**Krane’s Categorization of Disease + A lot of Extras**

**Kidney Disease**

- **Acute Renal Failure**
  - Pre-Renal
    - Sodium Excretion <1%
    - BUN/ Creatinine > 20
    - CHF, Cirrhosis, Edema
  - Renal Intrinsic
    - Sodium Excretion >2%
    - BUN/Creatinine < 10
  - Post-Renal
    - Labs aren’t that useful

- **Intrinsic Kidney Disease**
  - Glomerular Disease
    - Urinalysis: Proteinuria + Hematuria
    - Spot Test Ratio >1.5, 24 Urine contains > 2.0g/24hrs
  - Nephrotic Syndrome
    - >3.5g protein / 24 hrs (huge proteinuria)
    - Hypoalbuminemia
    - Hypercholesterolemia
    - Edema
  - Nephritic Syndrome
    - Hematuria and Proteinuria (<3.5)
    - RBC Casts
    - Salt and Water Retention = HTN
    - Reduced GFR

**Meleg-Smith’s Hematuria** Break Down

- **Hematuria**
  - RBCs Only
  - Tumor
  - Imaging
  - Lithiasis (Stones)
  - Chemical Analysis
  - RBC + Crystals
  - RBC + WBC
  - RBC+ Protein

**Casts in Urine**

- Red Cell Casts
- White Cell Casts
- Muddy Brown Casts
- Glomerulonephritis
- Pyelonephritis
- Acute Tubular Necrosis

**Path Renal Outline**

See Krane's Chart, Above
**Congenital Anomalies**

- **Agenesis Of the Kidneys**
  - Bilateral Agenesis is incompatible with life found in stillborn infants. Without kidneys, amniotic fluid is not made, and the baby gets crushed. This is called *potter’s sequence*
  - Unilateral Agenesis is compatible with life without other abnormalities. The good kidney will become enlarged with hypertrophy, some develop sclerosis and renal failure

- **Hypoplasia**
  - Failure of the kidneys to develop to a normal size
  - Bilateral is extremely rare, Unilateral is still rare
  - Condition may be indistinguishable from an acquired atrophic kidney
  - True hypoplastic kidney has reduced lobes and pyramids (< 6) and no signs of scarring

- **Ectopic Kidneys**
  - Definitive mesonephros develops at ectopic foci, usually on pelvic brim or within pelvis
  - The ectopic kidneys are usually small and asymptomatic
  - May cause torsion or obstruction or ureter, predisposing for infection (Pyelonephritis)

**Horseshoe Kidneys**

- Fusion of the Kidneys produces a horseshoe-shaped structure continuous across the anterior of the aorta and inferior vena cava
- Most (90%) are lower pole fusion, while only 10% are upper pole fusion
- Risk for stone formation

**Cystic Diseases**

- **Cystic Renal Dysplasia**
  - Abnormality in metanephrotic differentiation
  - Characterized histologically by the persistence in the kidney of abnormal structures (cartilage, undifferentiated mesenchyme, and immature collecting ducts) and by abnormal lobar organization. **Large cysts surrounded by mesenchyme**
  - On gross, there are uni- or bi-lateral cysts, with extremely enlarged kidneys
  - If unilateral, there is a great prognosis if the affected kidney is removed; poor prognosis for bilateral involvement

Cystic diseases are presented out of order from Robbins so that each disease does not go onto the next page (reduces flipping back and forth)

- **Acquired (Dialysis Associated) Cystic Disease**
  - Caused by end-stage kidney disease with prolonged dialysis
  - Cortical + Medullary cysts that contain clear fluid or may bleed (hematuria)
  - Major complication = renal cell carcinoma from the walls of cysts
Path Renal Outline

- **Autosomal Dominant Polycystic Disease** = Adult form of Polycystic Kidney Disease
  - **Pathogenesis**
    - Autosomal Dominant Inheritance Pattern
    - Polycystic Kidney Disease Genes (PKD1 and PKD2) on chromosome 16 and 14, respectively, are implicated in the generation of cysts via polycystin protein abnormality leading to proliferation of different regions of the tubules
    - Exact mechanism unknown
  - **Morphology**
    - Bilaterally enlarged kidneys reaching enormous sizes (4kg/kidney reported)
    - Surface appears entirely cystic though histology reveals functional parenchyma
    - Arise from different regions of the tubules so cysts express variable epithelia
  - **Clinical**
    - May be asymptomatic until renal insufficiency announces presence
    - Hemorrhage may cause flank pain (bleeding into cysts) or insights investigation (hematuria) found especially with large palpable abdominal masses.
    - Extradrenal Cysts can be found
      - 40% occur in the liver from biliary epithelium and are asymptomatic
      - Some occur in the lungs or spleen; mitral valve prolapse in heart
      - Intracranial Berry Aneurysms account for 10% of deaths in these pts

- **Autosomal Recessive Polycystic Disease** = Childhood form of Polycystic Kidney Disease
  - **Pathogenesis**
    - Gene PHKD1 codes for fibrocystin expressed in adult/fetal kidneys liver/pancreas
    - Mutations screw up the collecting tubule + biliary epithelium differentiation
  - **Morphology**
    - Enlarged, smooth surfaced, tiny elongated cysts along the interior (cortex and medulla), perpendicular to the cortical surface.
    - Lined by cuboidal cells because all cysts come from the collecting tubules
    - Invariably Bilateral
  - **Clinical**
    - Highly fatal in infancy, obvious renal failure in all cases
    - 4 subcategories formed based on onset (perinatal, neonatal, infantile, juvenile)
    - Survivors develop congenital hepatic fibrosis (biliary epithelium in origin) with HTN and Splenomegaly

- **Simple (Localized) Renal Cysts**
  - These get mistaken for tumors because they create awkward radiographic shadows
  - They are translucent, grey, glistening, and lined by a single layered membrane
  - May bleed into them, causing pain and distention
  - Are usually small and cortical
**Path Renal Outline**

- **Medullary Sponge Kidney** = *innocuous medullary cystic disease*
  - Occurs in **adults** with unknown pathogenesis
  - Found incidentally on radiograph; increased risk of **stones**, hematuria, infection
  - Cysts consist of cuboidal epithelium from collecting tubules

- **Nephronophthisis-Medullary Cystic Disease Complex** = *malicious medullary cystic disease*
  - **Pathogenesis**
    - Juvenile = NPH genes make **nephrocystin** without a known pathogenesis though there are autosomal dominant and autosomal recessive forms
    - Adult = MCKD1, little is known
    - Induces cysts at the corticomedullary junction and interstitial fibrosis
  - **Morphology**
    - **Medullary Cysts concentrated to the corticomedullary junction** though small cortical cysts may exist
    - Cysts are lined by flattened cuboidal epithelium with inflammation or fibrosis surrounding it
  - **Clinical**
    - Affects kids, suspected in unexplained renal failure with Familial History
    - First **polyuria** and **polydypsia** reflecting inability to concentrate urine
    - Renal failure occurs in 5-10 years
    - Cysts may be too small to see on radiograph

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Pathologic Features</th>
<th>Clinical Features or Complications</th>
<th>Typical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Renal Dysplasia</td>
<td>None</td>
<td>Large Cysts on Kidney</td>
<td>Renal Failure</td>
</tr>
<tr>
<td>Adult polycystic kidney disease</td>
<td>Autosomal dominant</td>
<td>Large multicystic kidneys, liver cysts, berry aneurysms</td>
<td>Hematuria, flank pain, urinary tract infection, renal stones, hypertension</td>
</tr>
<tr>
<td>Childhood polycystic kidney disease</td>
<td>Autosomal recessive</td>
<td>Enlarged, cystic kidneys at birth</td>
<td>Hepatic fibrosis</td>
</tr>
<tr>
<td>Medullary sponge Kidney</td>
<td>None</td>
<td>Medullary cysts on excretory urograph</td>
<td>Hematuria, urinary tract infection, recurrent renal stones</td>
</tr>
<tr>
<td>Familial juvenile nephronophthisis</td>
<td>Autosomal recessive</td>
<td>Corticomedullary cysts, shrunken kidneys</td>
<td>Salt wasting, polyuria, growth retardation, anemia</td>
</tr>
<tr>
<td>Simple cysts</td>
<td>None</td>
<td>Single or multiple cysts in normal-sized kidneys</td>
<td>Microscopic hematuria</td>
</tr>
<tr>
<td>Acquired renal cystic disease</td>
<td>None</td>
<td>Cystic degeneration in end-stage kidney disease</td>
<td>Hemorrhage, erythrocytosis, neoplasia</td>
</tr>
</tbody>
</table>
Glomerular Diseases (this is a monster section that lasts for 7 pages)

- **Initiation**
  - Something has to initiate the inflammatory damages that induce glomerulonephritis
  - Events are any combination of the following
    - Antibody-Antigen Deposition = Type III Hypersensitivity, circulating Ag-Ab
      - Granular Immunofluorescence
    - Antibody-Basement Membrane = Type II hypersensitivity, Goodpasture’s
      - Linear Immunofluorescence
    - Antibody-Antigen Planted = Type II Hypersensitivity, Ag stuck in glomerulus
      - Granular Immunofluorescence
    - T Cell Damage = Type IV Hypersensitivity, reaction to Ag in endothelium
      - No Immunofluorescence, No immune Deposition
  - Pathogenesis
    - Short-term injury is cleared by Macrophages and the “itis” is limited
    - Long-term injury (Lupus) causes persistent damage that becomes chronic
    - Different injuries occur at different rates until GFR = 30-50%, then they progress

- **Progression**
  - Once GFR gets down between 30-50%, progression is basically constant, irrelevant of the severity or time course of the underlying insult that caused it
  - Target for therapy, since all diseases must funnel to one final progression mechanism
  - **Focal Segmental Glomerulosclerosis (FSGS)**
    - Leads to proteinuria and hematuria even if the initial insult was nonglomerular
    - Stems from a loss of renal mass from whatever cause (ischemia/Infarction, immune mediated fibrosis, etc.) and is a result of adaptive changes
      - Loss of renal mass results in hypertrophy of remaining glomeruli
      - Podocytes cannot grow with the glomeruli, losing filtration barrier
      - Proteins and cells are allowed to leak out, resulting in macrophage induced fibrosis, causing a reduction in renal mass
      - Cycle Repeats
    - Treated with Renin-Angiotensin System Inhibitors
  - **Tubulointerstitial Fibrosis**
    - Literally fibrosis of the tubules and interstitum, opposed to the glomerulus
    - There is a stronger correlation between the decline of renal function and the amount of tubulointerstitial fibrosis than with the original insult
    - Results from two mechanisms
      - Infarction of tubules, possibly from alterations of hemodynamics in the above condition (FSGS)
      - Activation of tubule cells either from proteinuria or other cytokines. Activated tubule cells express adhesion molecules and elute inflammatory cells that lead to fibrosis
**Acute Glomerulonephritis** = nephritic syndromes

- **Acute Proliferative Glomerulonephritis / Post Streptococcal Glomerulonephritis**
  - **Definition**
    - Diffuse proliferation of glomerular cells with the presence of leukocytes
  - **Pathogenesis**
    - Post-streptococcal A Beta-Hemolytic Pharyngitis OR Skin Infection
    - Formation of Antibody against M protein Antigen (ASO titer elevated) results in immune complex formation and deposition
    - Immune response results in an acute nephritic syndrome
  - **Morphology**
    - LM = Enlarged and Hypercellular glomeruli; Tubules often contain Red Cell Casts; LM is not entirely specific, use IF and EM
    - IF = shows granular deposits of IgM, IgG, and C3
    - EM = discrete, amorphous, electron dense deposit on the subepithelial side (which is the immune complex)
  - **Clinical Course**
    - Young child (6-10 years old) with malaise, fever, nausea and hematuria (cocoa-urine) 1-2 weeks after a Strep A infection, showing elevated ASO titers
    - 95% recover well as Ag-Ab is cleared with Fluid/Electrolyte therapy
    - 1% develop rapidly progressive glomerulonephritis (See below)
    - Prolonged and persistent Proteinuria/Abnormal GFR marks a poor prognosis
  - **Notes**
    - This can happen from other infections than Strep A, and are bacterial (Strep Pneumo Pneumonia), Viral (Hep B, Hep C, HIV), or parasite (Toxo, Malaria)

- **Rapidly Progressive (Crescentic) Glomerulonephritis**; “comes from Goodpastures”
  - **Definition**
    - Severe glomerular injury associated with the formation of crescents in most glomeruli and is not necessarily associated with one syndrome
  - **Pathogenesis**
    - It is immunologically mediated, subdivided based on immunological findings
      - **Type I** = Anti-GBM Antibodies as in Goodpastures; Anti-Collage Type IV
      - **Type II** = Immune Complex as in postinfectious, SLE, or Henolch-Schloen
      - **Type III** = Pauci Immune aka “other” without association to Anti-GBM or immune complex, but is associated with ANCA (p and c), as in Wegner’s
  - **Morphology**
    - Histo = Crescents = proliferation parietal cells, macrophages, PMNs, and fibrin strands between cells, all contained within bowman’s space
    - EM = wrinkled and ruptured basement membranes
    - IF = variable pattern depending on type: 1 = Linear, 2 = Granular, 3 = None
    - Gross = Enlarged and pale kidneys with cortical Petechial hemorrhage.
  - **Clinical Course**
    - All types: hematuria, red cell casts, proteinuria approaching nephrotic ranges
    - Rapidly progressive disease with loss of renal function
    - Treatment is plasmaphoresis (Type 2), otherwise steroids and cytotoxic drugs (anti-inflammation) is the way to go.

For Goodpasture's see the Inflammation Lecture on Hypersensitivity for complete detail and immunofluorescent pattern. Kaplan separates Cresentic from Goodpasture’s; Dr. Krane assumes Goodpasture’s = Crescentic; Robbins says Goodpasture’s is just one type of crescentic
Path Renal Outline

- **IgA Nephropathy** (Berger Disease)
  - **Definition**
    - Primary Renal disease where IgA deposits are found in the mesangium detected by immunofluorescence
      - Systemic Diseases, discussed later, can cause IgA deposition in the kidneys (Henoch-Schonlein Purpura)
  - **Pathogenesis**
    - Associated with a one particular form of IgA (IgA1)
    - Antigen recognition in mucosal membranes results in formation of IgA and IgA-complexes that circulate in the blood; inciting antigen is unclear
    - Liver decomposes polymeric IgA (usually exists as a dimer in mucosal lumen)
      - Liver disease can present with IgA deposition and glomerulonephritis
    - Some IgA become trapped in glomerulus leading to complement activation and glomerular injury.
  - **Morphology**
    - Microscopic changes are variable, but mesangial proliferation or overt crescentic glomerulonephritis may occur
    - Diagnosis is based on immunofluorescent stains for complement or IgA in the characteristic pattern shown to the left (granular mesangial pattern).
  - **Clinical Course**
    - Fairly benign causing microscopic hematuria or a proteinuria that can approach nephrotic ranges
    - Bouts are intermittent though eventual chronic kidney failure will result, often requiring decades for onset

- **Membranoproliferative Glomerulonephritis** (Type 1 Krane Taught, Type 1 + 2 in Robbins)
  - **Clinical**
    - Adolescents and Children
    - Low levels of serum compliment
    - Secondary to Hep B or Hep C, or can be a primary disease (poor prognosis)
    - Nephritic or Nephrotic
  - **Pathogenesis**
    - Immune complex deposition and/or C3 complement activation
    - Resultant immune response produces an inflammation reaction
  - **Morphology**
    - LM = Hypercellularity + Basement membrane thickening & splitting = tram-track
    - IF = IgG, IgM and C3 in a granular pattern pushed to the periphery
    - EM = Subendothelial Deposits (capillary lumen side, with the RBCs)

  Type II is essentially the same presentation, only is autoantibody mediated rather than circulating immune complex deposition
Path Renal Outline

**Nephrotic Syndrome**

- **Definition and pathogenesis**
  - An **initial event** causes a derangement of glomerular capillaries with increased permeability to protein, with resultant **proteinuria**
  - **Albumin** leaks out along with the proteinuria leading to decreased colloid pressure
  - **Edema** (periorbital + peripheral) result from the loss of colloid pressure with subsequent ADH/aldosterone fluid retention (because all fluid is in the interstitium, it “looks like” there is fluid depletion) exacerbating the edema
  - **Hyperlipidemia/cholesteremia** has a complex genesis, but exists in nephrotic syndrome
  - Patients are at an increased risk of infection

- **Membranous Glomerulonephropathy**
  - **Critical Concepts**
    - Most common cause of nephrotic syndrome in adults
    - Either is idiopathic or is secondary to an immune disease
    - Does not respond well to corticosteroids
  - **Definition**
    - Diffuse thickening of the glomerular capillary wall with accumulation of electron dense immunoglobulins with deposits on the Subepithelial side of the BM
  - **Pathogenesis**
    - Chronic Immune Complex-Mediated Disease
    - **Idiopathic** = MHC susceptibility + an unknown nephritogenic antigen
    - **Secondary** = LSE, drugs (penicillamine), tumors, metals (drugs/mercury), or infections (Hep C, Hep B, shistosomiasis, malaria)
  - **Morphology**
    - **LM** = Uniform and diffuse thickening of basement membrane
    - **EM** = dense deposits in **subepithelial side**, with the BM forming “spikes” into the deposit. “Spikes” will grow out and encompass the deposit forming **domes**
    - **IF** = **Immunoglobulins and compliment** in a linear granular pattern
  - **Clinical Course**
    - Usually **insidious onset** of nephrotic syndrome
    - Proteinuria is nonselective and **does not respond to corticosteroids**
    - Eventual sclerosis of glomeruli leads to elevated BUN, Creatinine, and HTN

- **Minimal Change Disease**
  - **Critical Concepts**
    - Most common cause of nephrotic syndrome in **children**.
    - Characterized by **effaced foot processes on EM** with a normal LM glomerulus
    - Enormously responsive to corticosteroids and remits after puberty
  - **Definition**
    - A childhood nephrotic syndrome that is characterized by effaced foot processes on EM resulting in massive proteinuria with a normal glomerulus on LM
Path Renal Outline

- **Pathogenesis**
  - Unknown, but there is some link to autoimmune or post-infection, even though these changes can be seen in the absence of immune deposition or infection

- **Morphology**
  - Light Microscopy shows a normal glomerulus without any changes
  - Electron Microscopy shows effaced foot processes, vacuoles, and “fused” podocytes, which are actually just flattened epithelium
  - IF shows **nothing**; there is often no immune deposition

- **Clinical Course**
  - Primary target is children, though adolescents and young 20s affected
  - Despite massive proteinuria, there is a preservation of renal function **without** hematuria or hypertension
  - Effectively treated by corticosteroids, and although resistance or dependence may develop, disease remits after puberty.

  - **Focal Segmental Glomerulosclerosis (FSGS)** now the disease, instead of “progression”.

    - **Definition**
      - Sclerosis of some, but not all (i.e. focal) glomeruli affecting only part of each affected glomeruli (i.e. segmental) with nephrotic syndrome

    - **Pathogenesis**
      - Possibly a progression from minimal change disease with similar effacement of podocytes but with the extra epithelial damage and sclerosis under LM
      - **Nephrin** genes code for cell adhesion interactions at the diaphragm and mutations in nephrin genes cause a collapse of the filtration barrier
      - **Proteinuria** results with subsequent entrapment of plasma proteins, resulting in hyalinosis and sclerosis of affected segments

    - **Morphology**
      - LM = parts of some glomeruli are eosinophilic (pink) with sclerosis ***
      - EM = Effacement of podocytes as in Minimal Change Disease (above, this page)
      - IF = IgM and C3 in sclerotic areas

    - **Clinical Course**
      - Affects adults and kids, usually blacks, associated with HIV, Hep B, Hep C
      - Does **not respond** to corticosteroids and **does not remit** spontaneously
      - Some will end with rapid-onset renal failure (2 years) while some may last as long as 10; renal transplantation or dialysis is inevitable

    - **Notes**
      - There is a **morphological distinct** variant that also involves complete glomerular collapse and sclerosis with the focal segmental changes of FSGS in HIV positive patients, called **collapsing glomerulosclerosis**.
      - The Renal Ablation FSGS that occurs after the removal of a diseased or healthy nephrotic segment caused by hypertrophy of the remaining segment was discussed above, the first time we encountered FSGS as a “progression.”
Path Renal Outline

**Hereditary Syndromes of Isolated Hematuria** – genetic Glomerulonephropathies

- **Alport’s** = Nephritic
  - **Definition**
    - X-linked disorder involving collagen formation characterized by renal failure, auditory disturbances, and eye problems (corneal atrophy, lens dislocation)
  - **Pathogenesis**
    - Defective **glomerular basement membrane** as a result of a defect in **type IV collagen synthesis**
      - Lack of alpha chains renders these patient immune to Goodpasture’s, since they lack the alpha-3 antigen
    - Defect is in particular of the alpha-5 chain of collagen type IV
  - **Morphology**
    - EM reveals changes; genetic screening determines disease
    - Full blown disease is shown on EM as **alternating thickening and thinning** glomerular basement membrane with lamination of the lamina densa
  - **Clinical Course**
    - Disease onset is at birth; symptoms to not occur until later in life
    - Associated with **Vision Abnormalities** and **Auditory Problems**
    - **Earliest signs** (microscopic hematuria) detected between 5-20 years
    - **Overt Kidney Failure** occurs between 20-50 years.

- **Thin Basement Membrane Disease** like alports, but not
  - Benign familial hematuria discovered by routine urinalysis
  - Diagnosis confirmed by EM demonstrating **thinning of Glomerular Basement Membrane**
  - Caused by a defect in Type IV collagen formation (alpha-3, maybe alpha-4)
  - α-5 Type IV collagen present and there are no ocular or auditory lesions (not Alport’s)
  - and there is no IgA immune deposition in the mesangium (not IgA Nephropathy)
  - **Prognosis is excellent** with a maintenance of normal renal function throughout life

**Chronic Glomerulonephritis** – the end point of all Nephrotic and Nephritic Syndromes

- Endpoint of all diseases discussed here, occurring at varying rates dependent on primary disease
- Histology may demonstrate pathology of the original disease, though chronic glomerulonephritis is characterized by **extensive hyalinization** and **fibrosis** of the glomeruli, demonstrated by large amount of collagen on a trichrome stain
- Because **hypertension** is often concomitant with chronic renal failure, **arterial sclerosis** may be present as well
- Inevitably, chronic renal failure leads to **uremia** with characteristic changes (pericarditis/secondary hyperparathyroid) Course is progressive renal failure, often with **hypertension**, eventual **edema**, and, without dialysis or renal transplant, death. Other signs of CKD (edema) may be present.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Presents</th>
<th>Clinical</th>
<th>Pathogenesis</th>
<th>Light Microscopy</th>
<th>Immunofluorescence</th>
<th>Electron Microscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Nephritic</td>
<td>95% Recover 1% Renal Failure</td>
<td>Antibody mediated; circulating antigen (ASO titer) Type III hypersens</td>
<td>Diffuse proliferation; leukocytic (PMNs) infiltration</td>
<td>Granular IgG and C3 in GBM and mesangium. “Lumpy-Bumpy”</td>
<td>Subepithelial humps</td>
</tr>
<tr>
<td>Goodpasture Syndrome (Type I Crescentic)</td>
<td>Nephritic</td>
<td>Plasmaphoresis &amp; Steroids. 95% Renal Failure</td>
<td>Anti-GBM COL4- A3 antigen (collagen type IV, alpha-3)</td>
<td>Crescents</td>
<td>Smooth Linear IgG and C3, “neon sign pattern”</td>
<td>No deposits; GBM disruptions; fibrin</td>
</tr>
<tr>
<td>Idiopathic RPGN (Type III Crescentic)</td>
<td>Nephritic</td>
<td>Painless Hematuria, Recurs</td>
<td>ANCA-associated; no circulating immune deposition or anti-GBM antibody.</td>
<td>Crescents</td>
<td>Linear or Granular, not very useful.</td>
<td>Same thing, not very useful, because there can be deposits, can be anywhere, or not be there at all.</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Nephritic</td>
<td></td>
<td>Unknown; may be associated with systemic IgA disease or Virus.</td>
<td>Granular deposition of IgA in mesangium</td>
<td>Mesangial and paramesangial dense deposits. Basically, you won’t use it.</td>
<td></td>
</tr>
<tr>
<td>Alport’s</td>
<td>Nephritic</td>
<td>Hearing Loss, Vision problems, Nephritic</td>
<td>X-linked disorder of type IV collagen alpha-5 (gene COL4- A5)</td>
<td>Not listed</td>
<td>Not listed</td>
<td>Alternating thickening and thinning of the basement membrane</td>
</tr>
<tr>
<td>Minimal Change (Lipoid Nephrosis)</td>
<td>Nephrotic</td>
<td>Kids, Steroids = Great Prognosis</td>
<td>Unknown, podocytes effacement</td>
<td>Normal</td>
<td>Normal</td>
<td>Loss of foot processes; Podocyte fusion/effacement</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Nephrotic</td>
<td>Adults, even with steroids = poor prognosis</td>
<td>Unknown. Most common in African Americans. Loss or renal tissue, Sickle Cell, Heroin, AIDS, obesity.</td>
<td>Focal (only some glomeruli) and segmental (only part of each glomerulus affected) sclerosis and hyalinosis.</td>
<td>Nonspecific</td>
<td>Subendothelial Deposits</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (MPGN Type I)</td>
<td>Nephrotic or Nephritic</td>
<td>Immune complex deposition and activation of IgG and complement</td>
<td></td>
<td>Mesangial Proliferation, Basement membrane splitting “Tram-Track Appearance”</td>
<td>(I) IgG + C3; C3 levels are lower in blood from complement activation</td>
<td>(I) Subendothelial deposits</td>
</tr>
<tr>
<td>Dense deposit disease (MPGN Type II)</td>
<td>Nephritic</td>
<td>Autoantibody: alternative complement pathway</td>
<td>End-stage of every disease listed above</td>
<td>Hyalinized/Fibrotic glomeruli that hides primary disease</td>
<td>Nonspecific</td>
<td>(II) Dense deposits</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>CKD</td>
<td>Dialysis and Transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Taken from Big Robbins, Modified to be easier to use (Kaplan helped a bit). Kaplan’s Med Essentials includes some other clinical clues and prognosis. It just didn’t fit with the information Robbin’s and Krane wanted you to know. RPGN = rapidly progressive glomerulonephritis.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Presents</th>
<th>Serum Complement</th>
<th>LM</th>
<th>EM</th>
<th>IF</th>
<th>Patho / Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poststrepococcal glomerulonephritis</td>
<td>Nephritic</td>
<td>Lowered</td>
<td>Hypercellular</td>
<td>Subepithelial deposits described as lumpy-bumpy</td>
<td>Granular IgG C3</td>
<td><strong>Children</strong> following an infection of group A Beta-Hemolytic Strep with elevated ASO Titors. Patients do well with conservative treatment. 95% recover, 1% goes on to renal failure.</td>
</tr>
<tr>
<td>Goodpasture Syndrome</td>
<td>Nephritic</td>
<td>No change</td>
<td>Crescents</td>
<td>Nonspecific</td>
<td>Linear BM Neon Sign Pattern</td>
<td>Anti-GBM autoantibody against collagen Type IV alpha-5. Presents with hemoptysis and hematuria, males in their 20s or 30s. Horrible prognosis though plasmaphoresis and transplant are tried</td>
</tr>
<tr>
<td>Rapidly Progressive Glomerulonephritis</td>
<td>Nephritic</td>
<td>No change</td>
<td>Crescents</td>
<td>Nonspecific</td>
<td>Nonspecific</td>
<td>There is a rapid progression to renal failure, usually following Goodpasture’s. it can result from Strep A infections, but most of them recover</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>Nephritic</td>
<td>No change</td>
<td>Mesangial Proliferation</td>
<td>Nonspecific</td>
<td><strong>Granular IgA in mesangium</strong></td>
<td>It is the most common nephritic syndrome world wide. Comes on after an upper respiratory infection. Henoch-Schlonlein Purpura present.</td>
</tr>
<tr>
<td>Membranoproliferative (I) = Immune Complex (II) = Dense Deposit</td>
<td>Nephritic or Nephrotic</td>
<td>Low Low Low</td>
<td>Tram-tracking of basement membrane</td>
<td>Nonspecific, type II has dense deposits</td>
<td>Granular C3 pattern</td>
<td>Slowly progressive disorder that is refractory to treatment. Type II has a circulating <strong>nephritic factor</strong> that binds to and destabilizes C3. Presents with blindness, deafness, hematuria in kids. It is a defect in collagen type IV alpha-5. It is a progressive disease refractory to treatment</td>
</tr>
<tr>
<td>Alport’s</td>
<td>Nephritic</td>
<td>No Change</td>
<td>Nonspecific</td>
<td><strong>Thickening and Thinning of BM</strong></td>
<td>Nonspecific</td>
<td>Presents with blindness, deafness, hematuria in kids. It is a defect in collagen type IV alpha-5. It is a progressive disease refractory to treatment</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>Nephrotic</td>
<td>No Change</td>
<td>BM thickening, Silver stain shows spikes</td>
<td>Spike and Domes, subepithelial deposits with BM extending Podocyte Effacement</td>
<td><strong>Granular Linear</strong> (looks like Goodpasture’s dotted)</td>
<td>Variable prognosis. Associated with HepB/HepC, heavy metals (gold mercury), drugs (penicillamine), and sickle cell disease</td>
</tr>
<tr>
<td>Minimal Change (Lipoid Nephrosis)</td>
<td>Nephrotic</td>
<td>No Change</td>
<td>Normal</td>
<td></td>
<td>Nothing</td>
<td>Most common in kids. Great response to steroids with a wonderful prognosis! Associated with heroin, AIDS/HIV, Renal Ablation. There is a poor response to steroids and it recurs in transplants. Most common nephrotic syndrome in African Americans.</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Nephrotic</td>
<td>No Change</td>
<td>Some glomeruli (focal) where not all of the glomerulus is effected (segmental)</td>
<td>Nonspecific</td>
<td>Nonspecific</td>
<td>Most common in kids. Great response to steroids with a wonderful prognosis! Associated with heroin, AIDS/HIV, Renal Ablation. There is a poor response to steroids and it recurs in transplants. Most common nephrotic syndrome in African Americans.</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>CKD</td>
<td>No change</td>
<td>Hyalinized/Fibrotic glomeruli that hides primary disease</td>
<td>Nonspecific</td>
<td>Nonspecific</td>
<td>End-stage of all diseases that are listed above. Anemia, Uremia, elevated BUN, elevated creatinine, proteinuria and HTN. Death.</td>
</tr>
</tbody>
</table>

Done again in a “how to answer the question” format. This was created from listening to Kaplan’s Lectures. I think its got less than the other table, but I ended up making this one to help get through Lippincott’s Review questions. Things in bold are the unique or buzzword association.
Glomerular Lesions Associated with Systemic Diseases

- **Lupus**
  - Lupus forms Antibody-Antigen complexes that deposit in the glomerular filtration barrier.
  - Macrophage activation leads to injury and eventual fibrosis of the glomerulus and even some vasculitides.
  - Renal Failure is one of the most severe complications in the kidney, giving rise to hematuria, acute nephritis, nephrotic syndrome, and hypertension

- **Henoch-Schonlein Purpura**
  - Probably a spectrum of disease related to IgA nephropathy (Berger’s)
    - IgA is deposited in the renal mesangium, sometimes C3
    - Henoch-Schonlein is also systemic while Berger’s is localized to kidney
  - Presents with Puritic skin rashes on extensor surfaces of arms and legs
    - Skin lesions contain necrotizing Vasculitis with microhemorrhage
  - Onset of 3-8 years with excellent prognosis unless ominous clinical signs are present (crescents or severe prolonged nephrotic syndrome)

- **Amyloidosis** (Associated with Multiple Myeloma)
  - Congo Red Positive and apple green birefringent patterns
  - Amyloid, usually the light chain (AL) is deposited in areas of large blood flow: glomerular capillaries and mesangium
  - Progresses to worsening renal failure with eventual termination from uremia
  - Seen under EM as massive basement membrane without deposits
  - Urinalysis shows heavy proteinuria (large Uprotein/Ucreatinine ratio) with only trace protein on dipstick
    - Dipstick picks up albumen only, Uprotein/Ucreatinine shows all protein
    - Light Chains are not albumen, but are protein!

- **Fibrillary Glomerulonephritis**
  - Looks like amyloid on histo, but without Congo Red or Apple Green Polarized Light
  - Does have IgG and C3 on Immunofluorescence
  - Unknown etiology

- **Essential Mixed Cryoglobulinemia**
  - IgG-IgM complexes induce Vasculitis and membranous glomerulonephritis
  - Associated with Hep C

- **Plasma Cell Dyscrasias**
  - Multiple Myeloma produces lots of monoclonal immunoglobulins
  - Lesions look like amyloid without Congo Red or Apple Green Polarized Light
  - Called light chain or monoclonal immune deposition

- **Bacterial Endocarditis**
  - Particularly occurring with rheumatic fever, circulating antigens cause immune deposition and nephritis

- Discussion of diabetic nephropathy begins on the next page
Path Renal Outline

- **Diabetic Glomerulosclerosis / Nephropathy**
  - **Definition**
    - Term applied to the array of vascular and renal lesions that occur concomitantly in the kidney (hyalinized arteriosclerosis, glomerular fibrosis, etc.)
  - **Pathogenesis**
    - Discussed in the endocrine section, the main cause of the damage is the same for diabetic angiopathy, with salient points related here
    - **Metabolic Defect**
      - Decreased Insulin = Increased Glucose
      - Increased Glucose = Proliferation of Type IV collagen (sclerosis)
      - Increased Glucose = Advanced Glycosylation End Products
    - **Hemodynamic Defect**
      - Increased glucose leads to increased filtration and GFR
      - Glomerular Hypertrophy ensues
      - Hypertrophy leads to sclerosis and loss of renal mass with resultant compensatory hypertrophy, leading to more sclerosis, etc.
  - **Morphology**
    - **Capillary Basement Membrane Thickening**
      - Part of the diabetic angiopathy
      - Concomitantly with tubular basement membrane thickening
      - Determined only by EM studies
    - **Diffuse Mesangial Sclerosis**
      - Mesangium proliferates, becomes thickened, then sclerotic
      - Occurs diffusely throughout the glomerulus
    - **Nodular Glomerulosclerosis**
      - Known is Kimmelstiel-Wilson disease
      - Mesangial Sclerosis becomes nodular and acellular
      - Nodules may impinge on capillaries leading to ischemia, deformation of the glomerular tuft, and tubular necrosis.
  - **Clinical Course**
    - **Early** findings are subtle microalbuminuria and an elevated GFR
    - Soon after, overt proteinuria develops, with eventual decline of GFR into end-stage renal failure
    - Systemic Hypertension may occur prior to proteinuria or microalbuminuria.
      - The hypertension may lead to the disease, may occur from, or simply exacerbate
    - Pancreatic transplantation can reverse the glomerulopathy associated with Type 1 DM
**Acute Tubular Necrosis**

- **Definition**
  - Clinicopathologic finding characterized morphologically by damage to *tubular epithelial cells* and clinically by a *acutely diminished renal function*
  - Most common form of acute renal failure
  - Occurs as either *Ischemic ATN* (trauma, sepsis, shock) or *Nephrotoxic ATN* (see causes)

- **Pathogenesis**
  - Ischemic ATN caused by an acute, severe loss of blood flow or obstruction, usually associated with trauma
  - Tubular Epithelial Cells have high metabolic demands (constant massive resorption and Na/K-ATPase)
  - Ischemic/Poisoned cells lose cell polarity inserting Na/K-ATPase on the luminal aspect, *increasing distal sodium delivery*, inducing vasoconstriction via tubuloglomerular feedback
  - Ischemic cells detach from the basement membrane, obstruct lumen, increase bowman’s hydrostatic pressure, decreasing GFR
  - Vasoconstriction further decreases GFR by constricting afferent arteriole

- **Morphology**
  - *Ischemic ATN* shows focal tubular epithelial cell necrosis and basement membrane eruption with large spaces of unaffected tubule in between
  - *Toxic ATN* shows focal, nonspecific necrosis particularly at the proximal tubule
  - In both cases more subtle findings are possible
    - Loss of Brush Border
    - Simplification of cell architecture
    - Cell Vacuolization and Enlargement

- **Causes** (Toxic)
  - *Rhabdomyolysis* following crush injuries or any other condition that breaks down muscle (cocaine, statins, cyclosporine, alcoholism). *Myoglobin* is released and is directly nephrotoxic
  - *Aminoglycosides* are directly nephrotoxic and cause acute renal failure in 15-20% of patients. These are reserved for life threatening gram negative sepsis
  - *Cisplatinum* and *Cyclosporine*, amongst other chemotherapeutic agents
  - *Contrast Dye* is hyperosmolar and, especially in the dehydrated state, can lead to nephrotoxicity in a patient with already diminished kidney function (diabetics)
  - *Crystal deposition* from either *tumor lysis syndrome* (lymphoma/leukemia) or from the ingestion of *ethylene glycol* (which forms oxalate $\rightarrow$ calcium oxalate stones)
Batuman, at Tulane, organizes this as

1. Evolution
2. Oliguria
3. Polyuric
4. Functional Recovery

Robbins combines Polyuric and Functional recovery

Clinical Course

- Because of the patchy nature of the ischemia, and the tendency to maintain basement membrane attachment of the unaffected cells, repair and resolution is likely given supportive care.
- Phases (disparity between Batuman’s 4 stages vs Robbin’s 3 stages)
  - **Evolution Phase**: a short period during which the nephrotoxic insult has not yet caused acute renal failure. There is a slight rise in BUN.
  - **Maintenance Phase**: sustained decreases in BUN and urine output (oliguria), a GFR ~ 0, and the inability to tolerate water loads. Electrolyte disturbances are common (hyper K). With proper management, the patient will push through this
  - **Recovery Phase**: Renal function begins to improve rapidly with resolution in a few weeks. There is an initial polyuria as water balance is restored (excess fluid that got jammed up is now allowed to exit). Beware hypot K
- Dialysis, though performed, does not increase survival or prognosis.
- Dirty Brown Granular Casts, also called “renal failure casts” are diagnostic for ATN

**Pyelonephritis and UTI** (they cause Tubulointerstitial Disease)

- **Definition**
  - Infection of the ureters and renal pelvis resulting in tubules, interstitium, and pelvis being affected by infection; kidneys = nephritis, pyramids= pyelo, bladder = cystitis
  - Can be divided into acute and chronic pyelonephritis

- **Common Etiology and Pathogenesis**
  - Bacteria
    - Gram negative bacteria via endogenous spread = E Coli, Proteus, Klebsiella, Enterobacter come from fecal flora, though Staph and others are possible
    - Can be spread hematogenously (rare) or through ascending infection from a lower urinary tract infection (common)
  - Ascending Infection
    - Begins with colonization of the urethra
    - Entrance to the bladder is achieved via catheterization (males) or from ascent through a small urethra (females)
  - **Vesicouretal Reflux** allows bacteria to gain access to ureters.
    - Congenital = malformed or incompetent valve
    - Acquired = Atony of the bladder
  - **Intrarenal Reflux** occurs with each contraction of the bladder, urine exiting the urethra and the ureters, pushing infection up (especially with outflow obstruction)
  - This is the introduction to Pyelonephritis in Robbins, which then diverges into chronic and acute pyelonephritis
Acute Pyelonephritis

- **Definition**
  - Infection of the kidney in the acute setting

- **Pathogenesis**
  - Invariably ascending infection though hematogenous spread is possible.
  - Description of vesicouretal reflux on last page described pathogenesis

**Acute Pyelonephritis Morphology**

- Hallmark = **patchy interstitial suppurative inflammation**, intratubular WBC aggregates (WBC casts on urinalysis) and **tubular necrosis**
- Affects the upper and lower poles more than the middle
- Abscesses are possible in gross or on the scope
- **Papillary necrosis** is seen in diabetics with distal pyramid necrosis
- Pyonephrosis is severe infection that totally occludes the lumen and outflow
- Healing brings variable scars to the affects cortex but **always shows fibrosis of the underlying renal pelvis and calyces**

**Acute Pyelonephritis Clinical**

- Males are more common when under 1 yo (congenital defects) and over 40 yo (catheterization and prostate problems); women more common in between
- **Dysuria/Frequency** with sudden onset pain in the **costovertebral angle** (“Flank Pain”)
- Culture shows bugs, urine shows WBCs (white cell casts)
- Patients come in and they are sick. Real sick. Fever, Malaise, etc.
- Treat with antibiotics against the cultured bug

Chronic Pyelonephritis

- **Definition**
  - Tubulointerstitial inflammation causes discrete, corticomedullary scars overlying dilated, blunted, and deformed calyces.

- **Pathogenesis**
  - **Ascending Infections** that constantly recur can cause chronic Pyelonephritis. The pathogenesis is the same as for acute, but they happen over and over again, worsening destruction of kidneys
  - **Obstructive Uropathy** prevents the flow of urine, giving bacteria a place to grow. If there is only one infection, but its allowed to grow and go crazy because of an obstruction, you can get the same chronic changes.
  - **Xanthogranulomatous** (rare) may mimic renal cell carcinoma in gross and histo

**Morphology**

- Corticomedullary scarring overlying dilated,blunted, or deformed calyx
- Sclerosis of arteries in affected regions
- Dilated, flattened epithelium filled with thyroid casts on histo

- **Clinical**
  - With reflux, there can be an insidious onset without symptoms
  - **FSGS** is possible with increased scaring; proteinuria is a poor prognostic finding
Tubulointerstitial Nephritis caused by Drugs (Allergic Nephritis)

- **Definition**
  - Immune mediated reaction (Hypersensitivity Type I and IV) to a variable number of drugs resulting in tubulitis and acute renal failure

- **Pathogenesis**
  - **It is not dose related**
  - Drugs acts as a **hapten** until concentrated in the tubules for excretion in urine whereby activation of IgE and T/B/Plasma cells in the localized area

- **Morphology**
  - Pronounced edema in the interstitum
  - **Eosinophils/Neutrophils** are present in large numbers
  - Granulomas may be present; various stages of necrosis and healing

- **Clinical**
  - **Fever, Rash, Eosinophilia, and Acute Renal Failure** (increased SrCr and oliguria) 2-40 (average 15) days after exposure to offending agent
    - NSAIDs, Synthetic Penicillins, others (Allopurinol)
  - Removal of Drugs leads to recovery and healing

Analgesic Nephropathy

- **Definition**
  - Chronic Renal Disease caused by excessive analgesic mixtures resulting in chronic tubulointerstitial nephritis and renal papillary necrosis

- **Pathogenesis**
  - **Phenacetin** and its metabolite **acetaminophen** injures cell by both **covalent binding** and **oxidative damage**
  - **Aspirin** cause downregulation of PGI₂, vasoconstriction, papillary ischemia (pyramids)
  - **Volume Depletion** exacerbates both
  - Papillary necrosis occurs first, followed by cortical tubulointerstitial nephritis

- **Morphology**
  - Depressed areas of cortex overlie **papillary necrosis**
  - Patchy (early) and total (late) necrosis of papilla on histo
  - Medulla shows interstitial fibrosis and inflammation, a product of obstruction caused by papillary sloughing into tubule lumen

- **Clinical**
  - People with headaches or muscle pains (analgesic users/abusers)
  - Papillary damage = inability to dilute urine/secrete acid = **metabolic acidosis**
  - Drug withdrawal = reversal and healing
  - Increased risk for **transitional cell carcinoma** of the renal pelvis
DISEASES OF THE BLOOD VESSELS

Benign Nephrosclerosis

- **Definition and Pathogenesis**
  - Sclerosis of the renal arterioles and small arteries associated with aging and HTN
  - Sclerosis from **medial** and **intimal thickening**
  - **Hyaline Deposition** from extravazation of plasma proteins through injured epithelium

- **Morphology**
  - Hyalinized Arterioles with typical arteriolar changes in HTN seen in cardio block
  - Kidneys are normal to **small** with a leathery appearance in gross

- **Clinical**
  - Usually inconspicuous but proteinuria, decreased GFR, and an increased risk towards chronic renal failure do exist

Malignant Hypertension Nephrosclerosis

- **Definition**
  - Renal disease with typical arterial changes associated with malignant hypertension

- **Pathogenesis**
  - Extreme BP = **endothelial cell damage**, increase permeability, platelet activation, fibrin extravazation, and necrosis, all summing up into **fibrinoid necrosis**
  - Hyperplastic Changes (**onion skinning**) results from compensatory changes
  - The kidney becomes **ischemic**
  - Ischemia results in activation of the Renin-Angiotensin-Axis, activation of ANGII and an exacerbation of HTN
  - Result is a viscous cycle leading to malignant arteriosclerosis

- **Morphology**
  - **Fibrinoid Necrosis** = eosinophilic, fibrin + necrosis without inflammatory cells
  - **Onion Skinning** = concentric duplication of the basement membrane

- **Clinical**
  - Diastolic BP > 130 mmHg, renal failure, papilledema, retinopathy
  - Proteinuria, maybe hematuria, presents at onset with **preservation of renal function**
  - Chronic condition results in **total renal failure** and uremic death

Unilateral Renal Artery Stenosis

Is uncommon, but is historically significant (animal models of constricted renal arteries produced increases in blood pressure in proportion to the amount of stenosis)

Results from **cardiovascular changes** (atheromatous plaques) that lead to a **decreased RBF**, elaborating ANGII via the RAS

- These patients to very well with **ACE-I** or **ARB** and surgery is **definitive therapy**
Thrombotic Microangiopathies = HUS/TTP

- Group of overlapping clinical manifestations
  - TTP = pentad = thrombocytopenia, Microangiopathic hemolytic anemia, thrombosis,
  - HUS = TTP without the neurologic symptoms but with renal failure
- Despite being pathogenetically distinct, HUS/TTP is considered one syndrome
- Pathogenesis is either from endothelial injury and activation or from platelet aggregation
  - vWF elaboration leads to clots
  - Decreased NO or PGI2 increases vasoconstriction and permits clots
  - Denudation of the endothelium results in exposure to thrombogenetic basement membrane
- Types
  - Classic (Childhood) HUS
    - **Causes**
      - E. Coli Hamburgers (O157:H7) containing shigga-like toxin
      - Toxin causes denudation of epithelium and decreased NO synthesis
    - **Clinical**
      - Sudden onset hematemesis and melena following a flu-like prodrome
      - Oliguria/Hematuria/Hemolytic Anemia may follow
      - Managed by dialysis, acute setting resolves itself, though long term prognosis is poor
    - **Morphology**
      - Fibrinoid necrosis of lobular arteries
      - Intermesangial hemorrhage
      - Intimal Hyperplasia and Thrombosis
  - Adult HUS
    - LSE/Antiphospholipid Antibodies = HUS without immune deposition
    - Infection
    - Complication of pregnancy = uncomplicated delivery results in spontaneous renal failure a day to 3 months later.
    - Vascular Renal Diseases = Wegner’s, scleroderma, HTN
    - Chemotherapy = cyclosporine, bleomycin, cisplatin
  - Familial HUS
    - There is a defect in complement regulatory proteins
    - Results in Complement (C3) activation, thrombosis, and capillary destruction
  - Idiopathic
    - Linked to platelet aggregation ADAMTS gene
    - Its idiopathic
Other Vascular Disorders

- **Atherosclerotic Ischemic Renal Disease**
  - Occurring especially in adults Bilateral renal artery stenosis causes renal ischemia
  - HTN may actually be absent, but with bilateral stenosis, ANGII is usually elevated
  - Avoid ACE-I and ARBs since the decrease in ANGII will dilate the efferent arteriole resulting in an increased RBF but a decreased GFR = acute renal failure.

- **Atheroembolic Renal Disease**
  - Emboli from atheromatous plaques proximal to renal artery (aorta, coronary angiography)
  - Causes no problems in healthy kidneys, but infarcts lead to ARF in diseases kidneys

- **Sickle Cell Nephropathy**
  - Sickling in the vasa recta decreases concentrating ability and increases thrombosis
  - Characteristics are hematuria, dilute urine, and proteinuria

- **Diffuse Cortical Necrosis**
  - Follows malignant HTN, Obstetric Emergencies, Septic Shock, and Extensive Surgery
  - Ischemia and necrosis is limited to cortex, with white infarcts
  - Thrombosis of glomerulus and renal artery; hemorrhage may be present

Infarcts
- Kidney is and “end organ” with little collateral circulation
- Infarcts are white and wedge-shaped.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Image</th>
<th>Presentation</th>
<th>Pathophys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Nephrosclerosis</td>
<td>Hyalinized arterioles (fibrous thickening)</td>
<td>Only after years to decades of HTN</td>
<td>Medial and Intimal thickening of arterioles, compensatory response to protective vasoconstriction against HTN.</td>
</tr>
<tr>
<td>Malignant Hypertension Nephrosclerosis</td>
<td>Onion Skinning (hyperplastic changes)</td>
<td>Diastolic BP &gt; 130 + other changes (ocular) from Cardio block</td>
<td>Extreme HTN induces fibrinoid necrosis and ischemia which leads to ANG II release, increasing blood pressure (viscous circle)</td>
</tr>
<tr>
<td>Unilateral Renal Artery Stenosis</td>
<td>Usually shown on arteriogram with dilated artery proximal to stenosis</td>
<td>Other kidney compensates, treat with ACE-I or ARB</td>
<td>Medial thickening and stenosis of the larger renal artery / muscular arteries.</td>
</tr>
<tr>
<td>Bilateral Renal Artery Stenosis</td>
<td>Hypoplastic / Small kidneys on CT or X-ray. Stenosed lumen with medial thickening</td>
<td>Severe HTN, high levels of ANG II, Aldosterone, and Renin</td>
<td>Patients are reliant on ANG II to maintain their GFR (increases resistance on efferent arteriole); DO NOT GIVE ACE-I or ARB</td>
</tr>
<tr>
<td>Childhood HUS</td>
<td>Platelet-fibrin clots within glomerular capillaries</td>
<td>Children who have a flu-like prodrome with hematemesis, melena, and hematuria</td>
<td>Enterohemorrhagic E Coli (O157:H7) ingestion contains shigga-like toxin</td>
</tr>
<tr>
<td>Adult HUS</td>
<td>Caused by a variety of things</td>
<td>Hematuria + Uremia in a Syndrome that follows infection, lupus, vascular renal diseases (Wegner’s), or even a normal pregnancy</td>
<td></td>
</tr>
<tr>
<td>Atheroembolic Renal disease</td>
<td>Swollen blue feet</td>
<td>Swollen purplish feet after some sort of aortic repair or coronary catherization</td>
<td>Manipulation of atherosclerotic aorta proximal to renal arteries produces cholesterol emboli that lodge in kidneys</td>
</tr>
</tbody>
</table>
**Metabolic Acidosis** (10 Page Handout from Simon)

- **Causes**
  - **Loss of HCO₃⁻**
    - Diarrhea causes loss from the GI tract
    - Proximal Tubular Acidosis or treatment with Carbonic Anhydrase inhibitor
  - **Decreased H⁺ Excretion**
    - Occurs during early renal failure (proximal tubule and collecting ducts)
    - Renal tubular acidosis creates a electrochemical barrier resistant to excretion
      - Aldosterone inhibition
  - **Acid Loading exceeding renal handling capacity**
    - Requires a large amount of acid consumption (toxicity from Salicylates, methanol, ethylene glycol) or endogenous production (lactic acidosis, diabetic Ketoacidosis)

- **Anion Gap**
  - Useful for differentiating Metabolic Acidosis into two forms, defined by the following formula
    \[ \text{Anion Gap} = [\text{Na}] - [\text{Cl}] - [\text{HCO}_3^-] \]
    - Normal is 10-12
  - **High Anion Gap** = addition of organic acids (not H⁺) such as lactic acid or ketoacids that consume the bicarb without affecting the chloride concentration
    - Severe Renal Failure
    - Lactic Acidosis from hypoxia produces lactate
    - Ketoacidosis seen in diabetics and malnourished alcoholics
    - Poisonings such as Salicylates, methanol, and ethylene glycol
    - Remembered by the mnemonic **MUDPILES** (Methanol, Uremia, DKA, Paraldehyde, Isoniazid, Lactic, Ethanol, Salicylates)
  - **Normal Anion Gap** = addition of volatile acids (HCl) that combine with HCO₃⁻ decreasing HCO₃⁻ levels but reciprocally increasing the chloride levels, effectively leaving the anion gap unchanged
    - **Diarrhea** causes a loss of HCO₃⁻ in the stool
    - Renal Tubule Acidosis
      - **Type I = Distal Defect.** There is no loss of HCO₃⁻ but instead there is an inability to acidify the urine (intercalated cells of distal tubule cannot secrete H⁺ and make HCO₃⁻). The urine is therefore never less than 6. Urine pH > 6
      - **Type II = Proximal Defect.** The proximal tubule normally reabsorbs all the filtered bicarbonate. In *fanconi’s syndrome* the proximal tubule is bunk, and cannot resorb bicarbonate. The distal tubule has limited capacity to resorb, so bicarb is lost in the urine until a serum level low enough to be reabsorbed by the proximal tubule is reached, Urine pH < 5.5. Also associated with Multiple Myeloma.
      - **Type IV = Aldosterone Defect.** It is the most common RTA associated with hyperkalemia. It is common in diabetic nephropathy, ACE-I administration, and urinary obstruction. Things that reduce Renin-Angiotensin Axis, block the effects of ANG II, decrease renal sensitivity to ANG II or reduce aldosterone activity.

*See page 21 for breakdown of all acidosis, alkalosis, and which lab values to look at*
Metabolic Alkalosis

- **Cause**
  - Maintenance Process + Generating Process
    - Normally, an alkali load (addition of bicarb or loss of acid) is easily accommodated by the kidneys. It requires a concomitant **maintenance process** (volume depletion is most common, renal failure is another) and a **generating process** (alkali load) to induce a metabolic alkalosis

- **Types**
  - **Chloride-Responsive** (urine chloride < 10)
    - Generating Process = Vomiting, NG Suction, or Diuretic Loss of NaCl
    - Maintenance Process = Volume Depletion
    - Volume depletion causes resorption of Bicarb, release of Aldosterone (which causes hydrogen secretion), and a decreased GFR. Combine that with a loss of acid from the GI tract and a loss of fluid from diuretics, and you’ve got metabolic alkalosis
  - **Chloride-Resistant**, associated with excess mineralcorticoids (urine chloride > 20)
    - Mineralcorticoid excess either from a **primary** issue (hyperaldosteronism/Cushings) or from a **secondary** issue (renal artery stenosis cause increased Renin-Angiotensin Axis) results in increased secretion of acid
  - **Post-Hypercapneic Metabolic Acidosis**
    - COPDers are chronic CO₂ retainers. This causes a respiratory acidosis that is offset by a metabolic alkalosis (increased bicarb from the kidneys). If the doctor then hyperventilates the COPD patient in order to fix an oxygenation problem, the patient will blow off CO₂ (no more acidosis) and be left with a lot of bicarb (creating a relative alkalosis) because CO₂ changes faster than HCO₃ does.
  - **Milk-Alkali Syndrome**
    - Consuming milk and antacids (antacids as in bicarb) leads to precipitation of bicarb in the kidneys

Respiratory Acidosis and Alkalosis

- Essentially, changes in respiratory rates or airway obstruction cause changes in CO₂ levels. Changes in CO₂ levels happen faster than bicarb compensation, so you are left with only CO₂ alterations.
- **Acidosis** occurs with **hypoventilation** (central, airway obstruction COPD, neuromuscular)
- **Alkalosis** occurs with **hyperventilation** (CNS system, Pregnancy)
Path Renal Outline

Possible Derangements

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>PCO₂</th>
<th>[HCO₃⁻]</th>
<th>Compensatory Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Acidosis</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>Renal HCO₃ Reabsorption</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>Renal HCO₃ Secretion</td>
</tr>
</tbody>
</table>

Henderson-Hasselbalch Equation: pH = pKa + Log([HCO₃⁻]/(PCO₂ * 0.03))

When compensated, the pH is normal, but CO₂ and bicarb are different. When uncompensated, pH is deranged, often with only a change in either CO₂ or Bicarb. This is dependent on the Henderson-Hasselbalch equation, below. The point is that if one thing changes (HCO₃ or CO₂) the other must change in the same amount in order for the pH to remain constant. The only variables, then, are bicarb and CO₂, everything else is constant. This is what you were asked to do in physio.

\[
pH = 6.1 + \log \left( \frac{[HCO₃⁻]}{0.03 \times PCO₂} \right)
\]

When bicarb changes, pCO₂ must change the same amount in order to keep the pH constant. The opposite is true as well.

Handling Acid Base questions is harder in Path than it was in Physio. The pH, bicarb, and CO₂ point you in the right direction. Now you have to use the anion gap (serum chloride), urine chloride, potassium and urine pH to determine what disease process is going on. Then you have to know something about it.
**Path Renal Outline**

**Na and Water** (20 page handout from Simon)

- **Normal Physio**
  - Segments of the kidney:
    - PCT = Isoosmotic, tAL/TAL = Diluting, DCT = Diluting, CD = variable
  - ADH regulates whether the CD is water permeable or impermeable
    - ADH is a polypeptide that is 9 aa in length, made by the hypothalamus and stored at the **posterior pituitary**
    - **Osmotic Stimuli** @ the hypothalamus induce ADH release
    - Baroreceptors detect drops in vascular fluid volume and induce ADH release.
    - Baroreceptors can have a stronger effect under extreme stimuli, but Osmotic Receptors are more sensitive in the minute to minute changes
    - Release of ADH leads to activation of V₂ (vasopressin) receptors, cAMP and insertion of** Aquaporin Channels**

- **Problems of Urinary Dilution** (fluid retention because you cannot get rid of water)
  - **General Pathogenesis**
    - Decreased delivery of urine to diluting segments
      - Dependent on **RBF** (shock) and **GFR** (renal function)
      - If the amount filtered is less, or the amount reabsorbed in the proximal tubule is less, then there is less water to be excreted at the CD
    - Decreased Na Reabsorption
      - Ask dude
    - Increased Permeability of Collecting Ducts
      - It is supposed to be controlled by ADH, so aberrant ADH production, or oversensitivity to ADH will produce a concentrated urine
      - Alternatively, **decreased urine flow** allows for the small amount of permeability there is to act, reabsorbing the water
  - **Specific Pathologies**
    - **Volume Depletion**
      - Loss of isotonic volume (hemorrhage) causes a ↓RBF = GFR = ↑Proximal Tubule reabsorption resulting in↓delivery of everything to CD
      - Unless water is taken on (thirst via **ANG II**) there will be no change in Na concentration; if water is taken on, then there will be hyponatremia
    - **CHF / Cirrhosis / Nephrotic Syndrome**
      - All these conditions cause some sort of edema such that total body water and total body sodium are normal, but the **effective circulating volume** is low.
      - This causes non-osmolar ADH release as well as a decreased delivery of urine to diluting segments from ↓RBF and↓GFR
Path Renal Outline

- **Chronic Renal Failure**
  - If you have crap GFR because of chronic renal failure, you cannot get water out of your body
  - Leads to fluid retention and hyponatremia

- **Hypothyroidism**
  - Controversial pathogenesis, though CO mimics CHF pathogenesis

- **Adrenal Insufficiency**
  - Aldosterone is responsible for sodium reabsorption at the cost of potassium in the CD. Deficiency results in volume depletion diuresis
  - Glucocorticoids play a role in CO, so without them there is BP
  - Together they induce a non-osmolar ADH release

- **Diuretics**
  - Included in this section because they induce hyponatremia
  - Loops block Na at the TAL, Thiazides at the DCT, resulting in volume depletion and hyponatremia along with hypokalemia

- **Syndrome of Inappropriate ADH (SIADH)**
  - ADH secreting tumors, CNS abnormalities, or pulmonary disease
  - Patients release to much ADH, are therefore fluid overloaded without edema with mild or undetectable hyponatremia
    - **Clinical**
      - Hyponatremia = Hypotonicity in most cases
      - Hypotonicity results in edema (water enters the more hypertonic compartment) resulting in cerebral edema that accounts for symptoms
        - Symptoms = lethargy, agitation, anorexia, seizures, etc.
        - Treatment = isotonic saline replacement. Hypertonic Saline + Lasix is a dangerous treatment used for severe, acute hyponatremia

- **Problems of Urinary Concentration** (you cannot concentrate it so you pee it out)
  - **General Pathogenic Mechanisms**
    - Increased urine delivery
      - Opposite of problems of urinary dilution.
      - If too much fluid is delivered, reabsorption may be inadequate
      - Includes increased flow rates as well as increased volume
    - **Inhibition of Sodium Reabsorption in TAL**
      - Required for countercurrent exchange and medullary hypertonicity
      - Contributes to washout
    - **Water Reabsorption problems**
      - Too little ADH, or a failure to respond to ADH means no water reabsorption
    - **Medullary Washout**
      - Countercurrent effect may be abolished by rapid flow rates or inhibited countercurrent exchange in the Loop of Henle
Specific Pathologies

Central Diabetes Insipidus
- Abnormally low [ADH] causes diuresis requiring polydypsia
- Caused by many things, though is often idiopathic or surgical, but always originating from the **CNS / Pituitary**

Nephrogenic Diabetes Insipidous
- Normal ADH but with a↓ responsiveness of the renal tubule
- X-Linked Defect of the V₂ (vasopressin) receptor possible
- More likely to be **damage to tubules** (such as in ATN)

Osmotic Diuresis
- Substance is filtered through the glomerulus but not reabsorbed in PCT
- Obligates water to **remain in lumen** in order to balance osmoles
- Increases urine flow rates (washout) and limits reabsorption
- Associated with **Mannitol, Contrast Dye,** and **Diabetic Glycosuria**

Protein Malnutrition / Cirrhosis
- Concentration of urine relies on **urea**
- Urea is made by the liver, in response to protein metabolism

Psychogenic Polydypsia
- Abnormal thirst reflex causes consumption of aberrant volumes of fluids leading to increased fluid delivery and the inability to concentrate.
- Renal response is appropriate (getting rid of excess fluid) but may risk electrolyte disturbances

Differential Diagnosis and Treatments

**Serum Osmolarity**
- Decreased in Psychogenic Polydypsia
- Increased in Central and Nephrogenic Diabetes Insipidous

**Water Deprivation Test**
- Restrict fluids for 24 hrs, measuring BP, Vital Signs, and weight regularly
- Once urine osmolality has plateaued, give a dose of ADH
  - Urine Osmolality results in Central Diabetes Insipidus
  - No change in Psychogenic or Nephrogenic
- Dangerous because patients who are volume depleted (diabetes insipidus) can become hypovolemic rapidly with water deprivation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tests</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Central Diabetes Insipidous  | ↑ Serum Osmolality from Water Loss  
  ↓ Increased Urine Osmolality with ADH | Administration of ADH analogs                 |
| Nephrogenic Diabetes Insipidous | ↑ Serum Osmolality from Water Loss  
  – Increased Urine Osmolality with ADH | Not very good; give diuretics to get rid of salt, diet changes to restrict salt |
| Psychogenic Polydypsia       | ↓ Serum Osmolality from Water intake  
  – Increased Urine Osmolality with ADH | Restrict fluids (conscious restriction)        |
Path Renal Outline

- Clinical
  - Hyperosmolar = Hypernatremia (exception is Diabetic Ketoacidosis)
  - Symptoms are the same as for hyponatremia, but are due to water loss from cells in the CNS, not edema.
  - If you cannot concentrate your urine, you lose water through the kidneys. You can also lose water through the GI and through sweat.
  - If you cannot take the water back on, sodium is reabsorbed, but water is not, you become hypernatremic

Potassium (10 page handout from Simon)

- Extrarenal Handling
  - Dietary consumption without Extrarenal mechanisms would lead to extracellular concentrations of potassium that are rapidly fatal even after one meal
  - Certain mechanisms are activated that adjust extracellular potassium that maintain homeostasis that does not require renal handling
    - Insulin goes the uptake of glucose and potassium
    - Beta-Adrenergic Stimulation (epi) not only is additive to the glucose metabolism of insulin, but also to the cellular uptake of potassium
    - Aldosterone (apparently in addition to the renal effects) increases uptake

- Renal Handling
  - Since potassium really isn’t consumed, what comes in through the diet, must pass out through urine and feces.
  - The main action of potassium handling in the kidney occurs in the principal cells of the collecting tubules
    - Basal Na/K-ATPase brings potassium into the cell and sodium out of the cell
    - Apical Na channels allow leak into the cell, which are pumped out the basal side
    - Apical K channels allow leak into the lumen
    - Overall effect is one sodium resorbed for one potassium lost
  - Aldosterone is the driving force to improve all electrolyte channels of the principal cells
    - Increases the Apical Na+ leak channels
    - Increase the Apical K+ leak channels
    - Increases the Na/K-ATPase channels
  - Urine Flow Rate also plays a role in renal excretion
    - Higher flow rates result in increased loss in potassium = “washout effect”
    - Decrease flow rates result in decreased loss in potassium

- Hypokalemia
  - Rarely a consequence of decreased dietary intake
  - Transcellular Potassium Shifts can occur with the administration of some diuretics, or even more so with the administration or release of insulin and epinephrine
  - True Potassium Defects
    - Diarrhea. GI loss through loose stool can account for loss of both dietary and extracellular potassium, up to 80mEq/L
Path Renal Outline

- **Vomiting.** Potassium is NOT LOST in the vomitus, but dehydration from fluid loss stimulates aldosterone which causes an excess of potassium loss. The effect of increase bicarbonate creates a more negative lumen to draw K+ out (minor)
- **Diuretics** are the most common cause of hypokalemia. They increase urine flow rates, clearing more potassium. Some (loop diuretics) directly inhibit reabsorption of potassium in the thick ascending loop of henle. Finally, volume depletion can lead to aldosterone release
- **Renal Artery Stenosis** causes a decreased flow through the kidney, elevated JGA activation with Renin-Angiotensin-Aldosterone activation
  - **Effects of Hypokalemia**
    - Muscle weakness and intestinal ileus at 2.5 mEq/L or less
    - Cardiac Conductivity alterations = heart block, afib, vfib, Vtach
    - Hypokalemia potentiates side effects of digitalis
    - Metabolic alkalosis may be perpetuated by hypokalemia
  - **Treatment**
    - Give them oral potassium, but monitor so you don’t overshoot.

- **Hyperkalemia**
  - **Causes**
    - *Increased Ingestion* or *Intravenous Infusion* usually cause a transient and mild hyperkalemia (unless you are trying to kill someone with potassium)
    - *Uncontrolled Diabetics* have decreased insulin production as well as osmolar gradients that shift electrolytes out of the cell. They most often have some dilemma with renal handling from diabetic nephropathy or osmolar changes
    - *Renal Excretion Problems* is the main cause of significant hyperkalemia.
      - **Reduced GFR** results in increased potassium excretion until GFR is so low that potassium can be sufficiently secreted (aka “I need Dialysis”)
      - **Severely decreased ECF Volume** causes a reduced GFR and urine flow rates. This is not the 17 year old girl who is vomiting, but the 34 year old man lost in the desert for a week
      - ***ACE-Inhibitors cause hyperkalemia*** along with “potassium sparing diuretics” such as Spironolactone.
      - *Pseudohyperkalemia* occurs when you squeeze your muscles (depolarization results in potassium release for repolarization or RBC hemolysis releases K) and the nurse is drawing your blood while you squeeze (localized hyperkalemia)
  - **Effects of Hyperkalemia**
    - Usually asymptomatic, even at high levels (as high as 7)
    - **Peaked T waves** then **widened QRS** on ECG is ominous for fatal arrhythmias
  - **Treatment**
    - Depends on level of hyperkalemia and pathophysiology that brought it on
    - For our case, diabetics require insulin and fluids (dilution and fluid shifts)
PROSTATE

Normal and info
- Prostate weighs 20 grams and is divided into 5 zones
- Tubular glands separated by fibromuscular stroma surrounded by a capsule
- Glands are lined by 2 layers of epithelial cells
- Normal growth is controlled by Dihydrotestosterone (DHT) a metabolite of Testosterone, made via the Leydig Cells and an enzyme called 5-alpha-reductase.

Inflammation of Prostate
- Acute Bacterial Prostatitis
  - Caused by E. Coli and sometimes Staph or Enterococcus from a lower UTI (cystitis)
  - Dysuria, Fever, Chills, Perianal pain; the prostate is tender and soft
  - Prostatic Secretions show greater than 9 neutrophils per high power view
- Chronic Bacterial Prostatitis
  - Frequent bouts of UTI → frequent prostatic infection
  - Dysuria, Pelvic Discomfort and Lower Back Pain
  - Infiltrates of plasma cells, lymphocytes, and macrophages
- Nonbacterial Chronic Prostatitis
  - Most common prostatitis occurring in all age groups of sexually active men
  - Shows negative cultures, but likely to be an atypical bug (mycoplasma/ Chlamydia)
- Granulomatous Prostatitis
  - Diagnosed histologically which may be necrotizing or nonnecrotizing
  - It may mimic prostatic carcinoma clinically, grossly, and histologically
  - It is often secondary to surgical manipulation (biopsy / TURP) or stromal infiltration of prostatic fluid.

BPH = Nodular Hyperplasia
- Definition
  - Common disorder defined as enlargement of prostate due to proliferation of glandular and stroma resulting in outflow obstruction from bladder
- Pathogenesis
  - With age, testosterone decreases, estrogen increases, and DHT stays the same
    - Estrogens increase sensitivity for the DHT receptors in prostate
    - Testosterone really doesn’t play any role
    - DHT (from Leydig cells) has an increased selectivity on epithelial nuclear androgen receptors that induce glandular and stromal proliferation
Path Renal Outline

- Morphology
  - Enlargement begins in the **transitional** and **periurethral zones**
    - Causes compression and obstruction of urethra
  - Gross = **large firm** grey white-tan with narrow central urethra and potential **prostatic calculi** (stones within the prostate)
  - Histo = **glandular hyperplasia** (with a **double layer of epithelial cells**) mixed with a **hyperplastic stroma**.

- Clinical
  - Men starting in their 50s, 90% have it by the 80s, blacks > whites, 25% asymptomatic
  - Presents with nocturia, urgency, hesitancy, inability to stop/dribbling
  - Rectal exam = firm rubbery mass
  - **Complete obstruction** results in **acute urinary retention** predisposing for **bladder hypertrophy, cystitis,** and **hydrourerter / hydrenephrosis**
  - It is **not premalignant**
  - Treatment = 5-alpha-reductase (testosterone → DHT) inhibitor or surgery (older tx)

**Adenocarcinoma**

- Pathogenesis
  - Idiopathic, multifactorial, a combination of environment and genes
  - **Androgens** play a role in activation of growth signals
  - **Susceptibility mutation** of unknown tumor suppressor mapped to 1q24-25

- Predisposing Factors (all increase risk)
  - Sex at an **early age,** with **multiple partners** plus **STD**
  - Mechanical Manipulation (**vasectomy**)  
  - Diets **high in fat** which may inhibit Vitamin A absorption
  - Urban Dwelling have increased risk of contraction and death due to potential exposure
  - Cadmium is a metal associated with carcinoma of prostate
  - Since northern European descent and countries get it more often, there must be something to do with **Vitamin D or Sunlight**
  - Smoking is **not linked** despite being the #1 cancer in men

- Clinical
  - Obstruction of the urinary tract presenting like BPH
  - **Firm, Discrete Nodules** on rectal exam
  - **Metastatic Disease** (anemia, bone pain, hypercalemia)
  - **Paraneoplastic Syndromes** = DVT, DIC, Nonbacterial Thrombotic Endocarditis
  - PSA and PAP levels are elevated in both BPH and Adenocarcinoma; **% Free PSA** is elevated in BPH, low in carcinoma. PSA and PAP are used as screens
  - Begin screening for whites at 50, blacks at 40
  - **Doubling time is slow** (~2-4 years) meaning it may remain asymptomatic for a long time, with an **excellent 10 year survival rate** (depending on stage)
  - Tx = surgery, radiotherapy, hormonal manipulation (anti-DHT)
  - **Prostatic Intraepithelial Neoplasia (PIN)** is a precursor for malignancy

[Image of Adenocarcinoma with caption: Don’t mistake these single cell layered tubules for renal tubules!]

[Image of Adenocarcinoma with caption: Enormous purple nuclei surrounding tubules with concretions. This is a high grade (7-9) Adenocarcinoma]
- **Morphology**
  - Found in **peripheral zones** with only a **single layer of epithelial cells**
  - May be difficult to see on gross, but palpable on rectal exam
  - Histo shows **prominent nucleoli, blue mucin, and perineural invasion**
  - **Grading** based on the Gleason Grading system which is determined by cellular architecture while staging is determined based on invasion and metastasis.
    - Take two samples, grade them, then add the score together
    - Benign = 2 (1+1), Malignant is 10 (5+5)
  - **Staging** is dependent on capsular or metastatic involvement

<table>
<thead>
<tr>
<th>Gleason Grading System</th>
<th>10-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Very Well Differentiated</td>
</tr>
<tr>
<td>II</td>
<td>Well Differentiated</td>
</tr>
<tr>
<td>III</td>
<td>Moderately Differentiated</td>
</tr>
<tr>
<td>IV</td>
<td>Poorly Differentiated</td>
</tr>
<tr>
<td>V</td>
<td>Very Poorly Differentiated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Almost nothing (5%)</td>
</tr>
<tr>
<td>II</td>
<td>Tumor confined to prostate</td>
</tr>
<tr>
<td>III</td>
<td>Capsular Involvement or Invasion to Seminal Vesicle</td>
</tr>
<tr>
<td>IV</td>
<td>Tissue invasion and metastasis (lymph node)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th>Epithelial Layer</th>
<th>PSA/PAP</th>
<th>Feel</th>
<th>Zone</th>
<th>Androgens</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPH</td>
<td>Double Cell Layer</td>
<td>Elevated or Normal</td>
<td>Nodular, Firm, Large</td>
<td>Periurethral, Transitional</td>
<td>Elevated Estrogen Pathogenic</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Single Cell layer</td>
<td>Elevated or Normal</td>
<td>Discrete Firm Masses</td>
<td>Peripheral</td>
<td>Elevated Estrogen Protective</td>
</tr>
</tbody>
</table>

**Other Malignancies of the Urinary Tract**

- **Carcinoma** is the most common of all cancers and has some interesting variants you should just recognize by name (mucinous and endometroid)
- **Rhabdomyosarcoma** is the **most common sarcoma** across the board
- **Leiomyosarcoma** occurs most often in children less than 20
- **Urothelial Carcinoma** can occur in anywhere there is transitional epithelium
  - Renal Pelvis, Urethra, Bladder Wall
  - Associated with Schistosomiasis infection (squamous cell carcinoma)
  - Associated with smoking and old age (transitional cell carcinoma)
  - Can lead to outflow obstruction, pyleonephritis, hydronephrosis
- Babies with a mass is usually Wilms’s tumor. However, if there is **elevated VMA** they have a **neuroblastoma**. This wasn’t in anything we learned, but came up in three different Qbanks. Good bonus pearl to know in case its on Step or a Bonus Question on the exam.
Urinary Tract Obstruction

- **Definition**
  - Uhm... duh? It can be unilateral, bilateral, complete, incomplete, intrinsic to the kidney, or an extrinsic thing compressing the ureters.

- **Causes**
  - **Urinary Calculi** = Kidney Stones (usually unilateral), ureter or renal pelvis
  - **Normal Pregnancy** = the parasite/tumor (the baby) compresses the ureters
  - **Benign Prostatic Hypertrophy** = cuts off flow at the urethra (see BPH section at end)
  - **Tumors** = prostate, bladder, uterus
  - Others, less important, listed on page 1012 of Robbins

- **Pathogenesis**
  - Generation of obstruction is dependent on the type of obstruction
  - **Hydronephrosis** = dilation and atrophy of the kidney associated with decreased outflow
    - Even with complete obstruction, GFR does not suffer as the fluid is simply reabsorbed into interstitum and perirenal space = severe dilation
    - High pressures from the dilation results in renal atrophy
    - Vascular complications are reversible; the initial injury is to the tubules
  - Obstruction leads to an inflammatory reaction with subsequent fibrosis

**Morphology**
- With complete obstruction there is no GFR and mild dilation of renal pelvis
- With incomplete obstruction there is constant filtration and massive dilation
- Early morphological changes are distended calyces and pelvis; later signs are the formation of thin walled cystic pockets
- **Interstitial fibrosis** on histologic preparation is seen along with tubular necrosis

- **Clinical Course**
  - **Acute Obstruction** provokes pain from rapid dilation of area immediately proximal; stones cause colic from ureter/capsule distension, prostate causes bladder symptoms
  - **Unilateral or Incomplete Obstruction** may remain asymptomatic leading to hydronephrosis, atrophy, and loss of renal function that could otherwise have been prevented with intervention. **Ultrasoundography** is critical to identify before damage
  - **Bilateral Partial Obstruction** presents with the inability to concentrate urine, reflected by polyuria and nocturia. This results from tubular atrophy and scarring associated with tubular interstitial nephritis
  - **Complete Bilateral Obstruction** results in the inability to produce urine (anuria or oliguria). When the obstruction is removed, massive salt concentrated diuresis occurs.
Urolithiasis, Renal Calculi, Stones

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Cause</th>
<th>Opacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Oxalate</td>
<td>75%</td>
<td>Hypercalcemia= high calcium blood</td>
<td>Radio-opaque</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercalciuria = high calcium urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperoxaluria = high oxalate urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypocitriuria = low citrate urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>They just happen sometimes, too</td>
<td></td>
</tr>
<tr>
<td>Struvite (Magnesium Ammonium Phosphate)</td>
<td>15-25%</td>
<td>Infection by Urea-Splitting Bacteria such as Proteus</td>
<td>Radio-opaque</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>5-10%</td>
<td>Hyperuricosuria = high uric acid urine</td>
<td>RADIOLUCENT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperuricemia = high uric acid blood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated with Leukemia Gout</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50% No Metabolic Abnormalities</td>
<td></td>
</tr>
<tr>
<td>Cystine</td>
<td>2%</td>
<td>Genetic Diseases that prevent reabsorption of amino acids (Cystinuria)</td>
<td>RADIOLUCENT</td>
</tr>
</tbody>
</table>

- **Definition**
  - The formation of solid crystals in the GU tract, most forming in the kidney, as a result of increased concentration of particles that precipitate out

- **Causes**
  - The most important determinant is an increased urinary concentration of the stones’ constituents such that it exceeds their solubility in urine (supersaturation)
  - Acidification of the urine and Low urine flow rates may also contribute
  - Absence of inhibitors, which has a long theoretical list, must also occur, since not all patients with high stone concentrations and low urine rates get stones.

- **Types and Pathogenesis**
  - **Calcium Oxalate Stones**, made of calcium and oxalate
    - Most common type of stone, 75% incidence
    - Associated with hypercalciuria with or without hypercalcemia
      - When both are present, it is a result of hyperparathyroidism, which can be a result of progressive kidney failure (see Ca/P, Chronic Kidney)
      - Renal impairment of calcium reabsorption or a hyperabsorptive intestinal tract can lead to hypercalciuria without hypercalcemia
    - A good chunk (20%) are associated with Uric Acid Secretion
      - May occur with or without hypercalciuria
      - Involves nucleation of the crystal in the collecting ducts
    - Some (10%) are associated with hyperoxaluria
      - Primary, or genetic form is less common
      - Overabsorption from diet (enteric hyperoxaluria) occurs even in vegetarians who have a diet rich in oxalates.
    - Hypocitriuria
      - Seen in diarrhea and metabolic acidosis may also lead to calcium stones
    - 15-20% have no known metabolic derangement
**Struvite Stones**, made of Magnesium Phosphate
- Caused by **urea-splitting bacteria**, aka, an infection
  - Increased ammonia from urea degradation in the tubules causes an alakalation of the urine, favoring Magnesium Ammonium Phosphate Salts
  - Forms the **largest kidney stones**
  - **Staghorn Calici**li occupying renal pelvis are caused by infection and are Struvite

**Uric Acid Stones**
- Common in patients who have conditions predisposing to hyperuricemia, such as **gout** or any **leukemias**, forming at a **low urinary pH**
- More than half of patients with Uric Acid Stones have no metabolic derangement
  - These are **radiolucent**

**Cystine Stones**
- Formed with genetic diseases that prevent reabsorption of proteins from the lumen
  - Ex. Cystinuria (we learned about it in physio, last semester)
  - Form at low Urinary pH

- **Morphology**
  - Most occur **unilaterally** at the **renal pelvis** or the **bladder**
  - Vary in size, <5mm small, 5-7mm intermediate, >7mm large
  - They may be smooth or jagged
  - **Staghorn Calici** are large, forming off a small stone in the pelvis, growing upwards, forming a cast of the pelvis and calyces

- **Clinical Course**
  - These cause **renal colic** which is intermittent, sharp **flank pain** that may radiate to groin
  - Hematuria may be present as the stone passes and shreds the ureter
  - Large stones do not pass and stay in pelvis, causing obstruction
  - Predisposition for infection

---

This CT shows a kidney with a bright dot in the center. Off to the top right, is another bright dot. This slice happens to show the kidney and the ureter, both with “something” radio-opaque in them. Stone.

We see a **dilated tubule** with **interstitial inflammation** (giant cell) with compressed tubules. When under polarized light, you will see that there is more than calcium.
TUMORS

Benign Tumors

- Renal Papillary Adenoma
  - Small (<5cm), pale, yellow-gray, well-circumscribed nodules within the cortex
  - Ultrastructurally (EM) appear as low-grade papillary renal cell carcinoma
  - Has papillomatous structures with numerous complex folds

- Renal Fibroma or Hamartoma
  - Tiny (<2 cm) Nonmalignant, grey-white firm nodules found within the pyramids
  - Looks like they came from interstitial cells, now full of fibrosis

- Oncocytoma
  - Epithelial tumor composed of large, eosinophilic cells with benign-looking nuclei and monster nucleoli
  - EM reveals massive amounts of mitochondria
  - While benign, it can get pretty big (12cm) and cause compression syndromes
  - Tumors are yellow to brown, well-circumscribed

Malignant Tumors

- Renal Cell Carcinoma
  - Pathogenesis
    - Most cancers are idiopathic, though some familial data has given rise to an understanding of renal carcinoma genesis. Good news, you don’t have to know it
    - The aged (after 40 but especially in 60+) who smoke are at greatest risk
    - Exposure to asbestos, petroleum, heavy metals has been implicated as well
  - Type and Morphology
    - Clear Cell Carcinoma (by far the most important of the three types)
      - Caused by a mutation in the VHL gene that causes von-Hippel-Lindau disease
      - Form from proximal tubular epithelium
      - Usually Unilateral
      - Masses are yellow because of the foam-like fat cells present in the tumor
      - Margins are ill defined, though it is often contained within the renal capsule
    - Papillary Carcinoma
      - Bilateral in most cases
      - The cancer associated with dialysis-associated cystic disease
      - Tumors are often hemorrhagic and cystic
      - Cuboidal or columnar epithelium arranged in papillary pattern
    - Chromophobe
      - Eosinophilic cytoplasm, perinuclear halo, localized to vasculature
      - Grow from interstitial cells (like oncocyto)ma
      - Excellent prognosis, but occur in only 5% of renal cell carcinomas
Clinical Course
- Often asymptomatic, discovered by CT scan or MRI for a nonrenal cause
- May reach massive sizes (10cm) before symptoms set in
- Symptoms = hematuria (which is the most reliable), flank pain, and mass = “classic triad”
- 25% of tumors have metastasized prior to discovery

Paraneoplastic Syndromes are huge in Renal Cell
- Polycythemia, Hypercalcemia, Hypertension, Cushings, and Feminization

Staging is dependent on local involvement

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Kidney</td>
<td>60-80%</td>
</tr>
<tr>
<td>Stage II</td>
<td>Kidney + Fat</td>
<td>15%</td>
</tr>
<tr>
<td>Stage III</td>
<td>Kidney + Renal Vein or Lymph</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

Treatment
- Total nephrectomy is usually curative without metastasis, but partial nephrectomy to preserve renal function has been done, and has been successful

Wilm’s Tumor (Nephroblastoma)
- Common childhood malignancy with peak age of 2 years old
- Causes by a loss of a Tumor Suppressor Gene (WT-1 or WT-2) Wilm’s Tumor
- Symptoms = abdominal mass + HTN/Nausea/Heamturia
- Gross = very large, demarcated mass, most are unilateral
- Micro = embryonic glomerular and tubular structures (blastema) surrounded by mesenchymal spindle cells.
- Prognosis of a unilateral tumor is good (90% survival) because we can determine how anaplastic the tissue is
  - Those that are largely anaplastic get chemo and surgery
  - Those that are mildly anaplastic don’t get chemo and do much better

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Pathogenesis</th>
<th>Age Range</th>
<th>Pearl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Cell Carcinoma</td>
<td>VHL gene, smoking, age</td>
<td>Elderly</td>
<td>Clear Cell most common, presents with hematuria, though most are asymptomatic</td>
</tr>
<tr>
<td>Wilm’s</td>
<td>Blastema of fetal kidney, abnormal wt gene</td>
<td>Babies/Kids</td>
<td>Enormous mass in an infant; Fetal Components in child kidney</td>
</tr>
</tbody>
</table>
Classical Presentations, Buzz-words, Tip-Offs.

This section is about how a case will be presented, and the things you should look for. Obviously, you are going to have to know something more than just the diagnosis (for example, “IgA Nephropathy has granular mesangial deposits”). These are presented in no particular order.

<table>
<thead>
<tr>
<th>Presentation / Buzz Word</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young 20s + Painless Hematuria</td>
<td>IgA Nephropathy</td>
</tr>
<tr>
<td>Hemoptysis (Coughing Blood) + Hematuria (Peeing Blood) + Crescents</td>
<td>Goodpasture’s</td>
</tr>
<tr>
<td>Child or Teenager with nephrotic syndrome</td>
<td>Minimal Change</td>
</tr>
<tr>
<td>Flank pain, fever, and WBC casts</td>
<td>Pyelonephritis</td>
</tr>
<tr>
<td>Flank pain radiating to the groin, usually male</td>
<td>Kidney Stone</td>
</tr>
<tr>
<td>Huge Uprotein/UCr ratio but “trace protein” on dipstick</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Large Abdominal mass in a child</td>
<td>Wilm’s Tumor</td>
</tr>
<tr>
<td>Hematuria, Flank Pain, Palpable Mass, usually old smoker or dialysis pt</td>
<td>Renal Cell Carcinoma</td>
</tr>
<tr>
<td>RBCs without Protein on Urinalysis in an adult = tumor</td>
<td>Renal Cell or Urothelial Cell Carcinoma</td>
</tr>
<tr>
<td>Onion-skinning of vasculature, sclerosis of glomeruli</td>
<td>Malignant HTN</td>
</tr>
<tr>
<td>Child with deafness, vision abnormalities, hematuria</td>
<td>Alport’s</td>
</tr>
<tr>
<td>2-14 weeks past a cold/flu, usually in a child</td>
<td>Post-Strep GN</td>
</tr>
<tr>
<td>Sepsis, Shock, Trauma, any form of hypotension, with or without Dirty Brown Casts</td>
<td>Acute Tubular Necrosis</td>
</tr>
<tr>
<td>“Arthritic Pain,” NSAID use, especially with recent upgrade in dose</td>
<td>Pre-Renal Azotemia</td>
</tr>
<tr>
<td>Long Term abuse of NSAIDs, multiple kinds, especially acetaminophen</td>
<td>Analgesic Nephritis</td>
</tr>
<tr>
<td>African American Male with Nephrotic Syndrome</td>
<td>FSGS</td>
</tr>
<tr>
<td>Elevated PSA is usually a trap, they want you to pick Prostatic Carcinoma</td>
<td>BPH</td>
</tr>
<tr>
<td>Polycythemia (most diseases of kidney produce anemia)</td>
<td>Renal Cell Carcinoma</td>
</tr>
</tbody>
</table>

I’ve left spots to add your own. Most of the time, in the kidney at least, the picture is pretty ambiguous. This is why I started this here. If we can get you some free diagnosis/points, it makes the rest of the exam a little less staggering.