

## Pathology Review Flash Cards Renal, LUT, Male Genital, Endocrine

Spring 2009

### Kidney Vascular and Congenital

- **Complete or bilateral renal agenesis:**
  - Rare condition, not compatible with life (stillborn infants)
  - Both kidneys are absent.
  - Results in oligohydramnios (decreased amniotic fluid), which occurs because the renal system fails to excrete fluid swallowed by the fetus.
  - Multiple fetal anomalies all caused by oligohydramnios and collectively known as the oligohydramnios, or Potter, sequence.
- **Unilateral renal agenesis:**
  - One kidney is missing.
  - Much more common than complete renal agenesis.
  - Contralateral kidney undergoes hypertrophy with progressive glomerular sclerosis.

### Kidney Vascular and Congenital

- **Renal ectopia:**
  - Abnormal location of a kidney, frequently in the pelvis.
- **Horseshoe kidney:**
  - The most common congenital kidney disorder
  - Occurs when kidneys are fused at lower pole.
  - As the kidneys ascend during development they frequently catch on the inferior mesenteric artery.
  - Fusion often results in obstruction or infection because of impingement on the ureters.

### Renal - Vascular

- **Benign hypertension**
  - Slightly small kidneys
  - Hyaline arteriosclerosis
- **Malignant hypertension**
  - Rapidly progressive severe HTN
  - Necrotizing arteriolitis
    - *Fibrinoid necrosis*
  - Hyperplastic arteriosclerosis

### Renal Artery Stenosis

- **Renal artery stenosis**
  - atherosclerosis
  - uncommon cause of hypertension (2-5%), (not renal failure)
    - constriction of one renal artery results in stimulation of renin
  - potentially curable by surgical treatment
- **Fibromuscular dysplasia of the renal artery**
  - fibromuscular thickening of the intima, media, or adventitia
  - medial type is more common
  - more common in women and at a younger age (3rd-4th decades)
  - may be single well-defined constriction or series of constrictions in middle or distal portion
- **Affected kidney ischemic, shrunken**
- **Ablative changes in normal kidney**
  - arteriosclerosis from the hypertension, focal segmental GN

### Fibromuscular dysplasia

- **Fibromuscular dysplasia** is a hyperplastic disorder that is usually bilateral, occurs in females, and primarily affects the carotid and renal arteries. Abdominal bruits are commonly heard.
- **Fibromuscular dysplasia** leads to renal artery stenosis, which leads to HTN and possible renal infarction. Renal infarction reduces nephron number, causing increased salt-sensitivity and further increase in HTN.

## Kidney Vascular and Congenital

- **Atheroembolic Renal Disease:**
  - Atheroembolic renal disease occurs when a piece of plaque from the aorta and/or other large arteries breaks off and travels through the bloodstream, blocking small renal arteries. Because renal blood supply has no collaterals, embolic obstructions are prone to producing infarcts which result in a decreased GFR and unilateral renal atrophy.
  - Atheroembolic renal disease is a common cause of renal insufficiency (poor kidney function) in the elderly.

## Kidney Vascular and Congenital

- **Renal Artery Aneurysm:**
  - A renal artery aneurysm is a bulging, weakened area in the wall of an artery to the kidney.
  - Most of these aneurysms are small (less than two centimeters, or about three-quarters of an inch) and without symptoms.
  - Renal artery aneurysms are uncommon, and are generally discovered during diagnostic procedures performed in relation to other conditions

## Autosomal Dominant Polycystic Kidney Disease

- Bilaterally enlarged kidneys with multiple expanding cysts that ultimately destroy the parenchyma
- Pathology
  - external surface appears to be composed entirely of cysts up to 3-4 cm
  - microscopically functioning nephrons exist between cysts
  - cysts arise from tubules and therefore have variable lining epithelium

## Autosomal Dominant Polycystic Kidney Disease

- Clinical:
  - Presentation (variable): 15-30 years old, flank pain, hypertension, hematuria, progressive renal failure
  - Large lesions are palpable
  - 40% have cystic disease of the liver (most common), spleen, pancreas, brain
  - Berry aneurysms in circle of Willis
  - 20% have mitral valve prolapse or other valvular abnormalities
  - No increase in renal cell carcinoma
  - Death due to uremia or hypertension

## Autosomal Recessive Polycystic Kidney Disease

- Pathology
  - Bilaterally enlarged kidneys with smooth external surface
  - On cut section, small cysts in cortex and medulla give kidney a spongelike appearance
  - Dilated channels at right angles to the cortical surface
  - Cysts originate from collective tubules and are lined by uniform cuboidal cells
  - Liver: epithelium lined cysts and proliferation of bile ducts

## Autosomal Recessive Polycystic Kidney Disease

- Clinical:
  - Prenatal and neonatal forms are fatal in infancy
    - Often due to pulmonary hypoplasia caused by oligohydramnios (also causes flattened facies, deformities of feet)
  - hepatic disease predominates in older children (may develop portal hypertension with splenomegaly)

### Other Cystic Kidney Disease

- **Multicystic renal dysplasia**
  - Most common, sporadic
  - Persistence in the kidney of abnormal structures including islands of cartilage, undifferentiated mesenchyme, and immature collecting ducts, with abnormal lobar organization
  - Unilateral or bilateral
  - Cysts and kidneys are variably sized
  - No liver disease

### Other Cystic Kidney Disease

- **Medullary sponge kidney**
  - Present to some degree in up to 1% of population
  - Cystic dilation of papillary ducts of the medulla
  - Bilateral in 70%; not all papillae are affected
  - Calcium oxalate crystals present in dilated collecting ducts
  - Stones, infection, or recurrent hematuria in 3<sup>rd</sup> or 4<sup>th</sup> decade
- **Acquired**
  - Associated with long-term dialysis
  - Cortical and medullary cysts; often contain calcium oxalate crystals
  - Increased incidence of transitional cell carcinoma
  - Usually asymptomatic

### Nephrotic Syndrome

- Syndrome of Glomerular dysfunction that is characterized by *increased loss of proteins in the urine* due to increased basement membrane permeability
- **CLINICAL MANIFESTATIONS**
  - **Massive proteinuria** without hematuria [ $>3.5\text{g/day}$ ]
  - **Hypoalbuminemia** [ $<3\text{g/dl}$ ]
    - **Generalized edema** – Due to ↓'d plasma oncotic pressure
    - Periorbital edema
    - Hypotension! & Activation of the Renin/Angiotensin System
  - **Hyperlipidemia and Hypercholesterolemia** – due to loss of lipoproteins and alterations in liver production of lipoproteins
  - Hyperlipiduria and Oval Fat Bodies
- Increase in Infections due to loss of low weight globulins and complement
- Loss of anticoagulants → hypercoagulable state

### Nephrotic Syndrome Disorders

- **Minimal Change Disease**
  - Most common cause of Nephrotic Syndrome in Children 2-6 yrs.
    - Treated with steroids
- **Pathology**
  - diffuse loss of foot processes of epithelial cells (visceral epithelial injury)
  - no changes seen by light microscopy
  - tubules are laden with lipid (secondary to hyperlipidemia) = "lipid nephrosis"
- severe **SELECTIVE** proteinuria with no loss of renal function; no hypertension or hematuria (Hypoalbuminemia)
- Resolves when children reach adolescence. Adults are slower to respond.
- in adults, associated with Hodgkin's disease, lymphoma, leukemia
- also secondary to NSAID therapy with acute interstitial nephritis

### Nephrotic Syndrome Disorders

- **Membranous Glomerulonephritis**
  - Occurs with chronic antigen-antibody mediated disease
  - Pathology
    - uniform, diffuse thickening of the glomerular capillary wall
    - irregular dense **SUBEPITHELIAL** deposits of **IgG and C3** between BM and epithelial cells with loss of foot processes
    - markedly thickened, irregular membrane
  - Clinical
    - nephrotic syndrome, hematuria, *hypertension*
    - progression results in sclerosis of glomeruli, rising BUN, relative reduction of severity of proteinuria, and development of hypertension
  - course variable; treat underlying condition

### Nephrotic Syndrome Disorders

- **Focal Segmental Glomerulosclerosis**
  - Minority of the glomeruli (focal); Sclerosis involving segments within glomeruli (segmental)
  - Pathology
    - focal detachment of the epithelial cells with denudation of the underlying GB membrane
    - hyaline thickening of *afferent* arterioles
    - IgM, C3 deposition in mesangium
    - accompanied by renal ablation for segmental glomerulosclerosis with tubular atrophy and interstitial fibrosis
  - Associated with
    - HIV/AIDS
    - Dysfunction of podocyte slit diaphragms in glomerular BM; dysfunction of nephrin and podocin caused by cytokines or toxins
  - Nonresponsive to corticosteroids

## Membranous Glomerulonephritis

- Most common nephrotic syndrome in adults
- **Etiology:** Idiopathic, drugs (NSAIDs), Carcinomas, Autoimmune disorders (nephrotic presentation of SLE), Infections (chronic hep B, hep C, syphilis, malaria)
- **Pathogenesis:** Type III hypersensitivity with complement activation.
  - subepithelial immune complex deposits “lumpy bumpy” appearance on immunofluorescence
  - complement activation damages glomerular membrane to produce nonselective proteinuria
  - Basement membrane is laid down over immune complex deposits leading to membrane thickening
- **Light microscope** shows diffuse thickening of the glomerular capillary wall throughout the entire glomerulus
- **Electron Microscope** shows: “spike and dome appearance” with silver stains

## Nephritic Syndrome

- Damage to the glomeruli leading to the formation of holes in the basement membrane. Results in damaged glomerular apparatus and subsequent bleeding into Bowman’s space
- **Clinical Symptoms:**
  - **Oliguria**(due to decreased GFR)
  - **Azotemia** (elevated creatinine and BUN)
  - **Hypertension** (due to retention of salt)
  - **Proteinuria** >150mg but <3.5g
  - **BUN/Creatinine** level of >15
  - **Hematuria** – best defined as *red cell casts* and RBC with dysmorphic membranes
    - Commonly defined as “smoky brown urine”

## Acute Proliferative

- Post-streptococcal GN
  - 1-2 weeks following Strep pyogenes infection
  - Malaise, nausea, fever, dark brown urine
  - Serum anti-streptolysin O (ASO) titers
  - Acute proliferative glomerulonephritis with glomerular hypercellularity, neutrophils
    - hypercellularity due to infiltration by leukocytes, and proliferation of endothelial and mesangial cells
  - Linear deposition of IgG and complement; subepithelial humps on EM
  - activation of complement is associated with low serum complement levels
  - immunofluorescence shows granular deposits of immunoglobulin, complement
  - resolves with conservative therapy; rarely progresses to RPGN (more often adults)

## Rapidly Progressive (Crescentic) Glomerulonephritis

- Characterized by rapidly declining renal function and onset of renal failure within weeks
- Presence of distinctive crescents made of infiltrating leukocytes, proliferating epithelial cells, and fibrin in most of glomeruli
- obliteration of Bowman’s space & compression of glomerular tuft
  - Eventual crowding out of the glomeruli = renal failure
- fibrin strands are prominent between the cell layers and crescent; distinct ruptures of the BM
- usually immune-mediated injury
  - type I – idiopathic, Goodpasture’s syndrome
  - type II – immune complex-mediated
  - type III – “pauci-immune” with anti-ANCA antibodies (Wegener’s, microPAN)

## Membranoproliferative Glomerulonephritis

- Characterized by hypercellular glomeruli caused by mesangial and endothelial cell proliferation and leukocyte infiltration
- “tram track” appearance of the capillary wall caused by reduplication of glomerular basement membrane
- Two Types
  - Type I
    - granular deposits of complement with or without immunoglobulin
    - Subendothelial electron-dense deposits
  - Type II
    - **C3 Nephritic factor:** IgG usually absent (alternative pathway)
    - Prominent electron-dense deposits along the lamina densa within the basement membrane (splitting of basement membrane)
- Features of nephritis and protein loss; hypocomplementemia
- Chronic immune complex disease, SLE

## IgA Nephropathy (Berger’s Disease)

- frequent cause of recurrent gross or microscopic hematuria
  - mild proteinuria is seen and nephrotic syndrome may develop
- Characterized by IgA deposition within the mesangium
- Often seen after respiratory, gastrointestinal, or urinary tract infection in children and young Adults
- lesions vary considerably
  - focal proliferative glomerulonephritis
  - focal segmental sclerosis
  - crescentic glomerulonephritis

## Diabetic Nephropathy

- Characterized by glomerulosclerosis and a range of nephropathies
  - non-nephrotic proteinuria, nephrotic syndrome, & chronic renal failure
- Also causes
  - arteriolar sclerosis
  - increased susceptibility to infection (papillary necrosis/Acute pyelonephritis)
  - tubular lesions
- Pathogenesis
  - thickened basement membrane and increased mesangial matrix
  - Increased amount and synthesis of collagen type IV and fibronectin
  - nonenzymatic glycosylation of proteins

## Diabetic Nephropathy: Pathology

- Capillary basement membrane thickening
  - diffuse glomerulosclerosis
    - diffuse increase in mesangial matrix with PAS positive deposit
    - continuous with hyaline thickening of arterioles
  - nodular glomerulosclerosis (Kimmelstiel-Wilson disease)
    - ovoid or spherical hyaline masses situated in the periphery of the glomerulus that lie within mesangial core
  - uninvolved lobules and glomeruli all show striking diffuse glomerulosclerosis
- arteriosclerosis – both afferent and efferent (in hypertension, only afferent)
- ischemic tubular atrophy, interstitial fibrosis, and contraction in size of kidneys

## Renal Amyloidosis

- **Renal Amyloidosis**
  - Subendothelial and mesangial amyloid deposits
    - Eventually obliterate glomeruli
  - Amyloid can be identified by special stains such as Congo Red and have bipolarized birefringence under polarized light
  - May present with nephrotic syndrome
  - Kidney size is normal or enlarged
  - Light. Assc with Chronic Inflammatory Diseases like RA, Multiple Myeloma

## Alport Syndrome

- Mainly X-linked recessive disorder involving defective GBM synthesis via abnormal Type IV collagen production
  - Mutation in  $\alpha$ -5 chain of type IV collagen
- Occurs in Adolescent or adult males by age 50
  - presents with nephritic syndrome, nerve deafness, lens dislocation and/or cataracts
  - Dark colored urine (hematuria), mild proteinemia
- Pathology
  - Irregular BM thickening and splitting of the lamina densa
  - Foamy change in tubular epithelial cells
  - Glomerular basement membrane shows attenuation with splitting of the lamina densa on EM
- Progress to chronic renal failure in adulthood

## HUS/TTP of the kidney

- Causes of HUS/TTP are variable but all result in:
  - Endothelial injury/activation → intravascular thrombosis capillaries/arterioles
  - Platelet aggregation
- Thrombi in renal vessels/glomeruli → renal failure
- Childhood HUS
  - E. coli 0157:H7 → verocytotoxin damages endothelium
  - Sudden onset hematemesis and melana, severe oliguria, hematuria, microangiopathic hemolytic anemia, neurologic changes
  - Kidney morphology: patchy or diffuse cortical necrosis, thickening/splitting of glomeruli capillary walls with fibrin deposits

## HUS/TTP of the kidney continued

- **Adult HUS**
  - Initial insult results from: infection (endotoxin/shiga toxin), antiphospholipid syndrome (SLE), placental hemorrhage w/ pregnancy, vascular renal disease, chemotherapy or immunosuppressive drugs
- **Idiopathic TTP**
  - Fever, neurologic symptoms (distinguishes TTP from HUS), hemolytic anemia, thrombocytopenic purpura
  - Genetic defect of enzyme involved in von Willebrand factor cleavage
  - CNS involvement dominates; renal involvement only 50% of time

## Acute Tubular Necrosis

- Most common cause of acute renal failure
- Acute focal tubular epithelial necrosis
  - Sudden lack of perfusion – crush injury, car accident
  - Exposure to toxic agents – Gentamicin, carbon tetrachloride, ethylene glycol, methanol, radiographic contrast agents
  - Ischemic changes – normal components of cell injury
    - Cell detachment, granular casts with Tamm-Horsfall protein
  - Changes are reversible, can have complete regeneration
    - Depends on integrity of tubular basement membrane

## Acute Tubular Necrosis

- 3 clinical phases – symptoms depend on degree of damage
  - Initiation – decline in urine output, increase in BUN
  - Maintenance – decreased GFR, U/O – increased  $\text{Na}^+$ ,  $\text{K}^+$ , water
  - Recovery – increase in output → cannot concentrate urine

## Interstitial Nephritis

- Caused by *sulfonamides, penicillins, ampicillins, cephalosporins, fluoroquinolones, isoniazid, rifampin, NSAIDs, loop diuretics*
- Occurs 2 weeks after drug use
- Maculopapular or diffusely erythematous rash, fever, eosinophils
- Mild proteinuria and hematuria
- Positive leukocyte esterase

## Tubulointerstitial Disease

- Interstitial Nephritis
  - Sulfonamides, penicillins, ampicillin, cephalosporins, fluoroquinolones (cipro, norfloxacin), isoniazid, rifampin, NSAIDs, loop diuretics
  - 2 weeks after use of the drug
  - Maculopapular or diffusely erythematous rash, fever, eosinophils
  - Eosinophils in urine
  - Mild proteinuria and mild hematuria
  - Leukocyte esterase
- Nephrocalcinosis due to hypercalcemia
  - Loss of concentrating ability
  - Progressive loss of renal function
  - Source of hypercalcemia
    - Metastatic disease to bone
  - May also have calcium oxalate stones

## Renal Cell Carcinoma

- Present with painless hematuria, flank mass, CVA tenderness
- Male dominant -6<sup>th</sup> to 7<sup>th</sup> decade
- Risk factors: smoking, *von Hippel-Lindau disease*
- Yellow mass in upper pole with cysts and hemorrhage
- Microscopic- clear cells that contain glycogen and lipids
- Tendency to invade renal vein- possibly to IVC and R heart
- Mets to: lung> lytic bone lesions> LN> liver/adrenal> brain
- Ectopic secretion of:
  - EPO→ polycythemia
  - Parathyroid-related peptide→ hypercalcemia

## Wilms Tumor

- Most common primary renal tumor in children
- Derived from mesonephric mesoderm
- Large, solitary well-circumscribed mass
  - necrotic gray-tan homogeneous tumor
  - Cyst formation and focal hemorrhage
  - Recapitulation of different stages of nephrogenesis
  - Bilateral and multicentric tumors associated with familial disease
- 2 hit hypothesis
  - Premalignant nephroblastomatosis followed by 2<sup>nd</sup> genetic insult
- Present with large, palpable abdominal mass in 2-5 year old
  - Hematuria after trauma, intestinal obstruction, hypertension

## Urothelial (transitional cell) carcinomas of renal pelvis

- 5-10% of primary renal tumors
- benign papillomas to frank papillary carcinomas
- because they lie within pelvis, discovered when small
  - early symptomology includes obstruction, hematuria, and fragmentation of tumor
- analogous to tumors of bladder, urinary tract
- may be multiple
- associated with analgesic nephropathy
- infiltration of wall of pelvis and calyces; prognosis is not good

## Renal - Infection

- Ascending Infection – E. coli; UT abnormalities
- Hematogenous dissemination
  - Patient ill with sepsis, or other site of infection
  - Wedge-shaped regions of yellow-white cortical necrosis
- Acute pyelonephritis
  - Fever, leukocytosis
  - Flank, CVA pain
  - WBC and WBC casts
  - Vesicourethral reflux important
  - E coli most common organism (non-obstructed)

## Renal - Infection

- Chronic pyelonephritis
  - Reflux nephropathy; vesicoureteral reflux
  - Coarse, irregular scarring
  - Blunting and deformity of calyces
  - Assymetric involvement of the kidneys
  - Loss of tubules with loss of concentrating ability resulting in polyuria
  - Inflammatory infiltrates (lymphocytes, plasma cells, neutrophils)
  - Interstitial fibrosis
  - Involvement of collecting systems, hydronephrosis may cause thinning of cortex

## Urinalysis

- **Specific gravity**
  - A normal specific gravity is between 1.01-1.025. It reflects the ability of the kidneys to concentrate urine.
  - The first sign in renal disease is a persistent SG <1.01
- **pH:**
  - The kidneys maintain a normal acid-base balance by reabsorbing a variable amount of sodium ions by the tubules and tubular secretion of hydrogen and ammonium ion exchange.
  - An acid urine with a pH < 6 can be seen in patients on a high protein diet, in acidosis, uncontrolled diabetes mellitus, and renal tubular acidosis.
  - An alkaline urine may be found either with urinary tract infections (Proteus) or possible bacterial contamination of an old specimen with urea-splitting organisms.

## Urinalysis

- **Protein:**
  - **Minimal proteinuria**- (< 0.5 grams per day)- associated with glomerulo-nephritis, polycystic disease of the kidneys, renal tubular disorders, the healing phase of acute glomerular nephritis, and latent or inactive stages of glomerulonephritis.
  - **Moderate proteinuria**, ( 0.5 grams to 3.5 grams per day) may be found in the vast majority of renal diseases, such as mild diabetic nephropathy, and chronic glomerulo-nephritis.
  - **Severe proteinuria**, (> 3.5 grams per day) is significant for nephrotic syndrome. It can also be seen in nephrosclerosis, amyloid disease, systemic lupus erythematosus, renal vein thrombosis and congestive heart failure.

## Urinalysis

- **Glucose:** the threshold of blood glucose is 250 mg percent. When glucose exceeds this number, the glucose transporters or the PCT saturate and sugar overflows into the urine. Glucose should not be found in the urine normally (except in pregnancy which will decrease the saturation capacity of glucose in the PCT)
- **Bilirubin:** the presence may suggest hepatocellular disease versus the presence of hepatobiliary obstruction or viral hepatitis
- **Urobilinogen:** small amounts are normal in the urine. An increase may be indicative of liver disease, congestive heart failure, or hemolytic anemia. An absence of urobilinogen indicates hepatobiliary obstruction

## Urinalysis

- **Nitrites:** usually sensitive for nitrogen releasing bacteria (E.Coli). Bacteria reduce nitrates to nitrite via a reductase enzyme.
- **Leukocyte esterase:** released from neutrophils in response to bacterial infections of the GU tract, sign of infection. (Urinalysis with positive Leukocyte esterase but negative bacterial cultures--> chlamydia).
- **Casts:** indication of tubular damage.
  - **RBC casts** =glomerular inflammation (nephritic syndromes)
  - **WBC casts** =tubulointerstitial nephritis, acute pyelonephritis, glomerular disorders.
  - **Granular** (“muddy brown”) **casts** = acute tubular necrosis.
  - **Waxy cast** =often very broad, are a sign of chronic renal failure.
  - **Hyaline casts** =nonspecific and often naturally occurring.
  - **Fatty casts** = nephrotic syndrome

## Urinalysis

- **Color:** affected by concentration of urine. Darker urine indicates either highly concentrated urine or the presence of bilirubin. Red urine indicates blood or myoglobin. Bright yellow urine may be secondary to vitamin intake.
- **Turbidity:** normal urine is clear. Amorphous phosphates or amorphous urates may cause urine to appear more cloudy or hazy.
- **Red blood cells:** normal should be 0-2. > 2 red blood cells may indicate trauma (stone), menstruation, infection, cancer, or nephritic syndrome.
- **White blood cells:** > 5-10 white blood cells may be an indication of inflammation or infection.

## Renal Obstructive Disease

- Obstruction → ↓ urine flow → ↑ medullary pressure  
→ ↓ tubular function → ↓ GFR
- Complications:
  - Hydronephrosis
  - Interstitial inflammation and fibrosis
  - Urinary stasis: ↑ d susceptibility to infection, stone formation
  - If chronic: pressure atrophy with cortical thinning and degeneration of the medullary pyramids
- Types:
  - Unilateral: may be asymptomatic until late
  - Partial bilateral: polyuria, dilute urine, salt wasting, tubular acidosis
  - Complete bilateral: oliguria, anuria

## Renal Obstructive Disease

- Congenital causes
  - Ureteral strictures
  - Posterior urethral valve
  - Ureteropelvic junction narrowing
  - Vesicoureteral reflux (also a cause of ascending renal infection)
- Acquired causes
  - Intrinsic: clots, stones, sloughed papilla, renal/ureteral neoplasms, ureteral strictures, neuromuscular disorders
  - Extrinsic: neurologic deficits, abdominal/pelvic neoplasms, medications (eg. Progesterone inhibits smooth muscle contraction.)

## Renal Obstructive Disease- Urolithiasis

- **Urolithiasis** – *stones formed with supersaturation state; favored by low urine volume and stasis; most unilateral (80%)*
- **4 main stone types:**
  - 75% calcium (calcium oxalate) **\*\*radiopaque\*\***
  - 15% triple or struvite (Mg ammonium phosphate)
  - 6% uric acid **\*\*radiolucent\*\***
  - 1-2% cystine
- Ca oxalate stone in presence of ↑uric acid secretion = *hyperuricosuric calcium nephrolithiasis*
- Struvite stones formed after infection by urea-splitting bacteria (e.g. Proteus and staph) → “staghorn” largest

## Renal Obstructive Disease- Pyelonephritis

- **Acute bacterial**
  - 85% gram neg bacteria (E. coli)
  - Nosocomial: Klebsiella, Pseudomonas
  - Symptoms: CVA tenderness, WBC casts, nitrites in urine
- **Chronic bacterial**
  - Often due to vesicoureteral reflux or obstruction
  - Thyroidization: tubules w/ colloid cast
  - Focal segmental glomerulosclerosis
- **Xanthogranulomatous pyelonephritis**
  - Foamy macrophages and plasma cells
  - Associated w/ Proteus infections



## Lower Urinary Tract - Other

- **Hemorrhagic cystitis**
  - Due to radiation or cytotoxic drugs (cyclophosphamide)
- **Chronic obstruction**
  - Leads to bladder hyperplasia, diverticuli, and trabeculae
- **Vesicoureteral reflux**
  - Improper insertion angle of ureter into bladder
- **Cystitis cystica/glandularis**
  - Cell nests form cystic structures in bladder wall
  - Glandularis: Colonic type metaplasia with goblet cells
    - May predispose to adenocarcinoma

## Lower Urinary Tract - Other

- **Malacoplakia**
  - Associated w/ chronic bacterial infection (eg. immunosuppressed)
  - Yellow plaques with foamy macrophages, multinucleated giant cells, Michelis-Gutmann bodies (dark blue staining mineralized concentrations)
  - PAS-positive material
- **Interstitial cystitis**
  - Chronic autoimmune cystitis (women)
  - Suprapubic pain, dysurea, urgency w/o infection
  - All layers of the bladder wall demonstrate fibrosis, inflammatory infiltrate with mast cells
  - Hunner ulcers

## Acute cystitis

- 85% Gram – , usually from fecal flora
- *E. coli* > *Proteus* > *Klebsiella* > *Enterobacter*
- *Staph. Saprophyticus* also common in women
- Associated with catheters, immunosuppression, obstruction/stasis (eg. BPH)
- Other causes:
  - Schistosomiasis (Middle East)
  - Candida, Cryptococcus (long-term antibiotics)
  - Chlamydia, Mycoplasma, Ureaplasma (non-gonococcal urethritis)

## Lower Urinary Tract Neoplasms

- **Transitional Cell Carcinoma (90% of bladder cancer):**
  - Can occur in renal calyces, renal pelvis, ureters, or bladder
  - Male to female ratio of 3:1, most at age 50-80, urban>rural
  - Associated w/ cigarette smoking, B-naphthylamine & other aniline dyes, long-term cyclophosphamide therapy, & long-term analgesic use (phenacetin abuse → TCC of renal pelvis)
  - Presentation: painless hematuria, obstruction (hydronephrosis, pyelonephritis)
  - Often multifocal at presentation
  - Tendency to spread by local invasion to adjacent structures, or may metastasize to liver, lungs, bone
  - Recurrence or new growth after excision is common

## Lower Urinary Tract Neoplasms

- **Transitional Cell Carcinoma (continued):**
  - Low grade: deletion of 9p/9q, loss of tumor suppressor gene
  - High grade: deletion of 13q/17p, mutations of p53 gene on 17p
  - Staging (extent of invasion at time of diagnosis) is most important factor in determining prognosis
    - depth of invasion: lamina propria, muscularis propria, microscopic extra-vesicular, gross extra-vesicular, invasion of adjacent structures
    - Once muscularis propria invasion occurs → 50% 5-year mortality rate

## Lower Urinary Tract Neoplasms

- **Transitional Cell Carcinoma (continued):**
  - Two distinct precursor lesions to invasive urothelial carcinoma:
    - Noninvasive papillary urothelial carcinoma - papillary growth lined by transitional epithelium with mild nuclear atypia and pleomorphism
    - Noninvasive flat urothelial carcinoma (called carcinoma in situ - CIS) - cytologically atypical malignant cells within a flat urothelium

## Lower Urinary Tract Neoplasms

- **Squamous cell carcinomas (3-7% of bladder cancer):**
  - Chronic irritation or chronic infection → squamous metaplasia
  - *Schistosomiasis hematobium* infection
  - Most aggressive and lethal form
- **Adenocarcinomas (rare):**
  - Associated w/ urachal remnants, bladder exstrophy & extensive intestinal metaplasia, histologically identical to GI adenocarcinoma
  - Signet-ring carcinomas - a rare & highly malignant variant
- **Benign leiomyomas and malignant sarcomas (rare):**
  - In kids – embryonal rhabdomyosarcoma (ex sarcoma botryoides)
  - In adults – leiomyosarcoma

## Prostatitis

- Young to middle-aged men
- Lower back pain, urinary/sexual dysfunction
- Chronic nonbacterial type most common (90%)
  - Unknown etiology
- Also acute/chronic bacterial type (5-10%)
- Normal-sized, smooth, tender prostate on rectal exam
- WBC's in prostatic secretions
- May lead to chronic cystitis, epididymitis, infertility

## Prostate – BPH (Benign Nodular Hyperplasia)

- Common in men > age 50, rubbery nodular enlargement on digital rectal exam
- **Not pre-malignant**, but can coexist with prostate cancer
- Symptoms: urgency, hesitancy, frequency, nocturia, dysuria
  - complications of urinary retention include UTI, cystitis, & hydronephrosis
- **Hyperplasia of both glandular epithelium and fibromuscular stroma** – compresses urethral lumen into vertical slit
  - Found in **periurethral and transitional zones** of prostate (inner zones)
- Increased Free fraction of prostate specific antigen (PSA)
- Dihydrotestosterone (DHT) level is the major trophic factor
  - Finasteride therapy inhibits 5 $\alpha$ -reductase, lowers DHT & **shrinks prostate**

## Prostate – Adenocarcinoma

- Also in men > age 50 (most common cancer of older men) increases w/ age, hard irregular nodule on digital rectal exam
- Increased Total PSA w/ decreased Free PSA and increased complexed PSA suggests malignancy
  - in BPH, Free PSA is increased in proportion to Total PSA
- Spread by direct local invasion and through blood & lymph
  - Local extension to seminal vesicles & bladder
  - Metastasis to obturator nodes and pelvic nodes via lymph
  - Metastasis to bone via blood
- **Osteoblastic** metastasis to lumbar spine (most common sites are axial skeleton, proximal femur & pelvis)
  - Alkaline phosphatase is elevated w/ bone metastasis from prostate

## Prostate – Adenocarcinoma cont'd

- Found in **posterior and peripheral zones** (away from urethra)
- Histology shows well defined glandular patterns
  - smaller and more crowded than benign glands, lined by single uniform layer of cuboidal or low columnar epithelium, absent outer layer of basal cells, enlarged nuclei w/ prominent nucleoli
  - perineural invasion often present
- **Gleason Grade** – used to predict indolent vs aggressive course
  - based on glandular patterns and degree of differentiation - 5 grades
  - Score = sum of two grades, dominant pattern plus secondary pattern  
(2 = most differentiated, 1+1 and 10 = least differentiated, 5+5)
- Androgens believed to play role in pathogenesis
  - Disseminated cancer may respond to endocrine therapy

## Cryptorchidism

- Undescended testicle (one or both)
- No spermatogenesis occurs because of  $\uparrow$  in temp within the body
- Associated with testicular atrophy and sterility
- Associated w/ $\uparrow$  risk of germ cell tumors, especially seminoma and embryonal carcinoma
  - Risk of germ cell tumors remains high, even after surgical correction

### Testicular Torsion (a.k.a. torsion of the spermatic chord)

- In torsion – spermatic chord twists – blood supply cut off
- Most men's testicles are attached posteriorly to scrotum by the mesochoonium
  - Without mesochoonium, testicle is free floating in the tunica vaginalis
  - Free to twist, allows for torsion
    - Called the "bell clapper" deformity – predisposes for torsion
  - Other risk factors – adolescence, strenuous physical activity
- Testicle will take on a bluish-black color
- Testicle will be drawn up into the inguinal canal
  - Due to shortening of the spermatic chord from torsion
- Cremasteric reflex will be absent
- VERY PAINFUL – surgery is imperative to save the testicle

### Penile Pathology

- Congenital:
  - hypospadias** (open on ventral surface),
  - epispadias** (open on dorsal surface); both assoc w/failed testes descent/other malform., predispose to infections
  - phimosis**: inflammatory scarring of prepuce causes the opening to be too small to retract; may cause secondary infection/neoplasm
  - paraphimosis**: constriction of glans penis after forced retraction of phimotic prepuce; causes urine retention

### Penile Pathology

- Infectious:
  - **balanoposthitis**: infection of glans penis/prepuce; assoc w/ phimosis
  - **HPV**
- Neoplasms:
  - **condyloma acuminatum**: benign wart (HPV 6/11); red, papillary;
  - **carcinoma in situ aka Bowen's disease**: plaque-like lesions with cellular atypia; no BM penetration; precancerous (HPV 16, 18)
  - **squamous cell carcinoma**: begins on glans penis/inner prepuce; starts as plaque→ papilla; slow-growing; invasive (HPV 16, 18)

### Pituitary Adenomas

- 10% of intracranial neoplasms, peak incidence 30's-50's
- Microadenoma < 1cm, Macroadenoma > 1cm
- Soft, well-circumscribed lesions; larger lesions may compress optic chiasm; 30% non-encapsulated and infiltrate adjacent bone, dura; functional status not reliably predicted by histological appearance
- Relatively uniform, polygonal cells arrayed in sheets or cords, connective tissue is sparse
- May produce over activity of overproduced hormones or loss of activity of other hormones due to secondary destruction of normal cells

### Pituitary Adenomas

Prolactinomas (30%)-most common	Hyperprolactinemia→ amenorrhea, galactorrhea, loss of libido, infertility
Growth Hormone Adenomas-2 <sup>nd</sup> most common	Children → Gigantism Adults → Acromegaly (tumors may become large)
Corticotroph Cell Adenoma	Cushing's Disease
Gonadotroph Cell Adenoma (10-15%)	Secrete hormones inefficiently and variably; LH deficiency = decreased libido in men, amenorrhea in women; usually found due to enlarged size and neurologic complication
Thyrotroph Cell Adenoma (1%)	Hyperthyroidism
Mixed Cell Adenomas	May be mixed population of cells or single population with mixed hormones
Non-functional Adenomas (20%)	Numerous mitochondria, infrequent secretory granules, present with mass effect or hypopituitarism

### Panhypopituitarism

- > 75% loss of pituitary parenchyma
- Causes
  - Tumors: pituitary adenoma, craniopharyngioma, etc.
  - Rathke cleft cyst: ciliated cuboidal ep. w/ goblet cells, proteinaceous fluid
  - Ischemic necrosis: Sheehan syndrome (postpartum) most common
  - Empty sella syndrome: secondary to adenoma or infarction
    - Primary form usually not associated with hypopituitarism
  - Hypothalamic lesions: neoplastic, infectious, autoimmune
- Effects
  - Reduced function of thyroid, adrenal cortex, and gonads
  - Pallor (decreased melanocyte stimulating hormone)

## Diabetes insipidus

- Underproduction of ADH → free water loss
- Causes: head trauma, neoplasms, surgery, idiopathic
- Symptoms:
  - Polyuria, polydipsia, dehydration
  - Brain shrinkage: somnolence, coma, death
  - Serum > 320-330 mOsm acutely w/ possible hyponatremia
- Diagnosis: Rule out diabetes, renal disease first
- Treatment:
  - Fluid replacement w/ normal saline
  - Rapid correction is dangerous

## SIADH

- Overproduction of ADH → increased water retention
- Causes: small cell lung carcinoma, other ADH-secreting tumors, lung disease, surgery, trauma, medications
- Symptoms:
  - Continued natriuresis in the face of hyponatremia
  - Increased total body water, but NO EDEMA
  - Cerebral edema: lethargy, weakness, seizures, coma, death
    - Dependent on rate of hyponatremia development
- Treatment:
  - Free water restriction and salt intake
  - Lithium carbonate or demeclocycline: ADH antagonists
  - If life threatening: hypertonic saline controlled to 125 mEq

## Hashimoto's Thyroiditis

- Chronic autoimmune hypothyroidism
  - middle aged women
- Thyrotoxicosis may occur at onset **T-cell mediated** + Antibodies against: thyroglobulin, thyroid peroxidase
- TWO types
  - 1 – **Goitrous** (most common): lymphocytic infiltrate and germinal center formation
  - 2 – **Atrophic**: gland fibrosis
- **Hurthle** Cells: abundant eosinophilic granules
- Increased risk of lymphoma

## Painless Subacute Lymphocytic Thyroiditis

- Subacute (6-8 weeks) autoimmune **hyperthyroidism**
- **Post-partum women**
- Antibodies against: thyroglobulin and thyroperoxidase
- **PAINLESS GOITER** (vs. subacute viral) containing lymphocytes but no germinal centers (vs. Hashimotos)
- 50% progress to Chronic Lymphocytic thyroiditis (Hashimotos)

## Grave's Disease

- Autoimmune hyperthyroidism
- TSH receptor- stimulating antibodies (IgG)
- Palpable, **diffuse GOITER**
  - Hypertrophy and hyperplasia
  - Diminished colloid
  - Some lymphocytic infiltrate
  - Inc. blood flow causes AUDIBLE BRUIT
- **Exophthalmos**
  - infiltrate & inc. GAG synthesis & EDEMA
- **Pretibial myxedema**
- TX: b-blockers, PTU, radiation, surgery

## Hypothyroidism & Hyperthyroidism

- Hyperthyroidism
  - most common cause is Grave's disease
  - Common signs and symptoms include weight loss despite increased appetite, diarrhea, heat intolerance
  - Serum TSH low, T3 and T4 elevated
  - Medical emergency: thyroid storm
- Hypothyroidism
  - most common cause is Hashimoto's disease
  - Common signs and symptoms include slight weight gain (not obese), constipation, cold intolerance
  - Serum TSH high, T3, and T4 are low
  - Medical emergency: myxedema coma.

## Goiter and Multinodular Goiter

- Diffuse, non-toxic, simple goiter
  - characterized by thyroid enlargement with excess colloid and absence of nodules
  - may be endemic (iodine deficiency) or sporadic.
  - It results from absolute or relative deficiency of thyroid hormone.
- Multinodular goiter may be toxic or non-toxic.
  - TMG and NMG have similar pathogenesis, a combination of environmental and genetic factors.
  - TMG characterized by one or more functional, TSH-independent nodules.
  - TMG may cause subclinical hyperthyroidism or a mild thyrotoxicosis.

## Thyroid Adenomas

- Benign, solitary, “Cold”, discrete masses
- Encapsulated with follicular epithelium
- Constitutive activation of TSH receptor signaling to increase cAMP
- Uniform appearing follicles with colloid

## Papillary Thyroid Carcinoma

- Most common thyroid cancer (75-85%)
- Papillae of fibrovascular stalk covered with cuboidal epithelium
- Orphan Annie nuclei-“ground glass” empty looking nuclei with finely dispersed chromatin
- Psammoma bodies-calcifications within papillae
- present as multifocal cold nodule-decrease in hormone synthesis
- Assoc w/radiation exposure
- Good prognosis; 10 yr survival >90%
- METS: cervical nodes (lymphogenous), lungs

## Follicular Thyroid Carcinoma

- 10-20% of all thyroid cancers (2<sup>nd</sup> most common after papillary)
- Most common single, encapsulated, COLD nodule with uniform small follicles with colloid
- Hurthle cells: cells with granular, eosinophilic cytoplasm
- Invades hematogenously to bone, lung, and liver
- Associated with iodine deficiency goiter
- Indistinguishable from follicular adenoma on FNA

## Medullary Thyroid Carcinoma

- 5% of thyroid cancers
- neurosecretory tumor of parafollicular or C cells
- produces calcitonin (tumor marker) is converted into amyloid (amyloidosis is key pathologic feature)
- associated with MEN II and III
- polygonal or spindle shaped cells form nests, trabeculae or follicles
- can present with paraneoplastic syndrome (pheochromocytoma)
- 5 year survival of 50%

## Anaplastic Thyroid Carcinoma

- <5% of all thyroid ca
- Undifferentiated in older patients
- Multinodular, aggressive, uniformly fatal
- Hx of Follicular Cancer
- See regional invasion and distant metastasis

### De Quervain's Painful Subacute Granulomatous Thyroiditis

- Post-viral hyperthyroidism (2-6 wks) → subacute (6-8 wks) hypothyroidism → complete recovery
- F>M, 30-50 yr. old
- Sudden or gradual onset thyroid enlargement and PAIN with fever, malaise, anorexia, myalgia
- T-cell mediated microabscesses → granulomas and giant cells → minor fibrosis

### MEN Syndromes

- MEN – Autosomal Dominant
  - MEN I – three p's: pituitary, parathyroid, and pancreas
    - Presents with kidney stones and stomach ulcers
  - MEN II – medullary carcinoma of the thyroid PLUS
    - IIA – MCT; Parathyroid hyperplasia; Pheochromocytoma (Sipple Syndrome)
    - IIB or III – similar to IIA, but distinct oncogenic mutation; also accompanied by neuromas or paragangliomas of the skin, oral mucosa, eyes, respiratory tract, GI tract
  - Familial medullary thyroid cancer; II and III associated with *ret* gene

### Primary Hyperparathyroidism

- Most common cause of nonmalignant hypercalcemia
- Most commonly occurs in Females >50 years of age
- Associated with MEN1 and MEN IIa
- Causes:
  - Adenoma (85%). sheets of chief cells with no intervening adipose; remainder of the gland (as well as other 3 parathyroids) will be atrophied. Most commonly involves right inferior parathyroid
  - Primary Hyperplasia- All four glands are involved
- Laboratory findings:
  - Both serum PTH and serum Ca<sup>2+</sup> are increased (abnormal)
  - Chloride:Phosphorus ratio >33

### Primary Hyperparathyroidism

- Clinical Findings
  - Most commonly present with calcium stones of the kidney
  - Nephrons can calcify leading to polyuria and renal failure
  - Peptic ulcers are seen because Ca<sup>2+</sup> stimulates gastrin which increases HCL
  - Acute pancreatitis due to activation of phospholipase by Ca<sup>2+</sup>
  - Osteitis Fibrosa Cystica- cystic bone lesions due to increased osteoclast activity, commonly seen in the jaw. Cause a "salt and pepper" appearance of skull on Xray
- Diagnose with Technetium-99m radionucleotide scan
- Treatment is surgical removal of adenoma

### Hypercalcemia/Hypocalcemia

- Hypercalcemia
  - Sx: fatigue, N/V, metastatic calcification, renal stones, short QT, wide T wave
  - Causes: HyperPTH (Squamous cell Ca of Lung, parathyroidoma), HCT use (high reabsorption), hyperVitaminD (high GI absorption), bone lysis (multiple myeloma, Paget's disease)
- Hypocalcemia
  - Sx: Tetany (Trousseau&Chvostek), spasticity, long QT
  - Causes: low PTH/VitD, defective VitD activation (liver/renal failure), HypoMg

### Adrenal Pathology

- ACTH levels cause adrenal cortex:
- Hyperplasia: pituitary or paraneoplastic ACTH-secreting tumors, 21-hydroxylase deficiency
- Atrophy: exogenous steroids, adrenal cortical adenoma (rest of gland shrinks), 2<sup>o</sup> adrenocortical insufficiency (which is defined as low ACTH)
- Note that adrenal can be small also from autoimmune destruction (Addison's) or large from metastatic tumors
- Adrenal medulla: only pathology is pheochromocytoma

## Adrenal Pathology

- Unilateral vs bilateral
- Yellow coloring
- Medullary metastasis and hemorrhage

## Adrenal - Cushing's Syndrome

- \*Hypercortisolism w/ 4 main causes (iatrogenic, pituitary, adrenal, ectopic)
- Iatrogenic (most common): corticosteroid tx (long term)
  - zona fasciculate (F) /reticularis (R) atrophy b/c ↓ ACTH secretion from ant. pituitary
  - NO androgen excess
- Pit. tumor: Cushing's DI – benign ant. tumor secreting ACTH → zona F/R hyperplasia (excess cortisol/androgen)
- Adrenal: tumor producing ↑ cortisol (most are monoclonal, benign)

## Adrenal - Cushing's Syndrome cont.

- Ectopic Cushing's
  - any non-pituitary Ca secreting ACTH
  - →most common: small cell Ca of lung (also bronchial carcinoid, thymoma)
  - neither low nor high dose dexamethasone can suppress cortisol (ACTH levels are ↑↑↑)
- Dx test= 24h urine free cortisol (\*gold standard)
- \*Sx: weight gain in adipose areas (moon facies & buffalo hump), muscle wasting as aa are shunted to gluconeogenesis, purple abdominal stria, osteoporosis, DM, hirsutism, HTN, psychological disturbances

## Hyperaldosteronism

- Primary Aldosteronism
  - Autonomous overproduction of aldosterone due to:
    - Aldosterone secreting adenoma (Conn's Syndrome)
      - Solitary, well-circumscribed lesions that are bright yellow on cut section
      - Lipid-laden cortical cells
      - Some nuclear and cellular pleomorphism; no anaplasia
      - Dx important because HTN can be cured surgically
    - Primary adrenocortical hyperplasia
      - Bilateral nodular hyperplasia of adrenal glands
  - Na<sup>+</sup> retention, K<sup>+</sup> excretion → HTN, hypokalemia
  - (-) feedback of renin-angiotensin → ↓ plasma renin

## Hyperaldosteronism continued

- **Secondary aldosteronism**
  - Activation of renin-angiotensin system by:
    - Decreased renal perfusion
      - Nephrosclerosis, renal artery stenosis
    - Arterial hypovolemia and edema
      - CHF, cirrhosis, nephrotic syndrome
    - Pregnancy
      - estrogen induced renin increase
  - Increased levels of plasma renin

## Adrenogenital Syndromes

- Congenital adrenal hyperplasia
  - Most commonly due to 21-hydroxylase deficiency
    - ↓ aldosterone, ↓ cortisol, ↑ androgens, ↑ ACTH
  - Salt-wasting syndrome w/ complete lack of enzyme
    - Hyponatremia, hyperkalemia, hypotension, cardiovascular collapse
    - Male=precocious puberty in boys, oligospermia in older males
    - Female=ambiguous genitalia in infants, virilization in girls/women
  - Simple virilizing adrenogenital syndrome w/ partial lack of enzyme
  - Morphology: bilaterally hyperplastic adrenals; brown cortex due to depletion of lipid
- Adrenocortical neoplasms
  - Androgen secreting adrenal carcinoma

## Adrenal Insufficiency

- Primary acute adrenocortical insufficiency
  - Acute stressor in patient with chronic insufficiency
  - Rapid withdrawal of exogenous corticosteroids
  - Adrenal hemorrhage
    - Vulnerable populations include: newborns, postsurgical patients with DIC, anticoagulated patients
  - Waterhouse-Friderichsen syndrome
    - Most often due to *Neisseria meningitidis* septicemia
    - Rapid adrenocortical insufficiency with massive bilateral adrenal hemorrhage
    - Adrenals converted to sacs of clotted blood
    - Hypotension, hyponatremia, hyperkalemia

## Adrenal Insufficiency continued

- Primary chronic adrenocortical insufficiency (Addison Disease)
  - Autoimmune adrenalitis
    - Scattered residual cortical cells in a collapsed network of connective tissue
    - Variable lymphoid infiltrate
  - Infections: TB, histoplasmosis, coccidioides, AIDS related (CMV)
    - Granulomatous inflammatory reaction with effaced architecture
  - Metastatic cancers: lung, breast, GI, melanoma, hemotopoietic
    - Normal architecture obscured by infiltrating neoplasm
  - Progressive destruction of cortex; 90% destroyed before sx evident
  - Increased ACTH → hyperpigmentation
  - Decreased aldosterone → Hyponatremia, hyperkalemia, volume depletion, hypotension
  - Decreased cortisol → hypoglycemia

## Adrenal Insufficiency continued

- Secondary adrenocortical insufficiency
  - Reduced output of ACTH due to disorder of the hypothalamus or pituitary
    - Metastatic cancer, infection, infarction, irradiation
  - Deficient cortisol and androgens
  - No hyperpigmentation because ACTH low
  - Normal aldosterone because stimulated by renin-angiotensin system

## Adrenal Medulla Tumors

- Pheochromocytoma
  - Sporadic (90%) or associated with MEN syndrome (10%)
  - Adrenal medulla or extra-adrenal paraganglia (paraganglioma)
  - Synthesize and release catecholamines (Epi, NE, dopamine)
    - ↑ blood pressure, tachycardia, palpitations, tremor which can be precipitated by stress, exercise, changes in posture, palpation of tumor
    - Complications: catecholamine cardiomyopathy and precipitation of CHF, pulmonary edema, MI, ventricular fibrillation, or CVA

## Adrenal Medulla Tumors

- Pheochromocytoma
  - Morphology
    - appear encapsulated
    - fibrous trabeculae w/ rich vascularization
    - yellow on cross section;
    - polygonal to spindle-shaped chromaffin cells;
    - stippled "salt and pepper" chromatin
  - Dx: ↑ urinary excretion of catecholamines and their metabolites (vanillylmandelic acid and metanephrines)

## Adrenal Medulla Tumors

- Neuroblastoma
  - Malignant tumor of neural crest cells in kids; N-myc oncogene
  - Adrenal medulla, sympathetic chain (midline), brain
  - 90% make catecholamines (dx similar to pheochromocytoma)
  - Sx: abdominal mass, fever, weight loss, HTN rarely



## Adrenal Medulla Tumors

- Neuroblastoma
  - Morphology
    - fibrous pseudocapsule or infiltrative
    - necrosis; hemorrhage
    - cells w/ dark nuclei and scant cytoplasm growing in solid sheet
    - Rosettes
    - secretory granules
  - Metastasize to liver, lungs, bone marrow, bones, skin
  - Prognosis largely determined by age and stage but a variety of gene abnormalities also contribute to outcome

## Type 1 Diabetes Mellitus

- Usually manifests early (<30); accounts for 10% of cases
- Hyperglycemia due to autoimmune destruction of pancreatic  $\beta$ -cells and resultant failure of insulin synthesis
  - T lymphocytes reacting against poorly defined  $\beta$ -cell antigens
  - Weak genetic predisposition but associated with HLA-DR3/DR4
  - Also associated w/ environmental factors (geographic, viral, toxins)
- Plasma insulin levels  $\downarrow$ ; require insulin therapy for survival
- Ketoacidosis more common with type 1 diabetes
- Pancreas morphology:  $\downarrow$  in number/size of islets; prominent lymphocytic infiltrate (insulinitis)

## Type 2 Diabetes Mellitus

- Often manifests later (>40); accounts for 80-90% of cases
- Hyperglycemia due to  $\downarrow$  responsiveness of peripheral tissues to insulin followed by worsening  $\beta$ -cell dysfunction
  - Genetic factors more important than type 1 but no HLA associations
  - Environmental factors: obesity, sedentary lifestyle, dietary habits
- Plasma insulin concentration is normal or often increased until late in the disease due to  $\beta$ -cell burnout
- Ketoacidosis is much less common
- Pancreas morphology: subtle reduction in islet cell mass; amyloid replacement of islets; fibrosis in later stages

## Non-enzymatic glycosylation in Diabetes

- Glucose binds to proteins on cell surfaces via ketoamine linkages
  - Amount of glycosylation directly related to degree of hyperglycemia
    - Glycosylated RBC's (A1c) can be measured to dx DM
  - Rearrange to form Advanced Glycosylated Endproducts (AGE's) that crosslink and bind to cell surface receptors of endothelium, monocytes, macrophages, lymphocytes, and mesangial cells
    - Cause chemotaxis, cytokine release, vascular leakage, thrombosis, increased synthesis of ECM, entrapment of LDL in vessel walls
  - Complications: Atherosclerosis, CAD, stroke, microvascular injury (neuropathy, nephropathy, retinopathy)

## Small Vessel Disease of Diabetes Mellitus

- Diabetes is a vascular disease
- Diffuse thickening of vessel basement membrane due to nonenzymatic glycosylation & disturbances of polyol pathways
- Capillaries become leaky
- Microangiopathy leads to diabetic nephropathy, retinopathy, and neuropathy
  - Renal: hyaline arteriosclerosis of both afferent and efferent vessels
  - Retina: microaneurysms, macular edema, hemorrhagic exudates, intraretinal angiogenesis (proliferative diabetic retinopathy), retinal detachment, glaucoma, blindness
  - Neuropathy: vasa nervorum
  - Arteriosclerosis leading to hypertension

## Large Vessel Disease of Diabetes Mellitus

- Accelerated atherosclerosis involving aorta and medium-large sized arteries
- Can result in:
  - CAD ( increase incidence of myocardial infarction)
  - Peripheral vascular insufficiency  $\rightarrow$  gangrene of lower extremities
  - Cerebrovascular disease ( ischemic strokes)
  - Renal artery stenosis

## Osmotic Damage and Infection in DM

- Osmotic damage occurs in insulin independent tissues:
  - Retina, kidney, and neurons
- Mechanism of osmotic damage:
  - Hyperglycemic state results in ↑ uptake of glucose in these tissues and subsequent conversion to sorbitol
  - Sorbitol draws water into cells and creates osmotic damage
- Results of osmotic damage:
  - Cataracts
  - Peripheral neuropathy (motor, sensory, and autonomic degeneration)
- Increased propensity for infections
  - Skin (furuncles, abscesses, gangrene), pneumonia, pyelonephritis
  - Fungal (Candida and Mucormycosis), TB, bacterial