Pathology of The Renal Systen

By the Pathology team

بسم الله الرحمن الرحيم

هذه المذكرة عبارة عن إعادة تنسيق وإضافة نوتات ومواضيع لمذكرة زملائنا من الدفعة السابقة ٤٢٧ الأعزاء.. لتتوافق مع المنهج المقرر من القسم

حرصنا فيها على إعادة صياغة كثير من الجمل لتكون سهلة الفهم وسلسة إن شاء الله..

وضفنا بعض النوتات المهمة

وأضفنا مواضيع موجودة بالـ **curriculum**

تعديل ٤٢٨ على المذكرة بواسطة اخوانكم:

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نتمنى منها الفائدة قدر المستطاع،

ولا تنسونا من دعواتكم !

After hours, or maybe days, of working hard, WE "THE PATHOLOGY TEAM" are proud to present "PATHOLOGY OF THE RENAL SYSTEM", I hope you guys like it ☺. Plz give us your prayers.

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part 1

THE NEPHROTIC SYNDROME

refers to a clinical complex that includes the following:

(1) massive proteinuria - daily loss of 3.5 or more in the urine
(2) hypoalbuminemia - plasma albumin levels less than 3 g/dL
(3) generalized edema - the most obvious clinical manifestation
(4) hyperlipidemia and lipiduria

- The initial event is a derangement in the capillary walls of the glomeruli, resulting in increased permeability to the plasma proteins
- In the normal kidney - the glomerular capillary wall, with its endothelium, basement membrane (GBM), and podocytes , acts as a barrier through which the glomerular filtrate must pass.
- Any increased in permeability allows protein to escape from the plasma into the glomerular filtrate. → Massive proteinuria
- Long standing proteinuria → hypoalbuminemia →drop in osmotic pressure → generalized edema → drop in plasma volume
- Compensatory to the drop of plasma volume, secretion of aldosterone, along with the reduced GFR and reduction of secretion of natriuretic peptides, promotes retention of salt and water by the kidneys → worsening the edema
- Repeating of this chain of events → accumulation of massive edematous fluid (anasarca)
- Hyperlipidemia may occur but its not really understood, most likely (but not certainly) because hypoalbuminemia triggers increased synthesis, abnormal transport and impairment of breakdown of lipoproteins.
- The lipiduria, reflects the increased GBM permeability to lipoproteins.

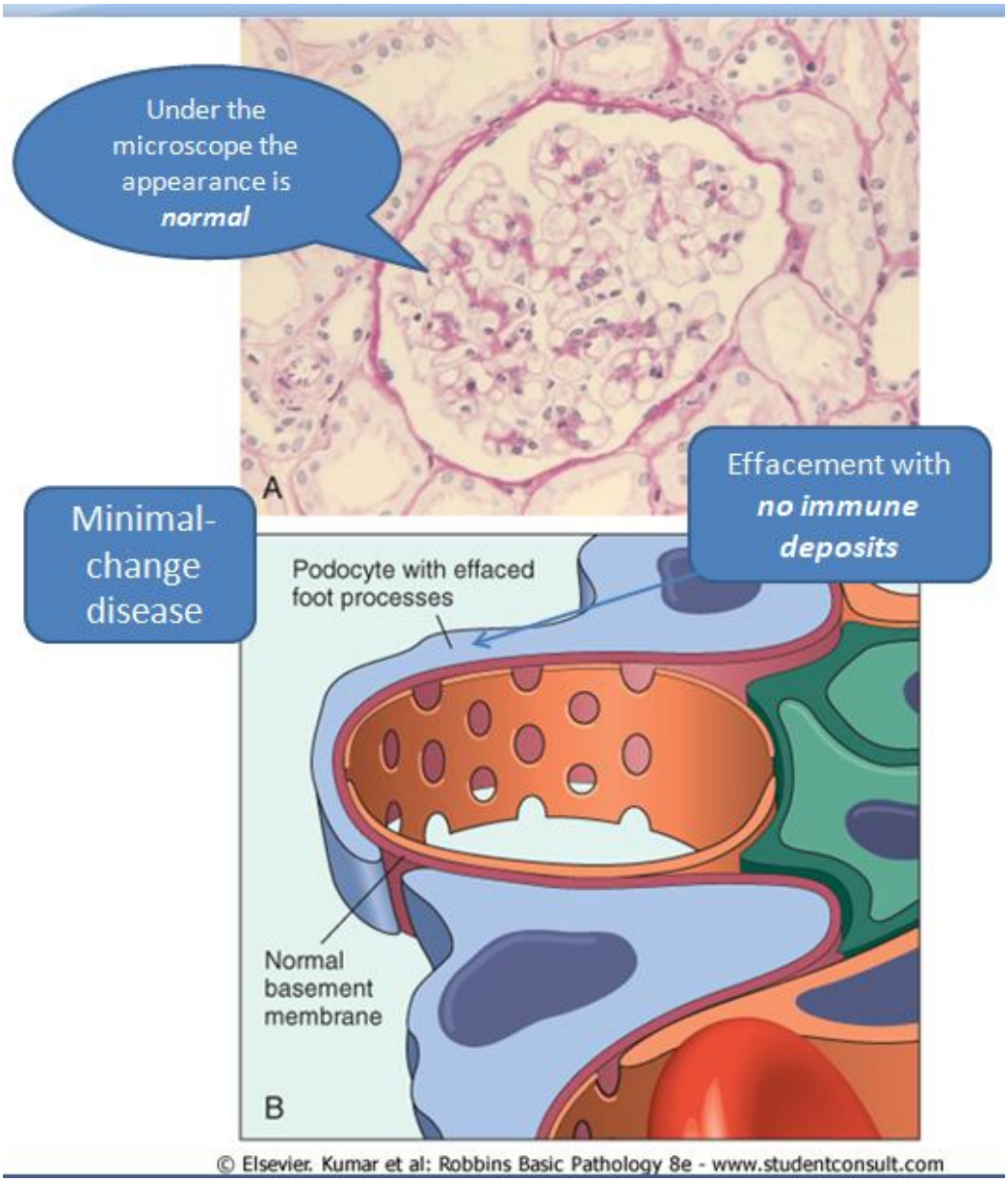
Causes of nephrotic syndrome :
- < 15 years old → almost always caused by a lesion primary to the kidney
- Adults → often associated with a systemic disease

Table. Causes of Nephrotic Syndrome

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

MINIMAL CHANGE DISEASE (MCD) (LIPOID NEPHROSIS)

- A benign disorder that is the most frequent cause of the nephrotic syndrome in children
- It is characterized by:
  - normal appearance of glomeruli under the light microscope
  - diffuse effacement of podocyte foot processes when viewed with the electron microscope
- It may develop at any age, but it is most common between ages 1 and 7 years.



Pathogenesis :

Based on some experimental studies, the proteinuria has been attributed to a T-cell derived factor that causes podocyte damage and effacement of foot processes. However, this is not established in the human disease. (they don`t really know ^^)

Morphology :

- The cells of the proximal convoluted tubules are often heavily laden with lipids and protein deposits, but this is secondary to tubular reabsorption of the lipoproteins (this appearance of the proximal convoluted tubules is the basis for the older term for this disease, lipoid nephrosis)

- Even with the electron microscope, the glomerular capillary wall appears normal.
- The only obvious glomerular abnormality is the uniform and diffuse effacement of the foot processes of the podocytes → The cytoplasm of the podocytes appears smeared
- The changes in the podocytes are reversible after remission of the proteinuria.
- There are also epithelial cell vacuolization, microvillus formation, and occasional focal detachments.

Clinical Course :

- There is no hypertension.
- Renal function is preserved.
- Selective proteinuria (mainly albumin loss)
- Prognosis is good → 90% of cases respond to a short course of corticosteroid therapy
- Proteinuria recurs in more than two thirds of the responders
- 5% develop chronic renal failure after 25 years
- Adults also respond to steroid therapy, but the response is slower and relapses are more common.

MEMBRANOUS GLOMERULONEPHRITIS (MEMBRANOUS NEPHROPATHY)

- It's the most common cause of nephrotic syndrome in adults.
- Slowly progressive & common between ages 30 and 50 years
- Secondary MGN occurs in association with :

  (1) infections (chronic hepatitis B, syphilis, schistosomiasis, malaria)

  (2) malignant tumors (carcinoma of the lung and colon and melanoma)

  (3) SLE and other autoimmune conditions

  (4) exposure to inorganic salts (gold, mercury)

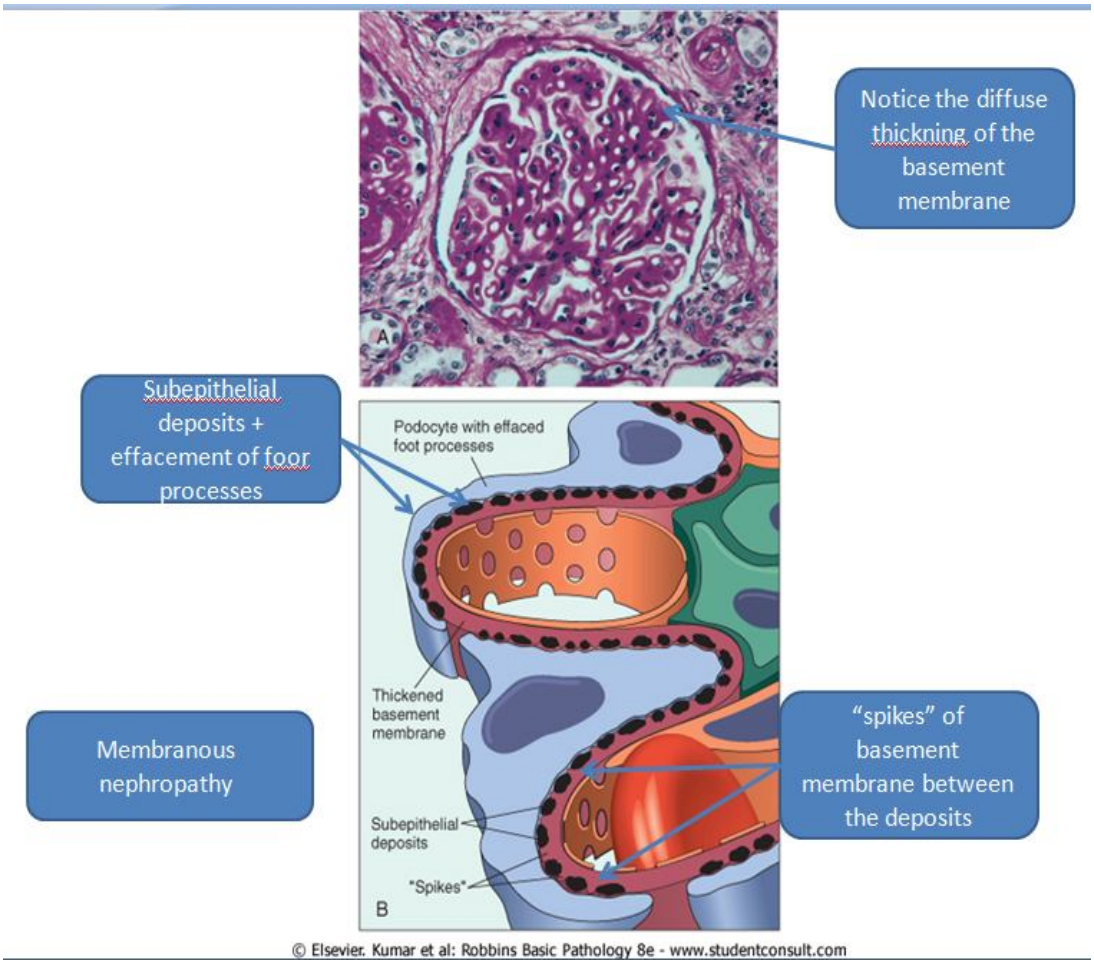
  (5) drugs (penicillamine, captopril, nonsteroidal anti-inflammatory agents)
- 85% of PRIMARY MGN are idiopathic

Pathogenesis :

- Non-idiopathic MGN is caused by exogenous (e.g., hepatitis B virus) or endogenous (DNA in SLE) antigen
- Idiopathic forms of MGN are thought to be induced by antibodies reacting in situ to endogenous or planted glomerular antigens.
- The lesions is similar to those of experimental Heymann nephritis (simply a MGN induced in rats).
- How does the glomerular capillary wall become leaky ? Absence of neutrophils, monocytes, or platelets and the presence of complement (C5b – C9) → direct action of complements on the glomerular epithelial cell → activation of glomerular mesangial and podocytes → liberation of proteases and oxidants that can damage capillary walls.
- The epithelial mediators also seem to reduce nephrin synthesis and distribution.

Morphology : (see fig. below)

- By light microscopy → diffuse thickening of the GBM (normal in early stages)
- By electron microscopy → the thickening is caused in part by subepithelial immunoglobulin-containing deposits that lie against the GBM
- Spike and dome pattern:
  Small, spikelike protrusions of GBM matrix that separate the deposits from each others
- As the disease progresses, these spikes incorporate the deposits into the GBM
- The podocytes lose their foot processes
- Later in the disease, the incorporated deposits are catabolized and eventually disappear, leaving cavities within the GBM. These cavities are later filled in by deposition of GBM-like material
- With further progression, the glomeruli become sclerosed and hyalinized.



Clinical course :

- Non-Selective proteinuria (in contrast to minimal change disease)
- proteinuria persists in over 60% of patients
- 40% of patients suffer progressive disease → renal failure in 2 to 20 years
- 10% to 30% have benign course with partial or complete remission of proteinuria.
- Patients do not respond to corticosteroid therapy .

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSG)

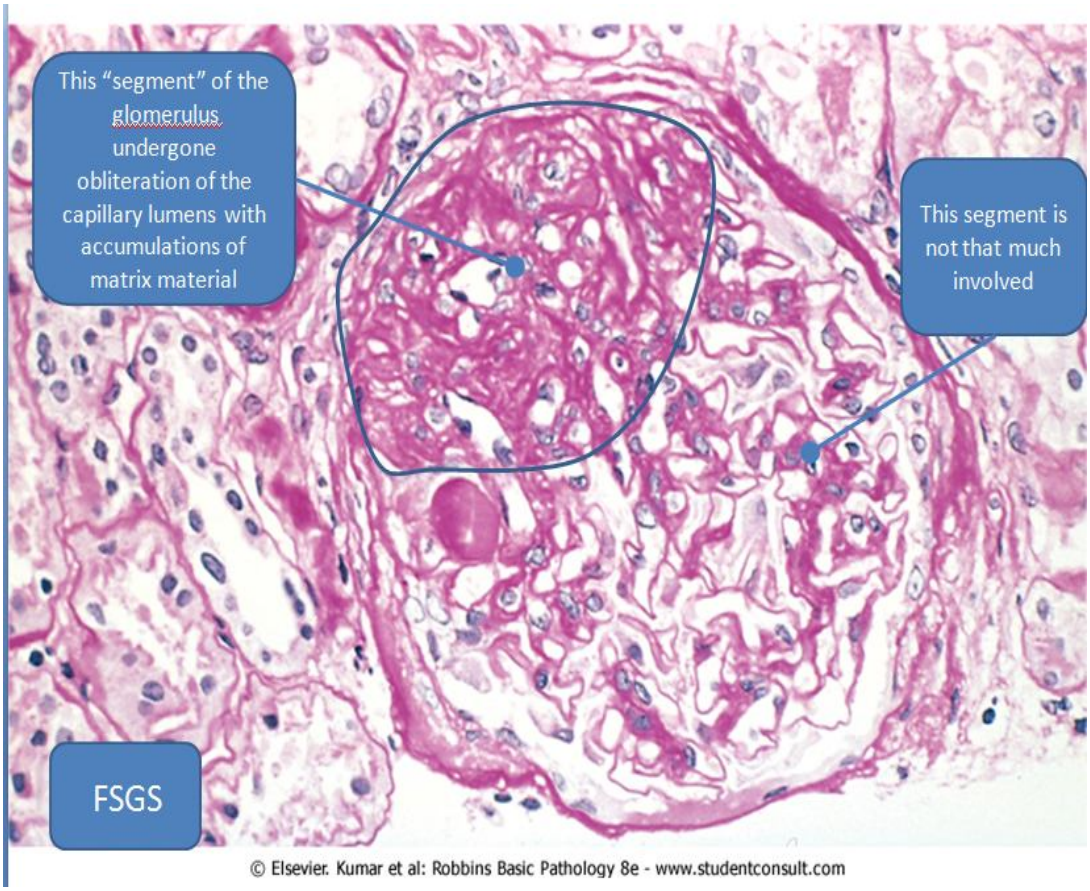
- Can be :
  (1) in association with HIV infection or heroin addiction
  (2) as a secondary event in other forms of GN
  (3) as a component of glomerular ablation nephropathy
  (4) in an inherited congenital form (Abnormal podocytes)
  (5) as a primary disease. (20-30% of all cases of the nephrotic syndrome)

Pathogenesis :

- Pathogenesis of primary FSG is unknown.
- Some believes that MCD and FSGN are part of continuum and MCD can transform into FSGN.
- Injury to the visceral epithelial cells (podocytes) and the resultant disruption of visceral epithelial cells is thought to represent the hallmark of FSG.
- As with MCD, permeability-increasing factors produced by lymphocytes have been proposed.
- Entrapment of plasma proteins and lipids in foci and reaction of the mesangial cell to such proteins and to fibrin deposits (hyalinosis & sclerosis)
- IgM and complement proteins are present

Morphology :

- At first, it affects only some of the glomeruli (hence the term "focal") and only the juxtamedullary glomeruli, eventually all levels of the cortex are affected
- Lesions occurring in some tufts within a glomerulus and sparing of the others (hence the term "segmental")
- Affected glomeruli show : Increased mesangial matrix, Collapsed basement membranes, and obliterated capillary lumens.
- Deposition of hyaline and lipid.
- As the disease progress, glomeruli become completely sclerosed (Global sclerosis).
- Immunofluorescence microscopy → immunoglobulins, usually IgM, and complement in the areas of hyalinosis
- Electron microscopy → effacement of foot processes and detachment of podocytes (greater than lipoid nephrosis).
- A macrophagic variant called **collapsing glomerulopathy** is being increasingly reported. It is characterized by collapse of the entire glomerular tuft and podocyte hyperplasia. This is a more severe form of FSGN that may be idiopathic or associated with HIV infection or drug-induced toxicities. It carries a poor diagnosis.



Clinical course :

- Hematuria and Hypertension (higher incidence than lipoid nephrosis)
- Non–selective proteinuria
- Poor response to corticosteroid (50% develop renal failure within 10 years)
- There is a little tendency for spontaneous remission of idiopathic FSGN.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)

- MPGN is manifested by
  - alterations in the basement membrane and mesangium
  - proliferation of glomerular cells
- 5% to 10% of cases of idiopathic nephrotic syndrome
- Some patients present only with hematuria or proteinuria
- Two major types of MPGN (I and II)

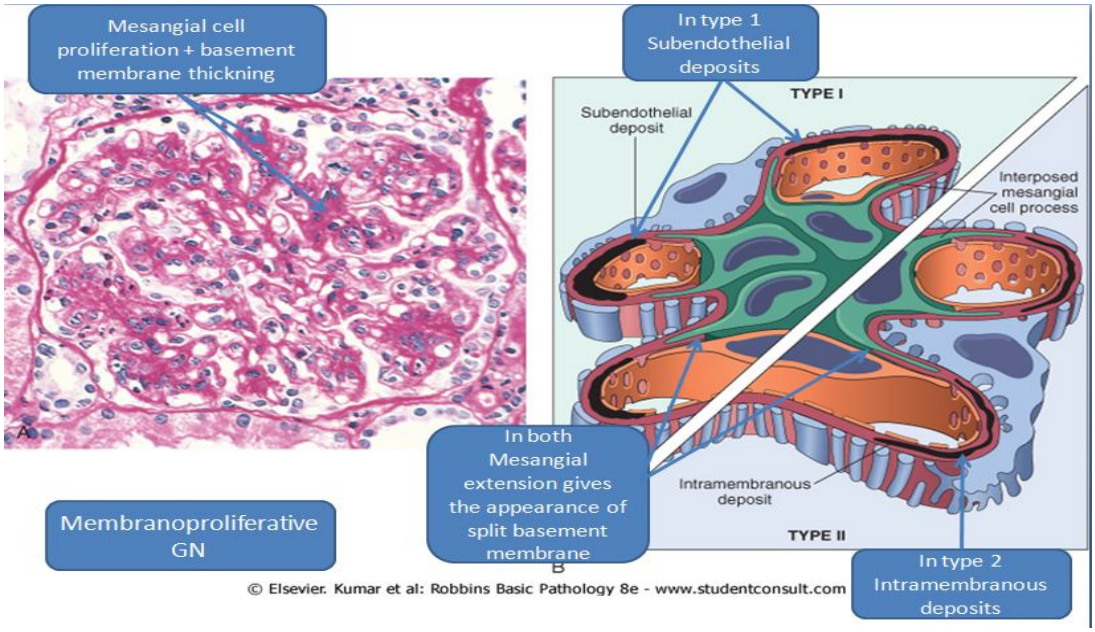
Pathogenesis :

- Type I : (more common 80%)
  Circulating immune complexes, akin to chronic serum sickness
  The inciting antigen is not known
  occurs in association with:
  - hepatitis B and C antigenemia
  - SLE
  - infected atrioventricular shunts
  - secondary infections with antigenemia
- Type II : (also known as **Dense deposit disease**)
- The fundamental abnormality appears to be excessive complement activation
- C3 nephritic factor (C3NeF) is an autoantibody and it is directed against C3 convertase (it's believed that it stabilize the enzyme and leads to uncontrolled cleavage) → activate the **alternative** complement pathway → elaboration of biologically active complement fragments
- Hypocomplementemia, more marked in type II, is produced in part by excessive consumption of c3 and in part by reduced synthesis of C3 by the liver.

Morphology :

By light microscopy : (Both types are similar)

- glomeruli are large and show proliferation of mesangial cells and endothelial cells.
- infiltrating leukocytes
- The GBM is thickened
- the glomerular capillary wall often shows a double contour or "tram track" appearance (evident in silver & PAS stains) caused by **"splitting" of the GPM** due to the inclusion within it of processes of mesangial and inflammatory cells extending into the peripheral capillary loops.



By electron microscopy :

(1) Type I (2/3 of cases)

- **Subendothelial electron-dense deposits**
- C3 is deposited
- IgG
- complement components (C1q and C4)

(2) Type II

- IgG is usually absent
- complement components (C1q and C4) are also absent
- C3 is present
- irregular lamina densa and subendothelial space of the GBM
- deposition of material of unknown composition (**Dense Deposit Disease**)

Clinical course :

- The principal mode of presentation is the nephrotic syndrome (in 50% of cases), although MPGN may begin as acute nephritis or mild proteinuria.

- Poor prognosis (worse in type II)
  - 40% develops renal failure
  - 30% develops renal insufficiency
  - 30% persistent nephrotic syndrome without renal failure

    (so, all are screwed :P)
- MPGN, usually type I, may occur in association with other known disorders (secondary MPGN)
  - SLE
  - Hepatitis B & C
  - Chronic liver disease
  - Chronic bacterial infection
- Idiopathic cases are believed to be associated with hepatitis C .

NOTE :

The most frequent systemic causes of nephrotic syndrome in adults are :

1. **Diabetes**
2. **SLE**
3. **Amyloidosis**

Diabetic Nephropathy:

Renal failure is second only to myocardial infarction as a cause of death from this disease. Three lesions are encountered:

1. glomerular lesions.
2. renal vascular lesions, principally arteriolosclerosis.
3. pyelonephritis, including necrotizing papillitis.

The most important glomerular lesions are:.

1) **Diffuse mesangial sclerosis**:
   - a diffuse increase in mesangial matrix along with mesangial cell proliferation with basement membrane thickening.
   - Found in diabetic people for over 10 years.
   - When glomerulosclerosis becomes marked, patients manifest the nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, and edema.

2) **Nodular glomerulosclerosis:**

- a glomerular lesion characterized by **ball-like deposits** of a laminated matrix situated in the periphery of the glomerulus.
- These nodules are PAS positive and usually contain trapped mesangial cells. (*the Kimmelstiel-Wilson lesion)*
- in almost 15% to 30% of long-term diabetics and is a major cause of morbidity and mortality.
- Unlike diffuse mesangial sclerosis, which is usually associated with hypertension and old age, nodular glomerulosclerosis can be introduced essentially to diabetes, if other nephropathies are excluded.
- Both the diffuse and the nodular forms of glomerulosclerosis induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular cortical surface.

3) **Renal hyaline atherosclerosis and arteriolosclerosis**

- constitute part of the macrovascular disease in diabetics**.**
- similar to those found throughout the body.
- affects both the afferent but also the efferent arterioles.
    - Efferent atherosclerosis almost only affects diabetics

4) **Pyelonephritis** (metioned later in the handout), both acute and chronic form, occur in nondiabetics as well as in diabetics but are more common in diabetics than in the general population, and once affected, diabetics tend to have more severe involvement.

SUMMARY

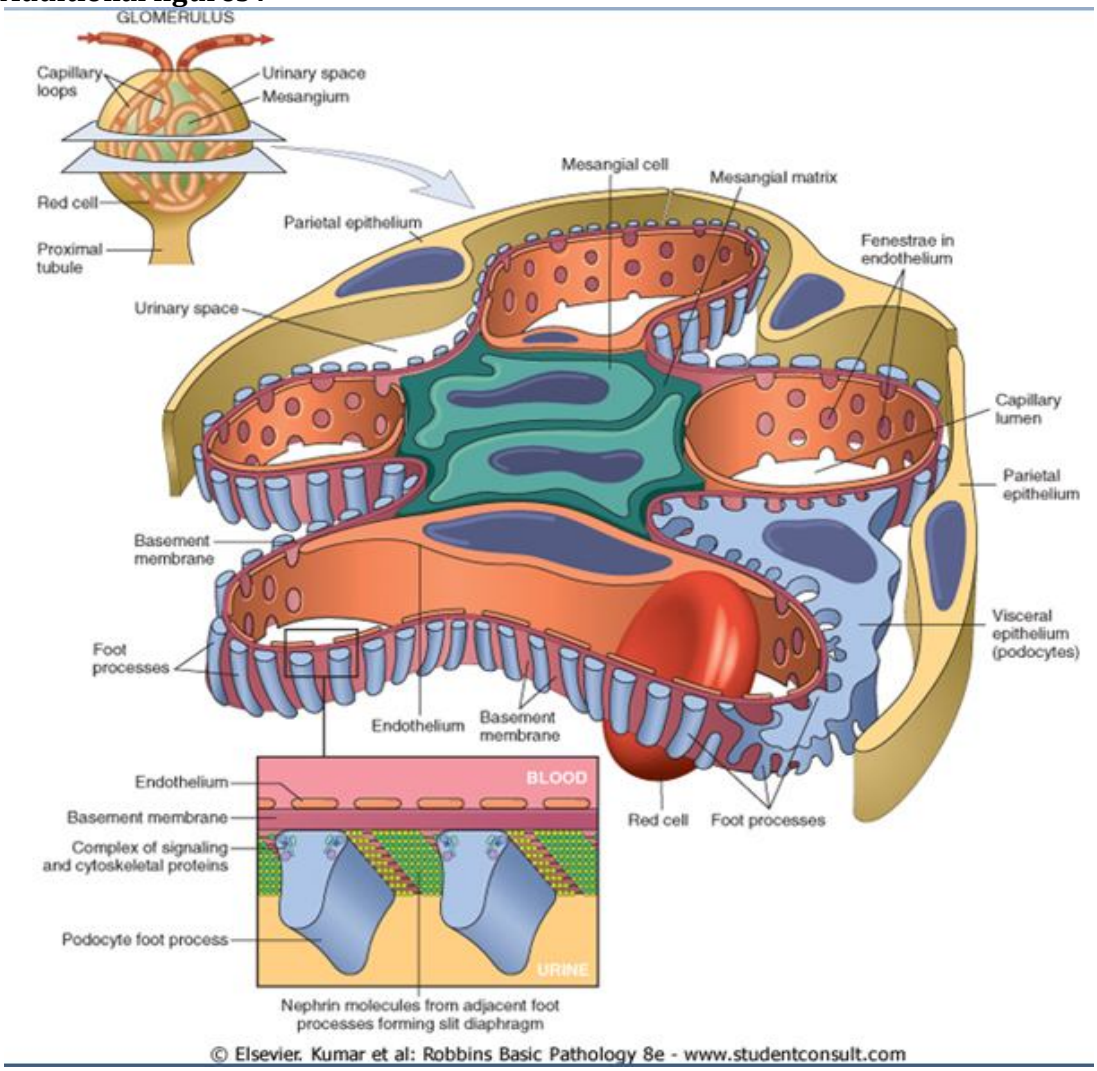
SUMMARY

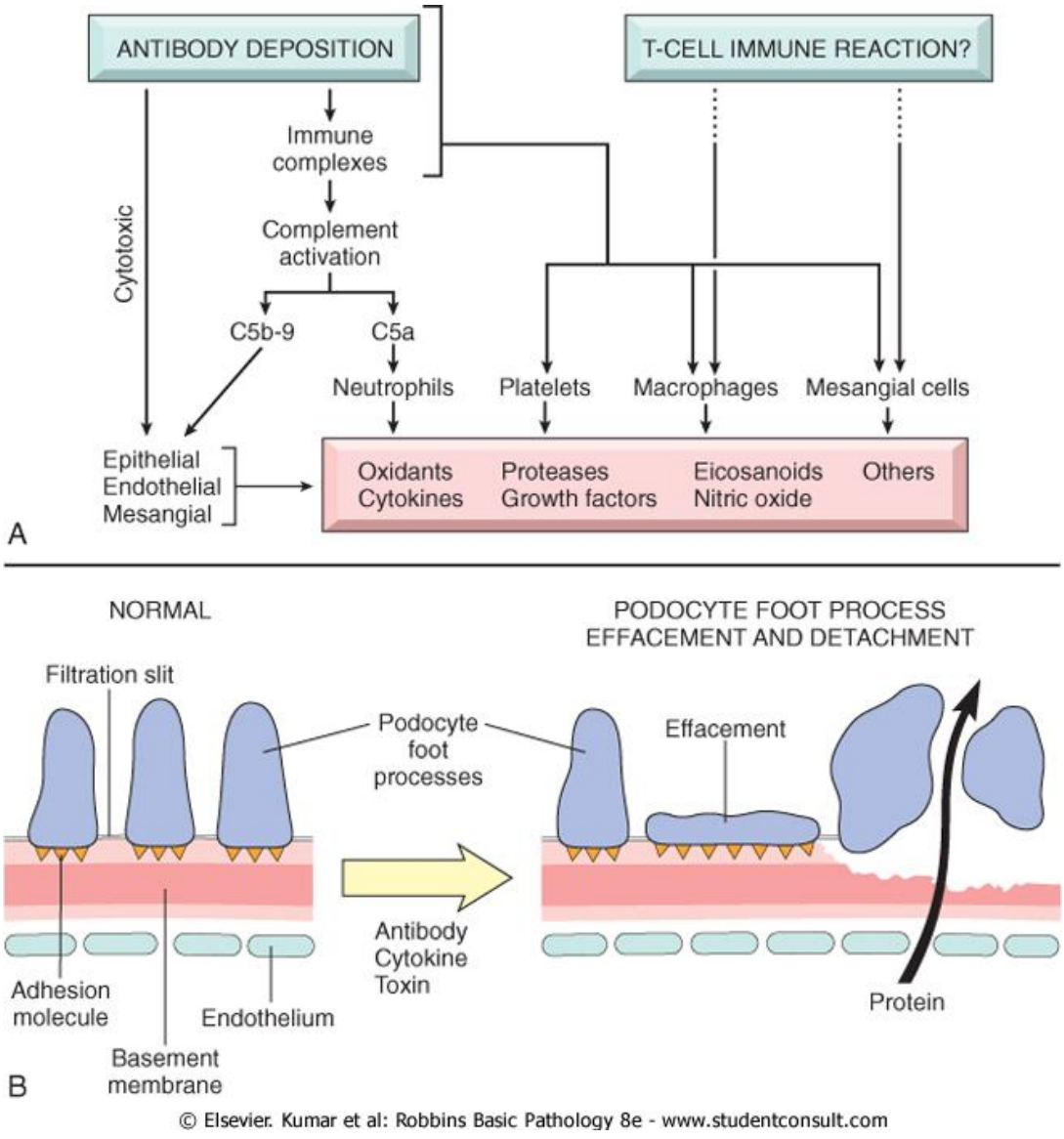
The Nephrotic Syndrome

- characterized by proteinuria, which results in hypoalbuminemia and edema.
- **Podocyte injury** is an underlying mechanism of proteinuria, and may be the result of nonimmune causes (as in MCD and FSGS) or immune mechanisms (as in MN).
- ***Minimal change disease*** *(MCD)* is the most frequent cause of nephrotic syndrome in children; it is manifested by proteinuria and effacement of glomerular foot processes without antibody deposits; the pathogenesis is unknown; the disease responds well to steroid therapy.
- ***Focal and segmental glomerulosclerosis*** *(FSGS)* may be primary (podocyte injury by unknown mechanisms) or secondary (e.g. as a consequence of prior glomerulonephritis, hypertension or infection such as HIV); glomeruli show focal obliteration of capillary lumens, hyaline deposits and loss of foot processes; the disease is often resistant to therapy and may progress to end stage renal disease.

- ***Membranous nephropathy*** *(MN)* is caused by an autoimmune response against an unknown renal antigen; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation; the disease is often resistant to steroid therapy.

Additional figures :





End of Part 5

Done by: by Assem " THE AWESOME" Kalantan

2nd part

Nephritic Syndrome

By TMA

Outline

1. General Characteristics of the Nephritic Syndrome

2. Primary Causes

   a. The Nephritides

      i. Acute Post-infectious Glomerulonephritis (Post-streptococcal GN)

      ii. IgA Nephropathy (Berger Disease)

   b. Rapidly Progressive GN (RPGN or Crescentic Glomerulonephritis-CrGN)
   3 immune causes:

      i. Type I (Anti-Glomerular basement membrane or Anti-GBM)

      ii. Type II (Immune Complex-Mediated)

      iii. Type III (Pauci-immune)

      iv. Summary of RPGN

   c. Chronic GN

General Characteristics of the Nephritic Syndrome

1. Hematuria
    a. Gross (may be a smoky brown urine)
    b. Microscopic
2. Oliguria
3. Azotemia
    a. Increased blood nitrogen
    b. Increased creatinine
    c. Decreased GFR
4. ***Some*** proteinuria (not as much as in nephrotic syndrome, **but** *may come close*)
5. Hypertension (b/c of decreased GFR and/or rennin released by ischemic kidney)

Some things you need to know:

- Primary glomerular disease affects the glomeruli first and last and rarely affects anything else

- Some systemic diseases (SLE-systemic lupus erythematosus) may be primary causes of the nephritic syndrome.

  Note: Secondary causes of Nephritic syndrome will not be discussed. Almost all primary causes are autoimmune.

Acute Post-infectious GN (Post-streptococcal)

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

It is an immune complex disorder. Diffuse proliferation and swelling of resident glomerular cells (Proliferative GN) is a strong characteristic. When the glomerular basement membrane (GBM) is also affected by this proliferation and swelling it becomes membranoproliferative GN (commonly seen when SLE is the primary cause).

Exogenous causative antigens include streptococcus, staphylococcus, pneumococcus, mumps, measles, chicken pox and hepatitis B and C. This is usually associated with a leukocyte infiltrate (commonly neutrophils).

Endogenous antigens show GBM thickening and are best exemplified by SLE.

During the active stage, look for IgG and complement deposits on the GBM (the excess deposit of complements results in hypocomplementemia).

Morphology:

The most characteristic change in post-infectious GN is a fairly **uniformly increased cellularity** of the glomerular tufts that affects nearly all glomeruli, hence the term "diffuse" (see figure). Increased cellularity of glomeruli because of proliferation and swelling of the endothelial and mesangial cells as well as a leukocytic infiltrate of monocytes and (mostly) neutrophils in the capillary walls. This may lead to capillary wall necrosis and a characteristic “crescent” formation in the urinary space in response to the inflammatory injury.

Immune complexes may be seen as subendothelial, intramembranous, occasionally mesangial but mostly subepithelial “humps” on the GBM. These usually clear over the next two months.

Clinical course:

Clinically, there is malaise, slight fever, nausea and a mild nephritic syndrome. Proteinuria may be severe enough to reach the level of that in the nephrotic syndrome (this doesn`t mean it will transform to nephritic syndrome). Gross hematuria with smoky brown urine (instead of being bright red) is one of the reasons the patient goes to see the doctor. Recall that strep. releases antistreptolysin-O. Antibodies (from now on I will use “Ab’s”) are raised against this and may be used in diagnosis. Recall that complements are low in the active phase. RPGN (part 2c) with the characteristic “crescents” or chronic renal disease may develop in some children. Note that chronicity is far more common in adults (again, uncommon in children). In adults 15-50% of all patients develop end-stage renal failure, in 1 to 2 decades.

IgA Nephropathy (Berger Disease)

- IgA nephropathy is the most common primary cause of GN
- It has a male to female ratio of 2:3 and is more common in whites than blacks.

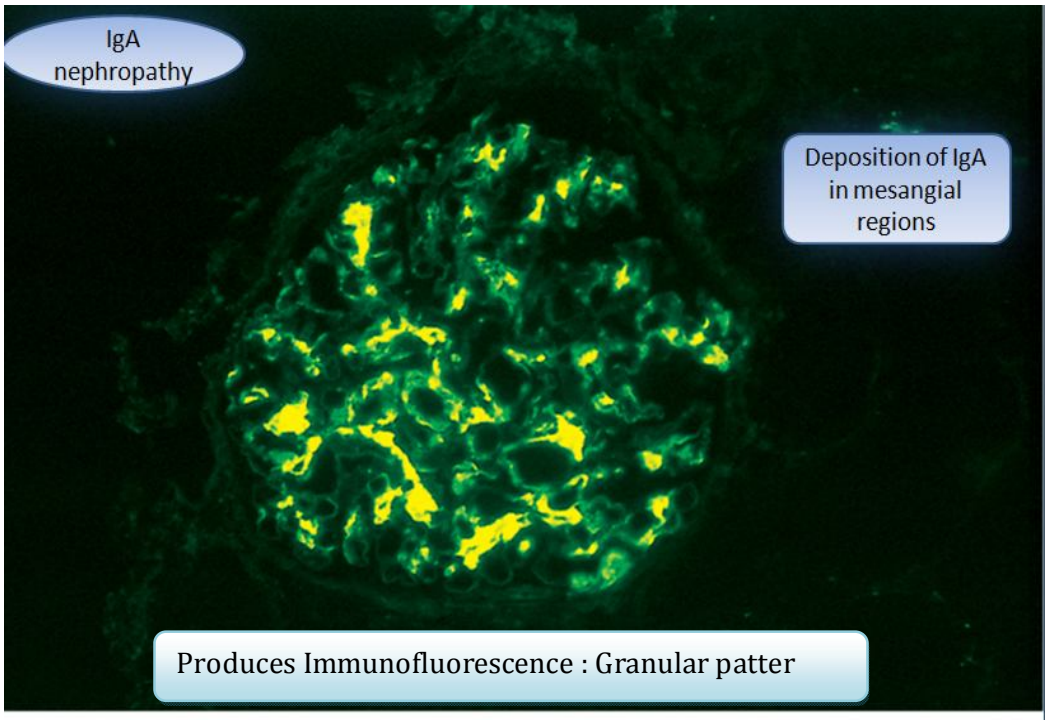
It affects children and young adults. An episode of gross hematuria (which last for a few days and recurs every few months) will develop within 1 or 2 days of a nonspecific upper respiratory tract infection. It is THE MOST COMMON GLOMERULAR DISEASE REVEALED BY BIOPSY and THE MOST COMMON CAUSE OF GROSS AND MICROSCOPIC HEMATURIA.

Some believe it to be a localized variant of Henoch-Schonlein purpura (this is systemic and characterized by a purpuric rash over-skin, abdominal pain-GIT, and arthritis-joints). Both, however, have the main feature of IgA deposition in the mesangium.

It may be a result of abnormal production of IgA from the marrow (recall that IgA is usually associated with secretion from the mucosa) or clearance (through abnormal glycosylation). Celiac disease (intestinal mucosal defects) or liver disease (decreased hepatobiliary IgA clearance) patients are at an increased risk of Berger's Disease, especially when the respiratory or GI tracts are exposed to environmental antigens. In half of all patients (with Berger's) there is increased serum IgA and an absence of complements C1q and C4 complements (suggesting activation of the alternative complement pathway). There may be a genetic predisposition.

Morphology:

Mesangial widening and inflammation of segments of some glomeruli (segmental or focal proliferative GN) or diffuse mesangial proliferation or, rarely, crescentic GN may be seen microscopically. The characteristic immunofluorescence picture is of **mesangial deposition of IgA,** often with C3 and properdin (see figure)



Clinical course:

More than half of patients have episodes of gross hematuria (after respiratory or GI or urinary infection). 30-40% have microscopic hematuria with or without proteinuria. Remember that the episodes last a few days and recur every few months. 25-50% of patients may eventually develop chronic renal failure.

Rapidly Progressive GN (Crescentic GN or CrGN)

It is a nephritic syndrome with rapid and progressive loss of renal function. Renal failure and death result in weeks to months.

Parietal cells of Bowman's capsule proliferate and, along with monocytes/macrophages infiltrate, takes on a crescentic appearance. Remember, in post-strep GN the infiltrate is in the capillary wall and is mostly neutrophils.

This form of GN may be found in:

1. streptococcal infection
2. lupus nephritis
3. good pasture's syndrome
4. vasculitis
5. cryoglobinemia
6. idiopathic

so, different etiologies and pathogenic mechanisms can cause it.
The autoimmune cause can be divided into three types:

Type I CrGN (Anti-GBM)

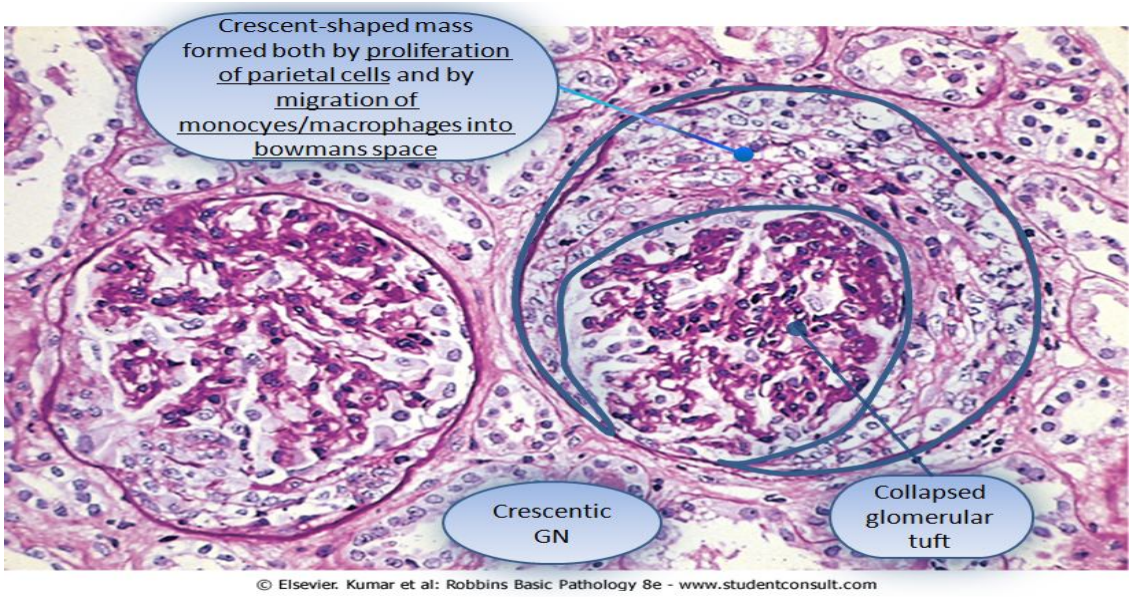
Deposits of IgG, often with C3, on the GBM. In some these also bind to pulmonary capillaries producing pulmonary hemorrhages associated with renal failure. When this occurs the condition is preferably called Good pasture Syndrome (if there is no pulmonary involvement it is a pure type I CrGN and is considered idiopathic).

Diagnose through the identification of Anti-GBM Ab's. Plasmapheresis is very beneficial to these patients as it removes the harmful Ab's.

Morphology:

The kidneys are enlarged and pale with petechial hemorrhages. Segmental glomerular necrosis and GBM breaks result. This, as well as the infiltrate (mostly monocytes/macrophages) causes the parietal cells of Bowman's capsule to proliferate giving rise to the **crescents** (a circumferential proliferation of epithelial cells and monocytes in bowman's capsule which occurs in response to fibrin leaked from damaged capillary loops). These crescents may scar as they obliterate the capsule and compress the glomeruli.

Immunofluorescence reveals IgG and C3 by linear staining.



Type II CrGN (Immune Complex-Mediated)

This could complicate any immune complex nephritide. Segmental necrosis, GBM breaks and crescent formation may be seen, but the factor that differentiates it from type I is that the healthy segments in glomeruli show signs of complex deposition (diffuse proliferation and leukocyte exudates in SLE or post-infectious GN, and mesangial proliferation in IgA nephropathy or Henoch-Schonlein Purpura). The granular appearance of the GBM or mesangium is described as being "lumpy bumpy" in immunofluorescence because of the Ig or complement deposition. Plasmapheresis **does not help**.

Type III CrGN (Pauci-Immune)

Pauci- refers to few or some. From the name you can imagine that there is not as much immune interaction. There are no anti-GBM Ab's or immune complexes to be found. The causative agent is the Anti-neutrophil Cytoplasmic Ab discussed in the vasculitides. So, type III CrGN may be a complication of *microscopic polyangiitis* or *Wegener granulomatosis*, but in most cases it is idiopathic (when it's limited to the kidney).

Morphology:

As in the previous two, there is segmental necrosis, GBM breaks and crescent formation. Healthy segments are normal and immunofluorescence is almost normal (God knows what this means, probably the ANCA).

Prognosis : poor.

Treatment : aggressive immunosuppression .

Summary of RPGN

It is a classic nephritic syndrome with pronounced oliguria and azotemia. Proteinuria may approach nephrotic levels. Patients may require long-term dialysis or kidney transplantation. In general, the lower the number of crescents (best if <80%) the better the prognosis.

Plasmapheresis may benefit some patients, especially those with type I RPGN.

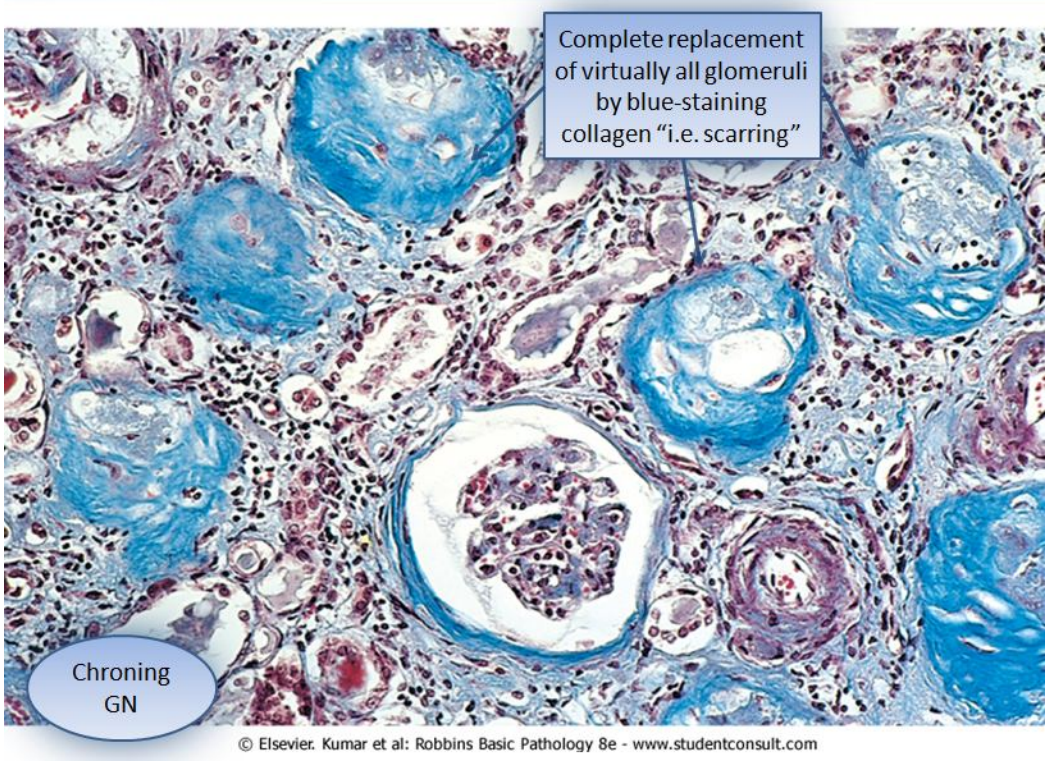
Chronic GN

This is not always a result of preceding glomerular inflammatory injury, but it is an important cause of end-stage renal failure (presenting as chronic renal failure). About a third to half of all patients on long-term renal dialysis or waiting for transplantation have chronic GN. 20% of all cases may arise with no prior history of symptomatic renal disease, and are usually young or middle aged adults.

Morphology:

Kidneys are symmetrically contracted, red-brown and diffusely granular. Advanced scarring of glomeruli sometimes leads to complete sclerosis and obliteration of glomeruli (see figure). There is marked interstitial fibrosis, atrophy and loss of many cortical renal tubules. Hypertension causes small and medium sized arteries to thicken with narrowing of the lumina.

The infiltrate seen here is lypho but very rarely plasma cells may also be found in the fibrotic tissues. In most cases by the time the condition is discovered it is impossible to tell where the lesion began in the kidney, lending the name of “end-stage kidneys”.



Clinical course:

Its onset is insidious and discovery is usually late by routine check-up. Transient nephritic or nephrotic syndromes may be seen, but what brings the patient is usually the edema that results from proteinuria. Sclerosis slowly limits the proteinuria, but never stops it completely. Hypertension may also bring the patient to do a check-up. Microscopic hematuria is usually present, but at this stage "grossly bloody urine is infrequent."

Renal dialysis and transplantation prevent the inevitable progression to uremia and death.

SLE Nephropathy :

Kidney involvement is one of the most important clinical features of SLE, with renal failure being the most common cause of death. The focus here is on glomerular pathology, although interstitial and tubular lesions are also seen in SLE.

The pathogenesis of all forms of **glomerulonephritis** in SLE involves deposition of DNA/anti-DNA complexes within the glomeruli. These evoke an inflammatory response that may cause proliferation of the endothelial, mesangial, and/or epithelial cells and, in severe cases, necrosis of the glomeruli. Although the kidney appears normal by light microscopy in 25% to 30% of cases, almost all cases of SLE show some renal abnormality if examined by immunofluorescence and electron microscopy.There are five patterns of glomerular disease in SLE (none of which is specific to the

disease): **class I**, normal by light, electron, and immunofluorescence microscopy (less than 5% of SLE patients); **class II**, mesangial lupus glomerulonephritis; **class III**, focal proliferative glomerulonephritis; **class IV**, diffuse proliferative glomerulonephritis; and **class V**, membranous glomerulonephritis.

Mesangial lupus glomerulonephritis (class II) is seen in 10% to 25% of cases and is associated with mild clinical symptoms. Immune complexes deposit in the mesangium, with a slight increase in the mesangial matrix and cellularity.

Focal proliferative glomerulonephritis (class III) is seen in 20% to 35% of cases, and, as the name suggests, lesions are visualized in only portions of fewer than half the glomeruli. Typically, one or two foci within an otherwise normal glomerulus show swelling and proliferation of endothelial and mesangial cells, infiltration by neutrophils, and/or fibrinoid deposits with capillary thrombi. Focal glomerulonephritis is usually associated with only mild microscopic hematuria and proteinuria; a transition to a more diffuse form of renal involvement is associated with more severe disease.

Diffuse proliferative glomerulonephritis (class IV) is the most serious form of renal lesions in SLE and is also the most common, occurring in 35% to 60% of patients. Most of the glomeruli show endothelial and mesangial proliferation affecting the entire glomerulus, leading to diffuse hypercellularity of the glomeruli, producing in some cases epithelial crescents that fill Bowman's space. When extensive, immune complexes create an overall thickening of the capillary wall, resembling rigid **"wire loops"** on routine light microscopy. Electron microscopy reveals electron-dense subendothelial immune complexes (between endothelium and basement membrane. Immune complexes can be visualized by staining with fluorescent antibodies directed against immunoglobulins or complement, resulting in a granular fluorescent staining pattern. In due course, glomerular injury gives rise to scarring (glomerulosclerosis). Most of these patients have hematuria with moderate to severe proteinuria, hypertension, and renal insufficiency.

Membranous glomerulonephritis (class V) occurs in 10% to 15% of cases and is the designation for glomerular disease characterized by widespread thickening of the capillary wall. Membranous glomerulonephritis associated with SLE is very similar to that encountered in idiopathic membranous nephropathy. Thickening of capillary walls is caused by increased deposition of basement membrane-like material, as well as accumulation of immune complexes. Patients with this histologic change almost always have severe proteinuria with overt nephrotic syndrome.

Allograft rejection of the transplanted kidney:.

Recognition and Rejection of Organ Transplants (Allografts)

The graft rejection response is initiated mainly by host T cells that recognize the foreign HLA antigens of the graft, either directly (on antigen presenting cells (APCs) in the graft) or indirectly (after uptake and presentation by host APCs).Types and mechanisms of rejection:

1. *Hyperacute rejection.* Preformed antidonor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure.
2. *Acute cellular rejection.* T cells destroy graft parenchyma by cytotoxicity and DTH reaction.
3. *Acute vascular rejection.* T cells and antibodies damage graft vasculature.
4. *Chronic rejection.* Dominated by arteriosclerosis, this type is probably caused by T-cell reaction and secretion of cytokines that induce proliferation of vascular smooth muscle cells, associated with parenchymal fibrosis.

End of 2nd part

By TMA

Part 3

Urinary Tract OBSTRUCTION

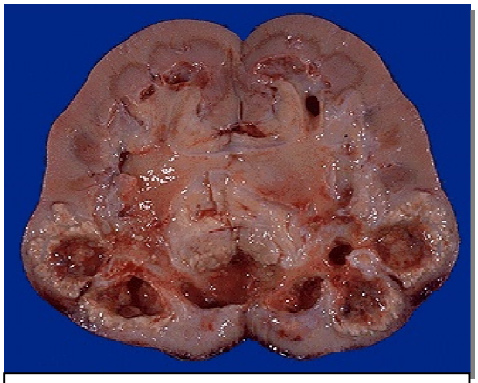
URINARY TRACT OBSTRUCTION

RENAL STONES (UROLITHIASIS)

- Calculus formation at any level of urinary collecting system, but most often calculi arise in the kidney.

PATHOGENESIS

- Composition
  - 80% of renal stones are composed of either:
    - Calcium oxalate
    - or calcium oxalate mixed with calcium phosphate.
  - 10% are composed of magnesium ammonium phosphate and;



A large kidney stone that obstructed the calyces of the lower pole of this kidney, leading to a focal hydronephrosis (dilation of the

  - 6→9% are either uric acid or cystine stones
  - In all cases, there's an organic matrix of **mucoprotein** that makes up about 2.5% of the stone by weight.
- **Causes** of stone formation (often obscure; particularly in the case of Calcium-containing stones):-
  - Supersaturation (↑ urine conc. Of stone constitutes)
  - 50% of the patients who develop calcium stones have **hypercalciuria** (absorptive hypercalciuria)

Not associated with hypercalcemia

Ca^{++} is absorbed from the gut in excessive amounts & promptly excreted in the urine .. this is why it's not elevated in blood.

some have a primary renal defect of Ca++ reabsorption.

- 5% to 10% of patients, there is **hypercalcemia** (due to hyperparathyroidism, vitamin D intoxication or sarcoidosis) and consequent **hypercalciuria** .
- 5% **hyperoxaluria** or **hypercitraturia** and the remainder are unknown cause**.**
- A **high PH** favor crystallization of calcium and formation of Mg ammonium phosphate stones .(NOT uric acid or cystine stone formation which favored by ↓ **PH**)
- **Excessive Uric acid** excretion in urine favors Calcium stone formation.
- **Magnesium ammonium phosphate** (struvite) stones almost always occur in patients with a persistently alkaline urine due to **UTIs**
- **Bacteria** may serve as **nidi** for the formation of any kind of stone. In particular, the urea splitting bacteria, such as proteus vulgaris and staphylococci
- In **avitaminosis A**, desquamated squamous from the **metaplastic epithelium** of the collecting system act as **nidi**
- **Gout** and diseases involving rapid cell turnover, such as **leukemias**, lead to high **uric acid levels** in the urine and the possibility of uric acid stone.
- **Cystine** stones, genetically determined defect in the renal **transport of certain amino acids** (cystine stones seen in acidic urine).
- **Lack of inhibitors of crystal formation** in urine (including Tamm-horsefall protein pyrophosphate, mucopoly-saccharides, diphosphonates and a glycoprotein called nephrocalcin)

MORPHOLOGY

- **Unilateral** in about 80% , often many stones are found in one kidney.
- Common sites of formation are renal **pelvis, calyces** and **bladder**.
- Tend to be **small** (average diameter 2 to 3 mm)
- May be **smooth** or **jagged**.

- Staghorn calculi.
  Occasionally, progressive accretion(increase in size) of salt lead 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 Mg-ammonium phosphates.

CLININCAL COURSE

- Large stones may be present **without producing symptoms** or significant renal damage (these large stones lodge in the renal pelvis).
- **Smaller stones** may pass into the **ureter**, producing a **typical intense pain** known as renal or ureteral colic.

  The pain is characterized by :

  1. paroxysms of flank pain radiating toward the groin.
  2. The clinical significance of stones lies in their capacity to obstruct urine flow or to produce sufficient trauma, to cause ulceration and bleeding .
  3. Fortunately, in most cases the diagnosis is readily made by radiological means.

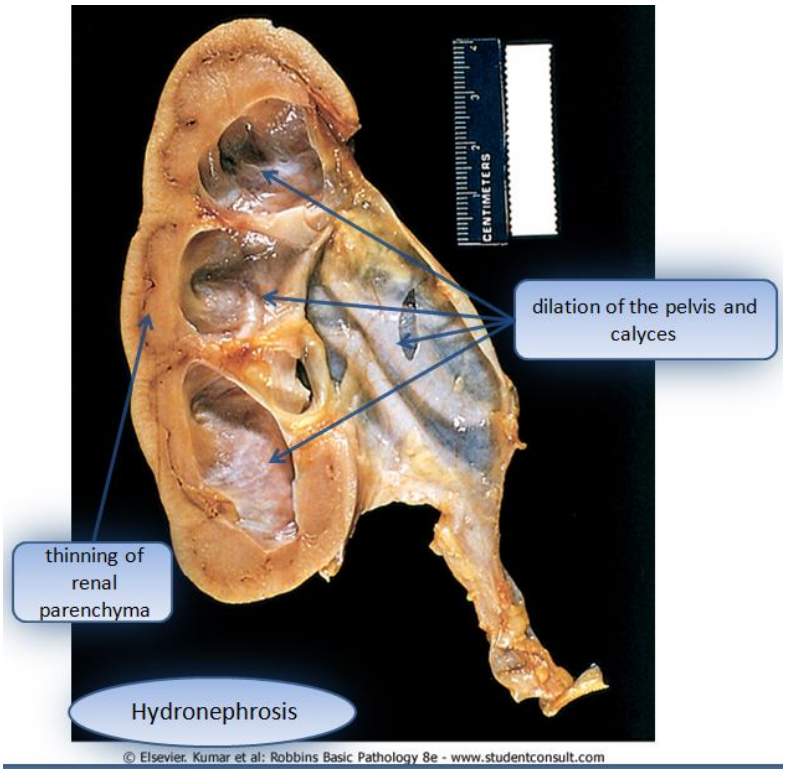
- Gross **hematuria**.
- Predispose the patient to **bacterial infection**.

HYDRONEPHROSIS

- **Dilatation** to the renal pelvis and calyces with **accompanying atrophy** of the **parenchyma**, **caused by obstruction** to the outflow of urine.
- May be **sudden** or insidious.
- The obstruction can occur at **Any level** of the urinary tract.
- **Bilateral hydronephrosis** occurs only when the **obstruction** is **below** the level of **ureters**.
- Even with complete obstruction, **glomerular filtration persists** for some time.
- Affected calyces and pelvis become **dilated**.
- **Compression** of the renal **vasculature**.
- The **most sever effects** are seen in **papillae** , because they are subject to the greatest increase in pressure.

- Initial **functional disturbances** are largely tubular, manifested primarily by **impaired concentrating ability**.
- Serious **irreversible** damage occurs in
    - about **3 weeks** with **complete** obstruction
    - in **3 months** with **incomplete** obstruction.
- **Causes:**

Congenital	Acquired
Atresia of the urethra	Foreign bodies: calculi, necrotic papillae.
Valve formations	Foreign bodies: calculi, necrotic papillae.
Renal ptosis with torsion or kinking of the ureter	Tumors and Hypertrophy: • Prostatic hypertrophy • Carcinoma of the prostate • Bladder tumors • Contiguous malignant disease (retroperitoneal lymphoma, carcinoma of cervix or uterus) • Nodular hyperplasia of the prostate
Aberrant renal artery	Inflammation: • Prostatitis • Ureteritis • Urethritis • Retroperitoneal fibrosis
	Neurogenic: Spinal cord damage with paralysis of the bladder
	Normal pregnancy: mild and reversible



- **Morphology (macroscopically):**
    - **Bilateral** or **Unilateral** hydronephrosis.
    - **Cortical thinning.**
    - Kidney may be **massively enlarged** and greatly **distended** pelvicalyceal system.
    - Renal **parenchyma is atrophied**, **obliteration of the papillae** and **flattening of the pyramids**.
    - When obstruction is **sudden** and **complete**, glomerular **filtration** is **compromised** relatively **early**, and renal **function may cease while dilation** is still comparatively **slight**
    - **Hydroureter (**dilated of the ureter**).**
- Morphology (**micro**scopically):
    - **Tubular dilation**, followed by **atrophy and fibrous replacement** of the tubular epithelium with relative **sparing of the glomeruli**.
    - **Glomeruli** also become **atrophic** and **disappear(**in severe cases**).**
      1. Become hyalinized only in the late stage of the disease.
      2. Chronic inflammatory cells may be present in the interstitium.

- **Clinical course:**
    - **Bilateral:**
        - **complete** obstruction produces **anuria**(non-passage of urine) which is soon brought to medical attention.
        - **Incomplete** obstruction causes **polyuria(**passage of large volumes of urine**) rather than oliguria**.
    - **Unilateral** hydronephrosis:
        - May remain completely **silent** for long periods **unless** the **other** kidney is for some reason **not functioning**.
    - Symptoms due to underlying cause such as renal calculi or an obstructing tumor draw attention to the hydronephrosis.

INFECTIONS OF THE URINARY TRACT AND KIDNEY

- A **urinary tract infection (UTI)** is a bacterial infection that affects any part of the urinary tract (*from the kidney downwards until the urethra !*)
- Although urine is a good environment for growth of many bacteria, it is normally sterile, and of course the urinary tract is sterile because it is flushed many times a day. Pathogens for UTI are those which attach to the epithelium and are not washed away.

PREDISPOSING FACTORS

- More in women than in men
    - *Women have shorter distance between skin (that contains bacteria) and the end of the urinary tract (urethra). 5 cm in women and 20 cm in men.*
- More in pregnant women.
- More in people around age 40

URETHRAL:

- Obstruction of the urinary flow (e.g. benign prostatic hyperplasia and uterine prolapse)
    - *In stasis of blood, there is absence of the (flushing) effect that washes away bacteria and stops its growth. So this residual urine will favor bacterial growth.*
- Urethral instrumentation (i.e. catheterization, cystoscopy)
    - *It may cause backflow of urine up the UTI.*
- Trauma to the urethra during sexual intercourse

VESICAL (urinary bladder)

- Incompetence of the vesicoureteral orifice
    - Congenital defect.

- Can be acquired in people with a flaccid bladder (could be due to spinal injury or diabetes)
- They cause

- Bladder dysfunction (can cause obstruction and vesicoureteral incompetence)

All of these cause stasis (just like obstruction) as well as *reflux of urine into the ureters.*

- This will also cause reflux into the renal pelvis and then into renal parenchyma.

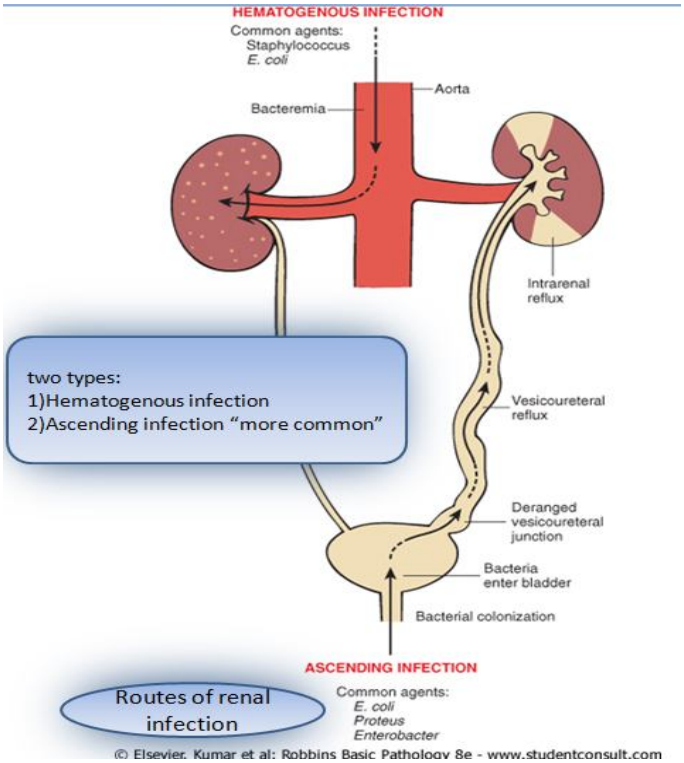
- Diabetic patients are more borne to UTIs because of less immunity and possible neurogenic bladder dysfunction.

SOURCE OF INFECTION

- The source of infection can be **hematogenous** (through the bloodstream, e.g. in septicemia or infective endocarditis), but ascending infection is more common.

PATHOGENESIS OF UTIS IN ASCENDING INFECTION

- Source of bacteria is usually in the perineal area
- Common causative agents are E.coli and other gram –ve bacilli
- The bacteria attach to the mucosal surface *(through fimbria)*
- They form colonies at the distal urethra.
- Then they move against the urine flow.
- These factors cause **ascending infection**.
- *When a UTI spreads retrograde from the bladder into the kidney, it may cause pyelonephritis.*



CLINICAL MANIFESTATIONS

- **Systemic Symptoms of infection:** Start at the onset and include chills, fever and malaise.
- **General Symptoms of UTIs:** *Irritation of bladder and urethra:*
  - dysuria, urinary frequency and urgency, suprapubic pain.
- **Urinary findings:** Polyuria and Baceriuria.

In UTIs involving the bladder (**acute** and **chronic cystitis**) there is:

- ⇨ Hypertrophic bladder
- ⇨ Trabeculation or thinning of the bladder wall
- ⇨ Markedly distended walls *(from retention of urine)*.

1. ACUTE PYELONEPHRITIS

It is a manifestation of UTI characterized by **Suppurative inflammation** of the kidney and renal pelvis, usually associated with lower tract infections as well.

ETIOLOGY:

- **Common: Gram negative** Ecoli(the commonest), proteus, klebsiella, pseudomonas, enterobacteria
- **Rare:** Strep. Feacalis & staph.

MORPHOLOGY:

Usually unilateral, but can be bilateral.

GROSSLY:

- Multiple**,** Discrete **,**Yellowish **and** Raised **abscesses**
  - May be scattered or limited to one region; or may coalesce to form a single large area of suppuration.

HISTOLOGICALLY:

- Suppurative necrosis (abscess formation) within renal parenchyma
  - (early stage: limited to interstitial tissue , later: abscess rupture into tubules)
- Large masses of intratubular neutrophils *(can be found in urine)*
- if there is a prominent obstruction, pus may fill renal pelvis, calyces and ureter ➔ "pyonephrosis".

CLINICAL FEATURES

- Usually patients do **not** develop renal failure because the infection is usually unilateral, so the other kidney is functioning.
- May become recurrent or chronic infection especially if is due to a predisposing factor and/or when it is bilateral.
  - These people have overwhelming sepsis and often, renal failure.

DIAGNOSIS: - pus cells (leukocytes) in urine. - urine culture

2. CHRONIC PYELONEPHRITIS

An Interstitial **inflammation** characterized by grossly visible **scarring** of **renal parenchyma** and **deformity of pelvic calyces**. It is an important cause of chronic renal failure

It has 2 forms:

1. **Chronic obstructive pyelonephritis:** caused by repetitive kidney infection that is predisposed by obstruction, with diffuse or localized obstructive lesions. This will lead to recurrent renal inflammation and scarring.
    a. *e.g. congenital urethral anomaly cause the disease bilaterally, and calculi and unilateral obstructive lesions of the ureter cause this disease unilaterally.*
2. **Chronic reflux-associated pyelonephritis (reflux nephropathy):** more common, results from superimposition of a UTI + congenital vesucoureteral reflux + intrarenal reflux.

MORPHOLOGY

- Unilateral or bilateral (even if bilateral, there is unequal involvement of the kidney), asymmetrical scar
- Patchy or diffuse scar involve pelvis or calyces or both

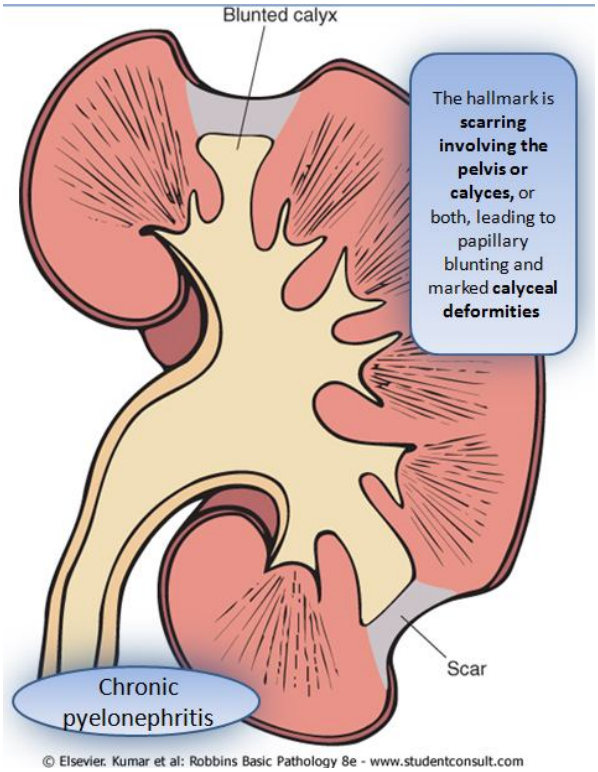
MICROSCOPICALLY

Nonspecific changes that may look like other tubulointerstitial disorders

- **Uneven interstitial fibrosis & chronic inflammatory cells.**
- **Dilation or contraction of tubule** (thyroidization)
- **fibrosis of calyceal mucosa**.
- **Vascular** change.
- Glomeruli normal OR focal sclerosis

CLINICAL COURSE :

- **Gradual** onset of:
    - Renal insufficiency.
    - Hypertension
    - Asymmetric contraction of the kidney (with blunting and deformity of the calyceal system
    - With or without bacteriuria
    - Polyuria, proteinuria, chronic renal failure.



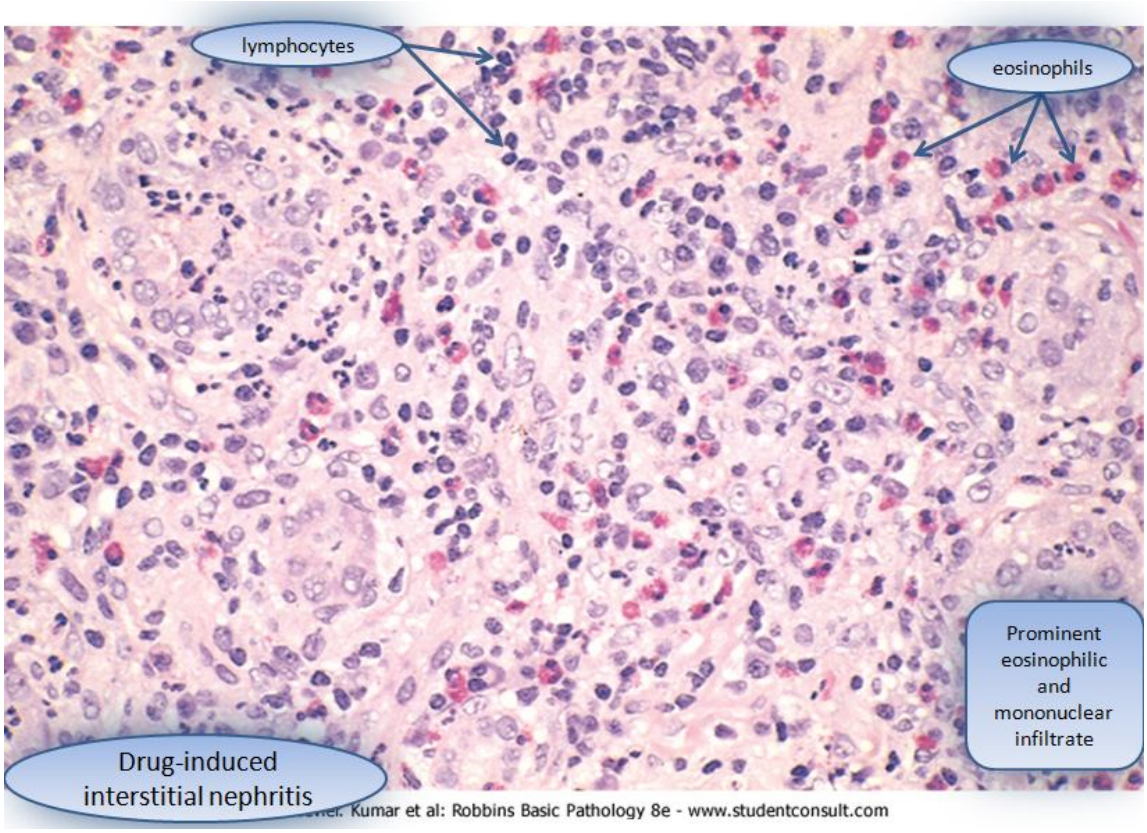
3. DRUG-INDUCED INTERSTITIAL NEPHRITIS

With the increase of the use of antibiotics and analgesics, it is important to talk about them (as well as other nephrotoxic drugs) causing renal injury.

- They cause 2 forms of diseases: *Acute Drug-induced interstitial nephritis* and *analgesic nephropathy*

3.1 ACUTE DRUG-INDUCED INTERSTITIAL NEPHRITIS

- **Pathogenesis:** Drugs become immunogenic and induce:
  - Hypersensitivity **type I** (IgE allergy against the drug)
  - Hypersensitivity type **type IV** (delayed type cell-mediated)
- **Morphology:** the *interstitium* is infiltrated with inflammatory cells (according to the type of hypersensitivity mediated (type I = eosinophils, etc…), (type IV= granolomas)
  - *Glomeruli:* normal, except in some cases of NSAIDS toxicity where the podocytes are affected, and nephritic syndrome develops.
- Signs & Symptoms:
  - **Fever**
  - **Eosinophilia (may be transient)**
  - **rash**
  - **renal abnormalities**
- Removal of offending drug usually recovers the patient ^_^.



3.2 ANALGESIC (PAIN RELIEF DRUGS) NEPHROPATHY:

- mixture of many medications for long time e.g. (aspirin, acetaminophen and codeine)
  ⇒ papillary necrosis.
- Complication of analgesic abuse is increased incidence of *transitional cell carcinoma* of the renal pelvis or bladder .

End of part 3
Done by Abo Malik

Part 4

Tumors of the kidney and urinary bladder

By A.Z.K

Introduction:

The most common malignant tumor of the kidney is renal cell carcinoma, followed in frequency by nephroblastoma (wilm's tumor). *Tumors of the lower urinary tract are about twice as common as renal cell carcinoma.*

Benign tumors:

1) **Renal papillary adenoma:**
   small, discrete (usually yellow) tumors are seen in 7% to 22% of autopsies. Histologically, consist of vacuolated epithelial cells forming tubules and branching papillary structures.

2) **Angiomyolipoma:**
   often associated with tuberous sclerosis (25% - 50% of patients), these tumors are considered to be hamartomas.

Malignant tumors:

Renal Cell Carcinoma:

- They arise from renal tubular epithelium, therefore, they are located mostly in renal cortex.

Most common from the sixth to seventh decades, and men are affected about twice as commonly as women. Renal cell carcinoma represent 85% of all primary malignant tumors of the kidney. *It arises from the renal tubular epithelium, and hence they are located in the cortex.* About 40% of the patients die of the disease.

RISK FACTORS:

- smocking
- hypertension
- obesity
- exposure to cadmium
- acquired polycystic disease (30-fold increased risk) : could be caused by chronic renal dialysis.

Based on the molecular origins of these tumors, the three most common forms are as follows:

1) Clear Cell Carcinomas:

- It could be bilateral in 40 – 60% of the population

The most common type (80% of renal cell cancers). They are made up of cells with clear or granular cytoplasm. The majority of them are sporadic, but they also occur in familial forms or in association with von Hippel-Lindau (VHL) disease. VHL disease is autosomal dominant and is characterized by predisposition to a variety of neoplasms , particularly to hemangioblastomas of the cerebellum and retina.

- VHL gene is a tumor suppressor gene present on chromosome 3.
- Mutation to this gene either familial (inherited) or sporadic results in the formation of cancer.

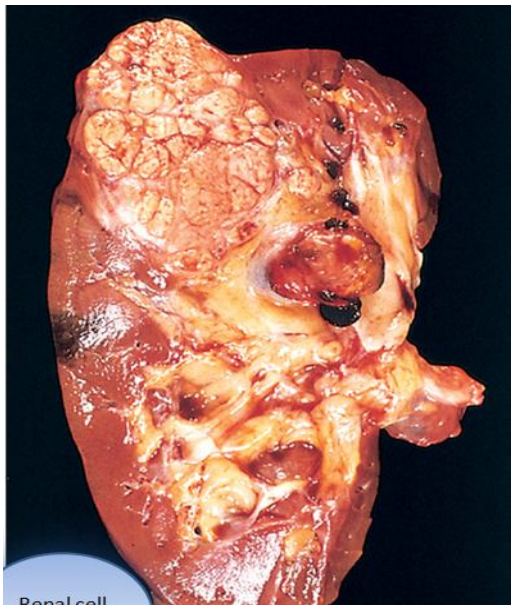
2) Papillary Renal Cell Carcinoma:

Comprises 10-15% of all renal cancers. They show a papillary growth pattern. These tumors are frequently *multifocal and bilateral and appear as early-stage tumors*. As clear cell carcinoma, the occur in familial and sporadic forms. The gene involved is MET proto-oncogene, located on the long arm of chromosome 7. This MET gene, which is a tyrosine kinase receptor for hepatocyte growth factor, is expressed in an increased amount (due to duplication of chromosome #7), which will result in an abnormal growth in the proximal tubular epithelial cells giving precursors of papillary carcinomas.

- **In familial cases**, there is duplication of chromosome #7 **+** active mutations.
- **In sporadic cases,** there is **ONLY** duplication of chromosome #7

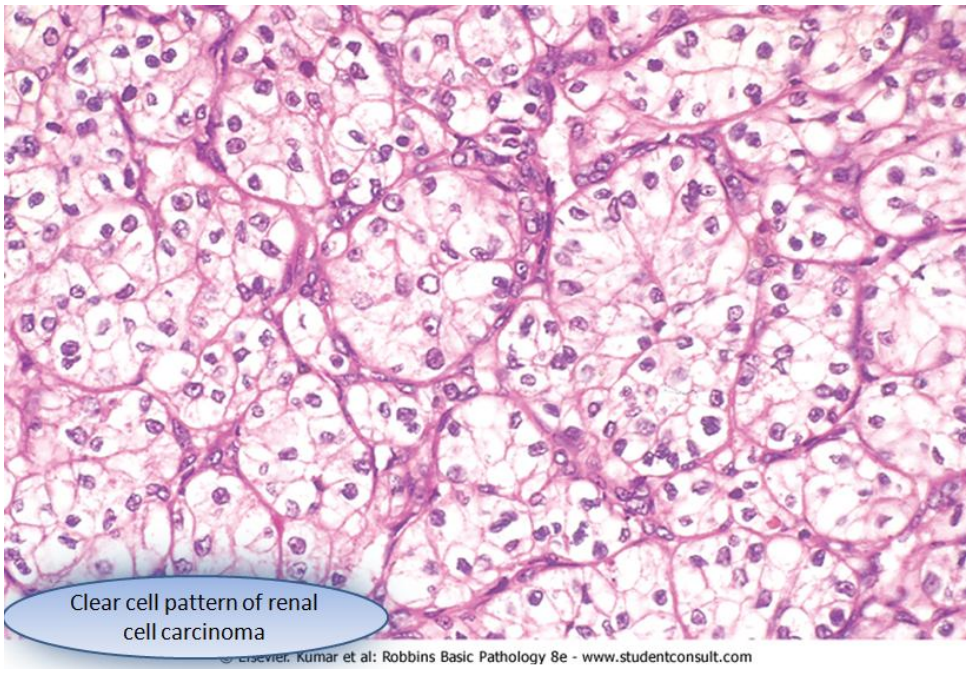
3) Chromophope Renal Carcinomas:

These are the least common, representing 5% of all renal cell carcinomas. They arise from intercalated cells of collecting ducts. These tumors are unique in having *multiple losses of entire chromosomes* including chromosomes 1, 2, 6, 10, 13, 17, 21. In general, chromophope renal cancers have a good prognosis.



MORPHOLOGY:

Clear cell cancers (the most common form) are usually solitary and large when symptomatic (spherical masses 3-15 cm in diameter). They may arise anywhere in the cortex. The cut surface is **yellow to orange to gray-white, with prominent areas of cystic softening or of hemorrhage,** either fresh or old. The margins of the tumor are well defined. The **tumor might invades the renal vein** and grows as a solid column within this vessel, sometimes extending in serpentine fashion as far as the inferior vena cava and even into the right side of the heart. And, it might also invade the collecting system. Occasionally, it might also invade the adrenal gland and Perinephric fat.



The tumor cells of clear cell renal cell carcinoma may appear almost <u>vacuolated</u> (full of lipid and glycogen) or may be <u>solid</u>. The classic vacuolated (lipid-laden), or clear cells are demarcated only by their cell membranes. The nuclei are usually small and round (see the figure). At the other extreme (i.e. solid) are granular cells, resembling the tubular epithelium, which have small, round, regular nuclei enclosed within granular pink cytoplasm. Between the extremes of clear cells and solid, granular cells, all intergradations may be found. The stroma is usually scant but highly vascularized.

Papillary renal cell carcinomas tend to be bilateral and multiple. They may also show gross evidence of necrosis, hemorrhage, and cystic degeneration. The cells can have clear or, more commonly, pink cytoplasm.

Chromophope-type renal cell carcinoma tends to be grossly tan-brown. Having very prominent, distinct cell membranes. The nuclei are surrounded by halos of cleared cytoplasm.

CLINICAL COURSE:

- The *most frequent presenting manifestation is <u>hematuria</u>, occurring in more than 50% of cases.*
- Extra-renal effects are *fever* and *polycythemia*, both may be associated with a renal cell carcinoma.
- Polycythemia result from elaboration of erythropoietin by the renal tumor.
- Uncommonly, these tumor can result in *paraneoplastic syndromes* (because of elaboration of hormones), some of these are hypercalcemia, hypertension, Cushing syndrome, feminization or masculinization.
- The prevalent locations for metastases are the lungs and the bones.
- The following triad is characteristic for renal cell carcinoma:
  1) painless hematuria
  2)palpable abdominal mass
  3) dull flank pain.

End of Part 4

Done by: AZK

Part 5

Wilms' Tumor

WILM'S TUMOR (NEPHROBLASTOMA) :

- derived of mesoderm.
- may be familial or sporadic.

Wilm's tumor is the most common primary kidney tumor in children. Most cases occur between the ages of 2 to 5 years. Wilm's tumor illustrates three important concepts of childhood tumors :

- the relationship between congenital malformation and increased risk of tumors
    - an increased risk of tumors in the presence of congenital malformation
- histologic similarity between the tumor and the developing organ
- the remarkable success in the treatment of childhood tumors

Each of these will be discussed next

As mentioned above, children that are born with congenital malformations are at high risk of developing Wilm's tumor. Three malformation syndromes will be discussed , WAGR syndrome ,Denys-Drash syndrome (DDS) , and Beckwith-Weidmann syndrome (BWS) .

1- WAGR syndrome

This syndrome is characterized by **A**nridia (absence of the colored part of the eye, the iris), **G**enital malformations, and mental **R**etardation. Patients with this syndrome have a **33% chance of developing Wilm's tumor.**

WAGR syndrome is associated with abnormalities in the *WT1* gene, the abnormality is loss of genetic material (deletion).

NOTE : WAGR stands for **W**ilms tumor, **A**nridia, **G**enital malformation and **R**etardation .

2- Denys-Darsh syndrome (DDS)

This syndrome is characterized by Gonadal Dysgenesis and Renal malformation.

Patients with this syndrome are at an extremely high risk of developing Wilms' tumor (~90%)

DDS is also associated with abnormalities in *WT1* gene, but here the abnormality is a mutation.

NOTE: DDS is a DOMINANT NEGATIVE syndrome. This means that a mutation in one gene (allele) will block the function of the other.

NOTE: WAGR syndrome and DDS both show abnormalities in the WT1 Gene but
in WAGR it is deletion while in DDS it is mutation.

3- Beckwith-Wiedemann syndrome :

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

The genetic locus that is involved in these patients is called "*WT2*" for the second Wilms' tumor locus.

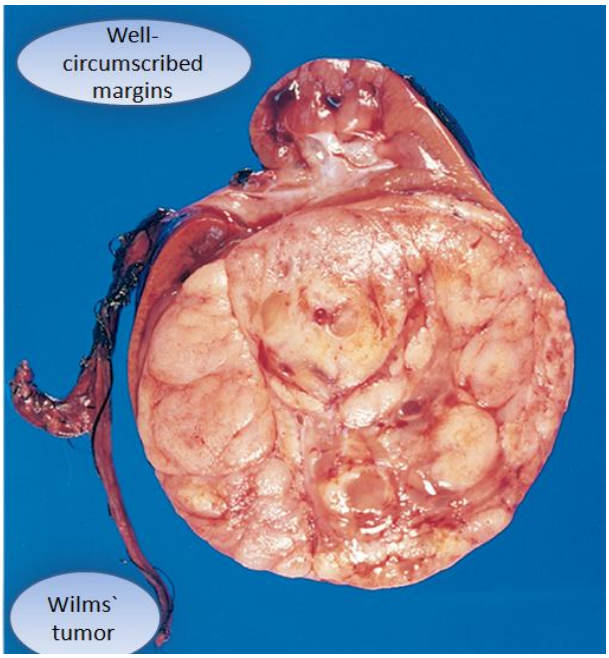
In addition to Wilms' tumors, patients with BWS are also at increased risk for developing hepatoblastoma, adrenocortical tumors, rhabdomyosarcomas, and pancreatic tumors

- Note :
  both WT1 and WT2 are located on chromosome #11 .

Morphology:

Grossly:

Externally: wilm's tumor tends to present as a large, solitary, Well-circumscribed mass. 10 % are bilateral or multicentric **at Diagnosis**.



Cut section : the tumor is soft, homogeneous, and tan to gray, With occasional foci of hemorrhage, cystic degeneration, and necrosis.

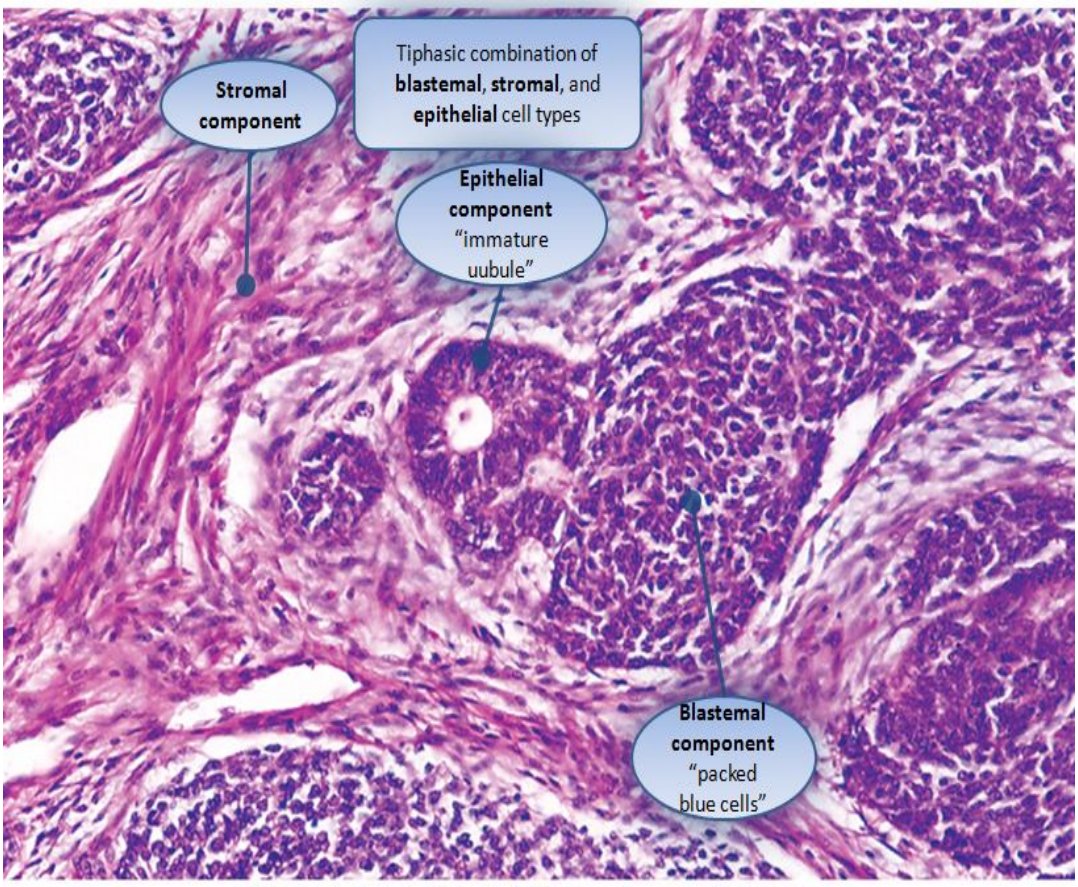
Microscopically:

Wilms' tumors are characterized by recognizable attempts to recapitulate

different stages of nephrogenesis (the stages of development may be repeated or different stages may be mixed). The classic **triphasic combination** of blastemal, stromal, and epithelial cell types is observed in most lesions, although the percentage of each component is variable.

The three types of cells that are present are:

1) Blastemal : appear as Sheets of small blue cells, with few distinctive features.
2) Epithelial : usually takes the form of **abortive tubules or glomeruli.**
3) Stromal : are usually fibrocytic or myxoid in nature, although skeletal muscle "differentiation" is not uncommon.



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Rarely, other heterologous elements are identified, including squamous or mucinous epithelium, smooth muscle, adipose tissue, cartilage, and osteoid and neurogenic tissue.

Approximately 5% of tumors contain foci of **anaplasia**. The presence of anaplasia correlates with underlying *p53* mutations, and the emergence of resistance to chemotherapy. The pattern of distribution of anaplastic cells within

the primary tumor (focal versus diffuse) has important implications for prognosis.

(Morphology continued)

Nephrogenic rests:

Are precursor lesions of Wilms' tumors and are sometimes present in the renal parenchyma adjacent to the tumor. Nephrogenic rests have a spectrum of histologic appearances, from expansile masses that resemble Wilms' tumors (hyperplastic rests) to sclerotic rests consisting mostly of fibrous tissue with occasional admixed immature tubules or glomeruli. It is important to document the presence of nephrogenic rests **in the resected specimen**, since these patients are at an increased risk of developing Wilms' tumors in the **contralateral** kidney**.**

Clinical Course:

1. Patient complaints
   - Commonly :
     Palpable abdominal mass that may extend to the pelvis
   - Less of ten :

     Abdominal pain
     Fever
     Hematuria
     Occasionally, Intestinal obstruction (due to tumor's large size)

2. Prognosis
   - generally very good, and excellent results are obtained with a combination of nephrectomy and chemotherapy.
   - Anaplasia is a harbinger of adverse prognosis :
     It could be either diffuse or focal
     Focal: good prognosis
     Diffuse: bad prognosis

TUMORS OF THE URINARY BLADDER AND COLLECTING SYSTEM:

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, but sometimes, tumor in the collecting system is clinically more important because of urinary flow obstruction; those in the bladder, however, are an even more frequent cause of death than are kidney tumors.

Classification:

1) Benign papillomas (rare)
2) Urothelial carcinomas

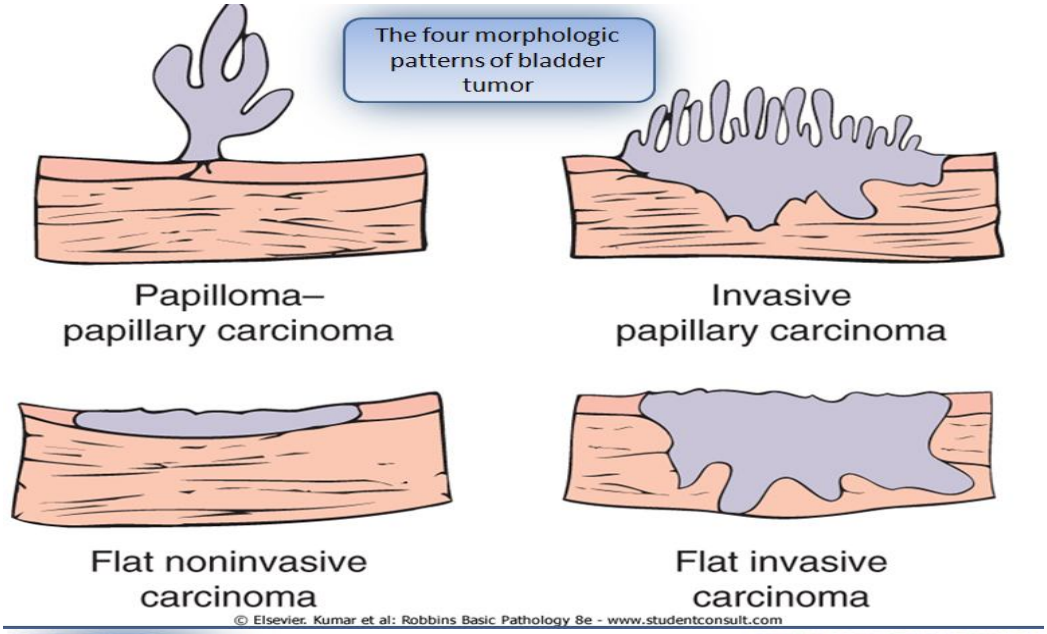
Morphology:

1) Benign papillomas :
   The very rare benign **papillomas** are 0.2- to 1.0-cm frond-like structures having a delicate fibrovascular core covered by multilayered, well-differentiated transitional epithelium

2) Urothelial carcinoma :
   - they range from papillary to flat, noninvasive to invasive, and low grade to high grade.
   - May be preceded by carcinoma in situ.
   - Grade II and III may spread to regional lymph nodes and may metastasize.

Low grade	High grade
Always papillary	Can be papillary or flat
Rarely Invasive	Invasive
May recur after removal	Covers large area of mucosa

Occasionally, these cancers show foci of squamous cell differentiation, but **only 5%** of bladder cancers are true **squamous cell carcinomas**.



Clinical course:

Painless hematuria is the dominant clinical presentation of all these tumors.

But since tumors of the bladder are more common than those of the collecting system , they are discussed first

1) Urinary bladder tumors:
    - They affect men about three times as frequently as women
    - usually develop between the ages of 50 and 70 years

- mutations involving several genes on chromosome 9 have been documented, p53 is the most common & FGFR3.
- bladder tumors are 50 times more common in those exposed to :
    - B-Napthylamine
    - Cigarette smoking
    - Chronic cystitis
    - Schistosomiasis of the bladder
    - Certain drugs (e.g. Cyclophosphamide)

The clinical significance of bladder tumors depends on their histologic grade and differentiation and, most importantly, on the depth of invasion of the lesion. Except for the benign papillomas, all tend to recur. Lesions that invade the ureteral or urethral orifices cause urinary tract obstruction.
As for the prognosis :

- low-grade shallow lesions : the prognosis is good after removal
- high-grade with deep penetration of the bladder wall: the prognosis is bad , the 5-year survival rate is **less than 20%**.

The overall 5-year survival rate for both types together is 57%.

2) Collecting System **(Renal Calyces, Renal Pelvis, Ureter, and Urethra):**
    - Less common than bladder tumors.
    - Causes urinary flow obstruction.
    - Present with :
        - Painless hematuria
        - pain in the costovertebral angle as hydronephrosis develops (if the tumor blocks the ureter).

    - 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%.

اللهم اني استودعك ما قرأت وما حفظت وما تعلمت، فرده لي عند حاجتي إليه
انك على كل شيء قدير، وحسبنا الله ونعم الوكيل.

End of Part 5

Done by: The DuDe