III. KIDNEY and URINARY TRACT PATHOLOGY

RENAL DISEASES

GLOMERULAR DISEASES. The functional complexity of the glomerulus is reflected in a wide variety of different, yet often related, clinical symptoms that result from glomerular injury. The common use of renal biopsy has changed the concepts of renal diseases, particularly in the case of glomerulopathies. A number of special stains and techniques are use to highlight morphologic and immunologic details in such biopsies for a clear cut diagnosis. These include the followings:

- The *periodic acid-Schiff stain (PAS),* which outlines the basement membranes of glomeruli and tubules and highlights the mesangial matrix.
- *Silver impregnation stains,* which also mark the glomerular and tubular basement membranes.
- *Immunofluorescence* and *immunoperoxidase studies,* which localize various types of immunoglobulins, antigens, complement, fibrin-related compounds, and cell surface markers, and the pattern of depositions: linear or granular or both.
- *Electron microscopy,* which is frequently essential in resolving the fine details of glomerular lesions.
- Other *special stains,* such as those for fibrin, collagen, amyloid, and lipids.

Glomeruli may be injured by a variety of factors and in the course of a number of systemic diseases (i.e. systemic lupus erythematosus, diabetes mellitus, hypertension etc.). These are termed *secondary glomerular diseases* to differentiate them from those in which the kidney is the only or predominant organ involved – *primary glomerulopathies.*

The clinical manifestations of glomerular disease are clustered into glomerular syndromes:

Nephrotic syndrome is characterized by heavy proteinuria, usually defined as the excretion of more than 3.5 g of protein per 24 hours. This heavy proteinuria leads to hypoproteinemia (hypoalbuminemia) and peripheral edema. Together, these three clinical findings comprise the classic nephrotic syndrome. A fourth symptom, hyperlipidemia, is also frequently associated with the nephrotic syndrome. The vast majority of cases of "pure" nephrotic syndrome (i.e. without features of the nephritic syndrome) result from glomerular diseases that fall under the category of *noninflammatory glomerulopathies.*

Nephritic syndrome is characterized by hematuria, either microscopic or visible grossly. Variable degrees of proteinuria (under 3.5 g/day), oliguria, and a decreased glomerular filtration rate (with resulting elevations in levels of blood urea nitrogen and serum creatinine) are usually present. Salt and water retention often results in hypertension and edema. In clear contrast to the nephrotic syndrome, the nephritic syndrome is most often associated with *inflammatory glomerular disease* (*glomerulonephritis).*

Renal failure. Acute renal failure and chronic renal failure are terms frequently used to describe the clinical manifestation of glomerular and other kidney disease. *Acute renal failure* refers to an acute decline in glomerular filtration rate, with

a resultant increase in blood urea nitrogen and serum creatinine values. It may result from damage to any portion of the kidney: glomeruli, tubules and interstitium. *Chronic renal failure* results from a large variety of renal diseases, including glomerular, tubulointerstitial, and vascular diseases.

A. Noninflammatory glomerular lesions are characterized by glomeruli that are normocellular or at most mildly hypercellular. These lesions are most often associated with proteinuria - frequently in the nephrotic range - and result from processes that interfere with the structural and functional integrity of any of the three components comprising the glomerular capillary wall: the endothelial cell, the basement membrane, and the epithelial cell. Noninflammatory glomerulopathies may be primary diseases involving only the kidney (minimal change nephrotic syndrome, focal segmental glomerulosclerosis, or idiopathic membranous nephropathy). They may also be components of a systemic disease such as diabetes mellitus, amyloidosis, multiple myeloma, or AIDS.

A. 1. Minimal change nephrotic syndrome (lipoid nephrosis) is a glomerular disorder characterized clinically by the nephrotic syndrome and pathologically by the fusion of epithelial foot processes. The loss of protein in the urine leads to hypoalbuminemia, and a compensatory increase in lipoprotein secretion by the liver results in hyperlipidemia. The loss of lipoproteins through the glomeruli leads to the accumulation of lipid in the proximal tubular cells, which is reflected histologically in a foamy cytoplasm (lipoid nephrosis).

It is largely a disorder of children, in whom it is the major cause of the nephrotic syndrome. However, the disorder also occurs in adults with significant frequency (20% of adults with the nephrotic syndrome). Neither the cause nor the pathogenesis of minimal change nephrotic syndrome is understood. Because of the association between the onset of the nephrotic syndrome and an allergic history, and the fact that the disease sometimes follows infection or exposure to allergens, involvement of the immune system has been postulated.

By definition, the light microscopic appearance of glomeruli in lipoid nephrosis is essentially normal. Electron microscopic examination of the glomeruli reveals total effacement of epithelial cell foot processes, the basement membrane being covered by a sheet of cytoplasm. No electron-dense deposits are seen.

Most adults and children show complete remission of proteinuria within 8 weeks of the initiation of corticosteroid therapy. There is no tendency to progress into chronic renal failure.

A. 2. Focal segmental glomerulosclerosis refers to a malady in which *some* glomeruli exhibit *segmental* areas of sclerosis in the capillary tufts whereas others appear normal. The majority of cases are of unknown etiology (idiopathic), few cases recognize heroin abuse or HIV infection as the cause.

By light microscopy, varying numbers of glomeruli show segmental areas of capillary loop obliteration. Adhesions to Bowman’s capsule are seen adjacent to these lesions. The mesangium is hypercellular. The frequent accumulation of a PAS-positive

material in the affected areas produces a lesion referred to as *hyalinosis*. This is a valuable finding in the differentiation of focal segmental glomerulosclerosis from a segmentally scarred focal glomerulonephritis.

By electron microscopy, diffuse effacement of epithelial cell foot processes is present; in addition there are folding and thickening of the basement membrane and capillary collapse.

Immunofluorescence studies show trapping of IgM and C3 in the segmental areas of sclerosis and hyalinosis.

A. 3. Membranous nephropathy is a disorder that is usually associated with the nephrotic syndrome and is characterized by diffuse thickening of the glomerular basement membrane. In fact, membranous nephropathy is the most frequent cause of the nephrotic syndrome in adults (30% of the case).

Although membranous nephropathy has been associated with many precipitating factors (tumors, SLE, hepatitis B, drugs), most cases are idiopathic. It is believed to be caused by the deposition of immune complexes from the circulation or the formation in situ of immune complexes within capillary walls.

By light microscopy the glomeruli are slightly enlarged, yet normocellular. Depending on the duration of the disease, the capillary walls are normal or thickened. In the early stages of the disease silver stains reveal multiple projections, or “spikes”, of argyrophilic material on the epithelial surface of the basement membrane. Such “spikes” represent projections of basement membrane material around the immune complexes, which do not stain with silver. As the disease progress the capillary lumina are encroached upon and glomerular obsolescence eventually ensues.

By electron microscopy, the progression of membranous nephropathy can be divided into 4 stages: I (small granular subepithelial deposits are along the basement membrane), II (“spikes” of basement protrude between deposists of electron-dense material), III (the electron-dense deposits are incorporated into the widening basement membrane) and IV (the basement membrane is markedly distorted, and the mobilization of the deposits has imparted a moth-eaten appearance to the membrane). If the lesion heals, the basement membrane is reconstituted and assumes the essential normal appearance, except for the increase thickness.

Immunofluorescence shows diffuse granular deposition of IgG and C3 in the glomerular loops.

A. 4. Diabetic glomerulosclerosis embraces the glomerular changes seen in diabetes. The alterations in diabetic glomerulosclerosis are an expression of the diabetic microangiopathy that occurs in many systemic small arteries, arterioles and capillaries. As in the systemic vessels, glomerular sclerosis is caused by the progressive accumulations of basement membrane material, a process that results in enlargement of the glomeruli. The pathogenesis of the lesion appears to be related to the severity and duration of hyperglycemia.

Proteinuria in diabetic glomerulosclerosis is initially mild and may remain so, although patients with nephrotic range proteinuria (over 3.5 g/day) usually progress to renal failure within 6 years.

The earliest detectable lesion of diabetic glomerulosclerosis is a thickening of the glomerular basement membrane, which can usually be detected by electron microscopy within 2 years of the onset of insulino-dependent diabetes. This is followed by a diffuse widening of mesangial areas, with the accumulation of a PAS-positive matrix. The glomerulus becomes enlarged and may appear hypercellular.

Diffuse glomerulosclerosis refers to enlarged glomeruli with expanded mesangial areas and diffusely thickened basement membranes.

Nodular glomerulosclerosis describes single or multiple nodules in the glomeruli. These are rounded, homogenous, eosinophilic masses in centrilobular areas. With time the nodules become acellular, in which case only a rim of peripheral mesangial nuclei is visible. Silver stains reveal a pattern of concentric lamination.

Diffuse glomerulosclerosis may occur alone or may be mixed with the nodular type. Concomitant with the development of glomerulosclerosis, insudative changes occur in both the adjacent arterioles and the glomerular tufts. These are manifested by hyaline arteriolosclerosis, which in diabetics uniquely involves both the afferent and efferent arterioles.

Electron microscopy reveals that the thickening of the capillary wall is caused by a widening of the basement membrane lamina densa, which may be many times its normal width. An accumulation of basement membrane-like material in the mesangium parallels the diffuse widening of the basement membrane and may become nodular and acellular.

A. 5. Renal amyloidosis refers to the deposition of diverse extracellular proteins in the kidneys (glomeruli are most frequently affected) a situation that results in altered permeability of the glomerular capillaries and proteinuria. Amyloid is conventionally defined as an eosinophilic (H&E stain) amorphous material that shows a characteristic apple-green color in sections stainned with Congo red and examined under polarized light.

Renal involvement is a prominent feature of most cases of systemic amyloidosis and consists initially of mesangial amyloid deposition that produces diffuse mesangial widening without hypercellularity. Progressively it spreads to obliterate capillary lumina. With increasing amyloid deposition, the glomeruli become enlarged with nodular deposits of eosinophilic material (non-PAS, but Congo red-stained = different from diabetic glomerulosclerosis). Finally, in advanced amyloidosis the glomerular structure is obliterated, with the glomeruli appearing as large, amorphous, eosinophilic balls.

Electron microscopy identifies amyloid as non-branching fibrils, first in mesangial areas, and then perpendicularly orientated on the epithelial aspect of the basement membrane with obliteration of the foot processes.

B. Inflammatory lesions of the glomerulus / glomerulonephritis, are characterized histologically by hypercellularity of the glomeruli, which may be either *diffuse* (post-infectious glomerulonephritis, membrano-proliferative glomerulo-nephritis, and some forms of lupus nephritis) or *focal* (IgA nephropathy and other

forms of lupus nephritis). The pattern of glomerular injury may also be global, that is, involving the entire glomerulus, or segmental, affecting only parts of it.

Clinically, glomerulonephritis are typically characterized by the nephritis syndrome, although in many cases, particularly with mild lesions, only part of the full-blown nephritic syndrome (e.g. hematuria) occurs. Occasionally proteinuria may predominate.

Pathogenetic, a number of mechanisms lead to inflammatory changes in glomeruli, including immunologic, thrombotic, toxic, and yet unknown disturbances. *Immunologic injury* can be of four basic types: (1) trapping of circulating immune complexes in a subepithelial location (confirmed electron microscopically by the presence of subepithelial "humps"); (2) in situ immune complex formation by the binding of circulating antibody to an antigen that has already deposited in the glomerular basement membrane; (3) activation of the alternative pathway of complement; (4) cell-mediated processes.

B. 1. Acute glomerulonephritis (postinfectious GN).

Acute glomerulonephritis refers to a glomerular disease that is characterized clinically by the sudden onset of the nephritic syndrome and morphologically by diffuse hypercellularity of the glomeruli. The disease is a sequel to infection with a variety of agents, for example staphylococci, pneumococci, spirochetes, and viruses, but the most frequent association is with certain strains of group A beta-hemolytic streptococci. The primary infections may be in either the pharynx or, especially in hot and humid environments, the skin. Acute glomerulonephritis most commonly affects children, and although in developed countries it is not seen as frequently now as in the past, it remains one of the most common renal diseases in childhood.

By light microscopy, diffuse enlargement and hypercellularity of the glomeruli are present during the first weeks after the onset of acute glomerulonephritis. The hypercellularity is due to the proliferation of both endothelial and mesangial cells and to the leukocytic infiltration by neutrophils and monocytes. The proliferation of mesangial cells result in an exaggeration of the normal lobular pattern. Crescents may be present, but they are usually sporadic and segmental. Tubulo-interstitial damage and inflammation occur in parallel with the glomerular changes. The blood vessels generally show no changes.

The characteristic ultrastructural features of acute postinfectious glomerulonephritis are subepithelial "humps". The humps are variably sized, dome-shaped deposits, which are situated on the epithelial aspect of the basement membrane. These deposits are invariably accompanied by mesangial and subendothelial deposits, which may be more difficult to find in the acute phase.

Immunofluorescence typically reveals granular peripheral reactions for IgG and C3 along the basement membrane, in locations corresponding to the humps.

The typical morphologic features of acute inflammation usually resolve by 8 weeks from the onset of the nephritis. However, a pattern of diffuse prominence of the mesangial matrix, which reflects mesangial hypercellularity, may persist for years. Generally, those patients who recover completely do so both clinically and

histologically by 3 years from onset. A small number of patients develop an unusually severe lesion that displays many crescents and progresses quickly to renal failure.

The issue of prognosis in acute glomerulonephritis has generated considerable controversy. Some investigators claim an overall complete recovery in more than 95% of patients, whereas others report that more than 50% of their patients develop some degree of chronic renal insufficiency, hypertension, or proteinuria. Although some degree of caution must remain with respect to the long-term prognosis of renal function, most data suggest that complete recovery, particularly in children, is the rule.

B. 2. Membranoproliferative glomerulonephritis

Membranoproliferative lesions are characterized by the combination of glomerular basement membrane thickening ("membrano-") and mesangial cell proliferation ("proliferative"). Although such lesions may be present initially as nephrotic syndrome, the prominent glomerular hypercellularity in membranoproliferative lesions clearly distinguishes them from the previously discussed noninflammatory primary glomerular lesions that cause nephrotic syndrome.

The light microscopic appearance of membranoproliferative lesions is similar in the majority of patients. Glomeruli are hypercellular, mainly due to mesangial cell proliferation. Variable infiltration by leucocytes is noted, and the glomeruli show prominent lobulation "lobular glomerulonephritis". Silver stains characteristically show a double contour to the peripheral basement membrane. This feature, which was previously described as "splitting" of the basement membrane, is a consequence of the marked inflammatory expansion of the mesangial area. As a result, the cells and matrix of the mesangium are forced peripherally into the capillary loops and insinuate themselves between the endothelial cells and the basement membrane, this process being called *mesangial interposition.*

Electron microscopy revels subendothelial and mesangial electron-dense deposits, and immunofluorescence demonstrates granular deposition of immunoglobulins (IgG, IgM) and complement in glomerular capillary loops and mesangium.

Membranoproliferative lesions occur primarily in older children and young adults, although they may also be seen in older adults. The clinical presentation may be either the nephrotic or nephritic syndrome or a combination of both. The vast majority of patients progress to end-stage renal failure, regardless of treatment.

B. 3. Lupus nephritis

Systemic lupus erythematosus is a chronic autoimmune disorder that primarily affects young women and is characterized by the involvement of many body organs. The variety of renal lesions in SLE is reflected in a wide spectrum of clinical manifestations, including the nephritic and nephrotic syndrome; the renal disease being one of the major prognostic determinants in patients with SLE (renal failure is the cause of death in over a third of the patients with SLE).

The morphologic alterations in lupus nephritis center on the glomeruli, because they bear the brunt of the immunologic assault. Cellular proliferation is typically mesangial and often irregular. Mild glomerular involvement is characterized by

diffuse mesangial expansion, with or without hypercellularity, and there is often a superimposed, segmental endothelial cell proliferation. More severe inflammation is manifested by enlarged, hypercellular glomeruli, enhanced lobulation, segmental areas of tuft necrosis, karyorrhexis, polymorphonuclear leukocyte infiltration, and crescent formation.

Heavy subendothelial deposits can usually be recognized at the light microscopic level by a marked thickening of the involved capillary wall, which results in a characteristic formation that has been called a "wire loop". Hyaline thrombi are also seen as eosinophilic plugs of material that seem to occlude the lumen of involved capillary loops. In areas of segmental necrosis, hematoxylin bodies, which are lilac-tinged fragmented nuclei, may be found. Hematoxylin bodies are considered to be the only pathognomonic light microscopic feature of tissue damage of SLE in the kidney and other organs. Because of the frequently episodic nature of this disease, it is not uncommon to see evidence of active proliferation and inflammation coexisting with older lesions, such as segmental scars and adhesions to Bowman's capsule.

By electron microscopy, immune complexes, which are particularly prominent in this disease, localize in mesangial, subendothelial, or subepithelial areas; by immunofluorescence microscopy IgG is the most frequently demonstrated immunoglobulin, although IgA and IgM are also usually present.

Some degree of interstitial inflammation is almost invariable in significant lupus glomerulonephritis. On occasion, the interstitial involvement may be a major morphologic feature, while the glomerular changes are only minor. Necrotizing arteriolar lesions are occasionally found in lupus nephritis, usually in association with a florid, diffuse, proliferative glomerulonephritis with crescents. The presence of a vascular lesion is associated with a poor overall prognosis.

B. 4. Focal glomerulonephritis

Focal glomerulonephritis is a morphologic term that refers to forms of glomerulonephritis in which only *some* of the glomeruli are involved. In this condition it is also common for the inflammation to be limited to *segmental* portions of the glomerulus. Focal glomerulonephritis may be produced by a number of conditions, including disorders that involve only or primarily the kidney (e.g. IgA nephropathy) and others that are systemic (e.g. Henoch-Schönlein purpura, lupus nephritis, systemic vasculitis, bacterial endocarditis).

IgA nephropathy (Berger disease) is a common form of focal glomerulo-nephritis. It is actually the most common form of primary glomerulonephritis in several parts of the world. The pathogenesis of IgA nephropathy is not understood, but a number of findings suggest a role for immune complexes. Genetic susceptibility may also play a role in the development of IgA nephropathy in some patients.

Ig A nephropathy is most common in young men, with a peak age of l5 to 30 years and usually presents as macroscopic (gross) or microscopic hematuria. Although once believed to be a rather benign disease, it is now clear that up to 20% of patients with IgA nephropathy progress to end-stage renal failure. Furthermore, the lesion, once diagnosed, does not spontaneously resolve and is not responsive to therapy.

IgA nephropathy is a mesangial proliferative lesion, meaning that mesangial cell proliferation and widening of the matrix are the sole or predominant light microscopic abnormalities in many of the cases. The involvement is usually focal. In most young children and in adults with mild disease, the proliferation of mesangial cells tends to be mild and is accompanied by a prominence of the mesangial stroma. By contrast, biopsy specimens from those patient destined to progress to renal failure often exhibit segmental necrosis of the glomerular tufts, crescents, and scarring. Particularly in such specimens, hyaline material, representing immune deposits, may be seen in the mesangium.

Ultrastructural examination confirms the mesangial cellularity and increased mesangial matrix. Immunofluorescence microscopy is essential in the diagnosis of IgA nephropathy and reliably demonstrates granular mesangial deposition of IgA, usually accompanied by C3 and sometimes by IgG, IgM, or both.

B. 5. Crescentic (rapidly progressive) glomerulonephritis

Crescentic glomerulonephritis is an ominous morphologic pattern in which the majority of glomeruli are surrounded by an accumulation of cells in Bowman's space. The crescent is an expression of fulminant glomerular damage and always leaves severe residual scarring. Clinically, most patients suffer a rapid and progressive decline in renal function. Irreversible renal failure with severe oliguria or anuria occurs within weeks unless adequate therapy is administered.

Crescentic glomerulonephritis is associated with a number of underlying conditions and should always prompt a search for other diagnostic features that allow a sub-classification. Idiopathic crescentic glomerulonephritis is essentially a diagnosis of exclusion that is made when there is no evidence of immune complex localization or vasculitis. On the other hand, there are specific primary glomerular and systemic diseases that can cause crescentic glomerulonephritis: membranoproliferative glomerulonephritis, IgA nephropathy, Henoch-Schonlein purpura, systemic vasculitis, and systemic lupus erythematosus; seldom poststreptococcal glomerulonephritis.

The glomeruli are by definition inflamed in crescentic glomerulonephritis. The crescents range from groups of cells filling only a segment of Bowman's space to circumferential masses of cells that completely surround the glomerulus. They evolve from a cellular to a fibrocellular form, and eventually scar to create a fibrous crescent. The cells in a cellular crescent, which range in shape from spindle to ovoid, are often intermingled with neutrophils and fibrin. The latter can invariably be demonstrated by immunofluorescence in active crescentic glomerulonephritis, the escape of fibrin into Bowman's space seems to be the most important trigger for glomerular crescent formation.

Within several weeks, enough organization has taken place in the crescent, so that a connective tissue matrix, which stains with silver, is mingled with the cells. Eventually, segmental crescents become incorporated into Bowman's capsule as a segmental fibrous collar or in the glomerulus as a segmental glomerular scar. Circumferential crescents result in globally scarred glomeruli.

C. Chronic glomerulonephitis (GN) is considered an *end-stage pool* of primary or secondary *glomerular disease* - most of them being described earlier in this chapter. The approximate proportion of patients with ongoing glomerular disease who progress to CG is as follows: poststreptococcal (1% to 2%); rapidly progressive (crescentic) (90%), membranous (30% to 50%), focal glomerulosclerosis (50% to 80%), membranoproliferative glomerulonephritis (50%), IgA nephropathy (30% to 50%).

Morphology of chronic GN. The kidneys are symmetrically contracted and have diffusely granular, pale cortical surfaces. On section, the cortex is thinned, and there is an increase in pelvic fat.

The glomerular histology depends on the stage of the disease. In early cases, the glomeruli may still show evidence of the primary disease (e.g. membranous nephropathy or membranoproliferative GN). However, there ensues hyaline obliteration of glomeruli, transforming them into acellular eosinophilic PAS-positive masses. The hyaline represents a combination of trapped plasma proteins, increased mesangial matrix, basement membrane – like material, and collagen. Because hypertension is an accompaniment of chronic GN, arterial and arteriolar sclerosis may be conspicuous. Marked atrophy of associated (to the sclerotic glomeruli) tubules, irregular interstitial fibrosis and lymphocytic infiltration occur.

The disease is relentlessly progressive; if patients with chronic GN are not maintained on continued dialysis or if they do not receive a renal transplant, the outcome is invariably death.

TUBULAR DISEASE: ACUTE TUBULAR NECROSIS (ATN)

Acute tubular necrosis refers to acute injury of the renal tubules that result in acute renal failure. ATN is the most frequent cause of the clinical syndrome of acute renal failure. Acute renal failure is a clinical term that defines an acute decline in the glomerular filtration rate, oliguria, and sometimes anuria, with rise in the blood urea nitrogen and serum creatinine levels.

Based largely on morphology, two subtypes of acute tubular necrosis are identified: *ischemic* and *toxic*.

Ischemic ATN occurs most often in response to shock or dehydration. It may also result from other causes, including the hepato-renal syndrome, sepsis, complications of renal transplantation, intravascular hemolysis, myoglobinuria secondary to crush injuries.

On gross examination, the kidneys in ischemic ATH are swollen and reveal a pale cortex and congested medulla. By light microscopy there are no pathologic changes in the glomeruli and vessels. The proximal tubules are dilated, with flattening of the epithelium and loss of the brush border. It is, therefore, difficult to distinguish proximal from distal tubules.

An important feature of ischemic ATN is that (despite its name) widespread necrosis of the tubular epithelium does not occur. Instead, the “necrosis” is more patchy, subtle and is reflected in individual necrotic cells within some proximal or

distal tubules. These single necrotic cells are shed into the tubular lumen, with resulting focal denudation of the tubular basement membrane. Distal tubules are dilated and frequently contain casts - some of the hyaline type, others finely granular (containing cellular debris).

During the recovery phase of ATN, tubular epithelium regenerates, leading to the appearance of mitoses, increased size of cells and nuclei, and cell crowding.

Toxic acute tubular necrosis. The kidneys are quite sensitive to toxins. Toxins known to cause ATN are heavy metals (mercury, bismuth, uranium), antibiotics (gentamicin, kanamycin, neomycin), organic solvents (ethylene glycol, carbon tetrachloride, dioxane).

In toxic ATN the morphologic features vary depending on the agent. With mercury, for example, there is nearly complete necrosis of all proximal tubular cells, which resolves if the patient survives. On the other hand, acute renal failure with some agents such as lithium is associated with virtually no morphologic changes in tubular epithelium. Between these extremes are most of the toxins, which result in varying degrees of epithelial cell damage, which may or may not correlate with clinical features.

VASCULAR KIDNEY DISEASES

Nephrosclerosis refers to the renal changes that occur with hypertension. No definition is completely accepted for hypertension, but a systolic pressure of 160 mm Hg and a diastolic reading of 90 are generally considered to represent unequivocal hypertension. Some degree of nephrosclerosis is usual in patients with prolonged hypertension and it may be severe enough to cause renal failure. Nephrosclerosis is separated into *benign* and *malignant* forms, corresponding to benign and malignant hypertension.

Benign nephrosclerosis is a consequence of renal ischemia. The kidneys are smaller than normal and affected bilaterally. The cortical surface exhibits a fine granularity, but coarser scars are also encountered. On cut section, the cortex is thinned.

Microscopically, many glomeruli appear normal, whereas others show varying degrees of ischemic changes, which is distinctly different from the lesions of intrinsic glomerular disease (e.g. glomerulonephritis). Initially, the glomerular capillaries are thickened and shriveled. Cells of the glomerular tuft are progressively lost. Collagen and matrix material are deposited within Bowman's space opposite the hilum. Eventually, the glomerular tuft is obliterated by a dense, eosinophilic globular mass enclosed in a scar, all within Bowman's capsule. Tubular atrophy, a consequence of the obsolescence of the glomerulus, is associated with fibrosis of the related interstitium. The pattern of change in the blood vessels of the kidney depends on the size of vessel involved. Large arteries down to the size of the arcuate arteries exhibit hyaline arteriolosclerotic changes of the intima, replication of the internal elastic lamina and partial replacement of the muscular coat with fibrous tissue (fibroelastic hyperplasia). Interlobular arteries show medial hypertrophy, in addition to the above

changes. Arterioles display hyaline thickening of the entire wall, so-called arteriolosclerosis.

Benign nephrosclerosis ordinarily is not associated with marked abnormalities of renal function, but a few of the many persons with "benign" hypertension progress to end-stage renal disease. Because "benign" hypertension has such a high prevalence, even the small proportion of these patients who develop renal insufficiency amounts to about one third of all patients with end-stage renal disease and most blacks with this complications.

Malignant nephrosclerosis refers to renal changes associated with *malignant hypertension*. There is no specific blood pressure that defines malignant hypertension, but a diastolic pressure greater than 125 mm Hg, the presence of renal changes and papilledema, and functional impairment of the kidney are generally accepted criteria. About half of the patients with malignant hypertension have an antecedent history of benign hypertension. The remainder includes patients with intrinsic renal diseases (such as pyelonephritis or chronic glomerulonephritis) and various systemic disorders (e.g. lupus erythematosus, scleroderma, polyarteritis). Occasionally, malignant hypertension arises *de novo* in apparently healthy persons. Malignant hypertension occurs more frequently in men than in women, typically around the age of 40.

The size of the kidneys varies from small to enlarged, depending on the duration of preexisting benign hypertension. The cortical surface characteristically displays petechiae, accounting for the name "flea-bitten" kidney. The cut surface is mottled red and yellow and occasionally exhibits small cortical infarcts.

Microscopically, malignant nephrosclerosis shows many of the changes of benign nephrosclerosis, but in addition the glomeruli frequently show fibrinoid necrosis, sometimes in continuity with the same process in the afferent arterioles. Subtotal infarction of glomeruli, with dilated capillaries stuffed with erythrocytes is common. Usually fewer than half of the glomeruli show acute, necrotizing, inflammatory lesions. Whereas the arterioles exhibit fibrinoid necrosis, the larger arteries reveal a lumen that is markedly reduced in size by profuse medial thickening, owing to cellular proliferation – “onion-skinning” and the accumulation of a collagen matrix (hyperplastic arteriolosclerosis).

Patients with malignant hypertension typically suffer headache, dizziness and visual disturbances. Gross and microscopic hematuria is frequent and proteinuria is virtually invariable. Progressive deterioration of renal function eventually leads to uremia.

(TUBULO)INTERSTITIAL DISEASES

Pyelonephritis (PN) is a combined inflammation of the tubules, interstitium, calyces, and renal pelvis and is one of the most common diseases of the kidney. It occurs in two forms. *Acute pyelonephritis* is caused by bacterial infection and is often associated with urinary tract infection (UTI). *Chronic pyelonephritis* is a more complex disorder: bacterial infection plays a dominant role, but other factors (vesicoureteral reflux, obstruction) are involved in its pathogenesis. Both, acute and

chronic pielonephritis are *focal* diseases, in between lesions the kidney appears normal. There are two routes by which bacteria can reach the kidneys: (1) through the blood-stream (*hematogenous infection*) and (2) from the lower urinary tract (*ascending infection*) - the most common cause of clinical pyelonephritis – resulting from a combination of urinary bladder infection with gram-negative enteric bacilli (*E. coli* in the first place), vesicoureteral reflux and intrarenal reflux.

Although the hematogenous route is the less common of the two, acute pyelonephritis does result from seeding of the kidneys by bacteria from distant foci in the course of septicemia or infective endocarditis. Hematogenous infection is more likely to occur in the presence of ureteral obstruction, in debilitated patients, in patients receiving immunosuppressive therapy, and with non-enteric organisms, such as staphylococci and certain fungi and viruses.

Acute pyelonephritis is always a result of a bacterial infection of the kidney. The symptoms of acute PN include costovertebral angle tenderness and systemic evidence of infection, such as fever and malaise. The peripheral leukocyte count is often elevated. The differentiation of upper from lower urinary tract infection is often clinically difficult, but the finding of leukocytes casts in the urine is diagnostic of PN.

On gross examination the kidneys of acute PN may have small abscesses on the subcapsular surface or large, wedge-shaped areas of coalescent suppuration. In areas where there has been severe reflux or obstruction, the cortex is thinned and the papilla blunted. The distribution of these lesions is unpredictable and haphazard, but in PN associated with reflux, damage occurs most commonly in the lower and upper poles.

Microscopically, the acute inflammatory process may extensively destroy the parenchyma, particularly the cortex, although vessels and glomeruli often show some resistance to infection. Collecting ducts, extending from the cortex into the medulla, are often filled with neutrophils, the latter, together with lymphocytes and plasma cells, being typically present in the interstitium.

Three complications of acute PN are encounter in special circumstances: *papillary necrosis* is seen mainly in eldery diabetics with urinary obstruction when one or all pyramids of the affected kidney shows gray-white to yellow necrosis of the tip or distal 2/3 that resembles infarction; *pyonephrosis* when there is total complete obstruction, so the suppurative exudates is unable to drain and thus fills the ureter, renal pelvis and calyces; and *perinephric abscess* that implies extension of suppuration beyond renal capsule into the perinephric tissue.

Chronic pyelonephritis is a chronic tubulointerstitial disorder in which there is gross, irregular, and often asymmetric scarring, together with deformation of the calyces and the overlying parenchyma. It often progresses to so-called *end-stage kidney* - a shrunken and fibrotic kidney insufficient to maintain renal function. In fact, about 15% of patients referred for renal dialysis or transplantation suffer from chronic pyelonephritis.

Chronic PN is divided into cases with some form of obstruction and those without. In cases with mechanical obstruction *(obstructive uropathy)*, the pathologic

changes are due to a combination of obstruction and infection, and grossly all of the calyces and the renal pelvis are dilated and the parenchyma is uniformly thinned - a condition termed *hydronephrosis*. The cases without obstruction are associated in large majority with vesicoureteral reflux (so-called *reflux nephropathy*), when the calyces from the poles of the kidney are preferentially expanded and are associated with overlying discrete to coarse scars that cause an indentation of the renal surface.

The microscopic changes involve primary and predominantly tubules and interstitium. The tubules show atrophy in some areas and hypertrophy in others or dilatation. Dilated tubules may be filled hyaline casts resembling colloid-containing thyroid follicles, a pattern called "thyroidization" / (pseudo)thyroidization. There are varying degrees of chronic interstitial inflammation and fibrosis. The glomeruli may be completely uninvolved, may have periglomerular fibrosis, or may be sclerotic. Arcuate and interlobular vessels disclose obliterative endarteritis in the scarred areas, and in the presence of hypertension hyaline arteriolosclerosis is seen in the entire kidney.

Reno-urinary tuberculosis is secondary to an active tuberculous lesions elsewhere the body reaching the kidney by hematogenous spread. The kidneys usually are involved along with other organs in acute milliary tuberculosis, but another form of renal tuberculosis *(tuberculous pyelonephritis)* also occurs, in which there is a chronic ulcerative and spreading lesion. This form is usually unilateral and due to embolic masses of organisms (Koch bacilli) arrested in the kidney that produce the first (not prominent) lesion in the cortex. By discharge of this lesion into a tubule, spread occurs to the medulla, where a caseous ulcerative tubercle appears on a renal papilla. From there, the mucosa of the pelvis, ureter and bladder are involved. Reinfection and extension to other portions of the kidney readily follow. Tuberculous stricture of the ureter and individual calyces leads to stasis of urine and hydronephrotic changes. There is progression of the tuberculous process in the kidney tissue through the stages of caseation, loss of tissue, ulceration and hydronephrosis.

The appearance of the kidney depends upon the stages of the process. In an early period, a few yellowish opaque tubercles are seen in the cortex and near the tip of a papilla. Later, caseous masses of varying size replace the renal tissue and the ragged hydronephrotic cavities contain thick creamy pus. The infected ureter becomes thick-walled, rigid, and stenosed. The bladder involvement begin at the ureteral opening and spreads as an irregular area of ulceration. The lesions of the ureter and bladder tend to heal if the infected kidney is removed.

HYDRONEPHROSIS

Hydronephrosis is defined as dilatation of the renal pelvis and calyces, flattening of the papillae and, in chronic cases, atrophy of the renal cortex. In the presence of hydronephrosis, the kidney is more susceptible to pyelonephritis.

It is always the result of urinary tract *obstruction*, whether from tumors, stones or some other causes. When the obstruction is sudden and complete, the reduction of

glomerular filtration usually leads to mild dilatation of the pelvis and calyces but sometimes to atrophy of the renal parenchyma. In the case of subtotal or intermittent obstruction, glomerular filtration is not suppressed, and progressive dilatation ensues. Grossly, the kidney may have slight-to-massive enlargement. The earlier features are those of simple dilatation of the pelvis and calyces. In far-advanced cases, the kidney may become transformed into a thin-walled cystic structure (with a diameter up to 15 to 20 cm) with striking parenchymal atrophy, total obliteration of the pyramids, and thinning of the cortex.

In early hydronephrosis the most prominent microscopic finding is dilatation of the collecting ducts, followed by dilatation of the proximal and distal convoluted tubules. Eventually the proximal tubules become widely dilated and loss of tubules is common – the picture of cortical tubular atrophy with interstitial fibrosis. Interestingly, the glomeruli are usually spared.

The clinical syndrome in bilateral acute and complete urinary tract obstruction is acute renal failure; in the case of bilateral chronic subtotal obstruction, chronic renal failure ensues. Many of these conditions are amenable to surgical interventions, so their prompt recognition is important. Unilateral, complete, or partial obstruction is often missed clinically because of the lack of symptoms, but left untreated, atrophy of an obstructed kidney is inevitable.

RENAL STONES (UROLITHIASIS)

The pelvis and calyces of the kidney are common sites for the formation and accumulation of calculi. Stones vary in composition, depending on individual factors, geography, metabolic alterations, and the presence of infection. For unknown reasons, renal stones are more common in men than in women. They vary in size from gravel, in which the stones may be less than 1 mm in diameter, to a large stone that dilates and casts the entire renal pelvis (“staghorn” stone).

Kidney stones may be well tolerated, but in some cases they lead to sever hydronephrosis and pyelonephritis. Moreover they can erode the mucosa and cause hematuria. The passage of a stone into the ureter causes excruciating flank pain, termed *renal colic*. Although until recently most kidney stones required surgical methods for their removal, ultrasonic disintegration (lithotripsy) and endoscopic removal are often effective alternatives.

RENAL TUMORS

BENIGN TUMORS arising in the soft tissue tumors of the kidney include *hemangiomas, lipomas, fibromas* and *leiomyomas*; these are often incidental findings noted at autopsy.

Angiomyolipoma is a well-known tumor in adults and has a strong association with tuberous sclerosis. Grossly, this tumor is yellow and bosselated, resembling renal cell carcinoma. They are well encapsulated and lack the areas of necrosis.

Microscopically, it displays an admixture of benign adipose tissue, smooth muscle and thick-walled vessels.

MALIGNANT TUMORS

Renal cell carcinoma (Grawitz tumor) is the most important neoplasm of the kidney, derived from the epithelial cells of the renal tubules. This tumor accounts for 90% of all cases of the renal cancers in adults. The incidence of renal cell carcinoma peaks in the sixth decade and is twice as frequent in men as in women.

Hematuria is the single most common presenting sign; the classic triad of hematuria, flank pain and palpable abdominal mass is found in less than 10% of patients. It is frequently associated with paraneoplastic syndromes (hyperparathyroidism, erythrocytosis, and hypertension). Often a patient with renal cell carcinoma initially presents with symptoms due to metastasis.

The overall survival in cases of renal cell carcinoma is approximately 40% at 5 years. Tumors with a papillary growth pattern or those composed of oncocytic cells have substantially better survival rates. The prognosis is worse if the tumor has penetrated the renal capsule to invade Gerota's fascia or has spread to regional lymph nodes or renal vein. Distant metastases are found most frequently in the brain, lung and bones. The treatment is essentially limited to complete operative removal.

On gross appearance, renal cell carcinomas arise more commonly in the upper lobe, usually as a solitary, unilateral lesion – spherical mass, 3 to 15 cm in diameter typically yellow orange white with large areas of hemorrhage and necrosis. The tumors are entire solid or focally cystic with sharply define margins. The histologic patterns are variable: solid, trabecular and tubular patterns of growth are common. The most frequent and characteristic neoplastic cell has an unusually clear cytoplasm, owning to the removal of glycogen and lipids by the water and organic solvents used in the preparation of the tissue. Frequently, there is little cellular or nuclear pleomorphism, although anaplastic sarcomatoid variants do occur.

Nephroblastoma (**Wilms tumor**) is a malignant mixed tumor of the kidney that is composed of mesenchymal and epithelial embryonal elements. It is one of the most common solid tumors in very young children and usually present before the age of 4 years, although it is occasionally seen in adults. The large majority (99%) of all cases is sporadic and the few familial cases exhibit autosomal dominant inheritance. Only 3% of sporadic cases are bilateral, contrasted with 20% of familial cases. Deletions of chromosome 11 have consistently been found in cases of Wilms tumor.

Most children with Wilms tumor present with a large abdominal mass, occasionally accompanied by abdominal pain or intestinal obstruction. Patients younger than 2 years of age tend to have a better prognosis. Invasion of the tumor beyond the renal capsule, noted at the time of surgery, is a negative prognostic indicator.

On gross appearance, Wilms tumor is usually large, with a bulging, pale tan cut surface enclosed within a thin rim of renal cortex and capsule.

Histologically the tumor is composed of elements that resemble three types of normal tissue: metanephric blastema, immature stroma (mesenchymal tissue), and

immature epithelial elements. Most nephroblastomas contain all three elements in varying proportions, but occasional tumors may contain only two or one of these elements.

The epithelial component presents as small tubular structures; rare immature elements resembling glomeruli are found. The stroma between the other elements is composed of undifferentiated spindle cells, although occasionally distinct differentiation of fibroblastic and striated muscle elements is seen. Bone, cartilage, adipocytes and muscle cells may be encountered.

Urothelial carcinoma of renal pelvis originated in urothelial epithelium of renal pelvis and calyces becomes clinically apparent as hematuria after fragmentation, or they may block the urinary outflow and lead to hydronephrosis and flank pain. Histologically, pelvic tumors are the exact counterpart of those found in urinary bladder (see further).

URINARY BLADDER DISORDERS

CYSTITIS is the inflammation of the urinary bladder and is the most common disorder of this organ encountered in clinical practice. In most cases, cystitis is secondary to infection of the bladder. Factors related to bladder infection and the development of cystitis include the age and sex of the patient, presence of bladder calculi, bladder outlet obstruction, diabetes mellitius, immunodeficiency, prior instrumentation or catheterization and radiation therapy or chemotherapy. The risk of cystitis in females is increased because of a short urethra, and especially during pregnancy. In the large majority of cases, E. coli, Proteus, Pseudomonas and Enterobacter are the cause of cystitis. Tuberculosis of bladder is always secondary to renal tuberculosis. Fungal cystitis may be seen in immunosuppressed patients.

The cystoscopic and histologic features of *acute* and *chronic* cystitis reflect the inflammatory process and are usually nonspecific.

Acute cystitis. Grossly, there is hyperemia of the mucosa, sometimes associated with exudate. When there is hemorrhagic component, the cystitis is designated *hemorrhagic* cystitis. This form of cystitis sometimes follows radiation injury or antitumor chemotherapy and is often accompanied by epithelial atypia. Adenovirus infection also causes a hemorrhagic cystitis.

The accumulation of large amounts of suppurative exudate may merit the designation of *suppurative cystitis.* When there is ulceration of large areas of the mucosa or sometimes the entire bladder mucosa, this is known as *ulcerative cystitis.*

Persistence of the infection leads to **chronic cystitis**, which differs from the acute form only in the character of the inflammatory infiltrate. There is more extreme heaping up of the epithelium with the formation of a real, friable, granular, sometimes ulcerated surface. Chronicity of the infection gives rise to fibrous thickening in the *tunica propria* and consequent thickening and inelasticity of the bladder wall.

The histologic findings of most of these variants of acute and chronic nonspecific cystitis are exactly those that can be anticipated in any such acute,

respectively chronic nonspecific inflammation. Mention may be made of special forms of chronic inflammatory reaction, the aggregation of lymphocytes into lymphoid follicles within the bladder mucosa and underlying wall, creating a variant of chronic cystitis known as *cystitis follicularis*. *Eosinophilic cystitis* is characterized by infiltration with submucosal eosinophils, together with fibrosis and occasionally giant cells. Finally, chronic specific cystitis seen in bladder tuberculosis, presents caseating granulomas.

URINARY BLADDER NEOPLASMS are mainly epithelial tumors, the large majority being urothelial / transitional cell as histogenesis and comprising more than 98% of all primary tumors of the bladder. They constitute a spectrum that begins with benign papillomatous lesions and extends through carcinoma *in situ* to invasive (Fig. 53) and metastatic transitional cell carcinomas.

Papillary urothelial / transitional cell carcinoma arises most frequently from the lateral walls and less often from the posterior wall. Tumors vary from small, delicate that are limited to the mucosal surface to larger, solid, invasive masses, which are often ulcerated. The papillary and exophytic cancers tend to be more differentiated, whereas the infiltrating tumors are usually more anaplastic. Histologically, urothelial / transitional cell carcinomas of urinary bladder are classified according to the World Heath Organization grading system:

- **Grade 1** papillary projections lined by neoplastic urothelial cells that show minimal nuclear pleomorphism and mitotic activity. The papillae are long and delicate, and fusion of papillae is focal and limited.
- **Grade 2** intermediate histo- and cytologic features between grade 1 (the best differentiated) and 3 (the poorest differentiated).
- **Grade 3** significant nuclear pleomorphism, frequent mitoses and fusion of papillae**.** Bizarre cells and focal sites of squamous differentiation are often seen.

Although invasion of the underlying bladder wall may occur with any grade of urothelial cell carcinoma, it is most frequent in grade 3 tumors.

Other types of tumors (**squamous cell carcinoma**, **adenocarcinoma**, mesenchymal tumors inclusive **embryonal rhabdomyosarcoma**) are uncommon in urinary bladder.

Metastatic tumors, especially by direct extension (from primary uterine cervix, prostate or colon tumors), but also from remote distance as malignant melanoma, carcinomas of the stomach, breast and lung are not uncommonly involving the urinary bladder.

IV. MALE GENITAL TRACT PATHOLOGY

ORCHITIS refers to acute or chronic inflammation of the testis, frequently in association with inflammation of the epididymis, and it is related to infections – *Chlamydia trachomatis, N. gonorrheae, E. coli, Pseudomonas, Mycobacterium tuberculosis, Treponema pallidum* - in the urinary tract (cystitis, urethritis, genitoprostatitis), which reach the testis and the epididymis through either the vas deferens or the lymphatics of the spermatic cords. It's worthy to note that the most common form of acute testicular inflammation caused by a virus is mumps orchitis, occurring in 20% of adult males with mumps.

In the **acute stage,** congestion, edema, and white cells infiltration (chiefly by neutrophils, macrophages, lymphocytes and plasma cells) characterize the inflammatory reaction. Although the process is more or less limited to the interstitial connective tissue, it rapidly extends to involve the seminiferous tubules, ductuli efferentes, ductus epididymis and may progress to frank abscess formation with suppurative necrosis of these structures. Fibrous scarring often follows such inflammatory involvement of the testis and epididymis, which can lead to permanent sterility or, in other cases, this acute nonspecific infection may become a chronic process.

Chronic orchitis can be either nonspecific, either specific (tuberculosis and syphilis). *Nonspecific granulomatous orchitis* appears as a moderately tender testicular painless mass mimicking a tumor. Histologically the orchitis presents noncaseating granulomas seen both within spermatic tubules and in the intertubular connective tissue. Skipping the missing caseous necrosis, the lesions resemble tubercles, but differ somewhat in having plasma cells and occasional neutrophils interspersed within the enclosing rim of fibroblasts and lymphocytes. *Tuberculosis* almost invariably begins in the epididymis, consecutive to hematogenous spreading from some other focus in the body, and may spread to the testis. Epididymis becomes swollen and sausage-like shaped. Histologically it's structure is substituted by many tubercle follicles that undergo caseation and coalesce, the entire organ being transformed into a massive caseating necrosis. Testicular lesions appear later and they consist also in caseating tuberculous granulomas. *Syphilitic orchitis* in both forms, acquired – tertiary stage – and congenital, takes two morphological patterns: the production of gummas or a diffuse interstitial chronic inflammation.

TESTICULAR TUMORS. Although rare, these entities are important because most of them are malignant and they occur in children and young adults. They are divided in two major categories: germ cell tumors (90 – 95%) and nongerminal tumors derived from stroma or sex cord. The most common types of germinal tumor are:

- **seminoma;** it has a homogeneous, gray-white, lobulated cut surface, replacing, in more than half of cases, the entire testis. Generally, the tunica albuginea is not penetrated. Microscopically, the typical seminoma presents sheets of uniform

"seminoma cells" arranged into poorly demarcated lobules by delicate septa of fibrous tissue containing lymphocyte infiltration. The "seminoma cells" are large, round-to-oval and have a distinct cell membrane, a clear or watery-appearing cytoplasm, and a large, central hyperchromatic nucleus. Mitoses are infrequent.

- **embryonal carcinoma;** grossly, the tumor is smaller than seminoma and usually doesn't replace the entire testis. On cut surface, the mass is often variegated, poorly demarcated at the margins, and punctuated by foci of hemorrhage or necrosis. Extension through the tunica albuginea into epididymis or spermatic cord is frequent. Histologically, the cells grow in glandular, alveolar, or tubular patterns, sometimes with papillary convolutions. The neoplastic cells have an epithelial appearance and are large, with "angry-looking" hyperchromatic nuclei having prominent nucleoli. In contrast to seminoma, the cell borders are usually indistinct, and there is considerable variation in cell and nuclear size and shape. Mitotic figures and tumor giant cells are frequent.
- **teratomas;** grossly are large, ranging from 5 to 10 cm in diameter, with a heterogeneous appearance, solid areas interspersed with cysts. Histologically, 3 variants are recognized, based on the degree of cellular differentiation:
  - (1) *mature teratomas,* composed of differentiated cells or organoid structures such as neural tissue, muscle bundles, islands of cartilage, clusters of squamous epithelium, structures of reminiscent of thyroid gland, bronchial or bronchiolar epithelium, and bits of intestinal wall, all embedded in a fibrous or myxoid stroma;
  - (2) *immature teratomas,* an intermediate stage between mature teratoma and embryonal carcinoma, is formed by elements of all 3 germ cell layers, incompletely differentiated and without any organoid arrangement;
  - (3) *teratomas with malignant transformation.*

PROSTATITIS Infections of the prostate result from the reflux of infected urine into the gland, following lower urinary tract infections.

Acute prostatitis, caused by gram-negative bacteria, especially *E. coli*, consists of an acute focal or diffuse suppurative inflammation in the prostatic acini and stroma (disseminated or coalescent abscesses + suppurative necrosis + interstitial edema + vascular congestion). Such inflammatory reactions may totally subside and leave behind only some fibrous scarring and calcification. Alternatively, they may become chronic or, in more severe cases, the abscesses may rupture into surrounding structures (urethra, rectum, ischiorectal fossa, perineum).

Chronic prostatitis may follow an acute episode, but is often of insidious onset. The nonspecific form is characterized by the aggregation of numerous lymphocytes, plasma cells, and macrophages, as well as neutrophils within the prostatic substance. The specific chronic inflammation of the prostate is represented mainly by tuberculous prostatitis with the classic morphologic reactions of caseating granulomas. Regardless the form, chronic prostatitis may undergo subsequent fibrosis with urethral obstruction.

NODULAR PROSTATIC HYPERPLASIA (BENIGN ENLARGEMENT) is an extremely common disorder in men over age 50 and it is characterized by the formation of large nodules in the periurethral region of the prostate, with the partial or complete obstruction of urinary flow.

The hyperplasia involves both the glandular tissue and the fibromuscular stroma, in varying proportions. The nodules appear exclusively in the middle and lateral lobes periurethral zone, weigh about 100 g and vary in color and consistency. In nodules with primarily glandular proliferation, the tissue is yellow-pink with soft, sponge-like consistency, and a milky white prostatic fluid oozes out of these areas. In those primarily due to fibromuscular involvement, the nodules are pale gray, tough, and don't exude fluid.

Microscopically the nodularity is produced by glandular proliferation (*adenoma*) ± glandular dilatation (*cysts*) or by fibro-muscular proliferation of the stroma (*fibroma, leiomyoma*) or, more frequent, by hyperplasia of all 3 tissues (*fibroleiomyoadenoma*). The epithelial element proliferation predominates in most cases and it takes the form of aggregations of small to large to cystically dilated glands, lined by two celullar layers an inner columnar, and an outer flattened epithelium, based on an intact basement membrane. The epithelium is characteristically thrown up into numerous papillary buds and infoldings.

The complications of nodular hyperplasia of the prostate consist of:

1. compression of the urethra with difficulty in urination – chronic retention of urine, attacks of acute retention, related to the accompanying urinary infection causing edema and congestion of the prostatic urethra.
2. cystitis and pyelonephritis.
3. secondary changes in the bladder: hypertrophy, trabeculation, diverticulum formation, stones.
4. hydronephrosis.

PROSTATE CANCER became the most frequent cancer diagnosed in American men, since 1990, surpassing the frequency of lung cancer for the first time, and the second leading cause of cancer death (after lung cancer). Of course, there is a considerable geographic variation in the incidence of prostatic cancer throughout the world, but what is common is the fact that it's a disease of elderly men, 75% of all patients with prostatic cancer diagnosis being 60 to 80 years of age.

The *etiology* of prostate carcinoma is unknown, but the principal focus of research interest is directed toward endocrine influences. The androgenic control of normal prostatic growth and the responsiveness of prostatic cancer to castration and exogenous estrogens support a role for male hormones in the pathogenesis of this neoplasm.

Carcinoma of the prostate is commonly multicentric and usually located in the peripheral (posterior) zone of the gland, often rendering it palpable on rectal examination.

The cut surface of the prostate shows irregular, yellow-white, indurated subcapsular nodules.

Spread of prostate cancer occurs by direct local invasion (involving the seminal vesicles and the base of the urinary bladder) and through the bloodstream and lymph (chiefly to the bones for e.g. lumbar spine, pelvis, ribs).

The majority of prostatic cancers are *adenocarcinomas* (counting for 98% of all primary prostatic tumors), originated in acinar epithelium. They are characterized by small-to-medium sized glands, which lack organization and infiltrate the stroma. Well-differentiated tumors show relatively uniform glands lined by a single layer of neoplastic epithelial cells. A single layer of cuboidal cells lining neoplastic acini is, in fact, the most employed criterion to establish the diagnosis of prostatic carcinoma. Progressive loss of differentiation of prostatic adenocarcinomas is characterized by:

(1) increasing variability of gland size and configuration,

(2) papillary and cribriform patterns, and

(3) rudimentary (or no) gland formation, with only solid cords of infiltrating tumor cells.

The spectrum of differentiation of prostatic adenocarcinomas has been formalized into several grading systems. The most widely used is the *Gleason grading system* – based on five histologic patterns of tumor gland formation and infiltration – has also a prognostic value: the lower the score, the better the outcome.