DISEASES OF THE TUBULES AND INTERSTITIUM

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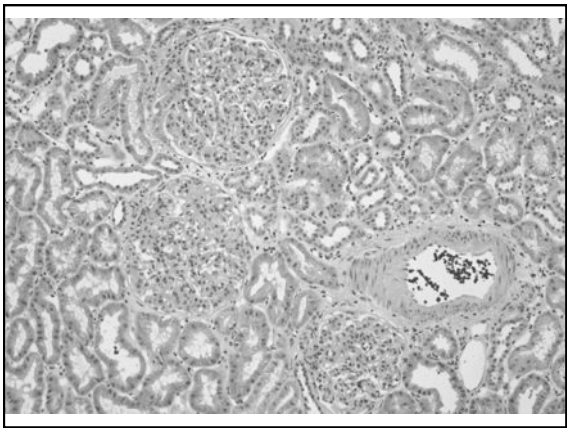
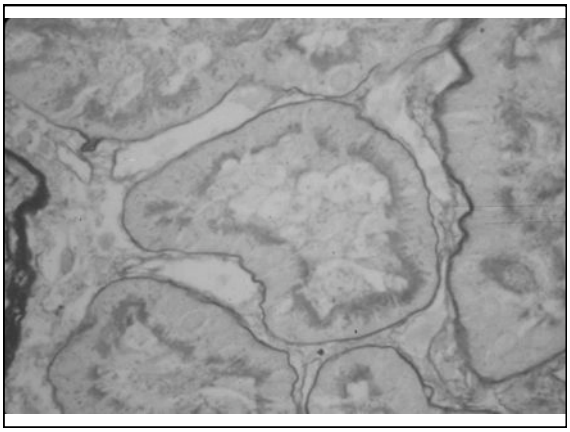
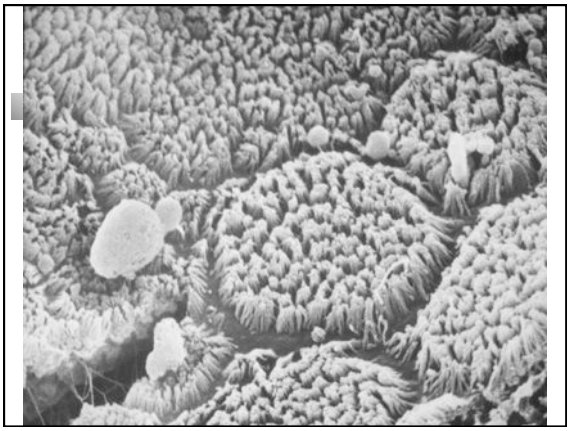
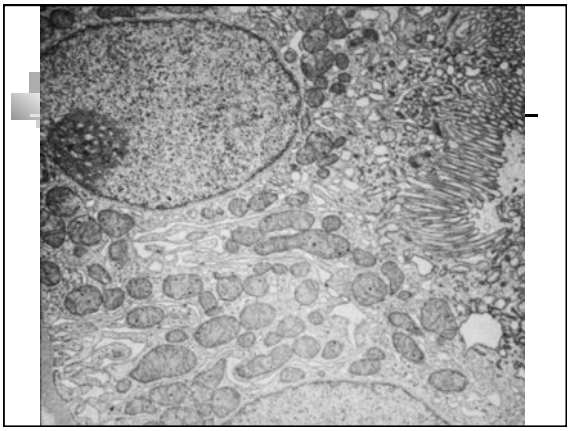
Mechanisms of Tubulointerstitial Disease

- 2 general categories:
  - Ischemic/toxic (non-inflammatory)
    - Acute tubular necrosis
  - Inflammatory
    - Tubulointerstitial nephritis
      - Infection, allergic/drug-induced, systemic disease (eg. Sarcoid), etc









Acute Tubular Necrosis

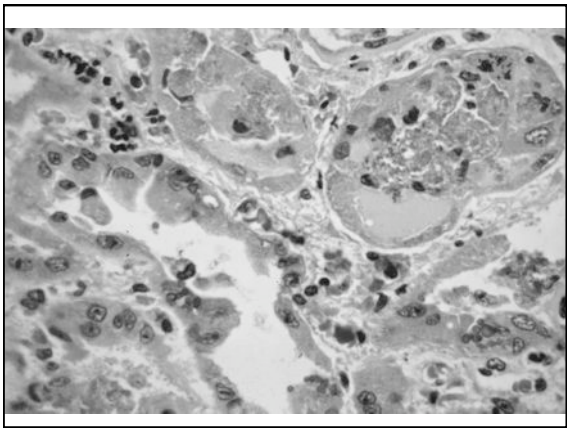
- Clinical-pathologic entity:
  - Clinical: ARF (#1 cause)
  - Oliguria / anuria
  - Minimal proteinuria & bland sediment
  - Increased FE Na
  - Pathology: tubular epithelial injury
    - Not necrosis

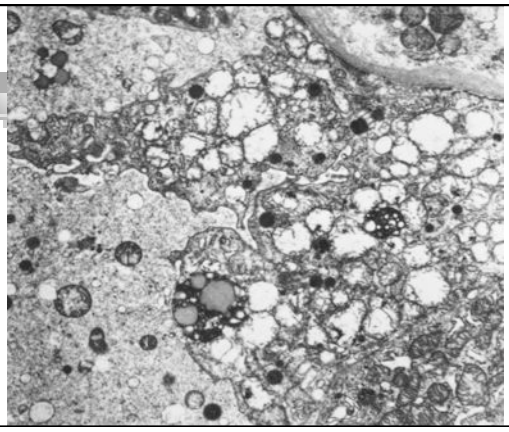
Acute Tubular Necrosis

- Predisposition of tubular epithelial cell
  - High metabolic activity/02 requirements
    - Prone to ischemic/hypoxic injury
  - Role in concentrating/reabsorbing filtrate
    - Increased exposure to toxins
- Two subtypes of ATN
  - Ischemic ATN
  - Nephrotoxic ATN

Ischemic ATN

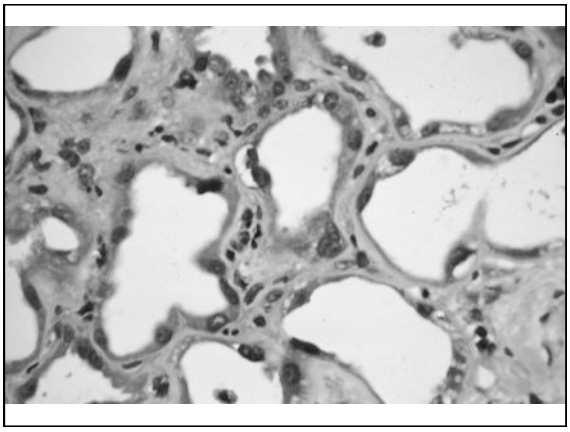
- Occurs in setting of decreased renal blood flow / hypotension
  - Trauma/severe blood loss, CHF, septic shock
- Pathology
  - Gross: P & S
  - Degenerative changes
  - Subsequent regenerative changes
  - Most severe changes in proximal tub and mTAL (makes sense)

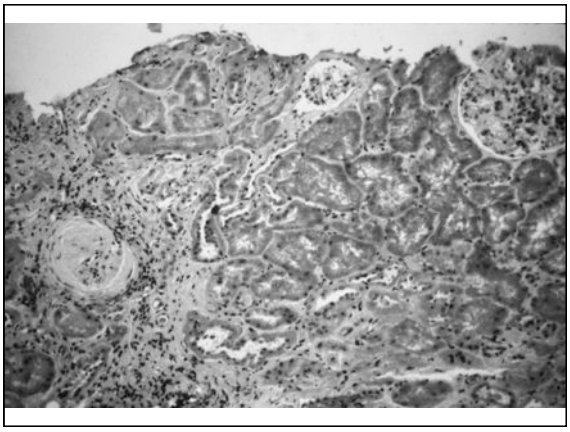


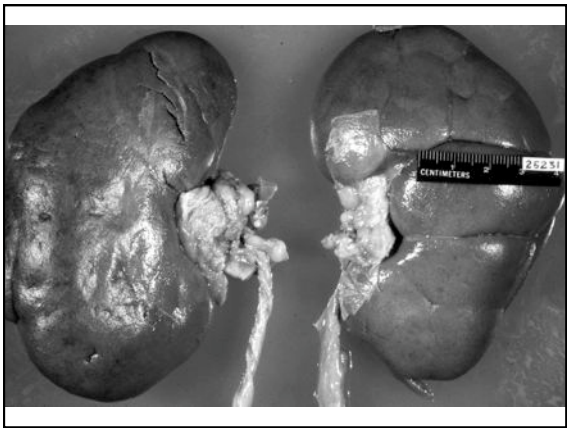


Clinical Phases of ATN

- Initiation
  - first 36 hours, dominated by initial event
- Maintenance
  - up to 3 weeks, oliguric, dialysis required
- Recovery ("diuretic phase")
  - increasing urine output – often substantial, electrolyte abnormali
- Prognosis: > 90% recovery if survive initiating event





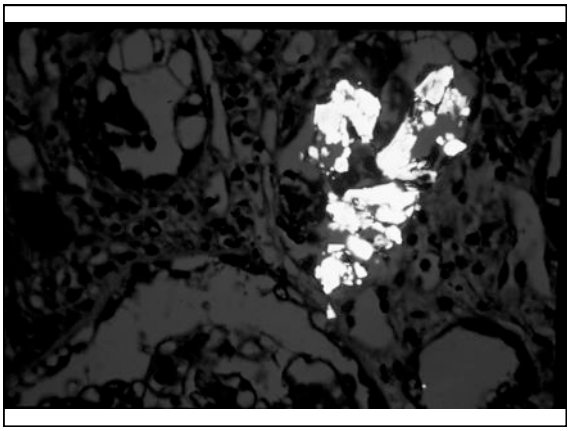


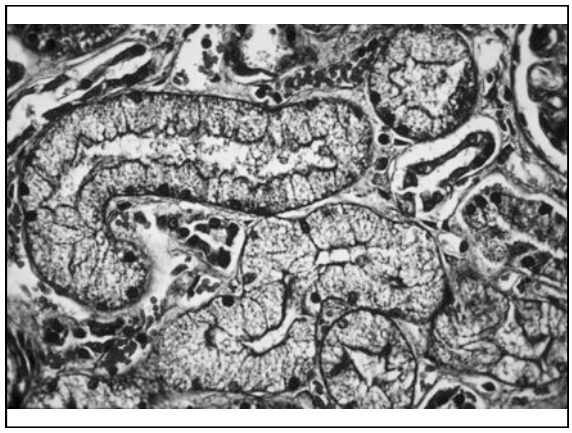
Nephrotoxic ATN

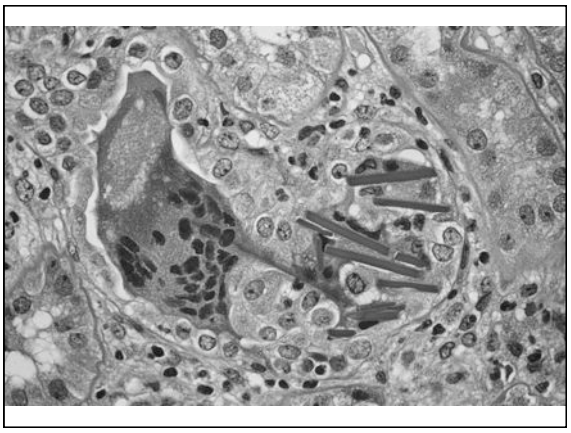
- Many toxins implicated
  - Heavy metals: Hg, Pb, gold, arsenic,...
  - Organic solvents: $CC1_4$, ethylene glycol
  - Therapeutics
    - antibiotics: gentamicin
    - antifungals: amphotericin B
    - chemotherapeutic agents: cisplatin
    - bisphosphonate: zoledronate
    - radiation & radiocontrast
    - pigments: Hgb, Mgb
    - abnormal levels of physiologic substances
    - osmotic agents: mannitol

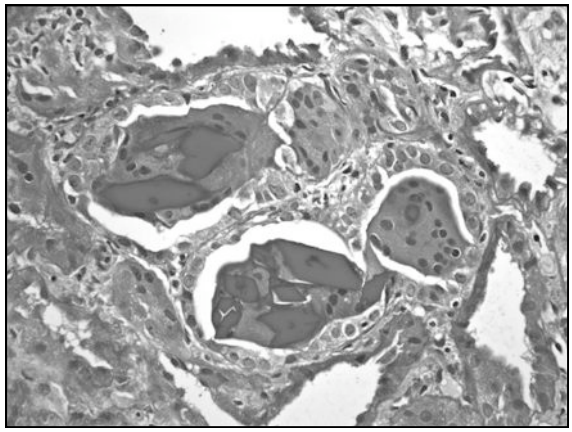
Nephrotoxic ATN

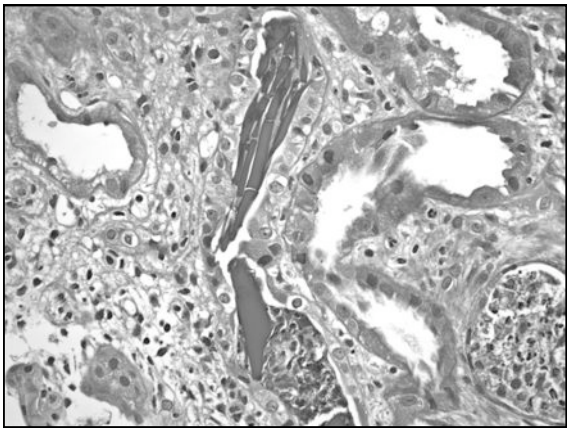
- Similar pathology to ischemic ATN
- Additional, toxin-specific findings:
  - Ethylene glycol
  - Osomotic agents/radiocontrast
  - Light chains
  - Hemoglobin/Myoglobin
- How does GFR decrease?

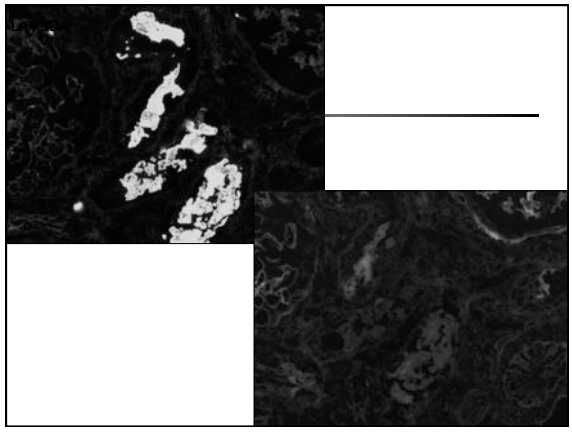


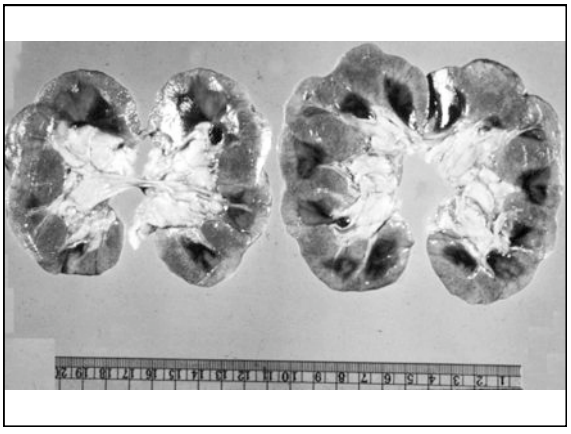


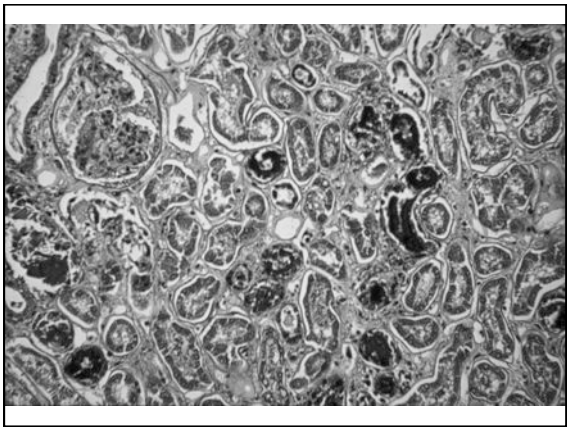












Tubulointerstitial Diseases

- Predominantly interstitial and tubular
  - secondarily involve glomeruli and vessels
  - low grade proteinuria
- A.K.A. Interstitial Nephritis
- Acute forms
  - inflammation, edema and tubular injury
- Chronic forms
  - inflammation, fibrosis, and atrophy
- Etiology: mainly infection or drug-induced

Drug-Induced Interstitial Nephritis

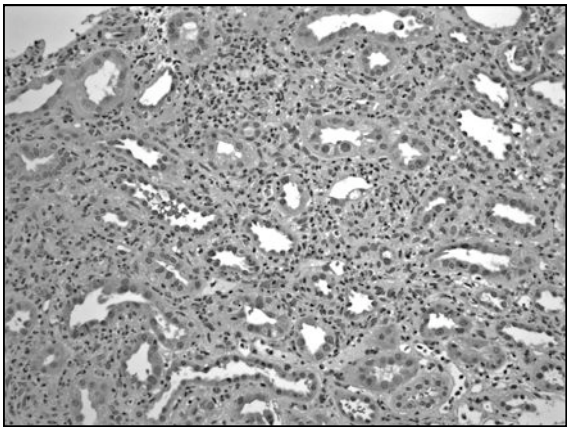
- Clinical: fever, eosinophilia, rash, & RI
  - Occurs 1-2 weeks following exposure
  - sterile pyuria (with eosinophils)
- Hypersensitivity reaction to drug
  - not dose related
- Resolves within weeks of withdrawal
  - Definitive proof: recurs with re-exposure

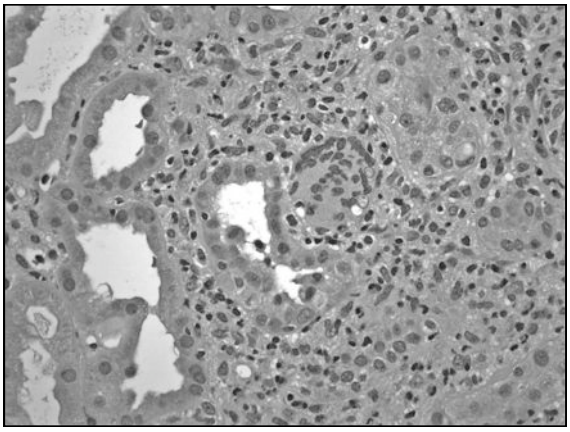
Drug-Induced Interstitial Nephritis

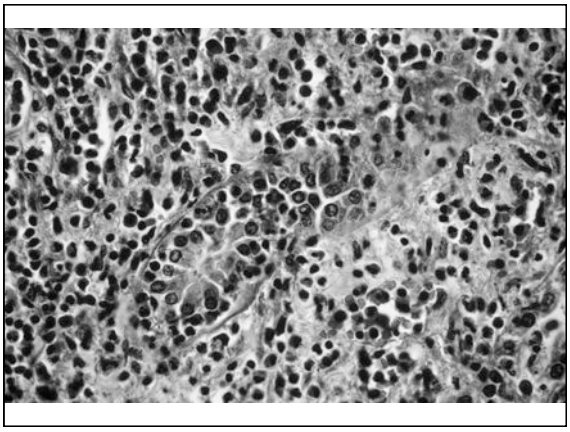
- Causative agents:
  - Antibiotics: synthetic penicillins, i.e. methicillin, ampicillin
  - Other antibiotics: i.e. rifampin, sulfonamides, vancomycin
  - NSAIDs
  - Diuretics: i.e. thiazides
  - Phenytoin
  - Others…

Drug-Induced Interstitial Nephritis

- Pathogenesis: cell-mediated hypersensitivity reaction (T's)
- Pathology
  - interstitial inflammation & edema
  - EOSINOPHLS
  - Tubulitis
  - +/- granulomas







NSAIDs

- Inhibit COX
- Multiple patterns of renal disease
  - Acute interstitial nephritis
  - Acute tubular necrosis
    - Loss of PG vasodilation / precip ATN in the setting of volume depletion
  - Minimal change disease (rarely MG)
  - Papillary necrosis
- Same nephrotoxicity for Cox-2 inhibitors

Acute Pyelonephritis

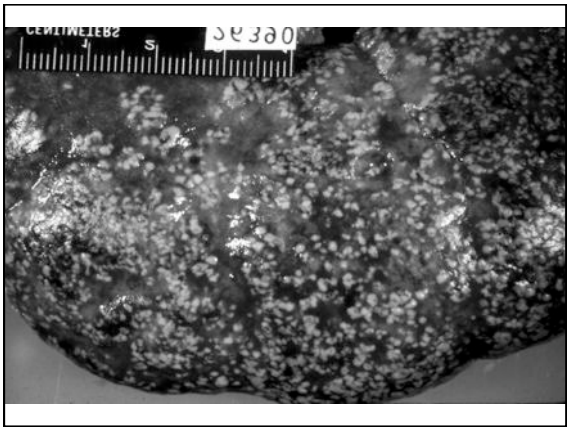
- **Acute suppurative infection of kidney**
- **Clinical: back pain, fever, pyuria, +/- RI**
  - **Urine cultures: confirmation / Ab sensitivity**
- **Route of infection**
  - **ascending > hematogenous**
  - **ascending starts in bladder as UTI (F>M)**
  - **hematog: septic emboli, bacteremia (F=M)**
- **Organisms**
  - **85% gram negative bacilli (#1 E. coli)**
  - **fecal flora**

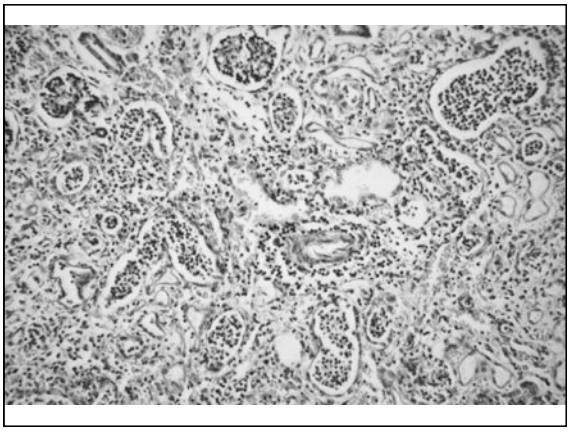
Acute Pyelonephritis

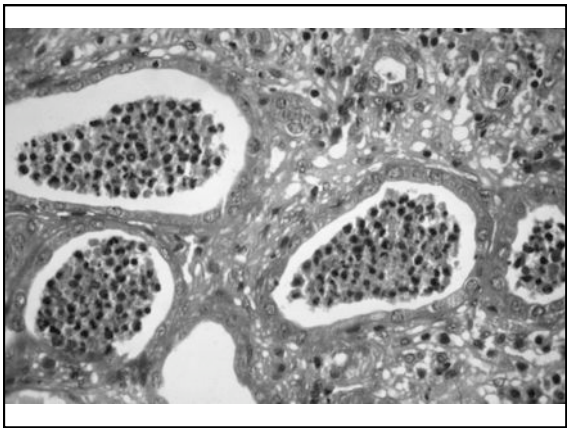
- **Increased risk of ascending infection in three clinical settings**
  - **Obstruction: BPH, tumors, pregnancy, neurogenic bladder (DM)**
  - **Instrumentation**
  - **Vesicoureteral reflux**
    - **50% UTI's in 1st year of life**
    - **congenital anomaly: intravesical portion of ureter lacks normal oblique course that prevents reflux**

Acute Pyelonephritis

- **Gross: normal size, +/- coalescent abscesses**
- **Micro: severe inflammation, PMN's**
  - **Microabscesses**
  - **PMN casts & tubulitis**
  - **Distribution:**
    - **Ascending: originates near medulla**
    - **Hematogenous: cortical**





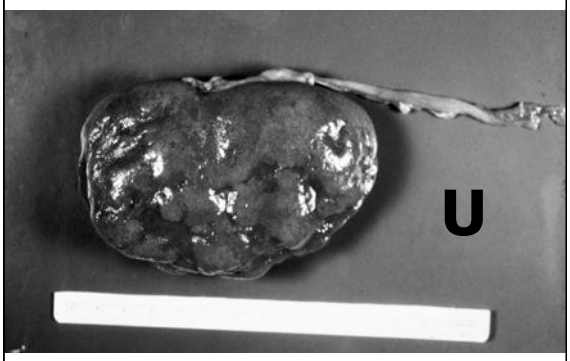


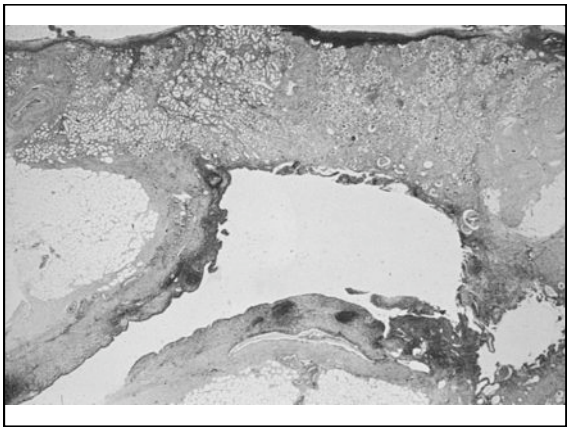
Chronic Pyelonephritis

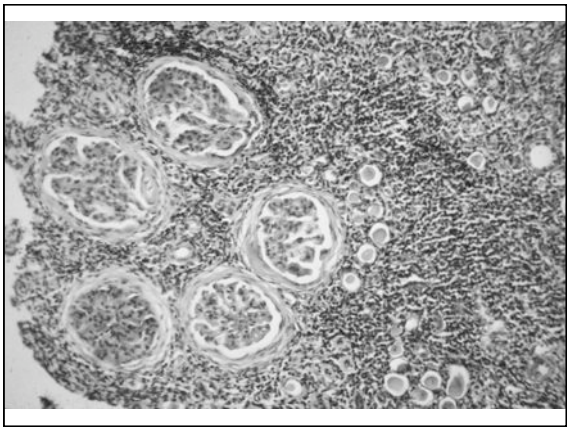
- Definition: chronic renal disorder with scarring, inflammation, and deformity of calyces/pelvis (ascending*)
- Gross: shrunken
  - Irregular, asymmetric broad/flat scars (U*)
  - Papillary blunting and calyceal deformity
- Micro:
  - Disproportionate tubulointerstitial scarring
  - Atrophic tubules with colloid casts ("thyroidization")
  - Chronic inflammation (not PMN's)

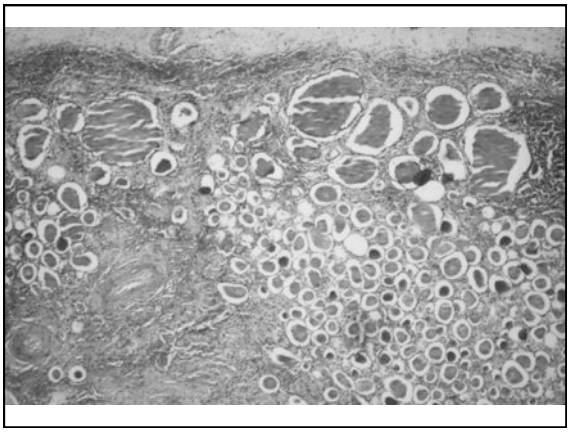
Chronic Pyelonephritis

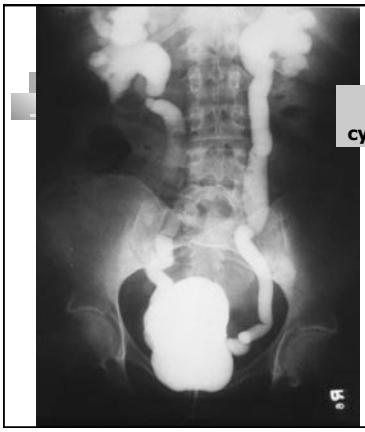
- Clinical
  - insidious onset of RI
  - +/- HTN, mild proteinuria, decreased urinary concentration, culture neg
  - Rarely follows "usual" acute pyelo
  - More common with persistent obstruction or VUR
  - +/- awareness of acute episodes
  - Rx: relieve obstruction / correct VUR, antibiotics as indicated







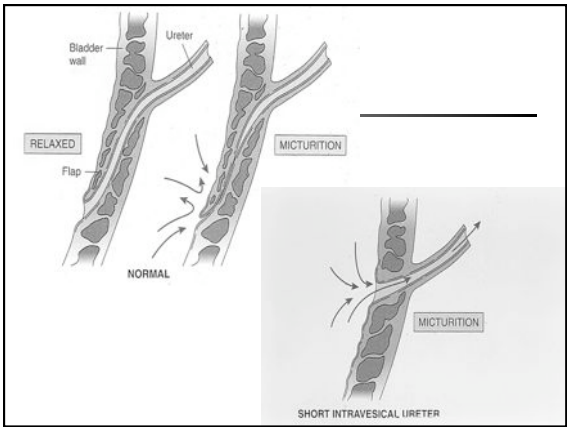


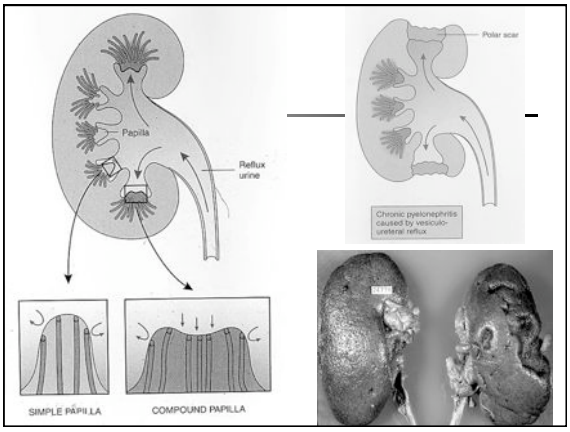


Voiding cystourethrogram

Vesicoureteral reflux (VUR):

- Congenital
- 50% UTI's < 1 yo



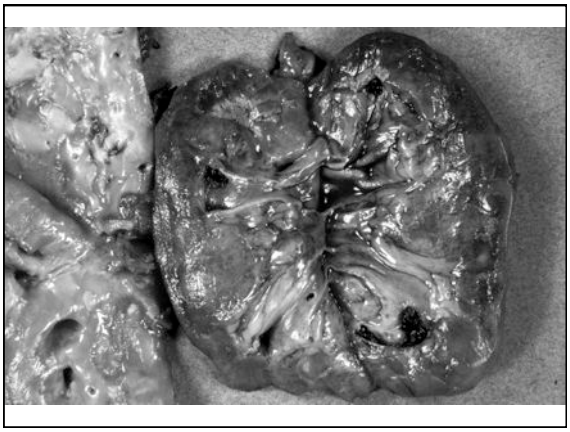


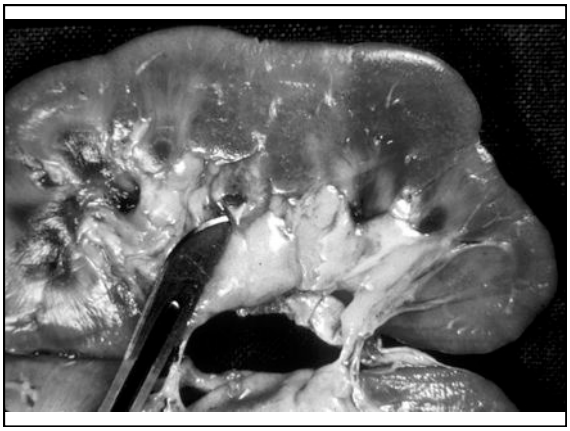
Tubulointerstitial nephritis in systemic disease

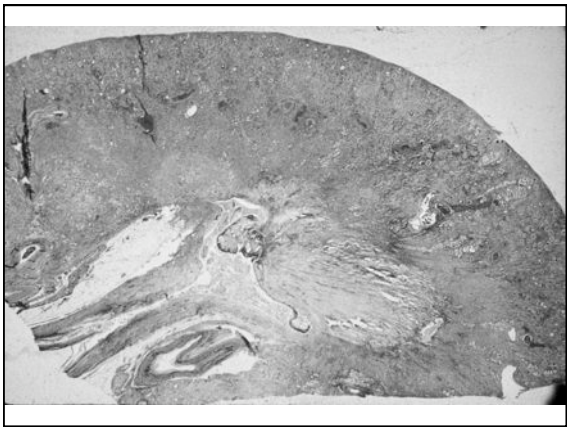
- Sjogren's syndrome
  - Systemic autoimmune disease
  - Frequent overlap with SLE or RA
  - Keratoconjunctivitis (dry eyes)
  - Xerostomia (dry mouth)
- Sarcoidosis
  - Multisystem granulomatous disease
  - Lungs, LNs, less commonly kidneys

Papillary Necrosis

- **Obstructive pyelonephritis**
- **Sickle Cell Anemia**
  - **medulla leads to sickling**
  - **sickling leads to medullary ischemia**
- **Analgesic abuse (phenaccetin*)**
  - **increased risk with combinations**
  - **direct toxicity and ASA-induced PG deficiency**
- **Diabetes Mellitus**







Cystic Diseases of Kidney

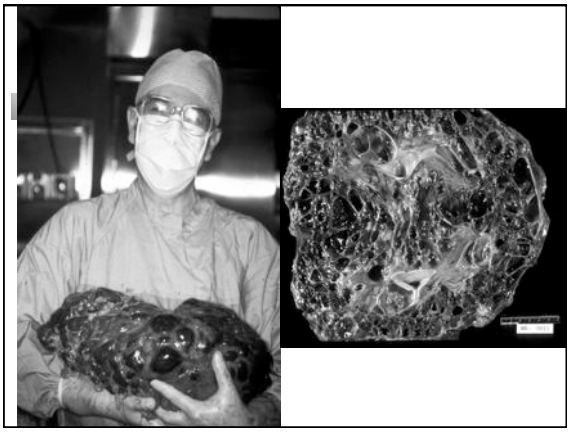
- Simple cysts
  - common post-mortem finding
  - as with all cysts, r/o RCC
- Dialysis-associated renal cysts
- Autosomal ***Dominant*** Polycystic kidney disease (mainly adults)
- Autosomal ***Recessive*** Polycystic kidney disease (children)

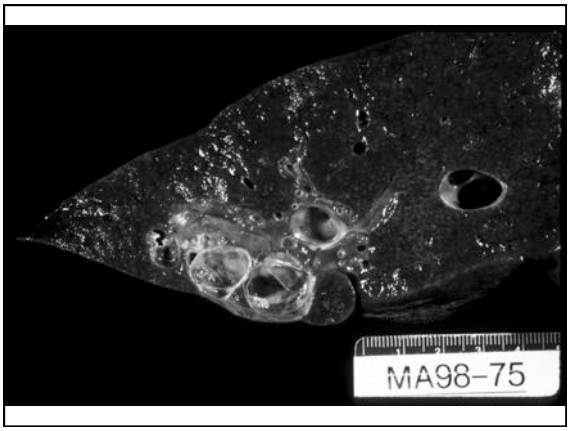
Autosomal Dominant Polycystic Kidney Disease

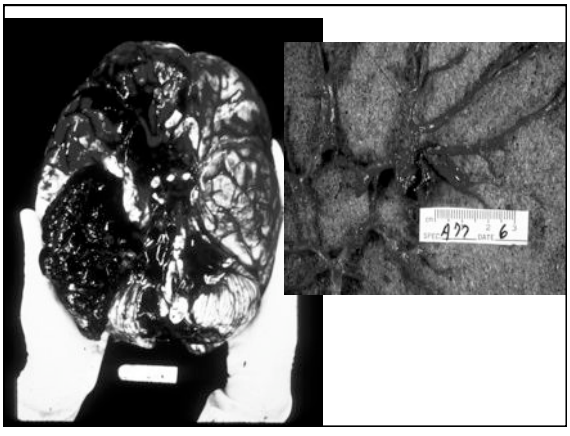
- Common: 1/500- 1/1000 live births
- Genes: Pkd1 on 16p; Pkd2 on 4
- Clinical:
  - typical onset at 20-40 years
  - HTN, RI, hematuria, and pain
  - 10% U.S. ESRD population
- Polycystic liver disease in 40%
- Cerebral artery berry aneurysms

Autosomal Dominant Polycystic Kidney Disease

- Gross: massively enlarged & cystic
- Micro: numerous cysts
  - predominantly distal tubular origin
- Etiology:
  - two-hit hypothesis
  - dysregulated, clonal tubular cell growth







Autosomal Dominant Polycystic Kidney Disease

- Rare
- Perinatal presentation (most)
- Typically rapid progression to ESRD
- Bilateral (like ADPKD)
- Liver involvement in majority
  - liver cysts & bile duct proliferation
  - if survive infancy: congenital hepatic fibrosis (cirrhosis)