e.g. hepatoblastoma.

**Gross features**
- WT tends to be large, well-circumscribed mass with soft, homogenous, tan to gray cut section accentuated with occasional foci of hemorrhage, necrosis and cystic degeneration.

  **Microscopic features**

- In WT there are attempts to recapitulate different stages of nephrogenesis.
- WT contain a variety of tissue components, but all derived from the mesoderm.
- The classic *triphasic combination* of blastemal, stromal, and epithelial cell types is observed in most lesions.
  - The blastemal component is represented by sheets of small blue cells
  - The epithelial component (differentiation) is represented by abortive tubules or glomeruli.
  - The stromal component is represented usually by fibroblastic cells or myxoid areas, although skeletal muscle "differentiation" and other mesenchymal elements may be seen.
- The presence of anaplasia correlates with underlying p53 mutations, and the emergence of resistance to chemotherapy.

  Clinically, there is a readily palpable abdominal mass, which may extend across the midline and down into the pelvis. Fever and abdominal pain, with hematuria, are less frequent. The prognosis of Wilms' tumor is generally very good, and excellent results are obtained with a combination of nephrectomy and chemotherapy. WTs with diffuse anaplasia, especially those with extra-renal spread, have the least favorable outcome.

### RENAL PELVIS, URETER, URINARY BLADDER & URTHERA

#### URETERS

**Congenital Anomalies** these are rare, and mostly of little clinical significance. However, some may contribute to urine outflow obstruction. *Incompetent ureterovesical junction* predisposes to pyelonephritis. The majority of *double ureters* are unilateral and of no clinical significance. A *congenital ureteropelvic junction obstruction* is the most common cause of hydronephrosis in infants and children. There is agenesis of the kidney on the opposite side in a significant number of cases. *Diverticula* are saccular outpouchings acting as pockets of stasis and secondary infections. *Hydroureter with elongation and tortuosity* may be congenital leading to hydronephrosis if untreated.

**Ureteritis** may be one component of UTI. With long-standing chronic ureteritis, there may be aggregation of lymphocytes in the subepithelial region causing fine granular mucosal surface (ureteritis follicularis), or the mucosa may become sprinkled with tiny cysts (ureteritis cystica). Identical changes are found in the bladder. The two most common tumors and tumor-like lesions are fibroepithelial polyps and leiomyomas. Primary malignant tumors are similar to those arising in the renal pelvis, calyces, and bladder; the majority are transitional cell carcinomas. They cause obstruction and are most frequently during the sixth and seventh decades. They can be multiple and may occur concurrently with similar tumors in the bladder or renal pelvis.

**Obstructive lesions of the ureters**

A great variety of pathologic lesions may obstruct the ureters and give rise to hydroureter, hydronephrosis, and sometimes pyelonephritis. The more important causes include

1. impacted small stones
2. strictures (congenital or acquired),
3. primary carcinoma,
4. pregnancy,
5. retroperitoneal fibrosis & cancers of the rectum, bladder, prostate, ovaries, uterus and cervix.

Sclerosing Retroperitoneal Fibrosis is a fibrous proliferative inflammatory process encasing the retroperitoneal structures including the ureters and causing hydronephrosis. Two thirds of the cases are idiopathic. The remaining cases are attributed to drugs (ergot derivatives, β-adrenergic blockers), adjacent inflammatory conditions or malignant disease. It may be associated with mediastinal fibrosis, sclerosing cholangitis, and Riedel thyroiditis. This suggests that the disorder is systemic in distribution but preferentially involves the retroperitoneum. An autoimmune reaction, sometimes triggered by drugs, has been proposed.

**URINARY BLADDER**

**Congenital anomalies**

**Diverticula** are pouch-like evaginations of the bladder wall that may be *congenital*, but more commonly acquired due to persistent urethral obstruction (e.g. prostatic hyperplasia or neoplasia). In both forms, there are frequently multiple sac-like pouches that range from less than 1 cm to 10 cm in diameter. Most diverticula are small and asymptomatic, but may be sites of urinary stasis that predispose to infection and the formation of bladder calculi.

**Exstrophy** is a developmental failure in the anterior wall of the abdomen and the bladder, so that the bladder communicates directly through a large defect with the surface of the body. The exposed bladder mucosa may undergo colonic glandular metaplasia and is subjected to infections. There is an increased risk of carcinoma.

**vesicoureteral reflux** is the most common and serious anomaly that contributes to renal infection and scarring.

**Congenital fistulas** are abnormal connections between the bladder and the vagina, rectum, or uterus.

**Persistent urachus** refers to failure of the urachus to close in part or in whole. When it is totally patent, a fistulous urinary tract is created that connects the bladder with the umbilicus. Sometimes, only the central region of the urachus persists, giving rise to urachal cysts. Carcinomas, mostly adenocarcinomas, may arise in such cysts.

**ACUTE & CHRONIC CYSTITIS**

The common etiologic agents of *bacterial cystitis* are the E. coli, followed by Proteus, & Klebsiella. Women are more likely to develop cystitis due to their shorter urethras. Bacterial pyelonephritis is frequently preceded by cystitis, with retrograde spread of microorganisms into the kidneys and their collecting systems. *Tuberculous cystitis* is almost always a consequence of renal tuberculosis. *Fungal cystitis* is usually due to Candida albican. It is particularly seen in immunosuppressed patients or those receiving long-term antibiotics. *Schistosomal cystitis* (Schistosoma haematobium) is common in certain Middle Eastern countries, notably Egypt. Viruses (e.g., adenovirus), Chlamydia, and Mycoplasma may also be causes of cystitis.

**Predisposing factors of cystitis include**

1. Urinary obstruction e.g. prostatic hyperplasia, bladder calculi, tumors
2. Cystocele or diverticula
3. Diabetes mellitus
4. Instrumentation
5. Immune deficiency.

**Hemorrhagic cystitis** sometimes complicates cytotoxic antitumor drugs (e.g. cyclophosphamide). *Radiation cystitis* is due to radiation of the bladder region.
Most cases of cystitis take the form of nonspecific acute or chronic inflammation of the bladder. **Gross features**

- There is hyperemia of the mucosa.
- *Hemorrhagic cystitis* shows in addition a hemorrhagic component; this form is sometimes follows radiation injury, antitumor chemotherapy, or adenovirus infection.
- *Suppurative cystitis* is characterized by the accumulation of large amounts of suppurative exudate.
- *Ulcerative cystitis* refers to cystitis associated with ulceration of large areas of the mucosa, or sometimes the entire bladder mucosa.
- Persistence of the infection leads to chronic cystitis, which shows red, friable, granular, sometimes ulcerated mucosa. Chronicity is also associated with fibrous thickening and inelasticity of the bladder wall.

**Microscopic features**

- In acute cystitis there are the expected features of acute inflammation.
- In chronic forms there is chronic inflammatory cells infiltration with fibrosis.
- Variants of chronic cystitis include *Follicular cystitis* and *Eosinophilic cystitis*.

  **Schistomal cystitis:** urogenital bilharziasis is caused by *S. haematobium*. Eggs are deposited in the superior rectal vein. From there, they pass through anastomoses into the veins of the wall of urinary bladder. There they cause granulomatous cystitis with eosinophilic infiltrate & fibrosis. These granulomas are visible under endoscopy as minute granules referred to as “sand grain” cystitis. The eggs eventually die in the tissue with regressive calcification. The condition may be complicated by:
  a. Extensive fibrosis that may impinge on the ureteric orifices with eventual hydronephrosis
  b. Carcinoma of bladder that is frequently squamous in type; as this form of cystitis can be associated with squamous metaplasia of the native transitional epithelium.

**Special Forms of Cystitis**

These are distinctive by either their morphologic appearance or their causation.

1. **Interstitial Cystitis (Hunner Ulcer):** a painful form of chronic cystitis occurring most frequently in women. Cystoscopy shows fissures and punctate hemorrhages in the mucosa, sometimes with chronic mucosal ulcers (Hunner ulcers). Infiltration by mast cells is characteristic of this disease. The condition may be of autoimmune origin.
2. **Malakoplakia** is characterized macroscopically by soft, yellow, slightly raised mucosal plaques 3 to 4 cm in diameter and histologically by infiltration with large, foamy macrophages with debris of bacterial origin (mostly *E. coli*). In addition, laminated mineralized concretions (Michaelis-Gutmann bodies) are typically present. Similar lesions have been described in other organs e.g. colon, lungs, bones. It occurs with increased frequency in immuno-suppressed transplant recipients and as a result of defects in phagocytic or degradative function of macrophages.
3. **Polypoid Cystitis** is an inflammatory condition resulting from irritation to the bladder mucosa mostly by indwelling catheters. The urothelium is thrown into broad, bulbous, polypoid projections as a result of marked submucosal edema.

**METAPLASTIC LESIONS**

*Cystitis Glandularis and Cystitis Cystica:* these terms refer to common lesions in which nests of transitional epithelium (*Brunn nests*) grow downward into the lamina propria and undergo transformation of their central epithelial cells into columnar epithelium lining (*cystitis glandularis*) or cystic spaces lined by urothelium (*cystitis cystica*). The two processes often coexist. In a variant of cystitis glandularis, goblet cells are present (*intestinal metaplasia*).
Both variants are common microscopic incidental findings in relatively normal bladders and are not associated with an increased risk of adenocarcinoma. Two forms of metaplasia occur in response to injury
1. Squamous Metaplasia
2. Nephrogenic Metaplasia (Nephrogenic Adenoma): the urothelium may be focally replaced by cuboidal epithelium, which can assume a papillary growth pattern with subjacent tubular proliferation.

TUMORS OF THE URINARY BLADDER AND COLLECTING SYSTEM (Renal Calyces, Renal Pelvis, Ureter, and Urethra)
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 a more frequent cause of death than are kidney tumors.

Gross features
Four morphologic patterns are recognized that range from small benign papillomas to large invasive cancers. These tumors are classified into
1. Benign papilloma (rare)
2. Papillary urothelial neoplasms of low malignant potential, and
3. Urothelial carcinoma (low and high grade)

Papillomas are very rare, small (up to 1 cm) benign tumors with frondlike structures having a delicate fibrovascular core covered by multilayered, well-differentiated transitional epithelium. Such lesions are usually solitary. They rarely recur once removed.

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

Low-grade carcinomas are always papillary and are rarely invasive, but they may recur after removal.

High-grade carcinomas can be papillary or occasionally flat; they may cover larger areas of the mucosal surface, invade deeper, and have a shaggier necrotic surface than do low-grade tumors. Occasionally, these cancers show foci of squamous cell differentiation, but only 5% of bladder cancers are true squamous cell carcinomas. Carcinomas of grades II and III infiltrate surrounding structures, spread to regional nodes, and, on occasion, metastasize widely.

Painless hematuria is the dominant clinical presentation of all these tumors. They affect men three times more frequently than women and usually develop between the ages of 50 and 70 years.

Risk factors of bladder cancer are
1. Exposure to β-naphthylamine (50 times increased risk).
2. Cigarette smoking
3. Chronic cystitis
4. schistosomiasis of the bladder
5. Certain drugs (cyclophosphamide).

A wide variety of genetic abnormalities are seen in bladder cancers; of these, mutations involving several genes on chromosome 9, p53, and FGFR3 are the most common.

The prognosis of bladder tumors depends on their histologic grade and the depth of invasion of the lesion; the latter is much more important. Except for benign papillomas, all tend to recur after removal. Lesions that invade the ureteral or urethral
orifices cause urinary tract obstruction. Overall 5-year survival is 57%. With deep penetration of the bladder wall the 5-year survival rate is less than 20%. Papillary tumors occur much less frequently in the renal pelvis than in the bladder, they nonetheless make up to 10% of primary renal tumors. Patients present with painless hematuria, and may develop hydronephrosis. Infiltration of the walls of the pelvis, calyces, and renal vein worsens the prognosis. Despite removal of the tumor by nephrectomy, fewer than 50% of patients survive for 5 years. Cancer of the ureter is fortunately the rarest of the tumors of the collecting system. The 5-year survival rate is less than 10%.