Development and Congenital abnormalities:

- Kidney has a complex development, is derived from mesoderm (intermediate layer)
- 3 successive excretory systems: pronephros (non-functional in humans), mesonephros, metanephros
- Metanephros – definitive kidney
- Kidney is derived from 2 parts: metanephric blastema (gives rise to nephrons) and ureteric bud (gives rise to the collecting duct system)
- Congenital kidney abnormalities are common – 10% of all people are born with potentially significant malformations of the urinary system
- CAKUT = congenital anomalies of the kidney and urinary tract
- Agenesis = absence, bilateral or unilateral
- Hypoplasia = small size
- Ectopic = abnormal location, pelvis
- Horseshoe = fused kidneys
  - common 1:500-1000 autopsies
  - lower > upper pole, inferior mesenteric artery

Renal cystic diseases

- Age
- Incidence
- Complications
- Gross appearance: reniform versus irregular shape
- Bilateral versus unilateral versus segmental

Cystic diseases:

- Cystic renal dysplasia
- Polycystic kidney disease: adult, childhood
- Acquired cystic disease (dialysis-associated)
- Localized, simple cysts, cystic carcinoma
- Hereditary syndromes
- Extra-renal involvement

Renal dysplasia:

- Aberrant nephronic differentiation
  - NOT related to neoplasia but a developmental abnormality
  - Dysplasia versus hypoplasia versus polycystic:
    - abnormal development (dysplasia)
    - small size but otherwise normally developed (hypoplasia)
    - cystic but without dysplastic elements (polycystic)

Renal dysplasia = abnormal metanephric differentiation

Multicystic dysplastic kidney: noncommunicating cysts of varying size separated by dysplastic parenchyma and the absence of a normal pelvocaliceal system; associated with ureteral or ureteropelvic atresia (closed passage)
Cystic renal dysplasia - summary:
- Sporadic
- Incidence 1:1000-2000
- Abnormality in metanephric differentiation - persistence of immature elements: cartilage, immature collecting tubules, abnormal lobar organization
- Associated abnormalities: uretero-pelvic junction obstruction, ureteral agenesis/atrophia, other
- Unilateral, bilateral, at times segmental
- Grossly: kidney(s) enlarged, irregular shape – “bunch of grapes”

Impact on lung development:
- Agenesis, Bilateral dysplasia
- Oligohydramnios (decreased amniotic fluid)
- Hypoplastic lungs
- Potter’s syndrome: facial features (flat face, low set ears), developmental defects in extremities

Childhood Autosomal Recessive Polycystic Kidney Disease – ARPKD

1. Typical presentation: renal, liver failure
   - perinatal, neonatal, infantile, juvenile subcategories
2. Epidemiology:
   - rare, incidence 1:20,000
3. Etiology/pathogenesis:
   - PKHD1 gene, 6p, fibrocystin
4. Pathology:
   - bilateral, reniform shape, enlarged, cysts in the cortex and medulla
   - cross-section – sponge-like appearance, saccular dilatation of collecting tubules
   - liver: cysts + portal fibrosis + proliferation of portal bile ducts leading to congenital hepatic fibrosis
5. Tests:
   - radiology
6. Prognosis:
   - renal/liver failure at birth, infancy, juvenile
7. Treatment:
   - transplantation

APKD – Adult Polycystic Kidney Disease

1. Typical presentation: asymptomatic or pain, colic, mass, hemorrhage
   - Hematuria, progressive renal failure, polyuria, HTN, low proteinuria (<2g)
2. Epidemiology: common: 1:400-1000 live births, 6-10% of ESRD in N. America/Europe, 1/800-100 population carries a mutation
3. Etiology/pathogenesis: autosomal DOMINANT, high penetrance genetically heterogeneous: chromosomes 16(PKD1) and 4(PKD2), other?
   - PKD1 (85%) earlier onset of renal failure, more severe
   - PKD2 later onset of renal failure
PKD1 – polycystin 1, function? Cell-cell, cell-matrix interactions
PKD2 – polycystin 2, regulation of intercellular Ca^{2+} levels
abnormalities in cell differentiation
4. Pathology: bilateral, reniform shape, enlarged, mass of cysts, functioning
nephrons dispersed between the cysts, hepatic cysts (40%), intracranial berry
aneurysms (4-10% of deaths), mitral valve prolapse (20-25%)
5. Tests: radiology
6. Prognosis: renal failure middle/late life depending on mutation

Cystic renal diseases - incidence:
- dysplasia 1:1000-2000
- ARPKD 1:20,000
- APKD 1:500-1000
Reniform shape: ARPKD, APKD
Bilateral: ARPKD, APKD, dysplasia - +/-
Segmental: dysplasia +/-
Associated abnormalities
- ureter – dysplasia
- liver: ARPKD, APKD

Medullary diseases with cysts
1. Medullary sponge: relatively common, innocuous
2. Nephronophthisis-medullary cystic disease complex:
   pediatric onset CKD (chronic kidney disease), autosomal recessive

Acquired (dialysis-associated) cystic disease: cortical & medullary cysts
Renal Cell Carcinoma (RCC): 7%/10yrs

Simple cysts:
- very common, multiple or single
- Differential Diagnosis – cystic renal cell carcinoma
- Hemorrhage, pain, calcification

Renal cysts in hereditary syndromes:
- Von Hippel-Lindau Disease
- Tuberous sclerosis

Kidney tumors:
- Malignant – all tumors presumed malignant until proven otherwise!!!
- Pediatric versus adults
- Renal parenchymal versus urothelial

Benign kidney tumors:
- Oncocytoma
- Angiomyolipoma
Oncocytoma:
- Benign
- 10% of renal tumors
- Origin: distal nephron
- Gross: mahogany brown with central scar
- Microscopic: eosinophilic cytoplasms on H&E, abundant mitochondria by electron microscopy

Angiomyolipoma (AML):
- Vessels/smooth muscle/fat (radiologic diagnosis)
- Tuberous sclerosis versus sporadic

Tuberous Sclerosis:
- TSC1 - Hamartin 9q34
- TSC2 - Tuberin 16p13
- Cutaneous angiofibromas, polyps, cysts

Angiomyolipoma: poorly formed vessels+ smooth muscle+fat in variable proportions, most = benign. Smooth muscle and melanocytic markers

Associated benign tumors: brain, kidneys, heart, liver, eyes, lungs, skin

Larger AML tumors can rupture with bleeding

Renal Cell Carcinoma (RCC) – presentation:
1. Clinical presentation:
   - Triad: costovertebral pain, mass, painless hematuria
   - Incidentally discovered – radiologic work-up for OTHER reasons: gall bladder surgery, etc…
   - Fever, malaise, weakness, weight loss
   - Paraneoplastic syndromes: polycythemia, hypercalcemia, HTN, hepatic dysfunction, feminization/masculinization, Cushing syndrome, eosinophilia, leukemoid reactions, amyloidosis
   - Presentation with metastases: lungs, bones

2. Epidemiology:
   - 2-3% of all cancers in adults
   - 65,000 new cases/yr; 40% die of the disease
   - 6-7th decade
   - M>F, 2:1
   - Risk factors: tobacco, obesity, HTN, occupational exposure
   - Chronic renal failure with acquired cystic disease 30-fold increase of risk
   - Most sporadic
   - Familial 4%

3. Etiology/pathogenesis:
   Clear cell type:
-3p, somatic mutation/hypermethylation induced inactivation of the VHL gene (von Hippel-Lindau, tumor suppressor gene)
- loss of VHL gene results in accumulation of the transcription factor HIF-1α (hypoxia inducible factor - 1α) and over-expression of HIF-1α target genes which facilitate cellular adaptation to tissue hypoxia
- VHL gene in development of both sporadic and familial clear cell RCC
- origin from proximal tubular epithelium

Other kidney cancers: chromosomal gains (papillary, met oncogene), losses (chromophobe)

VHL (von Hippel-Lindau) syndrome:
- tumors with high vascularity + clear cells
- hemangioblastoma (central nervous system/cerebellum/spine)
- angiomatas of the retina
- pheochromocytomas (some), other
- 1:40,000, autosomal dominant
- many different alterations in the VHL gene (3p25) with correlation between specific inactivation and phenotype
- age @ onset 37 yrs versus 61 yrs in sporadic RCC
- multiple bilateral cysts & tumors

Control of HIF-1α by VHL:
- under normoxic conditions VHL ubiquitinates HIF-1α, leading to ubiquitin-mediated proteolysis and degradation by the proteasome
- in hypoxic cells, such as those found in tumors, HIF-1α ultimately initiates the transcription of hypoxia-induced genes, including those which promote
  - cell survival under anaerobic conditions
  - angiogenesis
  - metastasis

4. Pathology: dependent on carcinoma type:
- Clear cell carcinoma RCC (Renal Cell Carcinoma) (aka conventional) - 65%;
- Papillary renal cell carcinoma: 10-15%;
- Chromophobe renal cell carcinoma: 5%; chromosomal losses
- other

Renal Cell carcinoma, clear cell type, most common, 65%
Gross: orange; microscopic clear cells

Papillary RCC:
- better prognosis than clear cell RCC
- Papillary architecture
- Hereditary (Familial) - multiple bilateral tumors
- cystic
- Trisomies 7, 16, 17
- Chromosome 7 – MET oncogene

Chromophobe RCC:
Mechanisms of Human Disease
Renal Path V
October 29th, 2018
Maria M. Picken, M.D., PhD

• 5%
• Multiple chromosomal losses
• Distal nephron
• Morphologic overlap with oncocytoma
• Prominent cell membrane “vegetable-like”
• Better prognosis than clear cell and papillary RCC

5. Tests: radiology
6. Prognosis: stage and tumor type dependent
7. Treatment: RCC is extremely chemo-resistant hence surgery has been a mainstay of therapy including metastasectomy (lungs) and cytoreductive surgery combined with immunotherapy and/or targeted therapy
   • Immunotherapy with cytokines: IL-2, IFN-α, checkpoint inhibitors
   • Targeted therapies:
     – multikinase inhibitors (Sunitinib, Sorafenib)
     – monoclonal antibodies to VEGF (Bevacizumab)
     – mTOR inhibitors (Temsirolimus, Everolimus)
mTOR: a central regulator of cancer cell growth, angiogenesis, and metabolism
   [mTOR = mammalian target of Rapamycin]

**Immune checkpoints** are regulators of the immune system
   • These pathways are crucial for self-tolerance, which prevents the immune system from attacking cells indiscriminately
   • Inhibitory checkpoint molecules are targets for cancer immunotherapy due to their potential for use in multiple types of cancers
   • Currently approved checkpoint inhibitors block CTLA4 (Cytotoxic T-Lymphocyte-Associated protein 4), PD-1 (Programmed Death 1) and PD-L1 (Programmed Death ligand 1)
   • For the related basic science discoveries, James P. Allison and Tasuko Honjo won the Nobel Prize in Physiology/Medicine in 2018

Checkpoint therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how cancer can be managed
Below – material on checkpoint inhibition is “good to know” even though it will NOT be included in the exam.
Figure: Upper left: Activation of T cells requires that the T-cell receptor binds to structures on other immune cells recognized as "non-self". A protein functioning as a T-cell accelerator is also required for T cell activation. CTLA-4 functions as a brake on T cells that inhibits the function of the accelerator. Lower left: Antibodies (green) against CTLA-4 block the function of the brake leading to activation of T cells and attack on cancer cells.
Upper right: PD-1 is another T-cell brake that inhibits T-cell activation. Lower right: Antibodies against PD-1 inhibit the function of the brake leading to activation of T cells and highly efficient attack on cancer cells.

Adult renal parenchymal tumors – summary:
- malignant until proven otherwise
- surgical treatment = mainstay, targeted and immune therapies evolving
- prognosis:
  - stage, nuclear grade, tumor histology
  - presence of regional nodal metastases
  - evidence of metastatic disease at presentation
  - patterns of metastases: lung, bone, brain, liver and adrenal gland
- classification evolving, role of molecular studies

Urothelial carcinoma:
- 5-10% of renal tumors = urothelial carcinoma
- adults
• renal pelvis, ureter, frequently also concomitant urinary bladder tumor
• hematuria
• analgesic nephropathy = risk factor

Wilms tumor:
1. clinical presentation: mass
2. epidemiology: pediatric, most common kidney tumor, <10 yo; peak: 2-5 yo
3. Pathogenesis: - mutations WT1, WT2; 75% in otherwise normal children; 25% children with developmental abnormalities Wilms tumor; recapitulates nephrogenesis, nephrogenic rests = putative precursor lesion of Wilms tumor
4. Pathology: abortive glomeruli/tubules/stroma
5. Laboratory tests: radiology
6. Prognosis: excellent, 90% 5 year survival
7. Treatment: surgery with/without chemotherapy depending on stage, chemosensitive

Pediatric malignancies 0-4 years:
• Leukemia
• Retinoblastoma
• Neuroblastoma
• Wilms tumor