

THE KIDNEY

Check out the Nephrotic_Nephritic_Syndromes Notes for a nice summary of Renal Diseases.

CYSTIC DISEASES OF THE KIDNEY:

- **CYSTIC RENAL DYSPLASIA:** Not true dysplasia.
 - **PATHOLOGY:** Abnormal mesenchymal (rather than epithelial) tissue found in the neonatal kidney. It is found along with cysts of varying size.
 - You will see grossly dilated ureters, due to obstruction.
 - **PATHOGENESIS:** Congenital malformation, caused by obstructed urinary flow in utero. Proper urinary flow is necessary for the fetal kidney to develop properly.
 - Nephrons don't form properly, and not all glomeruli connect to their respective tubules. Blind (disconnected) tubules become cystic.
 - **CLINICAL:** Most common cause of an abdominal mass in the neonate.
 - Bad prognosis. Baby will die early, and presentation is similar to Potter's Syndrome (**oligohydramnios**).
 - Must distinguish it from a Wilms tumor. Inject a contrast-dye into large kidney to distinguish them.
 - If the dye distributes into cysts, then it is renal dysplasia. If it doesn't, then it is probably a solid Wilms tumor.
- **POLYCYSTIC KIDNEY DISEASE (PKD):**
 - **AUTOSOMAL DOMINANT PKD (ADPKD):** A very common form of PKD that does not manifest until mid-adulthood.
 - **PATHOLOGY:** Formation of very large, disparate cysts.
 - Process can involve any part of the nephron.
 - **CLINICAL:** Renal failure occurs late-onset (adult) when it occurs, but it only occurs in about 50% of cases. The kidneys can withstand an incredible number of cysts before function is compromised.
 - **SYMPTOMS:**
 - **Nocturia** is a common early symptom, from Non-Oliguric failure.
 - Pain, due to bleeding infection, or rapid cyst growth.
 - **DIAGNOSIS:** CT-Scan is the best way to diagnose. Look for enlarged kidneys, cysts, or gross asymmetry between the two kidneys.
 - **ASSOCIATED CONDITIONS**
 - **Liver Cysts** are very common, about 50% of cases.
 - **Berry Aneurysms:** 10%
 - **TREATMENT:** These patients are often otherwise healthy and are ideal candidates for **dialysis** and/or **transplantation**.
 - In transplantation, the surgeons actually leave the old kidney in place!
 - **PATHOGENESIS:** Autosomal dominant. Penetrance of the disease is 100%. If you have the gene, you're sick.
 - **AUTOSOMAL RECESSIVE PKD (ARPKD):**
 - **PATHOGENESIS:**
 - **PATHOLOGY:** The cysts uniformly arise in the **collecting ducts**, rather than the whole nephron.
 - As compared to ADPKD, the cysts are diffuse and evenly distributed.
 - **CLINICAL:** Renal failure is virtually inevitable, usually occurring in childhood, but it can occur in adulthood.
 - **ASSOCIATED CONDITION:** Associated with congenital **Hepatic Fibrosis**.
 - **ACQUIRED PKD:**
 - **PATHOGENESIS:** Happens with renal failure patients on dialysis. The *other kidney* hypertrophies in response to unilateral kidney failure -----> healthy kidney hypertrophies -----> cysts form.
 - **CLINICAL: COMPLICATIONS**
 - **Renal Cell Carcinoma** is the most common complication. Renal tumors *do not* occur in the other forms of PKD.
 - If you were seeing anemia (due to renal failure) and you all of a sudden find a rising hematocrit, then suspect a renal cell carcinoma, secreting excess erythropoietin.

- **MEDULLARY SPONGE KIDNEY:** Congenital sponge-like cysts formed in renal medulla. It does not become symptomatic unless and until patients present with renal stones late in life.
- **MEDULLARY CYSTIC DISEASE COMPLEX (Nephronophthisis):** Also presents as cysts in the medulla, but this disease progresses to renal failure.
 - **PATHOLOGY:** Cysts around the corticomedullary junction, formed from the distal parts of nephrons.
 - **CLINICAL:** Patient presents with **polyuric renal failure** -- inability to concentrate urine.
 - Polyuria -----> JGA feedback shuts down glomerular filtration (the kidney thinks its peeing a lot do it inhibits filtration) -----> renal failure, uremia.
- **SIMPLE RENAL CYSTS:** That's just what they are.

RENAL FAILURE:

- **GENERAL PROPERTIES:**
 - High serum creatinine: Creatinine >> 1.0, indicating no glomerular filtration.
 - **Azotemia:** High BUN
 - **Uremia:** High frank urea in the blood, which can lead to encephalopathy in late stage.
 - **Anemia:** Anemia can occur due to no secretion of **erythropoietin** in damaged renal cells.
- **EPIDEMIOLOGY:** Statistically, the most important causes of renal failure:
 - Autosomal Dominant PKD (high incidence)
 - **Diabetes:** due to both glomerulosclerosis and pyelonephritis.
 - Glomerulosclerosis is from Diabetic nephropathy
 - Chronic pyelonephritis results from recurrent UTI's (due to sweet urine, lost bladder motility)
 - Analgesic Nephropathy (interstitial nephritis due to phenacetin analgesics); very common.
- **ACUTE RENAL FAILURE:** Most often occurs due to trauma, shock, or acute ischemia.
- **CHRONIC RENAL FAILURE:** End-stage renal disease

NEPHROTIC SYNDROMES: Non-inflammatory nephropathies.

- **NEPHROSIS:** Clinically characterized by **proteinuria**, loss of protein in the urine, usually due to loss of negative charge, or holes, in the glomerular basement membrane. Complications:
 - **Hypoalbuminemia**
 - **Edema**, resulting from hypoalbuminemia. *Don't treat it with diuretics! It is not an inflammatory edema.*
 - **Hyperlipidemia**, resulting from compensatory synthesis of lipoproteins in liver.
 - No hypertension.
- **MINIMAL CHANGE DISEASE (Epithelial Cell Disease):** Loss of negative charge on glomerular basement membrane, leading to idiopathic proteinuria.
 - **PATHOGENESIS:** Loss of negative charge on glomerular basement membrane leads to loss of epithelial **foot-processes**, which is only visible at the EM microscopic level.
 - **PATHOLOGY:** The glomerulus appears histologically normal, but GBM appears flattened on EM.
 - Size normally is *not* a barrier to the passage of albumin through the GBM. Normally *negative charge* is the only barrier.
 - **CLINICAL:** The condition is not diagnosed until severe proteinuria (edema) occurs.
 - **TREATMENT:** Treatment with **corticosteroids** is always quite successful.
 - **PROGRESSION:** Minimal Change Disease never progresses to renal failure. If it does, then the diagnosis should be changed Focal Segmental Glomerulosclerosis.
- **FOCAL SEGMENTAL GLOMERULOSCLEROSIS:** An extension of Minimal Change Disease, with same basic pathology.
 - **PATHOGENESIS:** Usually idiopathic, simply an extension of Minimal Change Disease with a worse prognosis. But, it can be caused by HIV or heroin.
 - **HIV-Associated Glomerulosclerosis:**
 - **Heroin-Associated Glomerulosclerosis:**
 - **PATHOLOGY:** In addition to loss of negative charge and flattening of epithelial foot-processes, we have:
 - **Glomerular Sclerosis:** Some Glomeruli are fibrotic, sclerosed, or totally obliterated. But, the damage is sparse:
 - **"FOCAL":** Only some nephrons are affected, whereas others are spared.
 - **"SEGMENTAL":** Only part of the glomerulus is affected. Half of the glomerulus may appear normal.
 - **Hyalinosis:** PAS-Positive material will appear in the affected glomeruli.

- **DIABETIC GLOMERULOSCLEROSIS (Kimmelstiel-Wilson Disease):** Negative charge on GBM can be lost in Diabetes, too.
 - **PATHOGENESIS:**
 - **Proteinuria:** Glycosylation of GBM proteins causes loss of charge on GBM -----> proteinuria.
 - **Progressive Renal Failure (lost filtration):**
 - **Mesangial Matrix** (kidney macrophages) builds up, and mesangial cells do not turnover.
 - **Microangiopathy:** Capillary lumen become compromised as a result of mesangial cell buildup. Also, stuff builds up in the lumen itself.
 - **Hyaline Arteriosclerosis:** Uniquely, both the afferent and efferent arterioles can become atherosclerotic in Diabetes.
 - **PATHOLOGY:**
 - Thickened basement membrane.
 - **CLINICAL:** Proteinuria occurs before renal failure. Hematuria is rarely or never seen.
- **RENAL AMYLOIDOSIS:** Accumulation of amyloid (crud) in the glomerular filter.
 - **PATHOGENESIS:** Amyloid builds up in capillary lumen, accumulates in GBM, and compromises filtration.
 - **CLINICAL:** Will see proteinuria early on, progressing to renal failure later.
 - **DIAGNOSIS:**
 - **Congo-Red Stain** will illuminate the amyloid and confirm Amyloidosis.
- **MEMBRANOUS NEPHROPATHY (Membranous Glomerulonephritis):** It's commonly called glomerulonephritis, but it is non-inflammatory.
 - **PATHOGENESIS:** **Immune Complexes** accumulate in the glomerular basement membrane -----> nephrosis and proteinuria. Ag-Ab complexes can come from multiple sources:
 - **Idiopathic (Idiopathic Membranous Nephropathy)**
 - **Endogenous Antigens:** **Tumor antigens** (association with **Colon Cancer**), lupus nephritis (dsDNA antigen).
 - **Exogenous Antigens:** **Hepatitis-B** is a well-established viral antigen. Also certain drugs.
 - **PATHOLOGY:** The disease is classified as non-inflammatory, because there is no cellular proliferation, of mesangial cells or GBM epithelial cells.
 - **Sub-epithelial humps:** Immune-complexes create little spikes in the basement membrane, outpocketings of GBM.
 - **Complement fixation** does occur.
 - **CLINICAL:** Clinical course ranges from complete remission, to recurring proteinuria, to renal failure.
- **NON-INFLAMMATORY HEMATURIAS:** Only two non-inflammatory conditions show any hematuria in the symptoms:
 - **ALPORT SYNDROME (HEREDITARY NEPHRITIS):**
 - **PATHOGENESIS:** Structural defect in **Type-IV Collagen**, leading to faulty glomerular basement membranes.
 - Weak basement membranes -----> capillaries leak -----> hematurias.
 - **CLINICAL:** **Hematuria** is common. Patient may also have auditory and ocular defects. Death from renal failure by age 40.
 - **THIN BASEMENT MEMBRANE DISEASE (BENIGN FAMILIAL HEMATURIA):** Idiopathic reduced thickness of basement membrane -----> recurrent hematuria.
 - **SYMPTOMS:** Patients will have recurrent hematuria in childhood or as young adults. They do not progress to renal failure.

NEPHRITIC SYNDROMES:

- **NEPHRITIS:** Inflammatory disease of the glomerulus. General symptoms:
 - **Hematuria**
 - **Oliguria.** Inflammation and edema lead to impaired filtration.
 - **Proteinuria**
 - **Hypertension** results from impaired filtration. Note that there is no hypertension in the Nephrotic Syndrome.
- **DIFFUSE GLOMERULONEPHRITIS:** Glomerulonephritis caused by general immune-mediated mechanisms (cell-mediated immunity and inflammation).
 - **ACUTE (POST-INFECTIOUS) GLOMERULONEPHRITIS:**

- **PATHOGENESIS:** The glomerulonephritis is not caused by immune complexes themselves, although immune complexes are present. The disease-process is **cell-mediated**, caused by inflammatory cells.
 - ***Streptococcus Pyogenes*** is the classical organism that results in post-infectious glomerulonephritis.
 - **Hepatitis-C (HCV)** can also cause it.
 - **PATHOLOGY:**
 - Sub-epithelial, sub-endothelial, and mesangial deposits of immune complexes.
 - Inflammatory cells found within the glomeruli will release hydrolytic enzymes leading to rupture of capillaries and hematuria.
 - Variable deposition of immune complexes in GBM
 - **CLINICAL: Hematuria** is presenting symptom, along with flank pain.
 - **DIAGNOSIS:** Glomerulonephritis can be distinguished by other hematuria-presenting disease (prostatitis, cystitis, UTI), by the presence of **red-cell casts** in the urine.
 - By definition, the acute disease regresses by itself, leaving no permanent damage.
 - **MESANGIAL PROLIFERATIVE GLOMERULONEPHRITIS:** Not a distinct disease entity, but rather a morphological / pathological designation.
 - **PATHOLOGY:** An extension of glomerulonephritis, where mesangial cells proliferate in response to the inflammation.
 - **Mesangial Cells:** Resident macrophages in the kidney. They both contribute to and respond to glomerular inflammation.
 - **Normal Functions:**
 - They contract to open and close the capillary lumens of the glomerulus.
 - They serve as phagocytes and APC's, and have the same surface-markers as macrophages.
 - **CLINICAL:** This can be chronic, going on for years without progressing to renal failure.
 - **MEMBRANOUS PROLIFERATIVE GLOMERULONEPHRITIS:** Not a disease entity, but rather a morphological designation.
 - **PATHOGENESIS:**
 - Immune deposits get under the endothelium, and inflammatory cells proliferate and cause the endothelial layer to swell.
 - Endothelial cells synthesize **more BM** in response -----> thickened BM on top of the edema -----> lost filtration.
 - **PATHOLOGY:** Severe extension of glomerulonephritis, where both mesangial cells and capillary endothelial cells proliferate in response to glomerular inflammation.
 - Basement membrane thickening
 - Prominent **hypercellularity** of glomerulus
 - Mesangial cell proliferation.
 - Capillary lumen can become occluded by membrane and mesangial proliferation -----> renal failure.
 - **CLINICAL:** Patients with this severe of disease progress to renal failure regardless of treatment.
 - **FOCAL GLOMERULONEPHRITIS:** Glomerulonephritis caused by specific etiologies and disease processes.
 - **SLE NEPHRITIS:** Renal disease (Nephrosis) caused by Lupus ranges from mild to severe.
 - **PATHOLOGY:** Anti-dsDNA immune-complex deposition in many tissues.
 - **Hematoxylin bodies** are light microscopic entities that are considered pathognomonic for Lupus.
 - **CLINICAL:** As classified by WHO, five classes of renal disease in SLE:
 - **CLASS I:** Histologically normal, but immune complexes would still be found on EM.
 - **CLASS II:** Purely mesangial. Immune complexes confined to mesangial areas.
 - **CLASS III:** Focal and segmental glomerulosclerosis. Lesions involves capillaries.
 - By definition, less than 50% of glomeruli are involved.
 - **CLASS IV: Diffuse proliferative glomerulonephritis.** The worst category. More than 50% of glomeruli involved, with rapidly worsening course.
 - **CLASS V: Diffuse Membranous Nephropathy.** Carries a good prognosis. Non-inflammatory Nephrotic Syndrome, with appearance similar to that of Membranous Nephropathy.
 - Thick **wire loop capillaries** are the characteristic finding of SLE nephropathy Type V.
 - **BERGER DISEASE (IgA NEPHROPATHY):**

- **EPIDEMIOLOGY:** Men, peak age at 30. Predominant in SE Asia. Also seen in U.S.
- **PATHOGENESIS:** Unknown pathogenesis. Must have genetic predisposition, and it is associated with liver disease.
- **PATHOLOGY:** Mild inflammation, IgA deposits in basement membrane. Inflammation is usually focal and segmental.
 - Inflammation is restricted to mesangium, hence it would be classified as a **Mesangioproliferative Glomerulonephritis.**
- **CLINICAL:** Patient tends to get recurrent bouts of hematuria, even after a mild infection like a cold. Anything that kicks up the levels of IgA will result in hematuria.
 - **PROGNOSIS** is variable. 20% develop renal failure within 40 years.
- **HENOCH-SCHONLEIN PURPURA:** Pathogenesis is identical to IgA Nephropathy *in the kidney*, but systemic manifestations differ.
 - **CLINICAL: SYSTEMIC MANIFESTATIONS**
 - Purpura of lower extremities
 - Polyarthralgia
 - Colicky abdominal pain, and bloody stools.
- **BACTERIAL ENDOCARDITIS:** Glomerulonephritis is a complication of subacute bacterial endocarditis, of *Staph Aureus* or *Strep Pyogenes* origin. Clinical severity is variable.
- **CRESCENTIC GLOMERULONEPHRITIS:** Morphological term for very severe glomerulonephritis.
 - **PATHOLOGY:** Crescents are formed as a regenerative mechanism, when whole glomeruli are destroyed and capillaries are ruptured.
 - **PATHOGENESIS:** May be found occurring with several disease entities:
 - **Idiopathic: Pauci-Immune Glomerulonephritis**
 - **Wegener's Granulomatosis:** Anti-Neutrophilic Cytoplasmic Antibodies (ANCA) will be found.
 - Goodpasture's Syndrome
 - **GOODPASTURE SYNDROME (Anti Glomerular Basement Membrane Antibody Disease):**
 - **PATHOGENESIS:** Auto-antibodies against the glomerular basement membrane (Type-IV collagen). Technically, it is called "Goodpasture Syndrome" when both the lungs and kidney is involved.
 - **CLINICAL:** Severe, crescentic glomerulonephritis.

TUBULOINTERSTITIAL DISEASES:

- **PYELONEPHRITIS:**
 - **PATHOGENESIS:** Several factors predispose to an ascending infection of urinary tract.
 - **Increased Residual Urine:** BPH, urinary obstruction, lost urinary motility due to Diabetes, all make it so that the bladder doesn't completely empty on micturition. The remaining urine collect bacteria and can seed infection.
 - **Bladder Reflux:** Abnormally short, perpendicular entrance of the ureter into the bladder wall.
 - **NORMAL:** Ureter enters at an elongated, oblique angle. *Pressure of micturition closes off the ureteral entrance*, preventing backflow of urine.
 - **SHORT INTRAVESICAL URETER:** Ureter entrance is perpendicular. Pressure of micturition tends to make urine reflux back into the ureters, causing infection.
 - **Interstitial Infection:** Bacteria tend to infect the **upper and lower poles** of the kidney, because that is where the renal papillae are *compound*, flattened, and therefore receptive to infection by bacteria.
 - Renal Papillae in the center of the kidney tend to resist infection, due to shape of papillae.
 - **PATHOLOGY:** Acute, pyogenic (PMN) inflammation of renal pelvis and tubules.
 - **CLINICAL: SYMPTOMS**
 - **Polyuria**, due to inability to concentrate urine.
 - Flank pain, costovertebral angle tenderness
 - **Hematuria**
 - **Leukocyte Casts** in urine indicates that the infection has ascended to the tubules, rather than just remaining in the lower urinary tract.
 - **CHRONIC PYELONEPHRITIS:** Longstanding pyelonephritis leads to **end-stage kidney**, a shrunken, fibrotic kidney that cannot maintain renal function.
- **ACUTE TUBULAR NECROSIS (ATN):** Acute damage to the tubules, from drugs (hypersensitivity), chemical toxicity, or ischemia.

- **PATHOGENESIS:** *ATN is not an inflammatory process*, but is rather due to ischemia.
 - **Prerenal:** Fall in renal blood flow, from hypotension or shock.
 - **Intrarenal:** Toxic injury to any part of the kidney nephrons, from glomerulus to collecting ducts.
 - **Postrenal:** Due to urinary obstruction. To cause ATN, it must be a complete obstruction, i.e. involving both ureters or common urinary outflow.
- **ISCHEMIC ATN:** Coagulation necrosis of renal tubules due to impaired blood flow or impaired filtration.
- **TOXIC ATN:**
 - **PATHOGENESIS:**
 - **Cisplatin** = Chemotherapeutic drug is directly nephrotoxic.
 - Heavy metals, such as Mercury or Lead
 - Organic solvents
 - **PATHOLOGY:** Characteristic properties
 - "Distalization" of proximal tubules; loss of brush-border.
 - Single-cell necrosis of disparate cells
 - Granular casts
- **DRUG-INDUCED (ALLERGIC) ACUTE INTERSTITIAL NEPHRITIS:** Dose-independent, immune-mediated hypersensitivity to a drug.
 - **PATHOGENESIS:** This is an inflammatory process, as opposed to ATN.
 - Lots of drugs can cause it, particularly NSAID's, **sulfonamides**, penicillins
 - **ANALGESIC NEPHROPATHY:** Chronic tubulointerstitial disease caused by analgesic drugs containing **phenacetin**.
 - **CLINICAL:** Common occurrence, and patients are at risk for developing **Renal Cell Carcinoma**.
- **MULTIPLE MYELOMA (Light-Chain Cast Nephropathy):** In Multiple Myeloma, IgG light chains can get filtered and form casts in the renal tubules.
- **URATE NEPHROPATHY:** Renal disease caused by deposition of urate crystals in renal tubules.
 - **PATHOGENESIS:** Anything causing increased Uric Acid in the blood.
 - Gout
 - Chemotherapy -----> higher DNA cell turnover rate -----> hyperuricemia
 - Leukemia and polycythemia similarly lead to hyperuricemia due to increased cell turnover rate.

RENAL VASCULAR DISEASES:

- **BENIGN NEPHROSCLEROSIS:** It is not always benign and can lead to end-stage renal disease.
 - **PATHOGENESIS:** **Renal Artery Atherosclerosis** is the most common cause.
 - Renal Artery Atherosclerosis -----> tubular injury due to ischemia.
 - **PATHOLOGY:** Ischemia leads to tubular necrosis and fibrosis. Affected kidney is small and fibrotic.
 - It may happen that the other (non-affected) kidney is smaller. This can happen when the Renin-Angiotensin system kicks in to compensate for the ischemic kidney. Then, the *other* kidney can't handle the increased load and becomes necrotic.
 - **HYPERTENSIVE RENAL DISEASE:** Benign nephrosclerosis occurring in conjunction with hypertension.
- **MALIGNANT NEPHROSCLEROSIS (HYPERTENSION):** The renal arterial changes occurring with Malignant Hypertension.
 - **PATHOGENESIS:** Diastolic blood pressure is at or above 125 usually.
 - **PATHOLOGY:**
 - **Fibrinoid necrosis** of the renal arterioles and the glomeruli.
 - **CLINICAL:** Hematuria and Proteinuria. Retinal changes, papilledema, headache, possible cerebral aneurysm are co-findings.
- **RENAL VASCULITIS:** Renal vascular damage due to any of a number of vasculitides: Polyarteritis Nodosa, Wegener's Granulomatosis, Hypersensitivity Vasculitis.
- **THROMBOTIC MICROANGIOPATHY:** Presence of thrombi in the renal vasculature.
 - **HEMOLYTIC UREMIC SYNDROME (HUS):** *E.Coli* bad strains. Symptom Cluster:
 - Acute Renal Failure
 - Thrombocytopenia
 - Hemolytic Anemia
 - **THROMBOTIC THROMBOCYTOPENIC PURPURA:** Similar to HUS, but more severe and with a worse prognosis.
 - **General Properties:**
 - It occurs in older people

- The kidney is involved to a lesser extent than in HUS
 - It affects many organs
- **SCLERODERMA:**
- **RENOVASCULAR HYPERTENSION:** Hypertension caused by renal vascular stenosis -----> increased renin. Treatable by impeding the Renin-Angiotensin system, or by fixing the stenotic vessel(s).
- **BILATERAL CORTICAL NECROSIS:**

UROLITHIASIS (RENAL STONES):

- **PATHOGENESIS:** More common in men than in women. Multiple causes:
 - **Calcium Stones:** most common. Can occur from hypercalcemia which leads to hypercalcuria. There is also **idiopathic hypercalcuria** in which high urine calcium occurs without hypercalcemia.
 - **Magnesium-Ammonium Phosphate:** Can result from infection with urease(+) bacteria -----> alkaline urine -----> renal stones.
 - **Urate Stones:** Hyperuricemia -----> renal stones. Occur in 25% of patients with Gout.
- **CLINICAL:** Stones may be asymptomatic, or can lead to severe hydronephrosis and pyelonephritis.
 - **Renal Colic:** Colicky (waxing and waning), excruciating flank pain of renal stones.
 - **HYDRONEPHROSIS** is the result of renal stones. Dilation of renal pelvis and calyces, and flattening of renal papillae.

RENAL CANCERS:

- **NEPHROBLASTOMA (WILMS TUMOR):** Malignant, mixed tumor of young children, composed of mixed mesenchymal and epithelial tumor cells.
 - **PATHOGENESIS:** **Wilms Tumor (WT) Gene** is a Tumor-Suppressor gene, deleted in the case of Wilms Tumor.
 - **PATHOLOGY:** Tumor contains three different elements:
 - Metanephric blastema
 - Immature epithelial elements.
 - Immature mesenchymal tissue (stroma)
 - **CLINICAL:** Child presents with large abdominal mass. Treat with chemotherapy and surgical resection. Survival rate is good for young (< 2 yrs) children.
- **RENAL CELL CARCINOMA:** Malignant tumor of renal tubular epithelial cells.
 - **PATHOGENESIS:**
 - **RISK FACTORS**
 - Cigarette smoking
 - Obesity, particularly in women.
 - **ASSOCIATED CONDITIONS:**
 - **Analgesic Nephropathy**
 - **Von-Hippel Lindau Disease**
 - **PATHOLOGY:** Uniform renal cells displaying clear cytoplasm. Yellow fleshy tumor on gross.
 - **CLINICAL:** Metastases is common. Tumor cells may become secretory.
 - **SYMPTOMS:** Hematuria, flank pain, palpable mass
 - Excessive erythropoietin -----> **Polycythemia**
 - **Paraneoplastic Syndromes** are common.

URINARY TRACT

DEVELOPMENT:

- **KIDNEY:**
 - **Mesonephric Duct:** Forms the ureter and Male GU tract.

- **Ampullary Bud** comes off the duct at four weeks. It induces the surrounding mesenchyme to form the **metanephric blastema**, which ultimately will form the kidney.
 - **INVERTED**: The mesonephric duct rotates during development, such that the superior part winds up being inferior, and vice-versa
 - **Superior Portion**: Forms the inferior Vas Deferens and Ejaculatory Ducts.
 - **Inferior Portion**: Forms the superior Vas Deferens and Ureter.
 - The kidney later migrates from the pelvis to the retroperitoneum.
 - **BLADDER: Urogenital Sinus** is divided into two portions, to become the rectum and the bladder.
 - **Urachus**: The former umbilical artery normally closes near the superior part of the UG sinus. Normally it attaches onto the superior anterior part of the bladder.
 - **Prostatic Epithelial Buds** form from invaginations of the epithelia around the UG sinus.
 - **Cloacal Membrane**: It induces the formation of the muscles of the anterior wall of the abdomen and the anterior bladder.
 - **CONGENITAL ANOMALIES**:
 - **PERSISTENT URACHUS**: Occurs when the umbilical artery fails to close.
 - Urine may flow directly out of the umbilicus, but this is very rare.
 - Urachus may be closed at one or both ends, forming a urine-filled **urachal cyst**.
 - **Urachal Adenocarcinoma** can develop as a complication. This bladder tumor tends to be on the dome of the bladder, instead of the lateral and posterior wall, like most other tumors.
 - **EXSTROPHY of BLADDER**: Improper formation of the **cloacal membrane**, leading to absence of anterior abdominal wall and anterior part of bladder.
 - Posterior wall of bladder is exposed to environment -----> chronic inflammation and squamous metaplasia -----> increased risk of squamous or adenocarcinoma of bladder.
 - **SYMPTOM: Epispadia** of penis usually is also found.
 - **EAGLE-BARRETT (PRUNE BELLY) SYNDROME**: The Eagle-Barrett syndrome is a relatively rare condition in which there is failure of normal development of the abdominal muscles and the smooth muscle of the ureters and bladder.
 - **SYMPTOMS**:
 - **Bilateral cryptorchidism**
 - Talipes equinovarus (club feet) and hip dislocation
 - Ureteral reflux -----> advanced hydroureteronephrosis is present.
 - **AGENESIS of the URETER**: The mesonephric duct does not form the metanephric bud. It *invariably results in agenesis of the kidney* too.
 - **URETERAL DUPLICATION**: About 0.8% of population, based on autopsy studies.
 - **Biphid Ureters**: Two calyceal-systems give rise to two separate ureters, which then fuse before entering bladder.
 - **Duplex Ureters**: The two ureters don't merge, so one of them is in the wrong place.
 - **ECTOPIC URETER**: The one that is misplaced may go into ejaculatory duct, vas deferens etc. It must be surgically removed.
 - **URETERAL SEAL**: Diverticulum or herniation around the ureter. It is common in ectopic ureter and often gets obstructed.
 - **UTEROPELVIC JUNCTION OBSTRUCTION**: *This is the most common cause of hydronephrosis in infants.*
 - 75% of cases: Usually a congenital deficiency of smooth muscle. Surgically treatable.
 - 25% of cases: Kidney malrotation -----> ureter obstructed by blood vessels.
 - **DIVERTICULUM of the RENAL CALYX**: Uncommon and asymptomatic. Cystic dilatation of the single calyx of the kidney.
 - **CONGENITAL MEGAURETER**: Congenital hydronephrosis. Catch-all term for massive dilatation of the ureter.
 - Dysplastic Ureter: Deficiency of myosin in ureteral smooth muscle -----> absent peristalsis and resultant dilatation of both ureters.
 - **URETERAL REFLUX**: The **trigone** is the area surrounding the **ureterocystic junction**, the entrance of the ureters into the bladder. When it contracts, it should prevent reflux of urine into the ureters.
 - **MUSCLE ARRANGEMENT**: Ureters have helical, peristaltic muscle, while bladder wall is longitudinal muscle.
 - **Waldeyer's Sheath** is another investment of muscle surrounding the ureteral opening. When it contracts, it prevents reflux of urine through the ureters.

- Long-term catheterization -----> weakening of the Trigone Muscle -----> ureteral reflux can occur.
- **MALPOSITIONED URETERS:** Ureters that insert onto the bladder at too perpendicular of an angle.
 - The normal bladder looks like a volcanic cone, while the bladder with malpositioned ureters looks more bowl-shaped (like a stadium).
- **Golf-Hole appearance:** On cystoscopy, this indicates both a malpositioned ureter and a weakened trigone. This leads to the worst case of ureteral reflux.

INFLAMMATORY DISORDERS:

- **FIBROEPITHELIAL POLYPS:** Papillary projections, lined with transitional epithelium, with fibrovascular core.
 - **EPIDEMIOLOGY:** Occurs in young people.
- **CYSTITIS:** Occurs in women because of short urethra.
 - **PATHOGENESIS:** Various causes
 - Urinary stones denude epithelium and expose the basement membrane, allowing bacteria to attach and predisposing to cystitis.
 - Bladder outlet obstruction, as in BPH.
 - Chemotherapy
 - Indwelling catheters
 - **Adenovirus** may cause cystitis in children, but viral cystitis is rare in adults.
 - **BUGS:**
 - Gram-negatives: *E. Coli*, *Proteus*, *Pseudomonas*, *Klebsiella*
 - Gram-positives: *Staph Saprophyticus*, Enterococci.
 - **POLYPOID CYSTITIS:** Polypoid lesions reflecting severe submucosal edema. Associated with indwelling catheters.
 - They usually go away after removal of the catheter.
 - **EOSINOPHILIC CYSTITIS:** Can occur in three situations:
 - Secondary to an allergic response in GI tract or peripheral eosinophilia (rare)
 - Secondary to a **transurethral resection**.
 - Adjacent to, and in response to, an **invasive carcinoma**. Always consider an invasive carcinoma when you see eosinophilic cystitis!
 - **CHRONIC INTERSTITIAL CYSTITIS (HUNNER ULCER):** Middle-aged women.
 - **PATHOLOGY:** Transmural, aseptic inflammation of bladder.
 - Urine cultures come back negative -- no bugs causing the inflammation.
 - Linear cracks in mucosa.
 - **Ulcer:** Bladder epithelium becomes denuded and can ulcerate. This can be treated with sulfa drugs.
 - **Fibrosis** prevents normal expansion of bladder. Cannot be treated.
 - **TREATMENT:** Give sulfa drugs, which aids in reepithelialization of bladder. Theory is that they are unable to sulfonate the GAG's and glycoproteins on the epithelium, hence these drugs help.
 - The treatment allows reepithelialization (heals the ulcer), but it does not stop the fibrosis.
 - **MALAKOPLAKIA:** Occurs with chronic cystitis.
 - **PATHOLOGY:** Looks like a chronic granulomatous response with no Giant Cells.
 - In bladder, grossly looks like a white or yellow, indurated lesion.
 - **Michaelis-Guttman Bodies:** PAS-Positive, calcified inclusions inside macrophages. They are lysosomes containing bacteria fragments.
 - They stain positive for iron, PAS, and calcium.
 - It usually occurs in the bladder, but can occur anywhere else too, especially in the UG tract.
 - **IATROGENIC CYSTITIS:** Induced by radiation or chemotherapy. Also known as **hemorrhagic cystitis**.
 - **Cyclophosphamide** shows *idiosyncratic* reaction (not dose-dependant) with the bladder in some people.

- **PATHOLOGY:** Edema, congestion, hemorrhage within four hours of administration of drug.
- **Radiation Cystitis:** Edema, vacuolized cytoplasm, fibrosis, nuclear abnormalities.

OBSTRUCTION: Urinary obstruction can occur at the level of renal pelvis, ureter, ureterovesical junction, urinary bladder or the urethra. Such an obstruction may cause hydronephrosis, hydroureter and predispose to urinary infections.

- **PATHOGENESIS:** Obstructions can be congenital, due to developmental anomalies or acquired; bilateral or unilateral.
 - **EXTRINSIC:** The ureter is compressed from outside
 - Pelvic tumors
 - Pregnancy
 - Retroperitoneal fibrosis
 - **BPH:** common.
 - **INTRINSIC:**
 - Ureteric tumors
 - **Urinary stones:** common
 - Blood clots
 - Detached renal papillae separated from the rest of the kidney by papillary necrosis.
 - **Urethral strictures** secondary to urethritis.

BENIGN LESIONS:

- **BRUNN LESIONS:**
 - **BRUNN BUDDS:** Invagination of surface epithelium into the lamina propria.
 - **BRUNN NESTS:** Invagination within the lamina propria. More progressed Brunn's Bud.
 - **CYSTITIS CYSTICA:** Results when Brunn's Nest closes over on itself, forming a cyst.
- **METAPLASIA:**
 - **CYSTITIS GLANDULARIS:** Cystitis Cystica that has undergone metaplasia to form glandular tissue. Differs from Cystitis Cystica only in the nature of the epithelia.
 - **COLONIC METAPLASIA:** Bladder glands look like mucinous glands. Occurs in paraplegics, and it leads to higher risk for adenocarcinoma.
 - **SQUAMOUS METAPLASIA:** It happens with *Schistosoma Haematobium* infection, and it can lead to Squamous Cell Carcinoma.
 - **NEPHROGENIC METAPLASIA:** Makes the bladder glands look like renal tubules.
 - **PATHOGENESIS:** Occurs after surgeries, and is probably a result of healing process.
 - **PATHOLOGY:** Cuboidal epithelium, with normal urothelium on top.
- **INVERTED PAPILLOMA:** Found near the trigone.
 - **PATHOLOGY:** In the polyp, transitional cell form back-to-back serpent-like glands. It looks like it would be cancerous, except they are lacking the thick epithelium (more than 8 cells thick) and fibrovascular stalks of cancerous papillomas.
- **BLADDER DIVERTICULUM:** Outpocketings of bladder can result from increased cystic pressure, in elderly men with BPH.
 - **Complication =** urinary stones can develop in the diverticulum.

MISCELLANEOUS URINARY DEFINITIONS (MUD):

- **Calculi:** A simple stone. Urinary calculi can occur in the renal collecting system, ureters or urinary bladder. These stones are composed of calcium oxalate, calcium phosphate, ammonium magnesium sulfate, urate crystals or cysteine.
- **Neurogenic Bladder:** An abnormally functioning bladder that has lost its autonomic innervation usually following spinal cord injury.

- **Enuresis:** Bed wetting. It is physiologic during the first 2 or 3 years of life. It may be functional or secondary to delayed neuromuscular maturation of the ureterovesical component, but it may present as a symptom of organic disease (e.g., infection, distal urethral stenosis in girls, posterior urethral valves in boys, neurogenic bladder).
- **Incontinence:** The patient may lose urine without warning; this may be a constant or periodic symptom. The more obvious causes exstrophy of the bladder, epispadias, vesicovaginal fistula, and ectopic ureteral orifice. Injury to the urethral smooth muscle sphincters may occur during prostatectomy or childbirth.
- **Filariasis:** An infection with *Wuchereria bancrofti* a threadlike nematode about 0.5 cm or more in length that lives in the human lymphatics. The patient suffers recurrent lymphadenitis and lymphangitis with fever and malaise. Not infrequently, inflammation of the epididymis, testis, scrotum, and spermatic cord occurs. Varying degrees of painless elephantiasis of the scrotum and extremities develop as obstruction to lymphatics progresses.
- **Nocturia:** Urination at night. Nocturia may be a symptom of renal disease related to a decrease in the functioning renal parenchyma with loss of concentrating power. Nocturia can occur in the absence of disease in persons who drink excessive amounts of fluid in the late evening. Coffee and alcoholic beverages, because of their specific diuretic effect, often produce nocturia if consumed just before bedtime.
- **PNEUMATURIA:** The passage of gas in the urine strongly suggests a fistula between the urinary tract and the bowel.
 - **PATHOGENESIS:**
 - **Vesico-enteric Fistulas:** Carcinoma of the sigmoid colon, diverticulitis with abscess formation, regional enteritis, and trauma cause most vesical fistulas.
 - **Urethro-enteric Fistulas:** Congenital anomalies account for most urethroenteric fistulas.

URINARY CANCERS:

- **TRANSITIONAL-CELL CARCINOMA of URETER:** 90% of ureter tumors are transitional cell carcinomas.
 - **EPIDEMIOLOGY:** Tend to occur in 6th to 7th decade.
 - Squamous Cell and adenocarcinomas are rare in ureter, but carry a worse prognosis when found.
- **TRANSITIONAL CELL CARCINOMA of BLADDER:**
 - **EPIDEMIOLOGY:** Predominantly a disease of white males.
 - 4th most common cancer in men, and 8th most common in women. 10% of all cancers.
 - **PATHOGENESIS:**
 - **Smoking** by itself can account for 50% of bladder cancers.
 - **Arylamines: 2-naphthylamine and 4-aminobiphenyl** are two arylamines, known to be carcinogenic, which are found in cigarette smoke.
 - **beta-Glucuronidases** in the bladder cleave previously conjugated arylamines, making them once again toxic when they hit the bladder. This mechanism explains why arylamine toxicity is specific to the bladder.
 - **Saccharin** has been shown to cause bladder cancer in rats when fed large doses.
 - **Occupational Hazard:** Rubber workers, leather workers, chemical workers, textile workers, painters, have all been associated with increased risk.
 - **Phenacetin:** Analgesic. Abuse after 10 or 20 years can lead to bladder cancer.
 - **Free Radicals:** Overall, free radicals seem to often play a role. They can attack deoxyguanosine and deoxyadenosine, causing point mutations in **ras** and **myc** oncogenes.
 - **THREE STAGES or SUBTYPES:**
 - **TRANSITIONAL CELL PAPILLOMA:** Low Grade *superficial* tumor. 80% of transitional-cell tumors.
 - **CLINICAL:** Although this is a low-grade tumor, 80% of patients will have a recurrence of another tumor in the future.
 - Only 20-30% of these patients will ultimately progress to invasive cancer.
 - **PATHOGENESIS:** Genetic defect on **chromosome 9**.
 - **PATHOLOGY:** This tumor may be classified as malignant or benign, depending on who you ask.
 - **TRANSITIONAL CELL CARCINOMA IN SITU:** Intermediate grade carcinoma. Flat lesion traversing the mucosa.
 - **CLINICAL:** 80% of these patients will ultimately progress to invasive cancer.

- **PATHOGENESIS:** Genetic defect in **P53 gene**, which is a different carcinogenesis than the papillary carcinoma above.
 - **PATHOLOGY:** Definitely malignant. The disease is diagnosed based on histology. The bladder wall isn't any thicker, but typical anaplasia is found.
 - **DIFFUSE** pattern carries poor prognosis and is very likely to become invasive, while **focal** pattern is much better.
 - **PAPILLARY TRANSITIONAL-CELL ADENOCARCINOMA:** Invasive, high grade carcinoma, having invaded the muscularis layer.
 - **PATHOLOGY:** It is usually found on the lateral walls of the bladder, not the posterior wall.
 - It can be endophytic or exophytic.
- **STAGING:**
 - **Ta:** Cancer is still within the mucosa. Recurrences are less common.
 - **T1a:** Cancer has passed the mucosa, into the lamina propria. Recurrences are common.
- **GRADING:**
 - **Grade 1:** Basically normal urothelium, except (1) it is greater than 8 cell layers thick, and (2) there is usually a fibrovascular stalk.
 - **Grade 2:** Intermediate. The surface layer of this bladder tumor appears disorganized. The cells shows variation in size and shape and the polarity of the nuclei has been lost.
 - Tends to be papillary or endophytic.
 - **Grade 3:** Highest degree of anaplasia; variety in architecture of cells. Tends to be exophytic and invading.
- **TREATMENT:** Radical cystectomy is normally performed if there is muscle invasion.
- **SQUAMOUS CELL CARCINOMA:** Occurs with *Schistosoma Haematobium*.
- **ADENOCARCINOMA:** Very rare. Likely to be urachal in origin (on dome of bladder) if it occurs.

URETHRA:

- **ANATOMY: Male Urethra**
 - **Prostatic Urethra**
 - Contains urothelium (transitional cells)
 - **Verumontanum (seminal colliculus):** an elevated portion of the urethral crest upon which open the two ejaculatory ducts and the prostatic utricle.
 - **Membranous Urethra**
 - Pseudostratified Columnar Epithelia line the membranous urethra.
 - **Cowper's Glands** empty into the membranous urethra.
 - **Penile Urethra**
 - Pseudostratified Columnar line most of the penile urethra.
 - Non-keratinized stratified squamous epithelia line the fossa navicularis and urethral orifice.
- **CONGENITAL ANOMALIES:**
 - **URETHRAL DIVERTICULA:** Mainly in women. Trauma may lead to sac-like evagination.
 - **Duplications of Urethra:** rare.
 - **FIBROEPITHELIAL POLYPS:** Congenital urethral polyps; arise in prostatic urethra near colliculus, and may cause obstruction. They can be removed surgically.
 - **POSTERIOR URETHRAL VALVE:** Mucosal folds projecting into the prostatic urethra, which may cause obstruction.
 - **SYMPTOMS:** Early on, dysuria and fever.
 - **enuresis** is seen in boys.
 - Late stage: Hematuria, inflammatory symptoms, eventually **hydronephrosis**.
 - **EPIDEMIOLOGY:** Not uncommonly seen in pediatric population.
 - **TREATMENT:** **Vesiculotomy** to relieve the pressure. Later trans-urethral resection, after the inflammation has healed.

URETHRITIS:

- **ACUTE URETHRITIS:** Dysuria with urethral discharge.
 - **PATHOGENESIS:** Sexually transmitted, in males.

- *Neisseria gonorrhoeae* = yellow discharge
 - *Chlamydia Trachomatis*, *Ureaplasma urealyticum* = white discharge.
- EPIDEMIOLOGY: Transmission risk of 17-20% for the male, with unprotected sex.
- **REITER SYNDROME**: In males, triad of **urethritis, conjunctivitis, arthritis**. Cause unknown. Treated conservatively. Disease waxes and wanes.
- **CARUNCLE**: Polypoid or sessile lesion in distal urethra of women.
 - PATHOLOGY: Consists of **granulation tissue** covered with hyperplastic partially ulcerated transitional or squamous cell epithelium.
 - CLINICAL: Treated with topical creams or removed. It may spontaneously resolve.
- **POLYPOID URETHRITIS**: Urethral counterpart to polypoid cystitis. Submucosal edema, associated with indwelling catheters.

NON-NEOPLASTIC DISEASES:

- **NEPHROGENIC METAPLASIA**: Just as in bladder.

MALE GU

SEX DISORDERS:

- GENETIC SEX
 - **TURNER SYNDROME:** XO genotype.
 - **MIXED GONADAL DYSGENESIS:** 1 defined gonad plus a contralateral streak gonad. Increased incidence of germ cell tumors.
 - **TRUE HERMAPHRODITE:** Both ovarian and testicular tissue present.
- PHENOTYPIC SEX:
 - **MALE PSEUDOHERMAPHRODITISM: Testicular Feminization Syndrome,** insensitivity to testosterone -----> phenotypic female with primary amenorrhea.
 - **FEMALE PSEUDOHERMAPHRODITISM: Androgenital Syndrome,** due to adrenal hypersecretion of androgens.

CRYPTORCHIDISM: Failure of testes to descend into scrotum.

- SYMPTOMS: Infertility.
 - 5-35X Risk of developing germ-cell tumors in untreated Cryptorchidism.
- TREATMENT: **Orchidopexy** = repositioning of testes into scrotum surgically. Should treat as early as possible (less than 1 yr old) to prevent occurrence of germ-cell tumor.

ORCHITIS:

- PATHOGENESIS: Often results from hematogenous spread of systemic diseases (bacteremia, viremia). Orchitis without epididymitis is thought to start this way.
- **GRAM(-) BACTERIAL ORCHITIS:** Most common, often secondary to Syphilitic orchitis.
- **SYPHILITIC ORCHITIS:**
 - **GUMMAS:** Granulomatous-type lesion in testicles, can occur with tertiary syphilis.
- **MUMPS ORCHITIS:** Occurs in 20% of adult male Mumps cases. Usually only unilateral.
- **GRANULOMATOUS ORCHITIS:** Non-caseating granulomas, may be an auto-immune reaction to sperm.
- **MALAKOPLAKIA:** Can occur in testes, as in other locales.

TORSION of the TESTES:

- PATHOGENESIS: Occurs when there is redundancy of the cord.
- PATHOLOGY: Will result in infarct of testicle if not quickly resolved.

GERM-CELL TUMORS:

- PATHOGENESIS: **Cryptorchidism** is a common risk factor for all germ-cell tumors.
 - They may occur in sites other than gonads, such as mediastinum, sacrococcygeal region, or even cranium.
- PATHOLOGY: **LDH Type-I** is elevated in many germ cell tumors.
- **SEMINOMA:** Adults.
 - **EPIDEMIOLOGY:** Seminoma accounts for 40% of all testicular tumors. It has a peak incidence in the 35-45 years age group.
 - **SUBTYPES:**
 - **CLASSIC SEMINOMA:** Most common type. Can metastasize to regional lymph nodes.
 - 5-15% of tumors contain scattered syncytiotrophoblast cells that secrete hCG.
 - **ANAPLASTIC SEMINOMA:** Different histologically, but same picture clinically as classic seminoma.
 - **SPERMATOCYTIC SEMINOMA:** The only testicular cancer to occur in elderly men. Is not known to metastasize.

- **PATHOLOGY:** Polygonal neoplastic cells that have clear cytoplasm, contain glycogen and resemble fetal gonocytes.
 - Syncytiotrophoblastic Differentiation: Seminomas often secrete **hCG** (80% of time) because they show some differentiation into syncytiotrophoblast. This is *not* a choriocarcinoma because that would require both syncytio- and trophoblasts.
 - Gross: Yellow, no necrosis.
 - Lymphocytic Inflammation: the tumor cells are arranged into solid nests surrounded by fibrous septa that are infiltrated with lymphocytes.
 - Cancer cells are clear and contain glycogen, which stains **PAS positive**.
 - **Granulomas** can be formed in response to seminomas, as a response to tumor antigens.
 - **TREATMENT:** The tumor is radiosensitive and can be cured in over 90% of cases.
 - **DDx = LYMPHOMA of TESTIS:** In an older male, you must consider lymphoma as well as seminoma for any tumor in testis. In a younger male, it is mostly likely a seminoma.
 - **EMBRYONAL CARCINOMA:** Usually occurs in conjunction with seminomas. It would be rare to see it by itself.
 - **EPIDEMIOLOGY:** The tumor has a peak incidence in the 25-35 year age group. Pure embryonal carcinomas are rare accounting for about 10-15% of all germ cell tumors.
 - **PATHOLOGY:** Undifferentiated cells resembling early embryonic cells.
 - Gross: Yellow with brown discoloration. Necrosis.
 - *No lymphocytes*, unlike seminoma. More nuclear crowding.
 - **Embryoid Bodies:** Contained in the tumor, they mimic what the embryonic tissue looks like in the blastocyst stage.
 - Can further differentiate into other tumors:
 - Teratocarcinoma
 - Yolk-Sac Tumor
 - Choriocarcinoma
 - **TERATOMA:**
 - **EPIDEMIOLOGY:** Rare in the testis. Usually found in pre-pubertal children.
 - **PATHOLOGY:** Benign lesion containing all three germ-layers, often containing hair, skin, eyes, anything else.
 - **SUBTYPES:**
 - **Mature Teratoma:** Benign, tends to occur in children.
 - **Immature Teratoma:**
 - **Teratoma with Malignant Transformation (Teratocarcinoma):** Rare, malignant, and tends to occur in adults.
 - **CLINICAL:** Age is most important prognostic indicator. Children have a good prognosis, and adults have a poor prognosis.
 - **ENDODERMAL SINUS (YOLK-SAC) TUMOR:** Most common germ-cell tumor in children.
 - **EPIDEMIOLOGY:** Children under age 5.
 - **PATHOLOGY:**
 - Numerous histological patterns seen:
 - Reticulated
 - Microcystic
 - Papillary myxoid
 - **Schiller-Duval Bodies:** Often present, they resemble fetal glomeruli.
 - **Alpha-Fetoprotein (AFP):** Tumor cells secrete AFP. AFP can also be found in teratocarcinomas, indicating the similar lineage of the two tumors.
 - **TREATMENT:** Surgical resection.
 - **TESTICULAR CHORIOCARCINOMA:**
 - **EPIDEMIOLOGY:** Rare.
 - **PATHOLOGY:** Highly malignant, composed of cytotrophoblast and syncytiotrophoblast cells. Highly invasive cells cause hemorrhage and necrosis of tissues into which they have spread.
 - **Human Chorionic Gonadotropin (hCG):** Choriocarcinoma cells secrete hCG, which helps to identify them. This is explained by their syncytiotrophoblast origin.

STROMAL TUMORS:

- **LEYDIG CELL TUMOR:** Most common stromal tumor of the testis. Usually benign.

- **EPIDEMIOLOGY:** Accounts for 1-3% of all testicular tumors.
- **PATHOGENESIS:** Unknown, but there is no association with Cryptorchidism.
- **PATHOLOGY:** Only 10% of tumors in adults are malignant. Malignancy cannot be predicted histologically, but only by behavior of the cancer.
- **SERTOLI CELL TUMOR:** Extremely rare. Usually benign (10% malignant).
 - **SYMPTOMS:**
 - Virilization is often seen in children
 - Gynecomastia may be present in 30% of adults. It can produce estrogen.
- **GONADOBLASTOMA:** Rare.
 - **EPIDEMIOLOGY / PATHOGENESIS:** Almost exclusively seen in patients with some form of gonadal dysgenesis (testicular feminization).
 - The majority of these tumors occur in patients under 30 years of age.
 - **SYMPTOMS:** Four-fifths of patients with gonadoblastomas are **phenotypic females**.
 - Males typically have cryptorchidism or hypospadias.

TESTICULAR ADNEXAE:

- **TESTICULAR TUNICS:**
 - **VARICOCELE:** Engorgement of veins in the pampiniform plexus of th testes.
 - **HYDROCELE:** Collection of clear, serous fluid in the scrotum. The fluid typically fills the space between the layers of the tunica vaginalis testis.
 - **HEMATOCELE:**
 - **SPERMATOCELE:**
- **EPIDIDYMITIS:** Painful swelling of one or both epididymides with fever and a variable incidence of dysuria and pyuria. In young men, usually associated with sexually transmitted urethritis (N. gonorrhoeae or C. trachomatis), in older men, most often associated with prostatitis (infections with coliform bacilli).
- **TUMORS OF EPIDIDYMIS:**
 - **Adenomatoid tumors** are most common and typically occur in the third and fourth decade of life.
 - **Leiomyomas** are the second most common tumor.
- **VASITIS NODOSA:**
- **LIPOMAS:** Typically benign and usually occur in spermatic cord.
- **SARCOMAS:**

PROSTATE:

- **ANATOMY:**
 - **Anterior Zone:** mostly stroma, little glands.
 - **Peripheral Zone:** 75% of all the glands in the prostate.
 - Location of most Prostatic Adenocarcinoma.
 - **Central Zone**
 - **Periurethral Glands:** A narrow sleeve of the proximal urethra.
 - **Transitional Zone:** Area surrounding prostatic urethra.
 - Location of most BPH

PROSTATITIS:

- **ACUTE BACTERIAL PROSTATITIS:** Usually gram(-) bugs.
 - **PATHOGENESIS:** Often occurs secondary to **bacteremia**.
 - **PATHOLOGY:** Tender, swollen, indurated prostate. Purulent prostatic secretions, usually caused by infection with coliform bacilli.
 - Often accompanied by bacteriuria.
 - **SYMPTOMS:** Fever, chills, perineal pain.
- **CHRONIC PROSTATITIS:** An imprecise term that encompasses a variety of syndromes.
 - **PATHOGENESIS:** Variable cause and clinical sequelae:
 - Chronic bacterial prostatitis
 - Chronic non-bacterial prostatitis
 - BPH: frequent complication.

- **PATHOLOGY:** Lymphocytic infiltrate.
- **SYMPTOMS:** Suprapubic pain, low back pain, dysuria, nocturia.
- **NON-BACTERIAL PROSTATITIS:** Most common prostatitis.
 - **PATHOGENESIS:** Usually unknown. Abnormal numbers of inflammatory cells found in their prostatic secretions, but no causative infectious agent can be found by culture or other means.
 - **Autoimmune:** Theory = may be an autoimmune attack against prostate.
 - *Trichomonas, Mycoplasma:* They may be responsible for the prostatitis in a minority of cases.
 - **DIAGNOSIS:** Made by excluding other causes of prostatitis.
- **GRANULOMATOUS PROSTATITIS:**
 - **NON-INFECTIOUS:** Inflammatory response to inspissated (thickened) concretions.
 - Allergic prostatitis often occurs here; eosinophils are common.
 - **INFECTIOUS:** Tubercular, fungal.

BENIGN PROSTATITIC HYPERPLASIA (BPH) (NODULAR HYPERPLASIA): *BPH is not preneoplastic.*

- **EPIDEMIOLOGY:** 75% of men have it by age 80. Some people say even higher. Especially common in African American men.
- **PATHOGENESIS:** Several theories
 - BPH may result from a combination of decreased testosterone and increased estrogen, occurring with old age. This may cause an increased sensitivity to DHT in the prostate.
- **PATHOLOGY:** Both glands and stroma proliferate, with a significant (5:1) stromal component.
 - **Gross:**
 - Hyperplasia appears **nodular**, with even proliferation of stroma and glandular components.
 - Hyperplasia nearly always occurs in the **transitional zone** of the prostate, beginning around the prostatic urethra, and going out peripherally.
- **SYMPTOMS:** Bladder-outlet obstruction. Hesitancy, dysuria, urgency, feeling of incomplete stream.
 - **Rectal Exam:** BPH feels like a soft padding over the base of the thumb. Cancer is rock-hard.
- **TREATMENT:**
 - **5-alpha-Reductase Inhibitors:** Finasteride (Proscar) inhibits the peripheral *conversion of testosterone to DHT*, thereby blocking the growth-effect of DHT on the prostate.
 - Clinical Trials have shown it effective in reducing prostate size and alleviating symptoms.
 - **Trans-Urethral Resection (TUR):** Core out middle part of the urethra, to open up the lumen. This results in **prostatic chips** which can be sent into Surg.Path. for analysis.

PROSTATIC ADENOCARCINOMA:

- **EPIDEMIOLOGY:** Common in U.S., rare in Asia. Incidence again highest in African American men.
 - Median age of diagnosis = 72 years old.
- **PATHOGENESIS:**
 - Dietary (supposed): Increase in dietary fats, decrease in fish oils.
 - Testosterone makes the cancer grow, but there is no evidence that high DHT can cause the cancer.
 - It may just be a natural consequence of aging -- some carcinoma is found in 80% of old men at autopsy.
 - **CYTOGENETIC Abnormalities:** Variety of them are seen.
 - Chromosome **8p22** deletion found in 70% of cancers.
 - **c-myc** oncogene involvement.
 - **POOR PROGNOSIS:** Two abnormalities associated with poorer prognosis.
 - Aneuploidy of chromosomes 7 and 8 is associated with poor prognosis.
 - Chromosome 16 has **Cadherin** and **Catenin** proteins, which are associated with poor prognosis when present.
- **PATHOLOGY:** Almost all carcinomas originate in the acini, in the Peripheral Zone of the prostate.
 - **Gross:** Usually yellow. It is solid -- not nodular as in BPH.
 - **GLEASON GRADING:**
 - **Grades:**
 - **Grade 1:** Near normal, minimal anaplasia.

- **Grade 2-4:** Intermediate grades.
 - **Grade 5:** No acini exist at all, maximal anaplasia.
 - SCORE: Add the major pattern + minor pattern to get final score. Final score of 1 thru 10, with 10 being worst.
- **PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN):** Pre-cancer. Lesion is confined to the acinus.
 - PATHOLOGY: *The basal cell layer is maintained* in PIN.
 - **Basal-Cell-Specific Keratin:** PIN will stain positive for it, since basal cells are present. Full carcinoma will stain negative, as basal cells are absent.
 - HISTOLOGICAL SUBTYPES:
 - **Tufting:** Most common
 - Micropapillary
 - Cribriform
 - Flat
 - EPIDEMIOLOGY: PIN develops early in life, from age 10-50.
- **PROSTATE SPECIFIC ANTIGEN (PSA):** Used to diagnose prostate cancer, and distinguish it from BPH.
 - PSA
 - STRUCTURE: A glycoprotein (mol wt 33,000) that is secreted in the cytoplasm of prostatic cells.
 - FUNCTION: Serine protease functions normally in aiding liquefaction of semen.
 - NORMAL VALUES: Upper limit of normal
 - Young adults: between 0 and 4 ng/mL.
 - 40-49 year-old: 2.5 ng/mL
 - 50-59-year-old: 3.5 ng/mL
 - 60-69-year-old: 4.5 ng/mL
 - 70-79-year-old: 6.5 ng/mL
 - **PSA DENSITY:** PSA levels divided by volume of prostate, to normalize for BPH. Densities greater than 0.15 are associated with 60% chance of cancer.
 - TWO SUBTYPES: The two subtypes cannot currently be differentiated.
 - **Complexed PSA:** Associated with cancer
 - **Free PSA:** Associated with BPH.
 - X-RAY DIAGNOSIS: Bone metastases can be seen on X-Ray and result in an elevated **Alkaline Phosphatase**.
- **TRANS-URETHRAL SONOGRAPHY (TRUS):** Diagnostic tool, to help diagnose cancers that aren't caught by PSA or rectal exam.
 - It can identify 60% of cancers even if they are nonpalpable, because of hypo-echogenic characteristics of these cancers. This is presumably because the compact, highly cellular nature of malignancy produces a minimal interphase between cells, and this creates minimal internal echoes. Transrectal ultrasound is also more accurate than DRE at detecting extracapsular extension.
- SYMPTOMS:
 - *Most cancers are indolent.* Less than 1% of men diagnosed with Prostate Cancer actually die of the disease.
 - METASTASIS to bone, lung, liver, spleen. Bone is most common site of metastasis.
- STAGING:
 - **Stage A:** Microscopic foci of anaplasia in an otherwise benign specimen.
 - A1: Focal anaplasia.
 - A2: Diffuse anaplasia.
 - **Stage B:** Clinically palpable nodule, but still confined to prostate.
 - B1: Focal lesion, one lobe.
 - B2: More than one lobe of prostate involved.
 - **Stage C:** Local invasion beyond the prostate capsule. No metastasis.
 - **Stage D:** Metastasis.
 - D1: Metastases to regional lymph nodes.
 - D2: Distant metastases.

CONGENITAL DISORDERS of PENIS:

- **PHIMOSIS**: Congenital or acquired inability to retract the prepuce, in uncircumcised penises.
- **EPISPADIA**: Urethra opens on dorsal aspect of penis. Surgically correctable and associated with infertility.
 - **PATHOGENESIS**: Often associated with **Exstrophy of Bladder**
- **HYPOSPADIA**: Urethra opens on underside (ventral) aspect of penis. Surgically correctable and associated with infertility.
 - Most common of the congenital penile anomalies.

SEXUALLY TRANSMITTED PENILE LESIONS:

- **CONDYLOMATA ACUMINATA (VENEREAL WARTS)**: **HPV**, usually type **6 and 11**.
 - **PATHOLOGY**: Condylomata resemble other warts and show acanthosis, papillomatosis, prominence of the granular layer, parakeratosis and keratosis. HPV can be demonstrated in the nuclei of the keratinocytes by immunofluorescence microscopy or electron microscopy.
- **GENITAL HERPES**: Herpes simplex virus is a double-stranded DNA virus that may cause persistent or latent infections. Most genital herpes infections are due to type 2 virus, although infection due to type 1 herpes virus, which is commonly associated with oral infections, has been reported in 10-25% of cases of genital herpes.
 - **PATHOLOGY**: Vesicles grouped on an erythematous base, not following a neural distribution, and associated with a previous history of such eruptions are pathognomonic for genital herpes.
- **GRANULOMA INGUINALE**: Granuloma inguinale, a sexually transmitted chronic infection of the skin and subcutaneous tissue of the genitalia, perineum, and inguinal area, has an incubation period of 2-3 months.
 - **PATHOGENESIS**: *Calymmatobacterium granulomatis*
 - **SYMPTOM**: A painful papule is the first sign of granuloma inguinale.
- **LYMPHOGRANULOMA VENEREUM**: *Chlamydia trachomatis*, immunotypes L1 - L3.
 - **SYMPTOMS**: A papule or pustule appears 5-21 days after sexual exposure. The disease is characterized by a transient genital lesion followed by lymphadenitis and, possibly, rectal strictures.

CANCER of PENIS:

- **SQUAMOUS CARCINOMA IN SITU**:
 - **BOWEN DISEASE**: Epidermal dysplasia on shaft of penis.
 - **SYMPTOMS**: **Erythematous plaque**
 - May progress to invasive cancer, but such progression occurs in only 10% of cases
 - **ERYTHROPLASIA of QUEYRAT**: Epidermal dysplasia on glans or prepuce.
 - **BOWENOID PAPULOSIS**:
 - **PATHOGENESIS**: **HPV-16**
 - **PATHOLOGY**: Lesions show less cytologic atypia than other forms of carcinoma in situ.
 - **TREATMENT**: Readily cured with topical antiviral ointments.
 - **PENILE INTRAEPITHELIAL NEOPLASIA (PIN)**:
- **GIANT CONDYLOMA of BUSCHKE-LOWENSTEIN (VERRUCOUS CARCINOMA)** Exophytic mass on gland of uncircumcised penis. Can be cured surgically.
- **SQUAMOUS CELL CARCINOMA**:
 - **EPIDEMIOLOGY**: Rare in the US -- less than 0.5% of all cancers in males
 - Common in South America, Africa and Asia, where it may be 10-20% of Male-GU cancers.
 - Age = 6th decade
 - **Circumcision** effectively prevents the disease, hence it is rare in U.S.
 - **PATHOLOGY**: Exophytic or endophytic with superficial ulceration.
 - **PATHOGENESIS**: One theory postulates that **smegma** (is that Yiddish?) accumulation under the phimotic foreskin results in chronic inflammation leading to carcinoma.

FEMALE GU

SEXUALLY TRANSMITTED INFECTIONS:

- BACTERIAL:
 - GONORRHEA
 - SYPHILIS
 - GRANULOMA INGUINALE
 - **CHANCROID**: Chancroid is a sexually transmitted disease caused by *Haemophilus ducreyi*. It is a well-established cofactor for HIV transmission, and 10% of patients with chancroid may also have syphilis or herpesvirus infection. One or more painful, dirty-appearing chancroid ulcers appear after the first few days of infection.
 - *GARDNERELLA*
 - *MYCOPLASMA*
 - *CHLAMYDIA*
 - CHLAMYDIAL URETHRITIS:
 - LYMPHOGRANULOMA VENEREUM:
- VIRAL:
 - HUMAN PAPILLOMAVIRUS (HPV) (CONDYLOMA ACUMINATUM):
 - HERPESVIRUS (HSV):
 - CYTOMEGALOVIRUS (CMV):
 - MOLLUSCUM CONTAGIOSUM:
- PROTOZOA:
 - TRICHOMONIASIS:

PELVIC INFLAMMATORY DISEASE (PID):

OTHER VAGINAL INFECTIONS:

- TUBERCULOSIS:
- CANDIDIASIS:
- ACTINOMYCOSIS:
- TOXIC SHOCK SYNDROME:

VULVA, VAGINA, CERVIX

VULVA:

- **BARTHOLIN'S GLAND CYST**: Obstruction of Bartholin's gland -----> cyst formation, infection, abscess.
 - TREATMENT: Incision, drainage, antibiotics.
- **LICHEN SCLEROSIS**:
 - PATHOLOGY: Painful white plaques on the vulva with atrophy.
 - Hyperkeratosis and blunting of rete ridges.
 - Homogenous, acellular zone in the upper dermis with a band of lymphocytes and plasma cells.
 - SYMPTOMS: Itching and dyspareunia.
- **SQUAMOUS HYPERPLASIA**: Benign.
 - PATHOLOGY: Thickened epithelium, hyperkeratosis. Granulosa layer becomes hypercellular.
- **LEUKOPLAKIA**: White patch on vulva. Differential diagnosis includes:
 - Lichen Sclerosis
 - Squamous Hyperplasia
 - Squamous Carcinoma *In Situ*
 - Squamous Cell Carcinoma

VULVAR TUMORS:

- **HIDRADENOMA:**
- **SYRINGOMA:**
- **VULVAR INTRAEPITHELIAL NEOPLASIA (VIN):** Vulvar dysplasia. Precursor lesion of Squamous Cell Carcinoma of Vulva.
 - **PATHOGENESIS:** Related to **HPV 6, 11, 16**
 - **SYMPTOMS:** Macules, papules, or plaques.
 - **GRADING:**
 - **VIN I:** Most differentiated.
 - **VIN II:**
 - **VIN III:** Highest degree of atypia.
- **SQUAMOUS CELL CARCINOMA of VULVA:**
 - **EPIDEMIOLOGY:** Most common cancer of the vulva (85%) and accounts for 3% of all genital cancers in women.
 - **PATHOLOGY:** Exophytic, ulcerative or endophytic. Usually is keratinizing.
 - **SYMPTOMS:** Pruritus, bleeding, ulcer, and a mass.
 - Prognosis is good: 90% survival with no metastasis.
 - Metastasis goes to inguinal or femoral nodes.
- **VERRUCOUS CARCINOMA (GIANT CONDYLOMA):**
 - **PATHOGENESIS:** **HPV 6**
 - **CLINICAL:** Good prognosis.
- **EXTRAMAMMARY PAGET DISEASE:** Rare
 - **PATHOLOGY:**
 - **Paget Cells:** Malignant, large, pale vacuolated cells, found scattered throughout the epidermis.
 - Usually remains confined to epidermis.
 - Stains: PAS-positive, mucin-positive
 - **SYMPTOMS:** Red, moist, weeping, pruritic lesion on labia majora.
 - *Other malignancies often co-occur with Paget's.* Check for other malignancies if you see the disease.
 - **TREATMENT:** Wide local excision. Usually curative.
- **MELANOMA:** Very rare.
 - **SYMPTOMS:** ABCD
 - Asymmetry of lesion
 - Borders are elevated
 - Color is brown or black
 - Diameter is unusually large.

VAGINA:

- **CONGENITAL ANOMALIES:**
 - **CONGENITAL ABSENCE**
 - **SEPTATE VAGINA**
 - **IMPERFORATE HYMEN**
- **ATROPHIC VAGINITIS:** Diminished estrogenic stimulation post-menopausal leads to atrophy and possible superimposed infection. Can be prevented with Post-Menopausal Estrogen Replacement Therapy (ERT).
- **VAGINAL ADENOSIS:** Change from normal squamous epithelium -----> glandular epithelium.
 - **PATHOGENESIS:** Associated with use of **diethylstilbestrol (DES)** during 10th - 18th weeks of pregnancy -----> female fetus will get Vaginal Adenosis.
 - **SYMPTOMS:** Appears as red area; glandular epithelium is not as thick.
 - *Increased risk for vaginal adenocarcinoma, which is otherwise a rare a cancer.*

VAGINAL TUMORS:

- **SQUAMOUS CELL CARCINOMA:** The most common cancer of the vagina.

- **PATHOGENESIS:** Associated with **HPV** infection.
 - Patients usually have had multiple sexual partners and early age at first intercourse.
- **STAGING: VAGINAL INTRAEPITHELIAL NEOPLASIA (VAIN)** is the precursor lesion to Squamous Cell Carcinoma. Term encompasses vaginal dysplasia and carcinoma *in situ*.
 - **VAIN I:** Mild, well-differentiated.
 - **VAIN II:** Moderate
 - **VAIN III:** Severe anaplasia. **Carcinoma *in situ***
 - **VAIN IV: Invasive Carcinoma**
- **PROGNOSIS:** Excellent prognosis, for localized lesions with no metastases.
- **CLEAR CELL ADENOCARCINOMA:**
 - **PATHOGENESIS:** Adenocarcinoma associated with *in utero* exposure to **Diethylstilbestrol**.
 - **PATHOLOGY:** "Clear cell" indicates glycogen-filled mucin-producing glandular cells.
 - **TREATMENT:** They are curable.
- **EMBRYONAL RHABDOMYOSARCOMA (SARCOMA BOTRYOIDES):**
 - **EPIDEMIOLOGY:** Rare, exclusively in infants and young children
 - **PATHOLOGY:** Made of primitive embryonal rhabdomyoblasts.
 - **SYMPTOMS:** Confluent polypoid masses resembling a bunch of grapes, protruding from the vagina.
 - **TREATMENT:** Good prognosis. Conservative surgery followed by chemotherapy.

CERVIX:

- **Transformation Zone:**
 - **Squamocolumnar Junction:** It can occur in the internal os or the external os.
 - **Endocervical Ectropion:** Reddish areas around the external os that are actually just extensions of columnar epithelium from the uterus. This is normal and can occur in women who have a transformation zone that is one the exocervix rather than endocervix.
 - **Squamous Metaplasia:** In women in whom columnar epithelium extends into the exocervix, the exocervical part can undergo squamous metaplasia, especially with age and childbirth. This effectively makes the squamocolumnar junction **recede** into the endocervix.
 - **Transformation Zone:** The area between the original squamocolumnar junction (before squamous metaplasia) and the new squamocolumnar junction is called the transformation zone.

BENIGN CERVICAL TUMORS:

- **ENDOCERVICAL POLYP:** Benign polyps usually located in the os. They bleed; surgical excision is curative.
- **MICROGLANDULAR HYPERPLASIA:** Closely packed glands without intervening stroma. Occurs with birth control pills or in pregnancy, it is caused by Progesterone and is *not* cancerous.
- **LEIOMYOMA:** One tenth of all uterine leiomyomas occur in cervix.

CERVICAL CANCERS:

- **CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN):**
 - **PATHOGENESIS: HPV 16, 18, 31, 33, 35**
 - Patients usually have had multiple sexual partners and early age at first intercourse.
 - **GRADES:**
 - **CIN-1:** Mild dysplasia. Abnormal cells in the lower third of the epithelium.
 - **CIN-2:** Moderate dysplasia. Abnormal cells in the lower and middle thirds of the epithelium.
 - **CIN-3:** Severe dysplasia, or carcinoma *in situ*. Abnormal cells diffusely involve more than two thirds of the epithelium.
 - **PATHOLOGY:** You see the cytologic features of HPV: Dysplasia, hyperchromatin, viral inclusions.
 - **TREATMENT:** Varies according to the disease stage.
 - Cryosurgery
 - **Cervical Conization:** Removal of mucosal layer of cervical tissue.

- Laser Vaporization
 - Hysterectomy
- **SQUAMOUS CELL CARCINOMA of CERVIX:** Most common cancer of cervix.
 - **PATHOGENESIS:** Usually evolves from CIN.
 - **PATHOLOGY:** Exophytic, ulcerating or infiltrative lesion.
 - May be either keratinizing or non-keratinizing.
 - **Keratin Pearls:** Can see islands of squamous cells in the stroma, indicative of Squamous Cell Carcinoma.
 - **SUBTYPES:**
 - **MICROINVASIVE SQUAMOUS CARCINOMA:** Generally carries a better prognosis. Two criteria in order to call it microinvasive:
 - Tumor ends less than 3mm from the overlying epithelium.
 - No vascular or lymphatic invasion.
 - **INVASIVE CARCINOMA:** Tumor greater than 3mm deep, and/or vascular or lymphatic invasion.
 - **SYMPTOMS:** Vaginal bleeding, discharge.
 - Metastasis: Tumor spreads by direct extension and through lymphatics.
 - **TREATMENT:** Varies with age. Same options as CIN. Radical hysterectomy is often required.
- **ADENOCARCINOMA of CERVIX:**
 - **EPIDEMIOLOGY:** Incidence is going up. Traditionally cited as 10% of cervical cancers, but now it may be more like 30-40%.
 - **PATHOGENESIS:** **HPV 16, 18** is implicated in pathogenesis. That explains the rising incidence of the cancer.
 - **PATHOLOGY:** Mucin producing glands with stromal invasion.

UTERUS

CONGENITAL ANOMALIES:

- **UTERINE AGENESIS:**
- **UTERUS DIDELPHYS:** Completely double-uterus, from lack of fusion of the two Mullerian ducts.
- **UTERUS DUPLEX BICORNIS:** Single Uterus with a common wall separating two endometrial cavities.
- **UTERUS SEPTUS:** Single uterus with a partial remain septum separating two hemi-cavities. Patient is at increased risk for spontaneous abortion.
- **BICORNUATE UTERUS:** Uterus with two horns and a single common cervix. Increased risk for premature birth.

ENDOMETRITIS: Inflammation of the uterus.

- **ACUTE ENDOMETRITIS:** Usually caused by ascending infection (sexually transmitted), abortion, or instrumentation.
- **CHRONIC ENDOMETRITIS:** Can be caused by IUD's, PID, abortion, instrumentation.
- **SYMPTOMS:** Pelvis pain, bleeding.
- **TREATMENT:** Often resolves on its own with menstruation to wash out the inflammation. If it doesn't, do cultures and give antibiotics.

ADENOMYOSIS: Endometrial glands and stroma located in the myometrium.

- **PATHOLOGY:** Looks like red, soft areas in the myometrium.
 - It can be confused with invasive carcinoma. Examine it histologically to distinguish them.
- **SYMPTOMS:** Can be asymptomatic, or dysmenorrhea.

ENDOMETRIOSIS: Presence of benign, ectopic endometrial tissue, outside the uterus.

- **PATHOGENESIS:** Theories as to the cause:
 - **Retrograde Menstruation:** Most accepted theory. Some tissue goes back through fallopian tubes and seeds in peritoneum.
 - **Intraoperative Implantation:** Resulting from surgery; surgical implantation of ectopic tissue.
 - **Lymphatic, Hematogenous Dissemination:** Some endometrial cells may spread through circulation and seed elsewhere.
 - **Celomic Metaplasia:** Metaplasia of peritoneal lining to endometrial glandular cells.
- **PATHOLOGY:**
 - Most common sites: ovaries, tubes, and broad ligaments. But, any site can be involved.
 - **Mulberry nodules:** Red-blue areas found during laparoscopy.
 - **Hemosiderin-laden macrophages** can also be found in the area, as the macrophages come in to try to clean up the mess.
 - **Glands with Stroma:** Endometriosis has normal-appearing tissue, glands with stroma. This distinguishes it from adenocarcinoma, which shows back to back glands, and little or no stroma.
- **SYMPTOMS:** Dysmenorrhea, dysfunctional uterine bleeding (DUB), dyspareunia and infertility.
 - Infertility results from adhesions in the tube and oviduct.

MENSTRUAL SYMPTOMS:

- **Dysfunctional Uterine Bleeding (DUB):** Abnormal vaginal bleeding, at any time, in which cause of the bleeding *lies outside the uterus*. The major cause is endometriosis.
 - **PATHOGENESIS:** Largely unknown. May result from endocrine disturbances.
- **Anovulatory Bleeding ("Breakthrough Bleeding"):** Bleeding occurring in the absence of ovulation.
 - **PATHOGENESIS:** For whatever reason, no ovulation leads to excessive estrogen and no progesterone, which leads to abnormal development of spiral arteries. When the estrogen levels then drop, the abnormal arteries can infarct, thrombose, or hemorrhage.
 - **AGE-GROUPS:** Common causes of DUB change with age:
 - Newborn: Due to maternal estrogen.
 - Child: Tumors
 - Reproductive Age: Stress, nutritional, tumors, endocrine disorders
 - Peri-Menopausal, Post-Menopausal: Tumors
- **Dyspareunia:** Pain during intercourse.
- **Dysmenorrhea:** Painful menstruation, or pain during menstruation.
- **Menorrhagia:** Excessive or profuse menses.

BENIGN UTERINE LESIONS:

- **ENDOMETRIAL POLYPS:** Benign overgrowths, mostly located on the fundus.
 - **PATHOLOGY:** Endometrial glands, fibromatous stroma, and thick-walled, dilated blood vessels.
 - **SYMPTOMS:** **Inter-menstrual bleeding** is the most common symptom.
 - **TREATMENT:** Curettage is usually curative.
- **LEIOMYOMAS (FIBROIDS):** *The most common GYN tumor.* Strictly benign.
 - **PATHOLOGY:** Firm, pale gray, *well circumscribed* whorled lesions, composed of smooth muscle fibers similar to the myometrium.
 - **Locations:**
 - **Intramural:** Located with myometrial wall.
 - **Subserosal:** Located outside the myometrium.
 - **Submucosal:** Located close to surface.
 - **SYMPTOMS:** Wide range of symptoms, from asymptomatic to abnormal uterine bleeding and pain requiring hysterectomy.
 - **TREATMENT:** Myomectomy.

UTERINE PRE-CANCER and CANCER:

- **ENDOMETRIAL HYPERPLASIA:** Pre-cancerous condition leading to adenocarcinoma.
 - **PATHOGENESIS:** Related to excessive levels of estrogen.
 - **SUBTYPES:**
 - **Simple Hyperplasia:** Crowding of glands. Glands are proliferative (more than 50% of field) and show crowding, but no atypia.
 - **Cystic Hyperplasia:** "Swiss-Cheese" hyperplasia is a variant.
 - Only 1% of cases progress to adenocarcinoma.
 - **Complex Hyperplasia:** Crowding of glands, with branching and irregular patterns. Still no cellular atypia.
 - 3% of cases progress to adenocarcinoma.
 - **Atypical Hyperplasia:** Complex hyperplasia with **atypia** nuclei -- mitotic figures, hyperchromatin, etc. Often see back-to-back glands.
 - *Frequent progression to adenocarcinoma.*
 - **TREATMENT:** This is usually cause for having the uterus removed. Milder cases can be treated with hormonal therapy (Tamoxifen?), to attempt to block the effects of estrogen on the uterus.
- **ENDOMETRIAL ADENOCARCINOMA:** *The most common GYN malignant cancer.*
 - **PATHOGENESIS:** Related to excess estrogen. Most risk-factors relate to excess estrogen:
 - Nulliparity, early menarche or late menopause.
 - Diabetes, hypertension.
 - Smoking
 - **PATHOLOGY:**
 - Growth pattern can be polypoid or diffuse. Hemorrhage and necrosis is common.
 - **SUBTYPES:**
 - **ENDOMETRIOID CARCINOMA:** Most common subtype. Well-differentiated, resembling endometrium.
 - **ENDOMETRIOID CARCINOMA with SQUAMOUS DIFFERENTIATION:** About 30% of cases.
 - **Papillary (Serous) Carcinoma:** Very poor prognosis. Usually presents with metastasis at time of diagnosis.
 - **Clear Cell Carcinoma:**
 - **Secretory Carcinoma:**
 - **GRADING:** International Federation of Gynecologic Oncologists (FIGO)
 - **FIGO 1:** Well differentiated, nearly 100% glands.
 - **FIGO 2:** Moderately differentiated. Shows both glands and sheets of cells.
 - **FIGO 3:** Poorly differentiated. Sheets of anaplastic cells with mitotic figures.
 - **SYMPTOMS:** Abnormal uterine bleeding is common complaint. Occurs in peri-menopausal and post-menopausal women.
- **ENDOMETRIAL STROMAL SARCOMA:** Rare stromal tumor, resembling leiomyomas. They do metastasize.
- **LEIOMYOSARCOMA:** Malignant counterpart to leiomyoma. Rare.
 - **PATHOLOGY:** Malignant smooth muscle cells, showing mitosis, necrosis, increased cellularity.
 - Gross: *Poorly circumscribed* lesion.
 - **SYMPTOMS:** Same broad range of symptoms as with fibroids.
 - **TREATMENT:** Radical hysterectomy.

OVERY and OVIDUCT

FALLOPIAN TUBES:

- **SALPINGITIS:** Usually caused by Pelvic Inflammatory Disease.
 - **COMPLICATIONS:**
 - **Hydrosalpinx:** Dilation of lumen of tubes, filled with clear fluid.
 - **Pyosalpinx:** Pus in tube

- **Fibrosis**
- **Tubo-ovarian Abscess**
- **ECTOPIC PREGNANCY:** Most often results from tubal strictures or fibrosis, secondary to PID.

CYSTIC LESIONS of OVARY:

- **SIMPLE CYSTS:** Majority are benign, but can be malignant.
 - **Follicle Cyst:** It can release estrogens, and looks just like a Graafian Follicle.
 - **Corpus Luteum Cyst:** Can release progesterone. Occurs in reproductive women. It is usually filled with blood, can hemorrhage, and must be removed.
 - **Epithelial-Inclusion Cyst:**
 - **Paratubal Cyst:** Cyst attached to the tube.
 - **Theca Lutein Cyst:** Commonly associated with high levels of hCG (choriocarcinoma, hydatidiform mole)
- **POLYCYSTIC OVARY SYNDROME (PCO) (STEIN-LEVENTHAL DISEASE):**
 - **PATHOGENESIS:** Obese women. Excess estrone production in adipose tissue triggers the change.
 - Adipose tissue -----> excess estrone -----> stimulation of GnRH and *suppression of FSH* -----> **high LH/FSH ratio**, which is characteristic of PCO.
 - **SYMPTOMS:** Classic triad of **Hirsutism, Amenorrhea, Obesity**.
 - Hirsutism: related to excess androgens
 - Amenorrhea, Infertility: Secondary to the screwed up LH/FSH ratio.
 - **PATHOLOGY:** Numerous subcortical cysts. No corpus luteum or corpus albicans can be found in ovary.

BENIGN OVARIAN TUMORS:

- **CYSTADENOMA:** Benign tumor.
 - **SEROUS CYSTADENOMA:** Cystic benign tumor.
 - **PATHOLOGY:**
 - **Unilocular**
 - Lined by **ciliated epithelium** -- tubal-like cells.
 - **MUCINOUS CYSTADENOMA:** Have mucin glands, similar to the endocervix.
 - **PATHOLOGY:**
 - **Multilocular.**
 - Lined by **columnar epithelium**.
 - **PSEUDOMYXOMA PERITONEI:** Seeding of the tumor in the peritoneum.
 - **PATHOLOGY:** Massive accumulation of gelatinous material in the abdominal cavity.
 - **PATHOGENESIS:** Mucinous Cystadenoma of the ovary, or Mucocoele in the appendix.
 - **TREATMENT** is surgical, and usually requires repeated operations.
- **BRENNER TUMOR:** Benign tumor, usually discovered incidentally.
 - **PATHOLOGY:** Composed of islands of transitional-cells, within fibrous stroma.
- **BORDERLINE TUMOR:** Tumor of low malignant potential. Excellent prognosis, despite histologic features that suggest malignancy. May be serous or mucinous.

OVARIAN ADENOCARCINOMA:

- **SUBTYPES:**
 - **SEROUS CYSTADENOCARCINOMA:** Most common malignant *ovarian* tumor. 30% of ovarian cancers.
 - Papillary Projections are common, with hemorrhage and necrosis.
 - **Multilocular**, when it is malignant, as opposed to unilocular when it is benign.
 - **Psammoma Bodies** are laminated, calcified concretions characteristically found in this tumor.
 - **MUCINOUS CYSTADENOCARCINOMA:** Third most common.

- Signet-Ring cells, or similar-looking cells, may be seen because these cells are mucin-producing.
 - Much larger than serous carcinomas.
 - Also multilocular.
- **ENDOMETRIOID ADENOCARCINOMA:** Second most common.
 - Resembles endometrial cancer histologically. Slightly better prognosis, but still bad.
- **CLEAR CELL ADENOCARCINOMA:** Rare.
 - May be associated with endometriosis
 - Very poor prognosis.
- **CLINICAL:**
 - **Bad prognosis.** As a group these tumors are bad, because they usually don't present until late-stage.
 - **CA-125** is a tumor-marker present in these tumors that is useful for *tracking the tumor*. It isn't too useful for diagnosis because it shows up in a lot of other instances, too.

STROMAL TUMORS: Mixed benign and malignant, mostly benign.

- **OVARIAN FIBROMA:** Benign. Most common ovarian stromal tumor, and the only non-secreting one.
 - **PATHOLOGY:** Solid, firm benign ovarian stromal tumor, composed of well-differentiated fibroblasts and collagen stroma.
 - It is the only one that does not secrete hormones.
 - **MEIGS SYNDROME: Ovarian Fibroma, Ascites, Pleural Effusion.** This complication can be found with this tumor.
- **THECOMA:** Benign.
 - **PATHOLOGY:** Circumscribed yellow-brown mass. Look similar to fibroma, but not as fibrotic.
 - **SYMPTOMS:** Occurs in peri- and post-menopausal women and produces lots of estrogen.
 - The excess estrogen can produce endometrial hyperplasia and *may lead to cancer*.
- **GRANULOSA CELL TUMOR:** May be malignant or benign.
 - **EPIDEMIOLOGY:** Rare. Found in middle-aged women.
 - **PATHOLOGY:** It produces estrogen, like a Thecoma, so it is yellow.
 - **Call-Exner Bodies:** Characteristic histologic pattern of tumor, arranged into follicles.
 - **CLINICAL:** Malignancy cannot be determined histologically. Watch the behavior of the tumor; if it metastasizes, then it's malignant.
- **SERTOLI-LEYDIG CELL TUMORS:** Rare tumor of "Low malignant potential."
 - **SYMPTOMS:** Occurs in younger age group.
 - Overall, 50% of patients present with hirsutism.
 - 5-yr survival = 60-70%
 - **SUBTYPES:**
 - **Sertoli-cell Tumor (Arrhenoblastoma):**
 - **Leydig-cell Tumor (Androblastoma):** Tumor is androgen secreting, and patient will present with hirsutism.

OVARIAN GERM-CELL TUMORS: Malignant tumors are quite rare, compared to their incidence in the testis.

- **DYSGERMINOMA:** Male counterpart to seminoma.
 - **PATHOLOGY:** Primordial germ cells
 - Clear glycogen-filled cytoplasm arranged in large nests.
 - **SYMPTOMS:** Occurs in younger women and has a very good prognosis.
- **ENDODERMAL SINUS (YOLK-SAC) TUMOR:** Rare and highly malignant.
 - **EPIDEMIOLOGY:** Rare, usually happen in young patients 10-12.
 - **PATHOLOGY:** Tumor resembles the mesenchyme of the primitive yolk-sac.
 - **alpha-Fetoprotein (AFP):** Means of both diagnosing the tumor and monitoring it.
 - **Schiller-Duval Bodies:** Characteristic structure resembling fetal glomeruli.
 - **TREATMENT:** Surgery is usually curative. Good prognosis despite being highly malignant.
- **CHORIOCARCINOMA:**
 - **EPIDEMIOLOGY:** Rare tumor, occurring in younger age groups.
 - **PATHOLOGY:** Very malignant, aggressive, and hemorrhagic.
 - Composed of neoplastic cytotrophoblastic and syncytiotrophoblastic cells.

- **Human Chorionic Gonadotropin (hCG):** Tumors secrete hCG which aids in identification.
 - **PATHOGENESIS:** Can be derived from the placenta (gestational choriocarcinoma) or the ovary.
- **GONADOBLASTOMA**
- **TERATOMA (DERMOID CYST):** Benign. Relatively common (relative to the other ones)
 - **PATHOLOGY:** All three germ-layers. More than 90% contain skin, sebaceous glands and hair follicles. Can be very large.
 - **EPIDEMIOLOGY:** 25% of all ovarian tumors with a peak incidence in the third decade.
 - **Struma Ovarii:** Dermoid cyst containing thyroid tissue. It is a unique cause of hyperthyroidism and can actually lead to ectopic thyroid cancer.
 - **SUBTYPES:**
 - **Mature Teratoma:** Most common and with best prognosis. Contains mature tissues.
 - **Immature Teratoma:** Contains embryonal tissue in addition to the mature tissue, and is more solid. Often contains neural tissue. Has a poorer prognosis.

KRUKENBERG TUMORS: Tumors metastatic to the ovary, most often originating from stomach.

- **PATHOLOGY: Signet-Ring Cells,** cells filled with glycogen, are usually seen, as the cancer cells are mucin-secreting.

PLACENTA and GESTATION

PLACENTA:

- **INFECTIONS:**
 - **PATHOGENESIS:** Placental infections result from complication of pregnancy.
 - **Premature Rupture of Membranes (PROM)** will result in ascending infection.
 - Induced abortions
 - Hematogenous spread: uncommon cause of placental infection.
 - Sexual intercourse during 3rd trimester. Probably a good idea not to do that.
 - **BUGS:** Hemolytic *Strep* and anaerobic *Strep* are the top two.
 - **TYPES:**
 - **Placentitis**
 - **Chorioamnionitis:** Infection of fetal membrane
 - **Funisitis:** Infection of umbilical cord.
- **ARTERIO-VENUS SHUNTING:** In monozygotic twins, sometimes one fetus will get the inordinate share of blood supply, resulting in complications (low birth weight, death) for the other twin.
- **ABRUPTIO PLACENTAE:**
- **PLACENTA PREVIA:** Embryo implants near the cervical opening, and placenta develops near the internal os.
 - **SYMPTOMS: Post-partum bleeding** is often very bad, as the placental vessels are easily sheared due to position of placenta.
 - **TREATMENT:** Pre-natal diagnosis (sonogram) can prevent bad complications at birth. Do elective C-Section.
- **PLACENTA ACRETA:** Abnormal adherence of placenta to the uterine wall. Placenta can remain adherent after delivery.
 - **SIMPLE PLACENTA ACRETA:** Attachment of villi to the myometrium without further invasion.
 - **PLACENTA INCRETA:** Villi invade the underlying myometrium.
 - **PLACENTA PERCRETA:** Villi penetrate the full thickness of the uterine wall.
 - **CLINICAL:** Attached placenta can result in life-threatening bleeding and may require hysterectomy.

TOXEMIA of PREGNANCY:

- PATHOGENESIS: Complex; multiple theories
 - Reduced resistance to the effects of Angiotensin II
 - Increased renin production.
 - Increased prostaglandins.
 - Placental production of a thrombogenic substance -----> possibly lead to DIC.
- PATHOLOGY:
 - Thrombosis, DIC leads to infarction of kidney, liver, and other organs.
 - May infarct the placenta itself.
- SUBTYPES:
 - **PREECLAMPSIA**: Mild toxemia.
 - **ECLAMPSIA**: Severe toxemia.
- SYMPTOMS: **Hypertension, proteinuria, edema**, and in its most severe form, **convulsions**.
 - Risk at first pregnancy is much higher than with subsequent pregnancies.
 - Delivery usually makes the symptoms alleviate. The goal is to try to get to delivery (perhaps induce early) before the eclampsia becomes bad.

SPONTANEOUS ABORTION: *A large number of spontaneous abortions are related to chromosomal abnormalities in the fetus.*

- **Threatened Abortion**: The pregnancy is hanging by a string. It may be able to be saved with some precautions.
- **Inevitable Abortion**: No intervention possible.
- **Missed Abortion**: Baby dies within the gestational sac and remains in the uterus. Curettage is required to evacuate the fetus.
- **Incomplete Abortion**: Parts of the fetal material remain in uterus.

ECTOPIC PREGNANCY:

- PATHOGENESIS: Fibrotic tubes from PID, usually.
- SYMPTOMS: Rupture and hemorrhage of tubes are most feared complication. Rupture usually occurs by 12 weeks.

TROPHOBLASTIC DISEASE:

- **COMPLETE HYDATIDIFORM MOLE**: Homozygous Diploid (XX, 46)
 - PATHOGENESIS: Results from the fertilization of an ovum that lacks functional DNA, hence *all chromosomes are paternal*.
 - EPIDEMIOLOGY:
 - Very young (younger than 15) and very old (older than 50) mothers are at increased risk.
 - Much more common in SE Asian women.
 - PATHOLOGY: Placenta has grossly swollen chorionic villi, resembling a bunch of grapes. Trophoblastic proliferation.
 - *No embryo* is present.
 - *Very high hCG levels*
 - SYMPTOMS: Present in second trimester of pregnancy with abnormal uterine bleeding.
 - COMPLICATION: Gestational **choriocarcinoma** can develop from it.
- **PARTIAL HYDATIDIFORM MOLE**: Triploid (X, 63)
 - PATHOGENESIS: Results from either two sperm fertilizing the same egg, or one primary spermatocyte (still diploid) fertilizing an egg.
 - PATHOLOGY: Embryo starts developing, but dies at about 10 weeks.
- **INVASIVE MOLE (CHORIOADENOMA DESTRUENS)**: More aggressive disease, rare.
 - PATHOLOGY: Invasion of the myometrium, and very large amounts of hCG.
- **GESTATIONAL CHORIOCARCINOMA**: Very rare.
 - PATHOGENESIS: Can arise from a complete hydatidiform mole.
 - PATHOLOGY: Very large, hemorrhagic tumor.

- Contains both cytotrophoblast and syncytiotrophoblast, as all choriocarcinomas do.
- No chorionic villi will be present.
- Secretes **hCG**, as other choriocarcinomas do.

THE BREAST

CONGENITAL DISORDERS:

- **SUPERNUMERARY NIPPLES:** Nipples or whole breast tissue dispersed along the axillary breast-line: from axilla, down mid-clavicular line, converging on inguinal region.
- **CONGENITAL INVERSION**

GYNECOMASTIA: Enlargement of the adult male breast usually caused by an excess of estrogenic hormones in circulation, as in cirrhosis or hormonally active tumors of the testis and adrenals.

GALACTOCELE: Cystic collection of milk, in lactating women. Milk collects and causes inflammation, to the point that it needs to be aspirated.

MASTITIS: Extreme breast tenderness encountered during lactation.

FIBROCYSTIC CHANGE: Very common.

- **EPIDEMIOLOGY:** Mid to late reproductive years.
- **PATHOGENESIS:** Normal cyclical effects of hormones and aging bring on the changes.
- **PATHOLOGY:**
 - **Histological Properties:**
 - Cystic dilatation of terminal ducts
 - Relative increase in fibrous stroma
 - Variable proliferation of terminal duct epithelial elements.
 - **Apocrine Metaplasia:** Epithelial lining of cysts often show characteristic change. No relation to cancer.
- **SUBTYPES:**
 - **NON-PROLIFERATING FIBROCYSTIC CHANGE:** No increased risk for cancer
 - **EPITHELIAL HYPERPLASIA:**
 - **Epithelial Hyperplasia with Atypia:** Shows a **4-5X** increased risk for cancer.
 - **Epithelial Hyperplasia without Atypia:** **1.5-2X** increased risk for cancer.
 - **SCLEROSING ADENOSIS:** Less common variant. Sclerosis and proliferation around the small lobules, which resembles carcinoma, but it isn't.
- **SYMPTOMS:** Lumps and tenderness, which are *hormone-sensitive* and responsive to changes in the menstrual cycle. This distinguishes the lump from a carcinoma, which does change in size or tenderness with the menstrual cycle.

BENIGN TUMORS:

- **FIBROADENOMA:**
 - **PATHOLOGY:** Composed of elongated ducts and hyperplastic stroma resembling intralobular connective tissue.
 - **EPIDEMIOLOGY:** Adolescents and young women. Most common benign neoplasm of the breast.
 - **SYMPTOMS:** Sharply circumscribed spherical nodule.
 - **Freely mobile:** The lump will move on palpation. This distinguishes it from a cancer, which is anchored to the stroma so it stays put.
- **INTRADUCTAL PAPILLOMA:** Benign solitary lesions within the ducts.
 - **EPIDEMIOLOGY:** Middle-aged and older women.
 - **SYMPTOMS:** Nipple discharge, nipple retraction. The lump is generally right beneath the nipple.

- TREATMENT: Surgical excision.

BREAST CANCER:

- EPIDEMIOLOGY: Most common cancer of U.S. females, and 2nd most common killer after lung cancer.
 - Peak ages of diagnosis: 45-49, 55-59.
 - PATHOGENESIS:
 - GENETIC FACTORS: Strong familial component.
 - HORMONAL FACTORS: **Estrogen** promotes breast cancer.
 - Thus, *early menarche, late menopause, and nulliparity* all increase the risk for breast cancer.
 - Multiparity and early menopause are both protective.
 - DIAGNOSIS: Non-mobile mass.
 - **Mammography** is especially useful in identifying **microcalcification**, which is characteristic of breast cancer.
 - CARCINOMA *IN SITU*: Risk for progressing to invasive cancer is **10X** that of normal.
 - **INTRADUCTAL CARCINOMA *IN SITU***: Arises in the terminal duct lobular unit, and has two subtypes.
 - **COMEDOCARCINOMA**: Composed of large, pleomorphic cells arranged around areas of central necrosis.
 - **Comedos**: Pimple-like. The necrotic material + PMN's can be squeezed from the tumor, just like pimples, hence the name. Also see atypia and necrosis, as would expect for carcinoma.
 - CLINICAL: It is easy to diagnose and carries a good prognosis.
 - **PAPILLARY-CRIBRIFORM CARCINOMA**: Tumor cells grow in papillary structures and form fenestrations within the distended ducts.
 - **Cribriform**: Glands are back-to-back and crowded, but still contained by the basement membrane.
 - **LOBULAR CARCINOMA *IN SITU***: Arising in the terminal duct lobular unit.
 - Monotonous-looking cells, as compared to comedocarcinoma.
 - **PAPILLARY CARCINOMA *IN SITU***: Rare and less dangerous tumor, originating in the larger branches of the duct system.
 - INVASIVE CARCINOMA:
 - **DUCTAL CARCINOMA**: The most common form of breast cancer, 65-80% of all cancers.
 - PATHOLOGY: Invasive carcinoma arising in terminal duct lobular unit.
 - Gross Specimen: Poorly defined margins, firm, gray or white specimen, which cuts with characteristic gritty sensation.
 - **Desmoplasia**: Calcification occurs in response to the cancer, making the lump larger and more visible on X-ray.
 - **LOBULAR CARCINOMA**: Second most common cancer.
 - PATHOLOGY: Invasive carcinoma arising in lobular epithelium.
 - **Indian Files**: Characteristic cords of monotonous cells infiltrating between stromal fibers, found in Lobular Carcinoma.
 - **MEDULLARY CARCINOMA**: Third most common cancer.
 - SYMPTOMS: Well-behaved tumor. Lumpectomy is usually curative.
 - PATHOLOGY: Circumscribed mass that lacks calcification on mammography.
 - **COLLOID (MUCINOUS) CARCINOMA**: Uncommon invasive breast carcinoma. Also has good prognosis.
 - **PAGET DISEASE of the NIPPLE**: Uncommon form of Ductal Carcinoma, which extends outward to involve the epidermis, nipple, and areola. Inflammation around nipple is seen; poor prognosis.
 - TREATMENT: Lumpectomy, mastectomy, radical mastectomy (including lymph nodes) if necessary.
 - **Tamoxifen**: Estrogen antagonist. If the tumor is estrogen-receptor positive, then Tamoxifen works in 70% of cases.
 - *Estrogen-receptor positivity correlates with a good prognosis*. This means that the tumor-cells are better developed, and they responsible to Tamoxifen.
- STAGING:
 - **Stage I**: Solitary tumor 2cm or smaller.

- **Stage II:** Tumor 2-5cm, without nodal masses, or with unilateral moveable nodal metastases.
- **Stage III:** Greater than 5cm, or with nodal metastasis, or any tumor with fixed nodal metastases, or any tumor with fixation to underlying chest-wall muscles.
- **Stage IV:** Any tumor involving chest wall, nodes other than axillary nodes, edema of the arm (blocked lymphatics), or distant metastases.
- METASTATIC PATTERNS: Axillary nodes -----> supraclavicular and infraclavicular nodes -----> internal mammary nodes -----> distant sites
 - Distant Sites: Lung and pleura, liver, bone, adrenals, skin.
- PROGNOSIS:
 - GOOD PROGNOSIS:
 - Estrogen-sensitive tumor (indicates cell maturity, and sensitivity to Tamoxifen)
 - Early menopause, multiparity
 - BAD PROGNOSIS:
 - Late menopause, nulliparity or late age at first childbirth.
 - **Cathepsin-D:** Presence of this proteolytic enzyme correlates with bad prognosis, as it probably facilitates invasion of the tumor.
 - **INFLAMMATORY CARCINOMA of BREAST:** Occurs secondary to dermal lymphatic invasion by the malignant cells, blocking the lymphatic drainage of the skin leading to lymphedema and thickening of the skin. Later will see redness, swelling, and tenderness. Very bad prognosis.
 - **Peau d'orange** - orange peel appearance of skin.

PHYLLODES TUMOR (CYSTOSARCOMA PHYLLODES):

- PATHOLOGY: A giant fibroadenoma. It may be benign or malignant.
 - Generally aggressive locally, but it does not metastasize.
 - Histology looks similar to a benign fibroadenoma, but the stroma is more hypercellular.