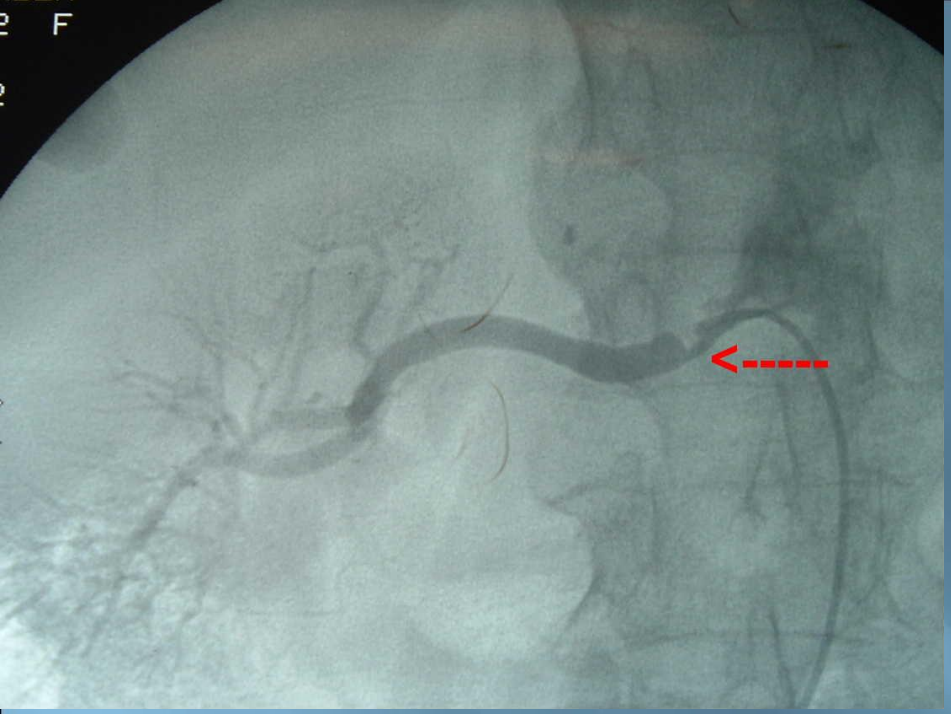
IN THE NAME OF GOD

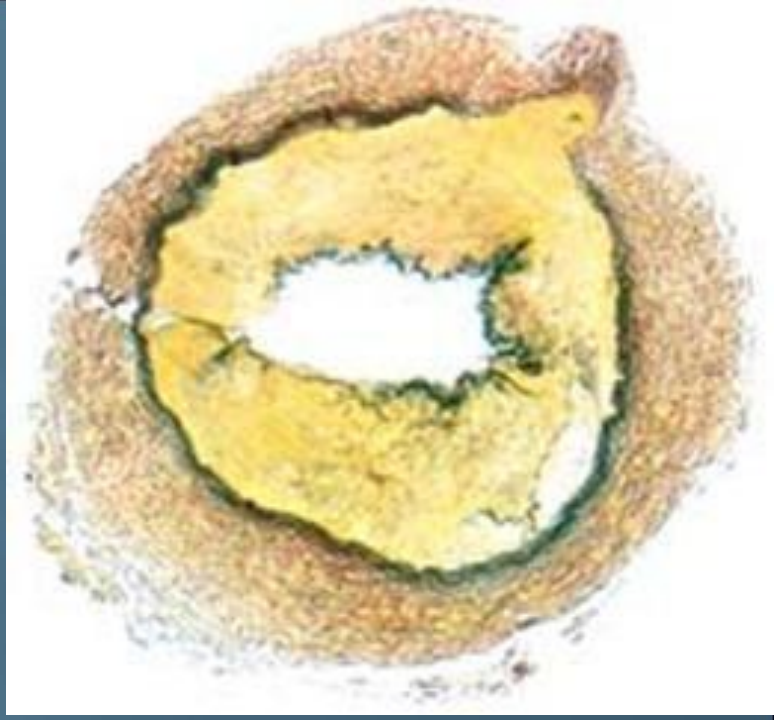
RENAL PATHOLOGY

Dr. Z. Vakili

Renal Artery Stenosis

- Rare cause of HTN
- SMALL Kidney
- 1) Plaque type is usual cause, yes regular old atherosclerosis
- 2) Fibromuscular "dysplasia" type:
  - INTIMAL HYPERPLASIA
  - MEDIAL HYPERPLASIA
  - ADVENTITIAL HYPERPLASIA
  - In younger women





PLAQUE, i.e.,

ATHEROSCLEROSIS

FIBROMUSCULAR

DYSPLASIA

Thrombotic Microangiopathies

- Damage to endothelial cells !!
- Diseases:
  a) childhood hemolytic-uremia syndrome (HUS)
  b) Thrombotic thrombocytopenic purpura

Thrombotic Microangiopathies

- Most follow intestinal infection (E. Coli)
- Disease is one of main causes of acute renal
- failure in children
- Vasoconstriction (decreased NO, increased
- endothelium, decreased PGI2)

ii) vasoconstriction also initiated via endothelial derived endothelin-1

iii) activation of endothelial cells increases adhesiveness to platelets, etc

iv) endothelial cells elaborate large multimers of vW factor $\rightarrow$ platelet aggregation

- Although the various diseases have diverse etiologies, 2 predominant factors →
  a) endothelial injury and activation, leading to vascular *thrombosis* and,
  b) platelet aggregation
  c) both of these causing vascular obstruction and vasoconstriction

1.- Endothelial injury

- activation can be initiated by a variety of agents, while some remain elusive
- a) denuding the endothelial cells, exposes vascular to thrombogenic subendothelium
  - i) ↓ NO, PGI2, enhance platelet aggregation and vasoconstriction

2.- Platelet Aggregation

- serum factors causing platelet aggregation

  a) large multimers of vW factor (secreted by endothelial cells)

  i) usually cleaved by ADAMTS-13 (vW factor-cleaving metalloprotease

HUS/TTP

1.- Classic childhood HUS (> 75%)

- bloody diarrhea → intestinal infection
    a) verocytotoxin-releasing bacteria
        i) Verocytotoxin-producing strains of E. coli (eg 0157:H7 or 0103);
        ii) Similar to Shigella toxin.
        iii) undercooked hamburger
        iv) "petting" zoos

- characterized:
    a) sudden onset (post GI or influenza infection)
    b) hematemesis
    c) melena
    d) severe oliguria
    e) hematuria
    f) hemolytic anemia (microangiopathic)
    g) hypertension in > 50% of cases

- Pathogenesis
    a) related to Shigella toxin
        i) affects endothelium
            - ↑ adhesion of leukocytes
            - ↑ endothelin and ↓ NO
            - endothelial lysis (inpresence of cytokines such as TNF
        ii) these changes favor thrombosis and vasoconstriction
        iii) verocytotoxin can directly bind to platelets and cause activation
- most patients recover in few weeks, with proper care (i.e., dialysis, etc); < 5% lethality

2.- Adult HUS

- associated with:
    - a) infection
        - i) typhoid fever
        - ii) E. coli septicemia
        - iii) etx or shiga toxin
        - iv) viral infections
    - b) antiphospholipid syndrome
        - i) SLE
        - ii) similar to membranoproliferative GN but w/out immune complex deposits
    - c) complication of pregnancy ("postpartum renal failure"

d) vascular renal disease
    i) systemic sclerosis
    ii) malignant hypertension
e) chemotherapeutic and immunosuppressive drugs
    i) mitomycin
    ii) cyclosporine
    iii) bleomycin
    iv) cisplatin
    v) radiation Tx

3.- Familial HUS

- recurrent thromboses (~ 50 lethality)
- deficit of complement regulatory protein
    a) Factor H

4.- Idiopathic Thrombotic Thrombocytopenic Purpura

- Manifested by:
    a) thrombi in glomeruli
    b) fever
    c) hemolytic anemia
    d) neurologic symptoms
    e) thrombocytopenic purpura

- defect in ADAMTS-13 (acquired or inherited)
  a) normally cleaves large vW multimers
    i) large vW factors promote platelet aggregation
- more common in women
- most patients < 40 years

- neurologic involvement is dominant feature
- renal involvement in ~ 50% of patients
    a) eosinophilic thrombi in glomerular capillaries, interlobular artery and afferent arterioles
    b) similar changes as with HUS
- exchange transfusion and steroid Tx $\rightarrow$ mortality rate to < 50%

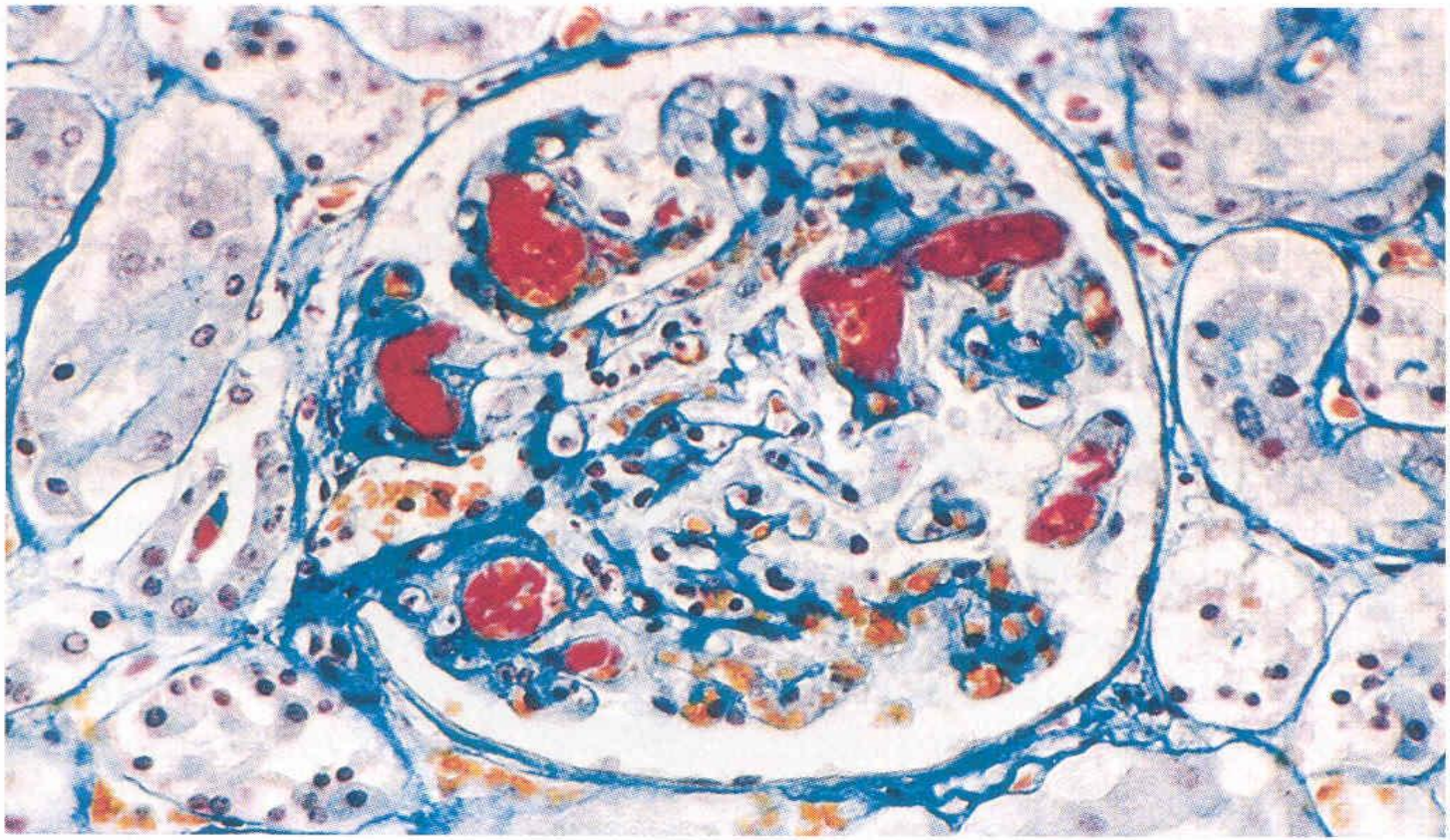


FIGURE 20–52 Fibrin stain showing platelet-fibrin thrombi (*red*) in the glomerular capillaries, characteristic of microangiopathic disorders.

Cystic Diseases

- Common and difficult to diagnose
- In adult polycystic disease – major cause of chronic renal failure
- Confused with malignant tumors

CYSTIC DISEASES

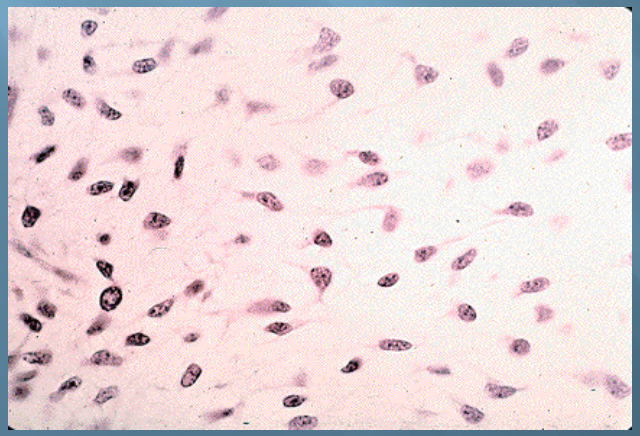
- CYSTIC RENAL "DYSPLASIA"
- Autosomal DOMINANT (AD-ULTS)
- Autosomal RECESSIVE (CHILDREN)
- MEDULLARY
  - Medullary Sponge Kidney (MSK)
  - Nephronopththisis-Medullary
- ACQUIRED
- SIMPLE

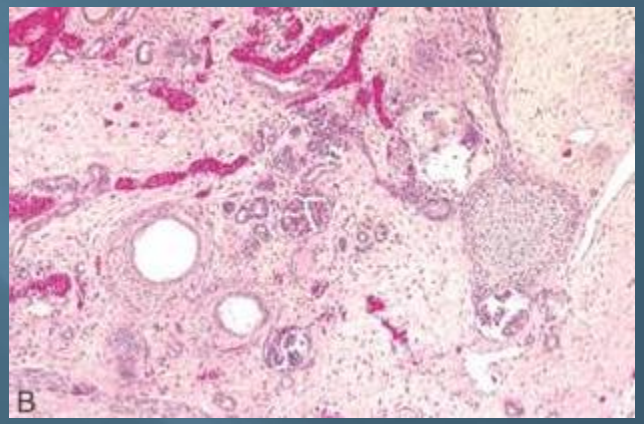
Cystic Diseases

- Simple cysts
- Adult polycystic kidney disease (autosomal dominant)
- Childhood polycystic kidney disease (autosomal recessive)

CYSTIC RENAL "DYSPLASIA"

- ENLARGED
- UNILATERAL or BILATERAL
- CYSTIC
- Have "MESENCHYME"
- NEWBORNS
- VIRAL, GENETIC (rare)





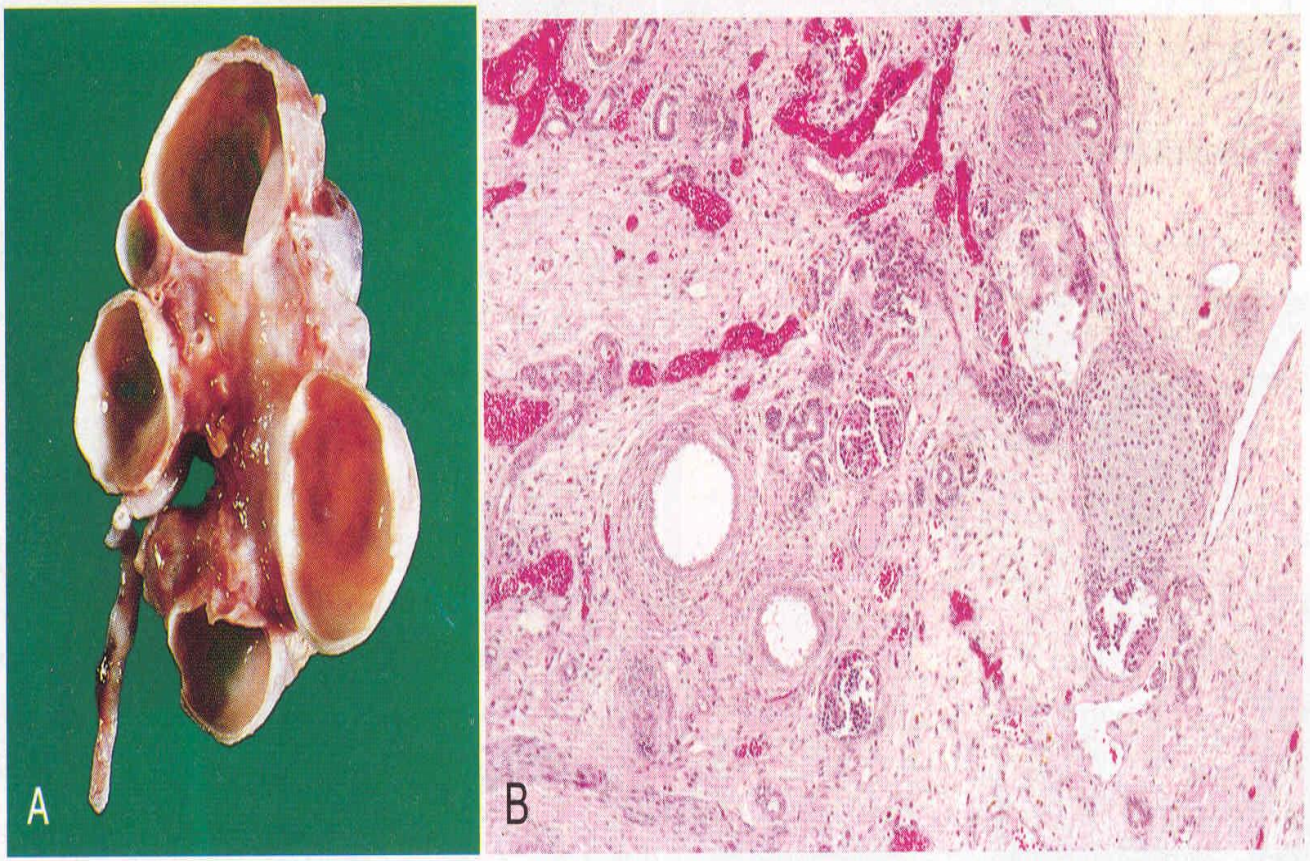


FIGURE 20–6 Renal dysplasia. *A*, Gross appearance. *B*, Histologic section showing disorganized architecture, dilated tubules with cuffs of primitive stroma, and an island of cartilage (H&E stain). (*A*, courtesy of Dr. D. Schofield, Children's Hospital, Los Angeles, CA; *B*, courtesy of Dr. Laura Finn, Children's Hospital, Seattle, WA.)

Adult polycystic kidney disease (autosomal dominant)

- Multiple expanding cysts of both kidneys that eventually destroy parenchyma of kidney
- Accounts for 10% of chronic renal failure

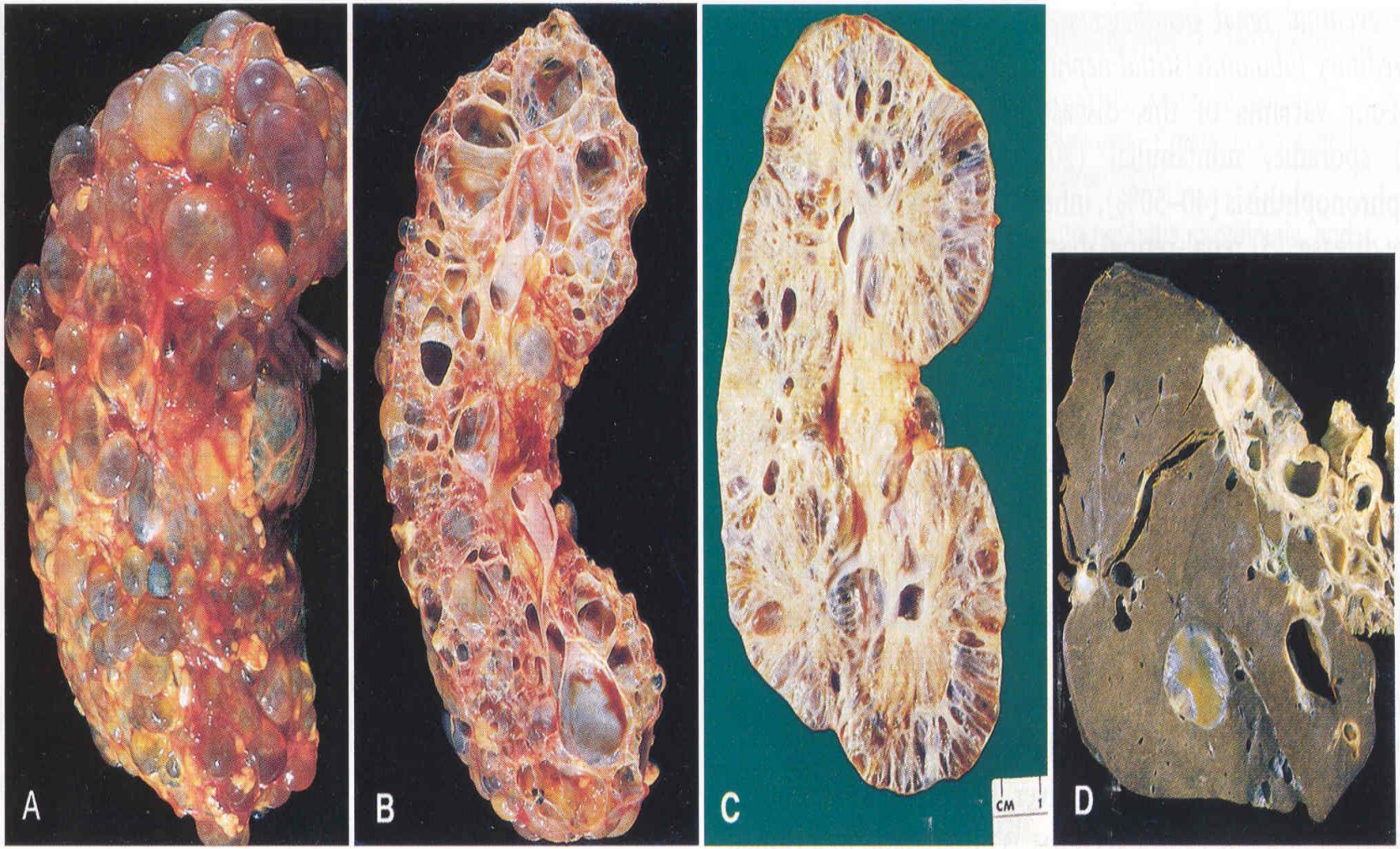


FIGURE 20–8 *A* and *B*, Autosomal-dominant adult polycystic kidney disease (ADPKD) viewed from the external surface and bisected. The kidney is markedly enlarged with numerous dilated cysts. *C*, Autosomal-recessive childhood polycystic kidney disease, showing smaller cysts and dilated channels at right angles to the cortical surface. *D*, Liver with cysts in adult PKD.

Adult polycystic kidney disease (autosomal dominant)

- In 90% of families, PKD1 (defective gene) is located on chromosome #16

  a) encodes for protein (polycystin-1), extracellular and is a cell membrane associated protein
  b) how mutations in this gene cause cysts formation is unclear

- Polycystin 2 (PKD2 gene) mutations also cause cyst formation

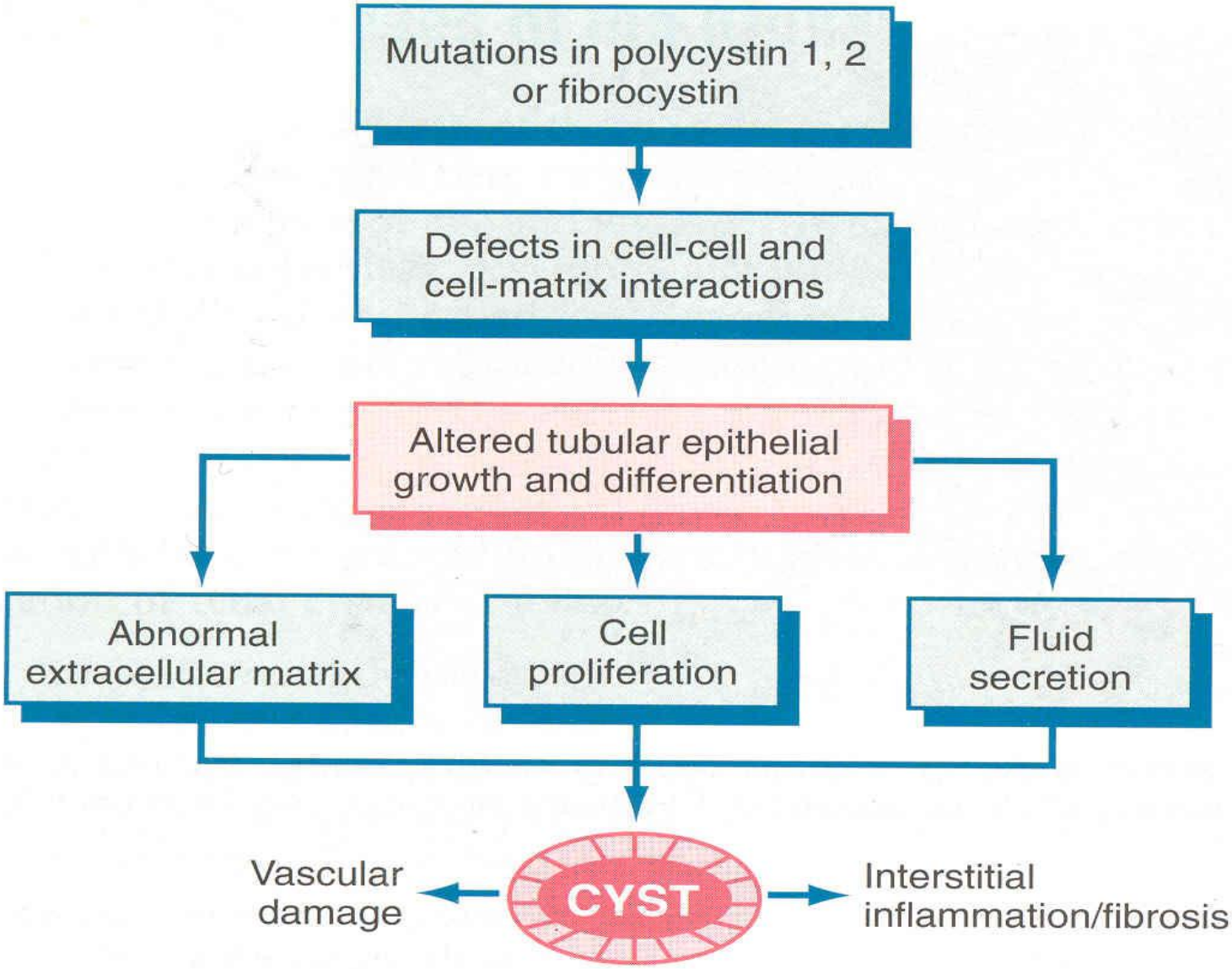


FIGURE 20–7 Possible mechanisms of cyst formation in polycystic kidney disease (see text).

Adult polycystic kidney disease (autosomal dominant)

- No symptoms until 4th decade by then,

  a) kidneys are very large

  b) common complaint is "flank pain"

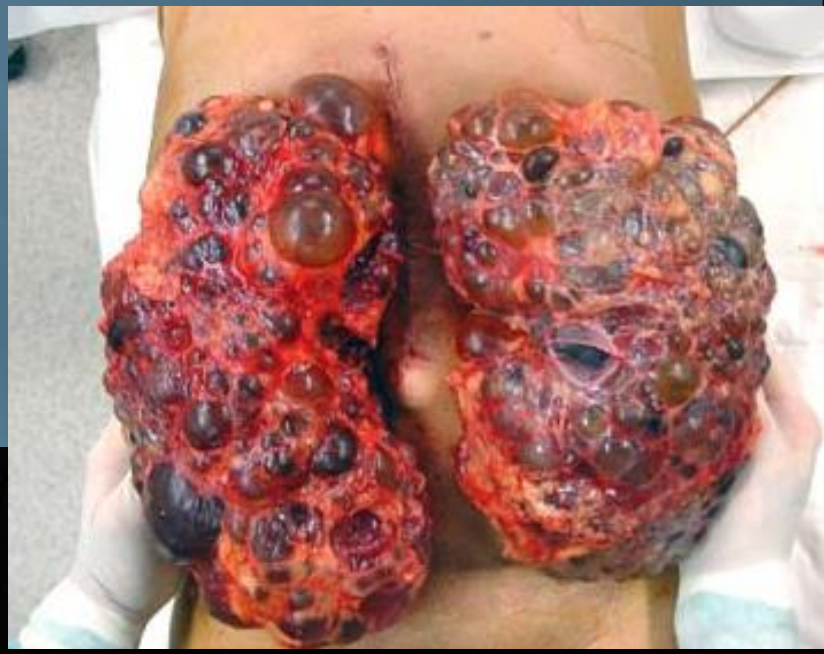
  c) hematuria

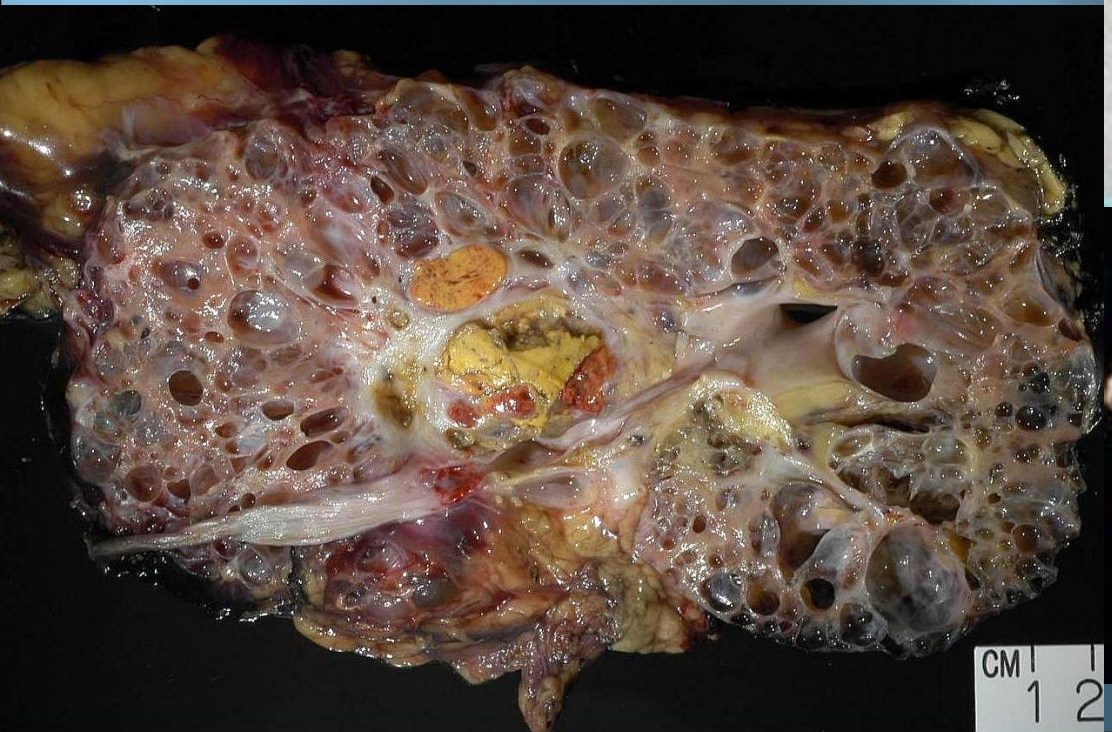
Adult polycystic kidney disease (autosomal dominant)

- d) most important complications
  - i) hypertension (~75% patients)
  - ii) UTI
  - iii) aneurysms in circle of Willis (10-30%) and risk for subarachnoid hemorrhage
  - iv) Asymptomatic liver cysts in ~30-40%
  - v) fatal disease (uremia or hypertension)
  - vi) progresses very slowly
  - viii) Treatment with renal transplantation

AUTOSOMAL DOMINANT

- HEREDITARY, PKD1, PKD2
- FOLLOWS AUTOSOMAL DOMINANT PEDIGREE
- COMPLEX GENETICS
- RENAL FAILURE in 50's

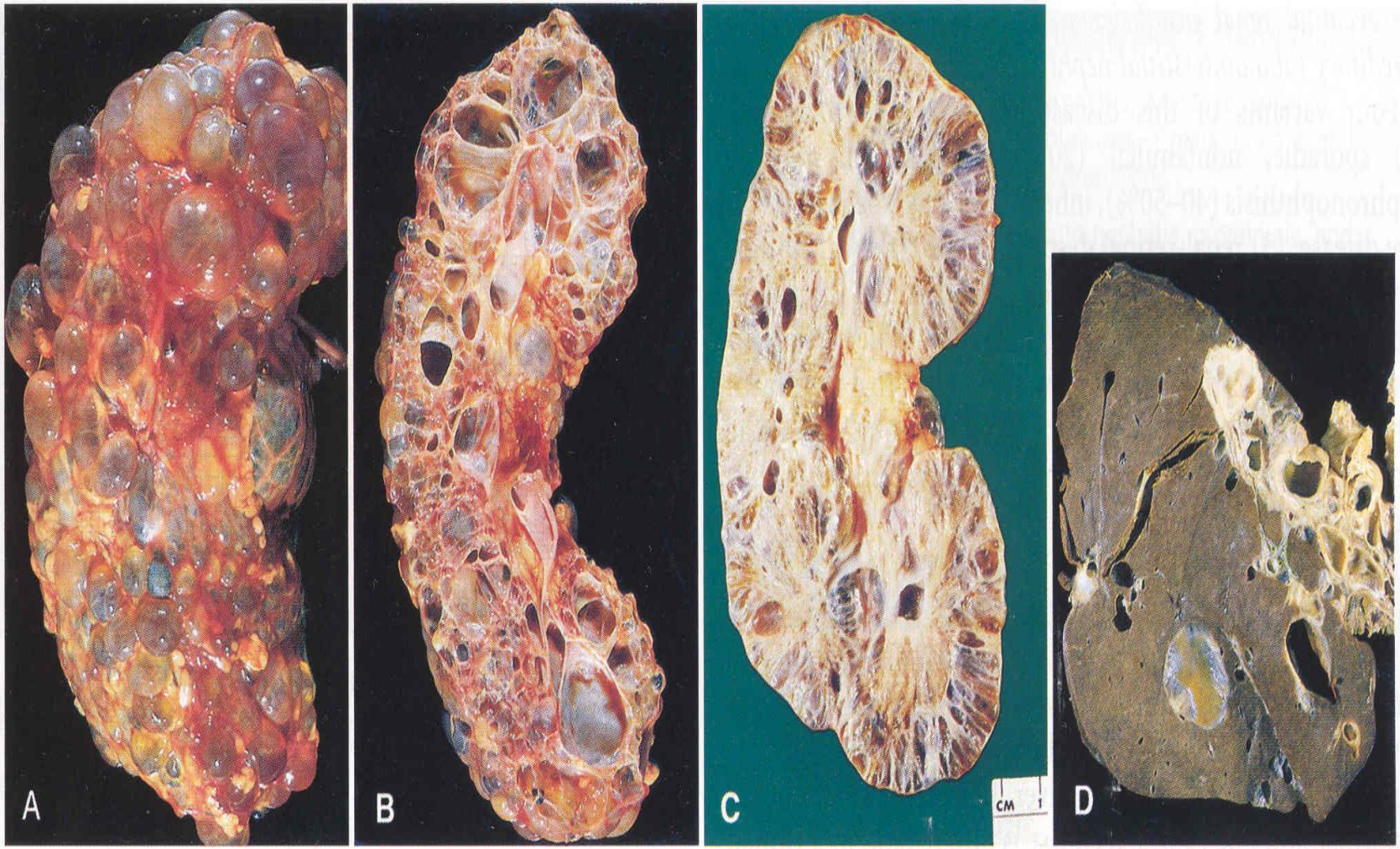




Childhood polycystic kidney disease (autosomal recessive)

- Rare
- Serious manifestations at birth and young infants may die quickly
  - a) pulmonary failure
  - b) renal failure

- Numerous small cysts in cortex and medulla
- Bilateral disease
- Many epithelial cysts in liver
- Patients who survive infancy develop liver cirrhosis (congenital hepatic cirrhosis)
- Unidentified gene location on chromosome 6p



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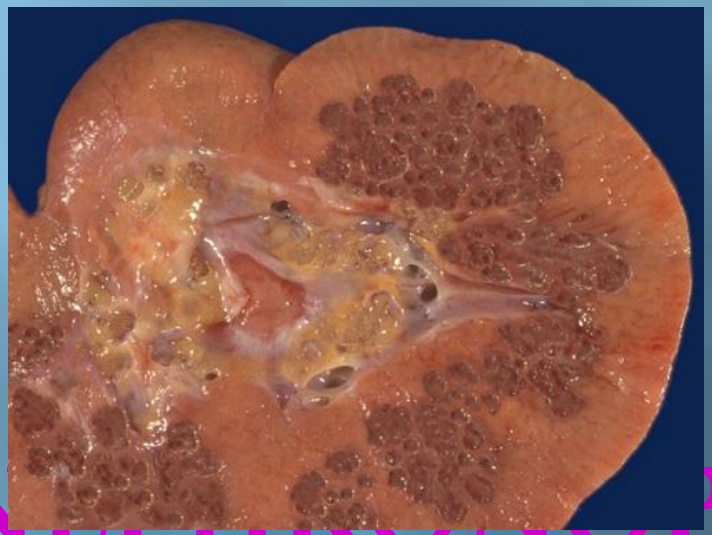
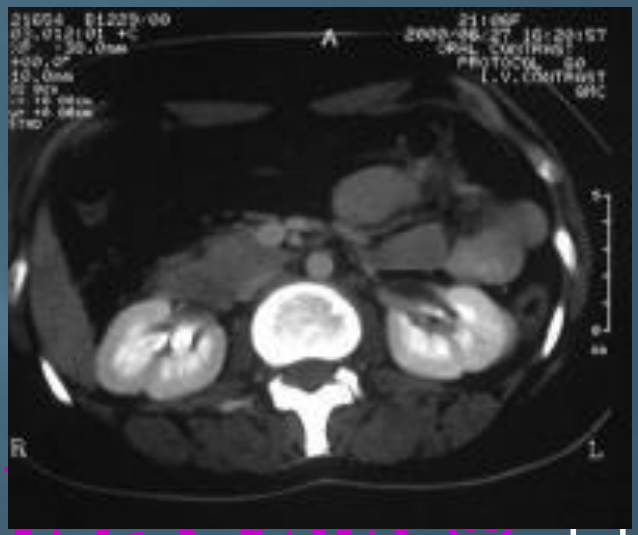
MEDULLARY CYSTS

MEDULLARY SPONGE KIDNEY (MSK), usually an incidental finding on CT or US





NEPHRONOPHTHISIS, cysts @ CMJ, hereditary (AR), progressive

Simple cyst

- a) Innocuous lesion
- b) Occur as single or multiple cysts
- c) Usually 1-5 cm diameter
- d) Clear fluid, smooth membrane, gray glistening
- e) Single layer of cuboidal cells
- f) Usually confined to cortex
- g) No clinical significance

- Importance to differentiate from tumors
    a) are fluid filled rather than solid
    b) have smooth contours
    c) almost always avascular

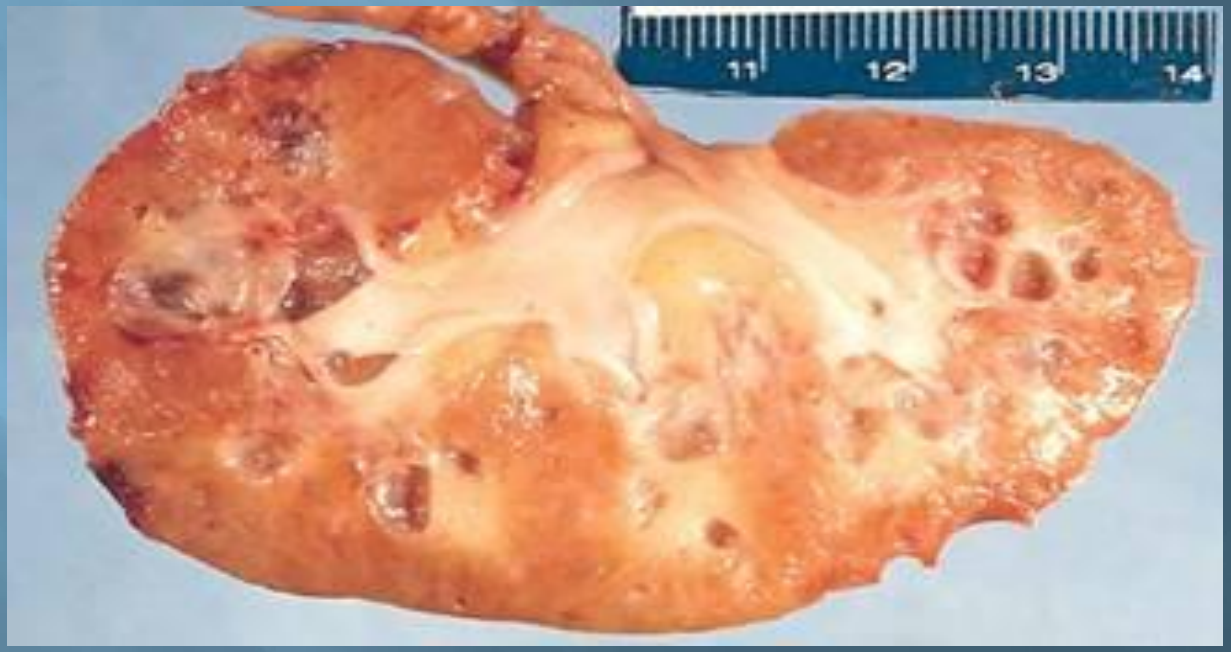
"SIMPLE" CYSTS

- Cortical
- Also called "retention" cysts
- Also "acquired"
- Incidental, asymptomatic
- VERY very very common

ACQUIRED (DIALYSIS)

- Occur in patients with end-stage renal disease who have undergone long term dialysis
- Occasionally, renal adenomas or adenosarcoma arise from these cysts

ACQUIRED (DIALYSIS)



Urinary Outflow-Obstruction

Renal Stones

- Urolithiasis: *Calculus formation at any level in urine collecting system, most often arise in kidney*
- Occur frequently (!1% of all autopsies)
- More common in males
- Familial tendency

Renal Stones

- ~75% of renal stone
  a) calcium oxalate
  b) calcium phosphate

- 15% composed of magnesium ammonium phosphate
- 6 % uric acid
- 1-2%cystine stones

- All stones composed of mucoprotein

- Cause of stones is obscure
  a) Supersaturation in urine of stones constituents (exceeds solubility)
  b) 50% of patients forming "calcium stones" do not have increased plasma Ca^{++} but do have high urine Ca^{++}
    i) most Ca^{++} absorbed from gut in large amounts (absorptive hypercalciuria)

ii) only 5-10% has associated hypercalcemia

- hyperparathyroidism
- Vit D intoxication
- Sarcoidosis (autoimmune disease)

c) Magnesium ammonium Phosphate stones

i) almost always occur in patients with alkaline urine due to UTI

ii) proteus vulgaris and staph split urea in kidney and therefore predispose patient to urolithiasis

- Gout and diseases involved with rapid cell turnover (e.g. leukemia) lead to high uric acid levels in urine and possibility of uric acid stones

- Acidic Urine (pH < 5.5)

- Stone formation 80% unilateral
- Hematuria and predispose to infection

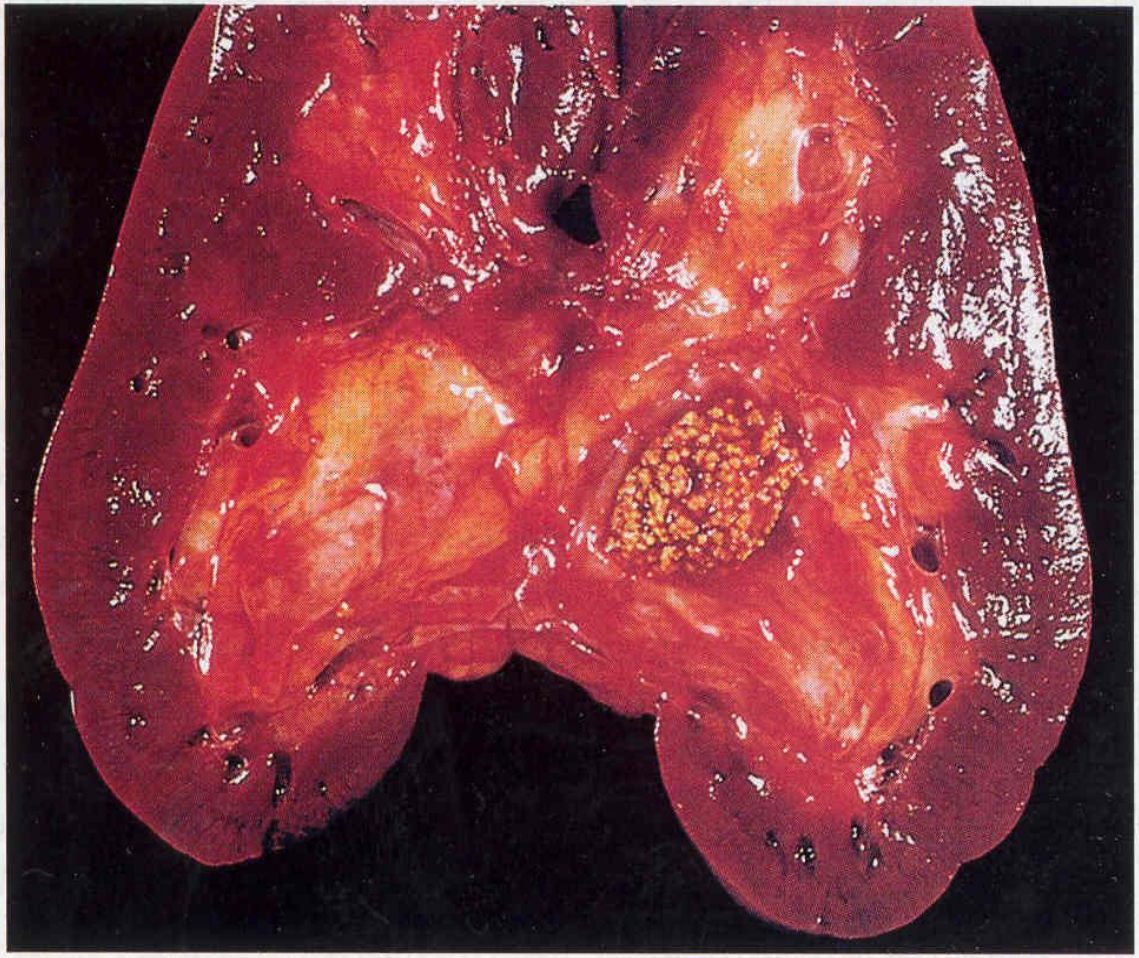


FIGURE 20–57 Nephrolithiasis. A large stone impacted in the renal pelvis. (Courtesy of Dr. E. Mosher, Brigham and Women's Hospital, Boston, MA.)

Hydronephrosis

- Dilation of renal pelvis and calyces with atrophy of parenchyma caused by obstruction of outflow of urine

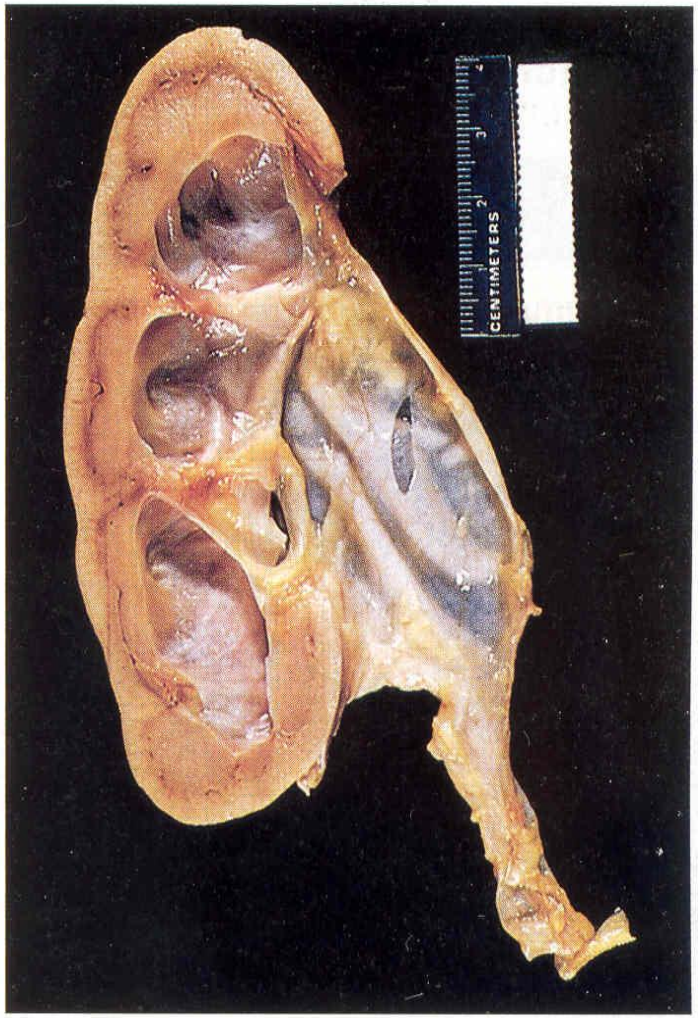


FIGURE 20–56 Hydronephrosis of the kidney, with marked dilation of the pelvis and calyces and thinning of the renal parenchyma.

Hydronephrosis

- Most common causes:
- a) congenital
  - i) atresia of the urethra
    - (absence of a normal body passage or opening from an organ to other parts of the body)

b) acquired

i) stones

ii) tumors

iii) inflammation

iv) spinal cord damage with paralysis of bladder

v) normal pregnancy

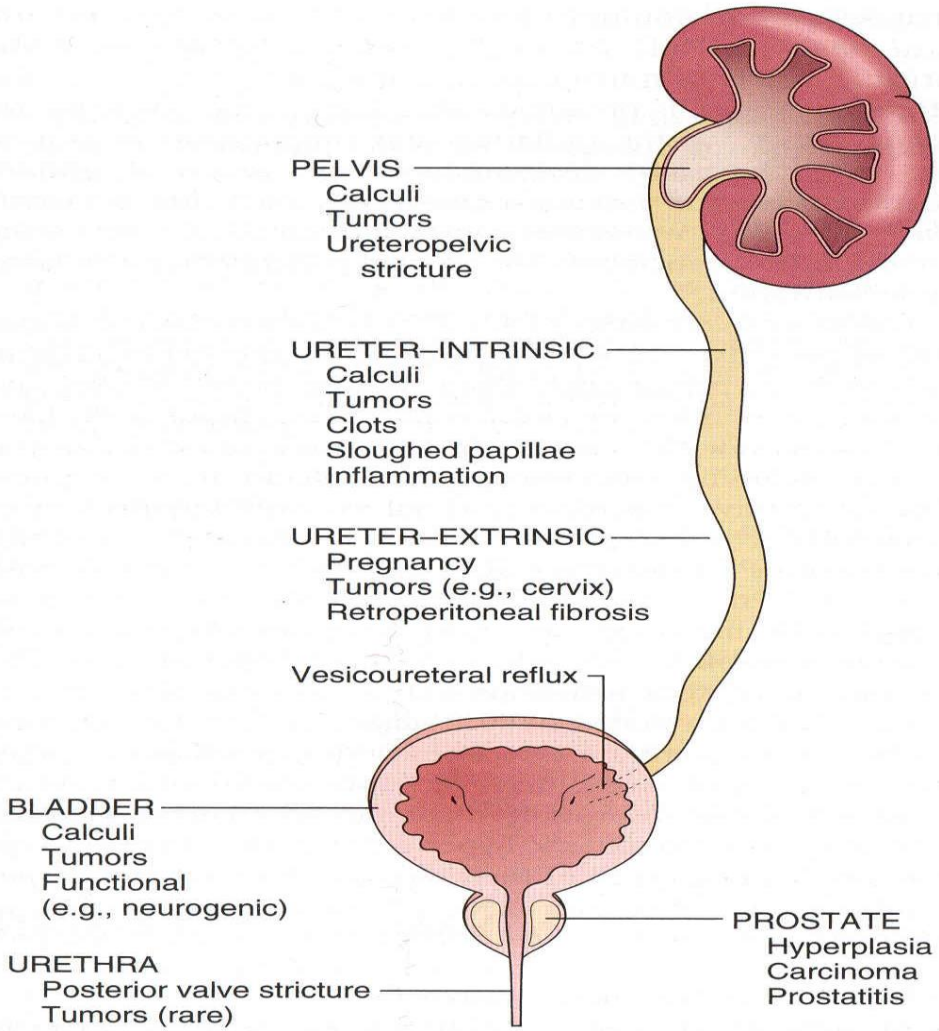


FIGURE 20–55 Obstructive lesions of the urinary tract.

ities of the ureter or bladder (often termed *dysfunctional obstruction*)

Hydronephrosis

- Bilateral nephrons only if blockage is below level or ureters
- Major problems are tubular with impaired concentration mechanisms
- Obstruction leads to inflammatory response
  a) interstitial fibrosis
- Complicating pyelonephritis is common

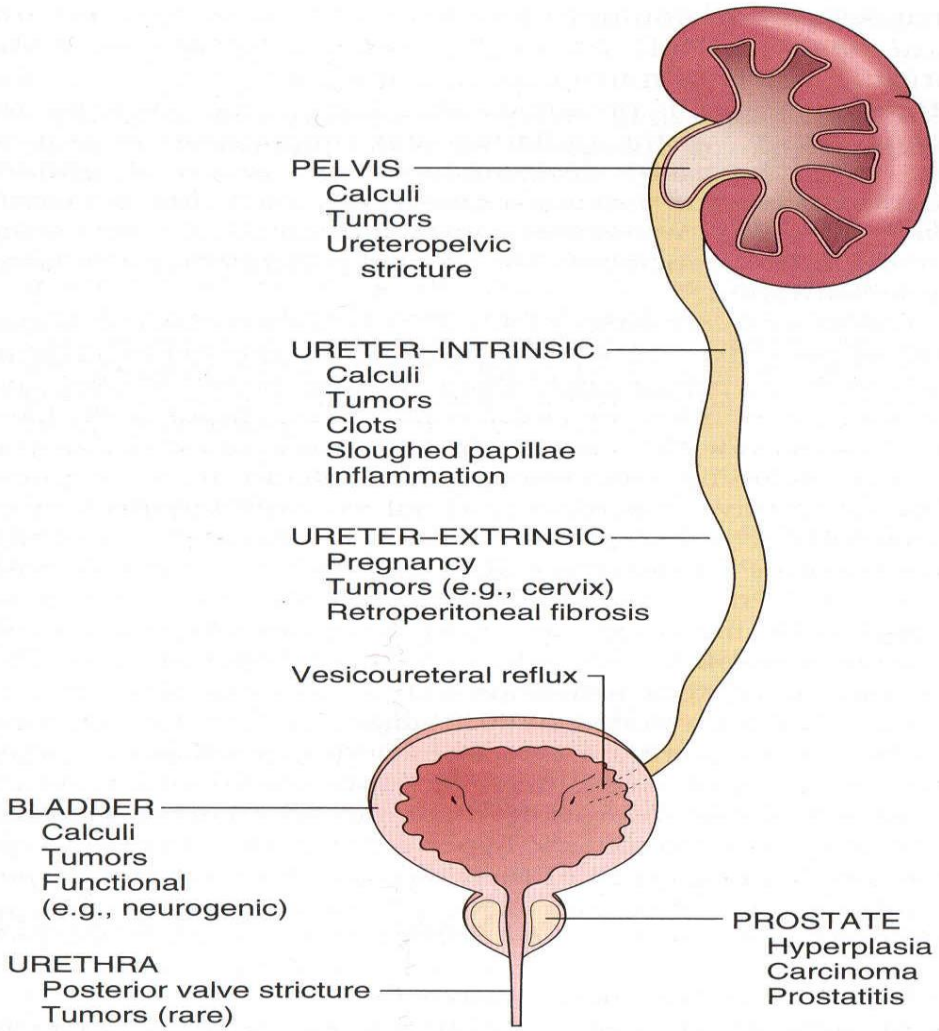


FIGURE 20–55 Obstructive lesions of the urinary tract.

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Tumors

- Most common malignant tumor is:

- a) renal cell carcinoma (80-85% of all 1° Ca in kidney)

  b) nephroblastoma (Wilms tumor)

  c) calyces and pelvis

- Tumor of lower urinary tract are 2x as common as renal cell Cancer

Renal cell Ca

- Derived from renal tubular epithelial cells
- a) located primarily in cortex
- 2-3% of all cell Ca in adults (~30,000 cases/yr)
- 6th to 7th decades in life
- Higher risk in smokers and occupational
- exposure to cadmium
- 30 fold increase in susceptibility in patients with
- polycystic disease

Classification:

1. *clear cell Cancer*

2.- Papillary renal cell Ca

3- Chromophobe Renal Carcinoma

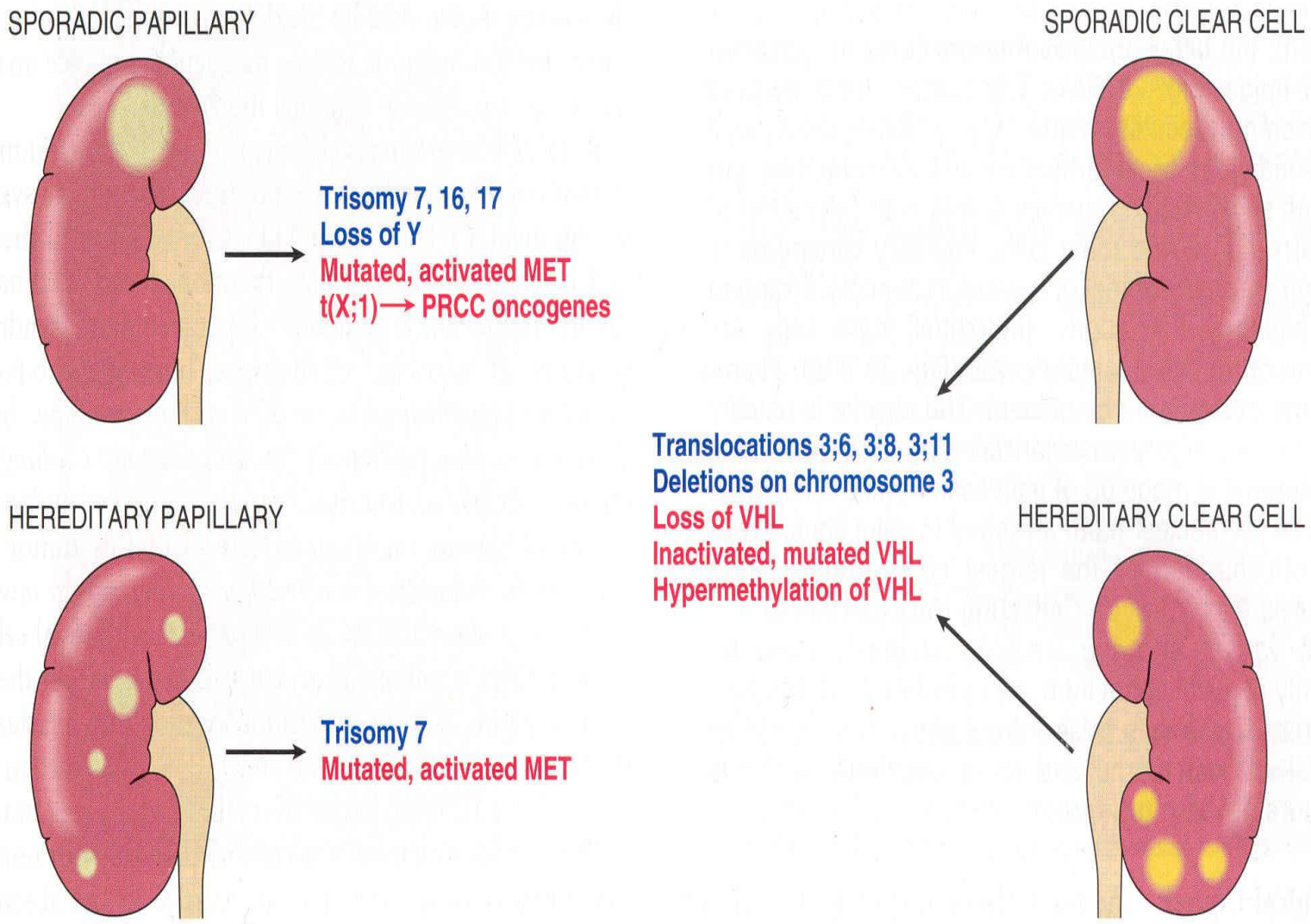


FIGURE 20–58 Cytogenetics (*blue*) and genetics (*red*) of clear cell versus papillary renal cell carcinoma. (Courtesy of Dr. Keith Ligon, Brigham and Women's Hospital, Boston, MA.)

1) *clear cell Cancer*

a) most common (70-80% renal ca)
b) most are sporadic
c) familial links (von Hippel-Lindau [VHL])
i) autosomal dominant disease
ii) predispose to a variety of CA – hemangioblastoma of cerebellum and retina
iii) genetic abnormality chromosome 3 (loss of tumor suppressor gene) –clear cell CA

2.- Papillary renal cell Ca

- 10-15% of all renal CA
- Multifocal and bilateral
- Both sporadic and familial forms
- No genetic abnormalities in chromosome 3
  a) Protooncogene on chromosome 7

3- Chromophobe Renal Carcinoma

- Least common (~5% of all renal cell CA)
- Cortical collecting ducts or their collated cells
- Stain more darkly than clear cell CA
- Lack of a lot of chromosomes (1,2,6,10,17,&21)
- Have good prognosis
- Renal cell CA are difficult to diagnose!
    a) Present with hematuria in ~50% of cases

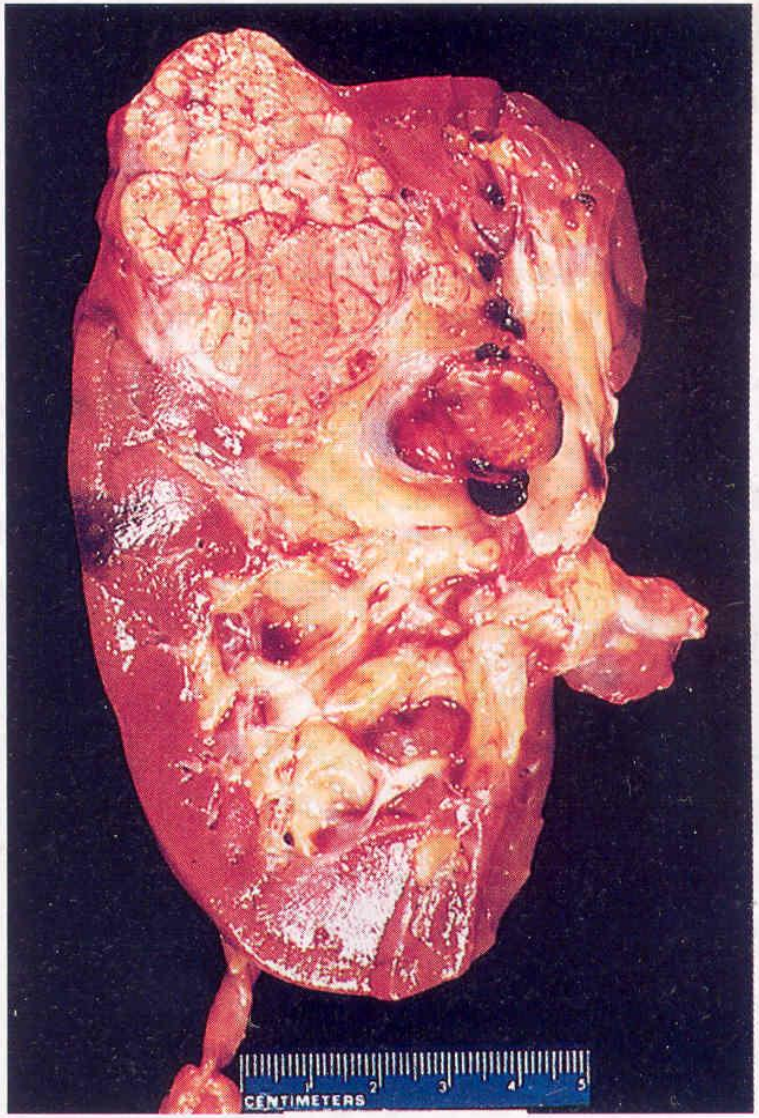


FIGURE 20–59 Renal cell carcinoma. Typical cross-section of yellowish, spherical neoplasm in one pole of the kidney. Note the tumor in the dilated thrombosed renal vein.

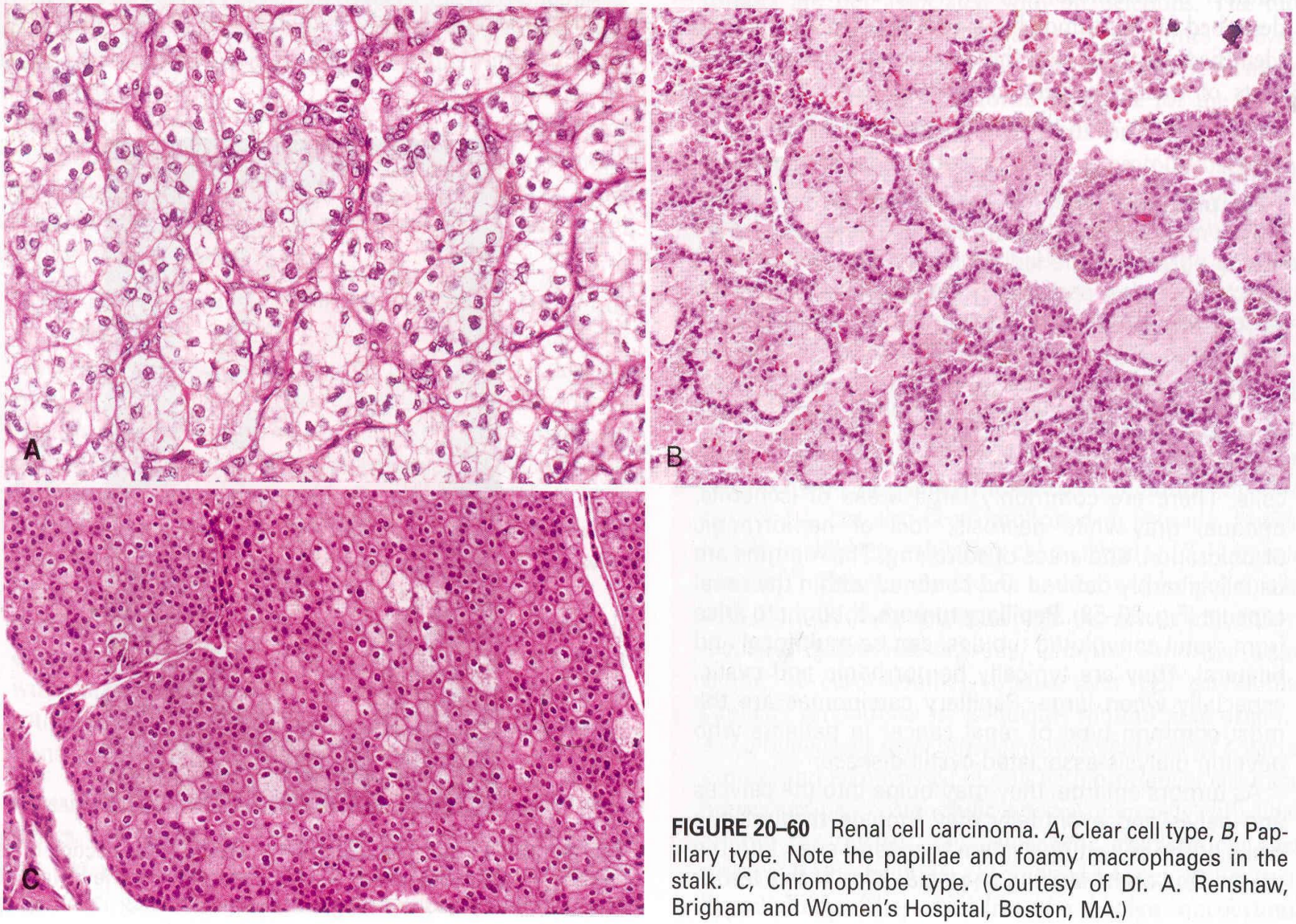


FIGURE 20–60 Renal cell carcinoma. *A*, Clear cell type, *B*, Papillary type. Note the papillae and foamy macrophages in the stalk. *C*, Chromophobe type. (Courtesy of Dr. A. Renshaw, Brigham and Women's Hospital, Boston, MA.)

b.Wilms tumor

- Occurs infrequently in adults
- 1/3 most common organ cancer in children <10 years, therefore, one of major cancers in children
- Sporadic or familial in nature
- a) autosomal dominant

c.Urinary bladder and collecting system tumors (Renal pelvis to urethra)

- Tumors in collecting system above bladder are uncommon
- Bladder Cancer more frequent cause of death than are kidney tumors

It is an aggressive and potentially fatal malignancy, reported as the 4th most common cancer in men, and the 8th in women.

accounting for more than 90% of bladder cancer.

Other less common types are squamous cell carcinoma and adenocarcinoma

The incidence rate of bladder cancer is highest in industrialized countries and areas where infection with the parasite *Schistosoma haematobium* is endemic

Peak age incidence of bladder cancer in general is in the 6th or 7th decade of life.

a) Bladder tumors

- i) small benign papillomas (rare)
- ii) large invasive CA
- iii) most recur after removal and kill by infiltrative obstruction of ureters rather than by metastasizing
- iv) Shallow lesion have good prognosis
- v) deep invasive Cancer, survival (5yr) is <20% with overall 5 yr survival at 50-60%

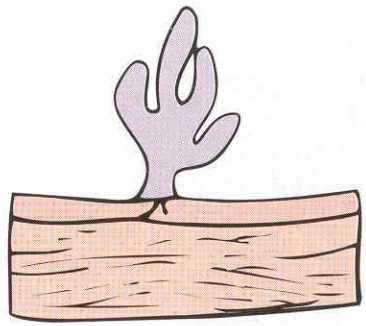
1) Cigarette smoking: 2 - 4 times.

2) Occupation: aromatic amine manufacture, dyestuff manufacture, rubber manufacture, painting, aluminum industry, leather industry and truck drivers.

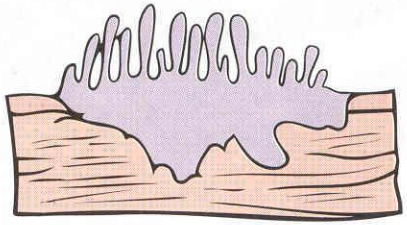
3) Infections: Schistosoma haematobium , 70% of all cancers are squamous; the remainders are transitional.

4) Drugs: phenacetin-containing analgesic drugs), or cyclophosphamide,

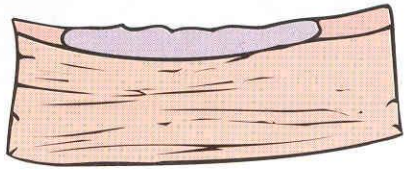
5) Family history of bladder cancer: First-degree relatives of bladder cancer patients have an approximately double risk of bladder cancer.



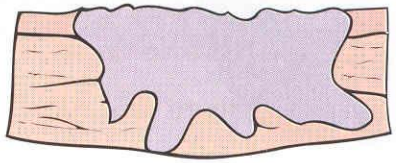
Papilloma–
papillary carcinoma



Invasive
papillary carcinoma



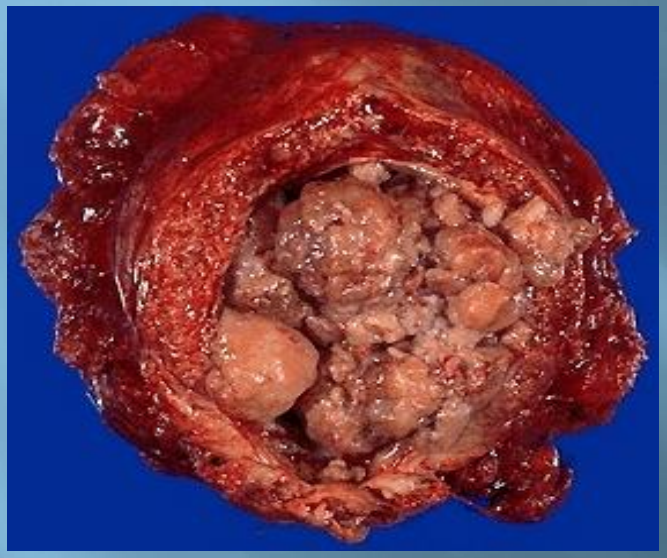
Flat noninvasive
carcinoma (CIS)



Flat invasive
carcinoma

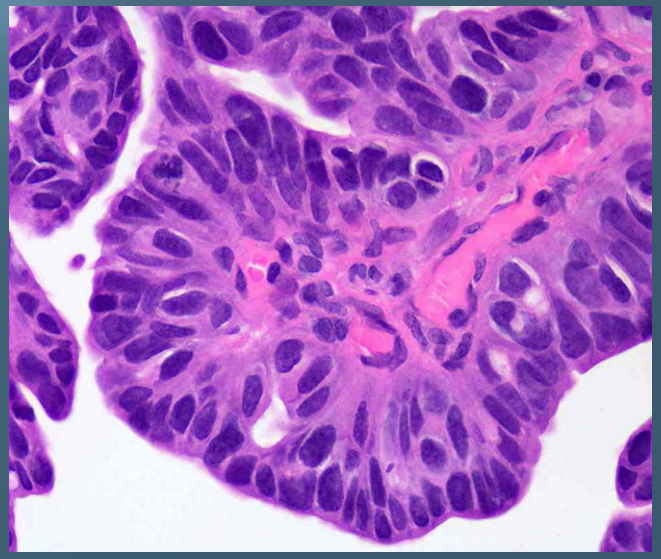
FIGURE 21–6 Four morphologic patterns of bladder tumors.

Morphology



Grossly

Microscopically



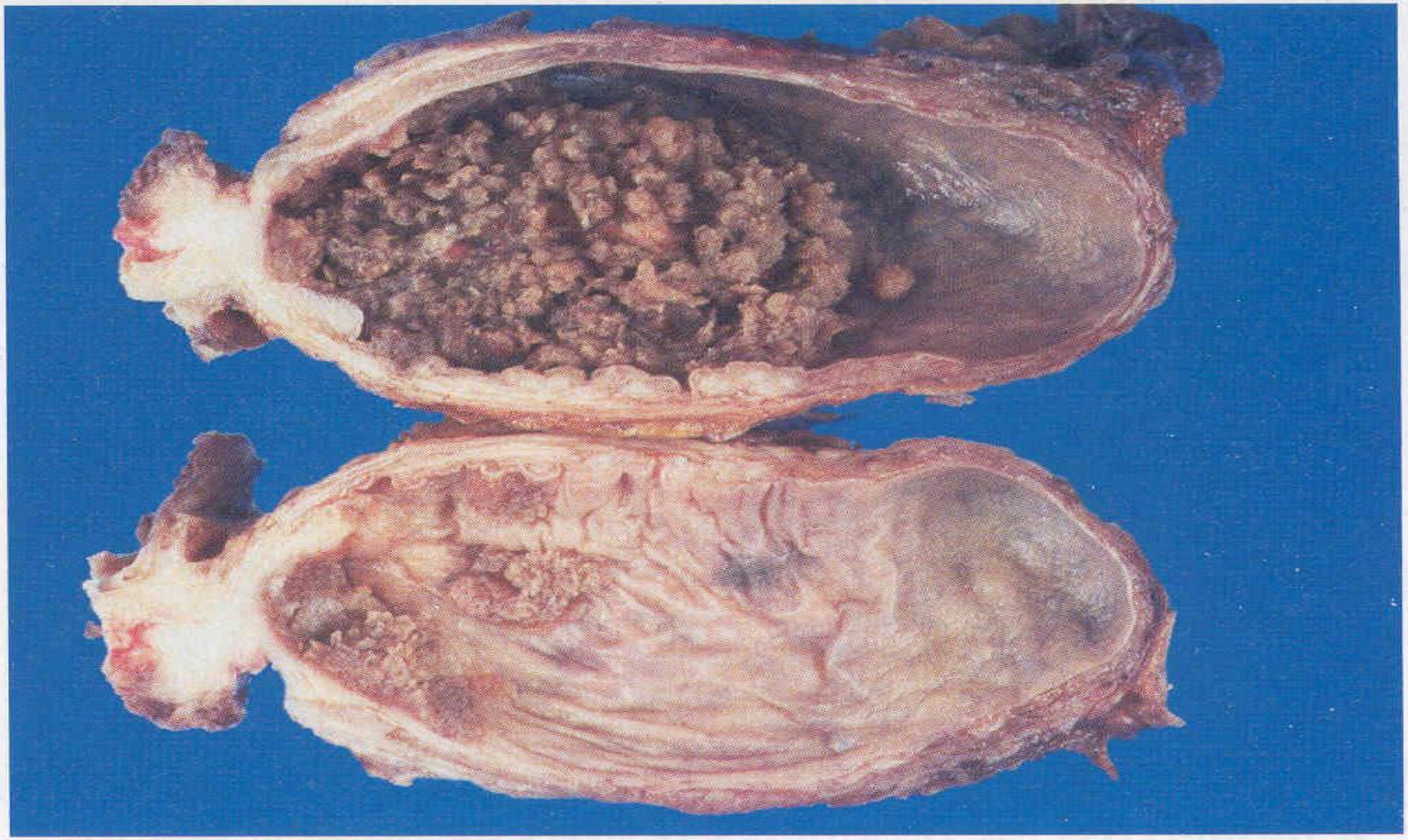


FIGURE 21–7 Cross-section of bladder with upper section showing a large papillary tumor. The lower section demonstrates multifocal smaller papillary neoplasms. (Courtesy of Dr. Fred Gilkey, Sinai Hospital, Baltimore, MD.)

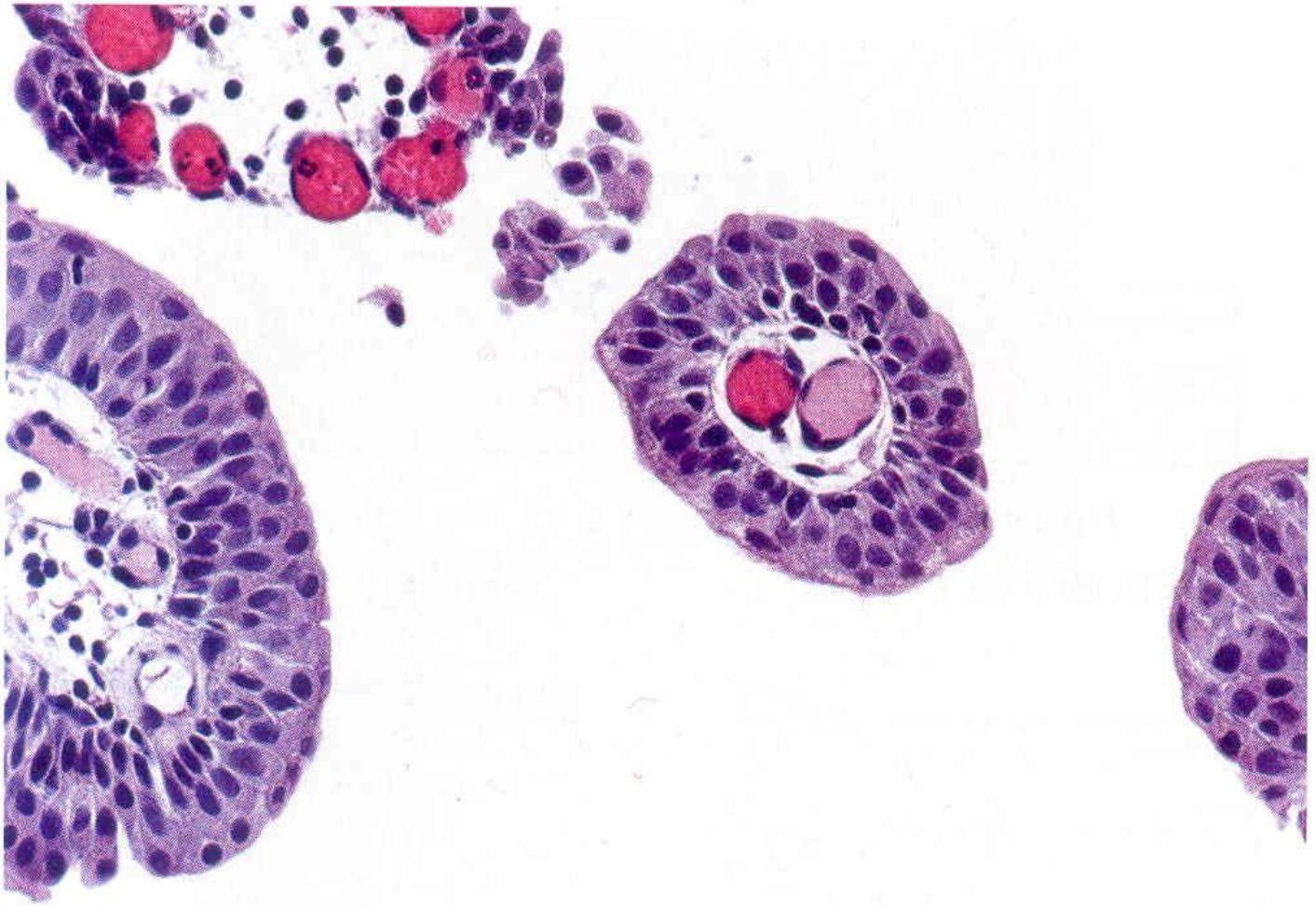


FIGURE 21–8 Papilloma consisting of small papillary fronds lined by normal-appearing urothelium.

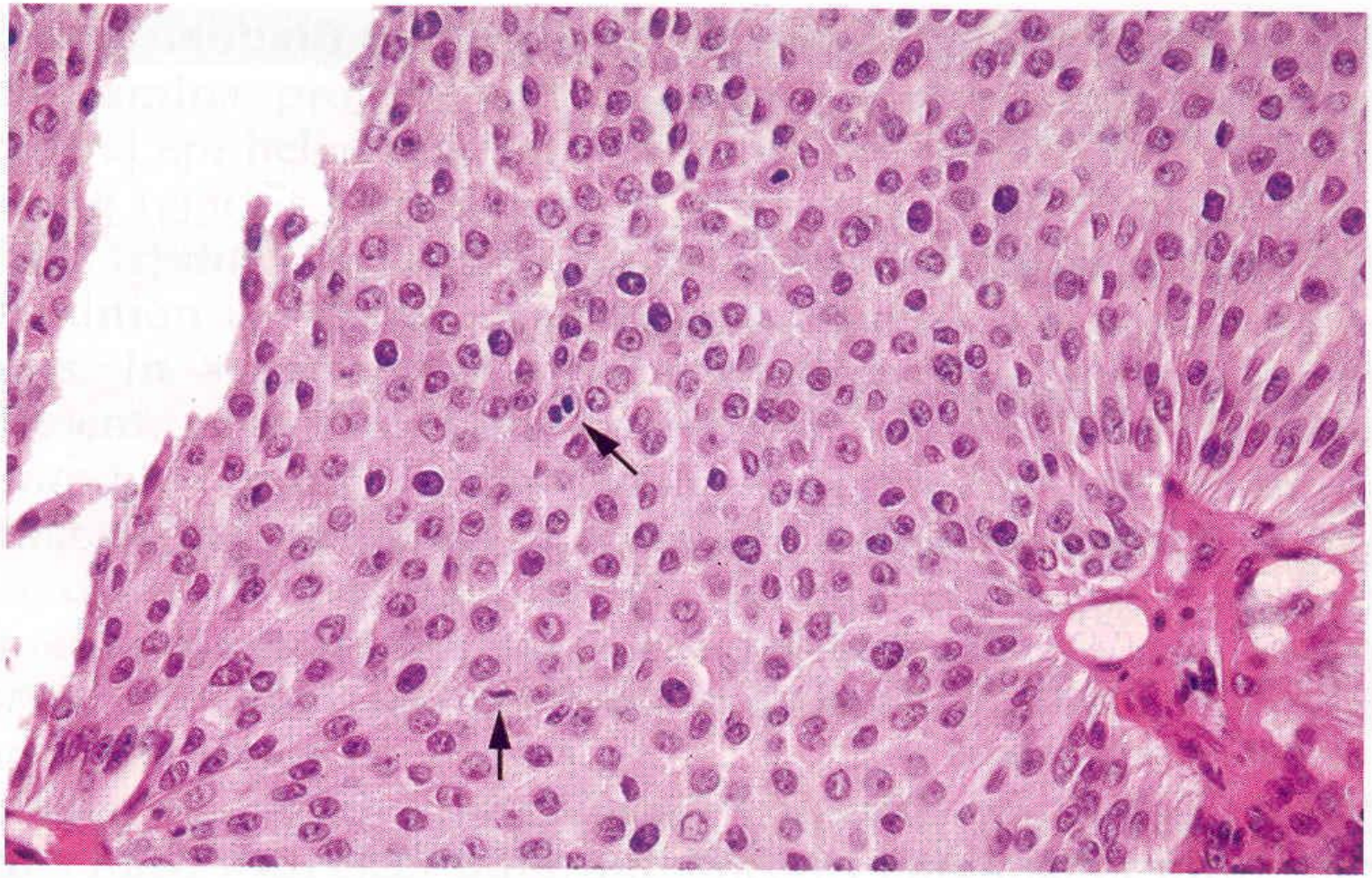


FIGURE 21–9 Low-grade papillary urothelial carcinoma with an overall orderly appearance, a thicker lining than papilloma, and scattered hyperchromatic nuclei and mitotic figures (*arrows*).

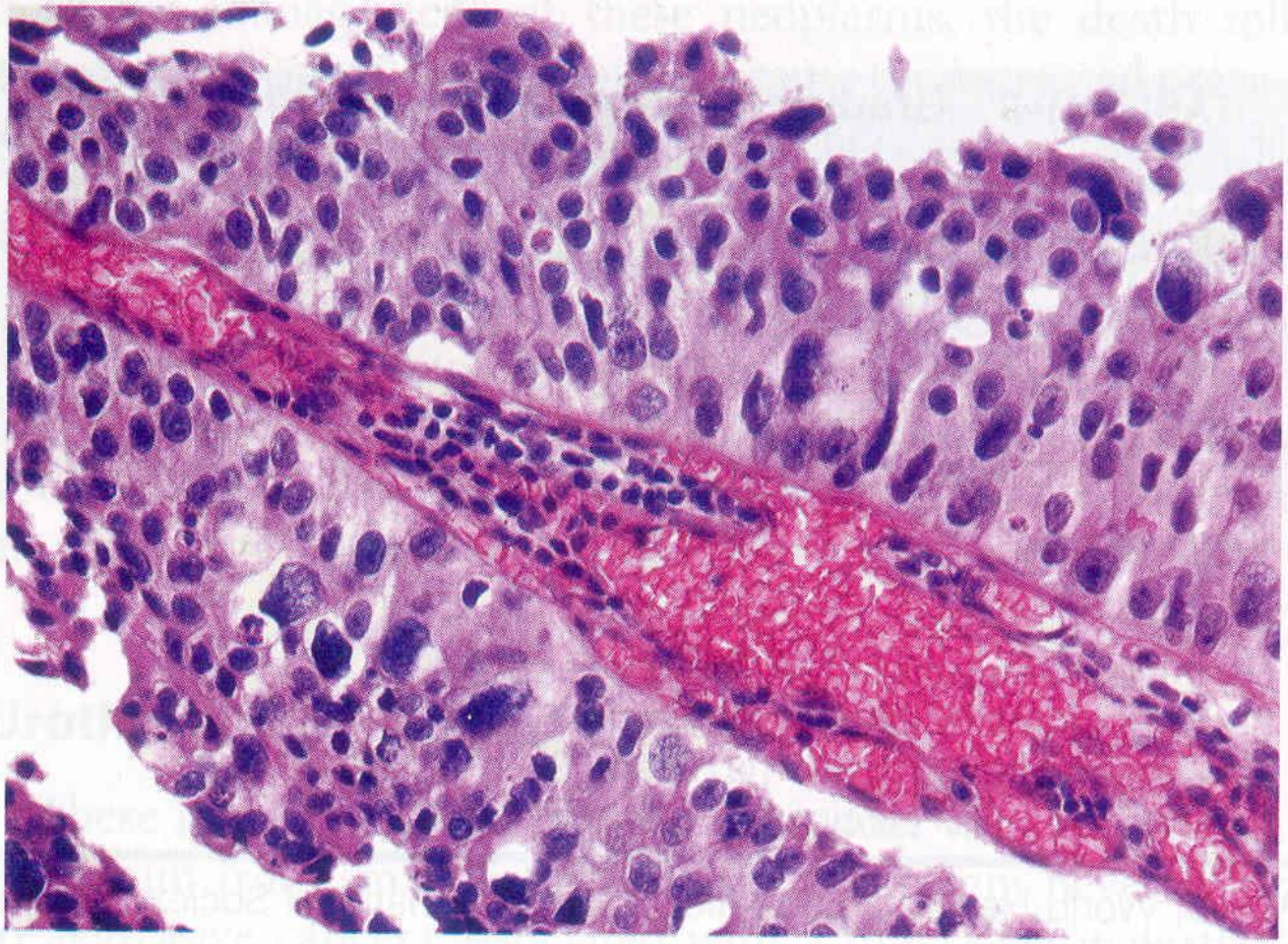


FIGURE 21–10 High-grade papillary urothelial carcinoma with marked cytologic atypia.

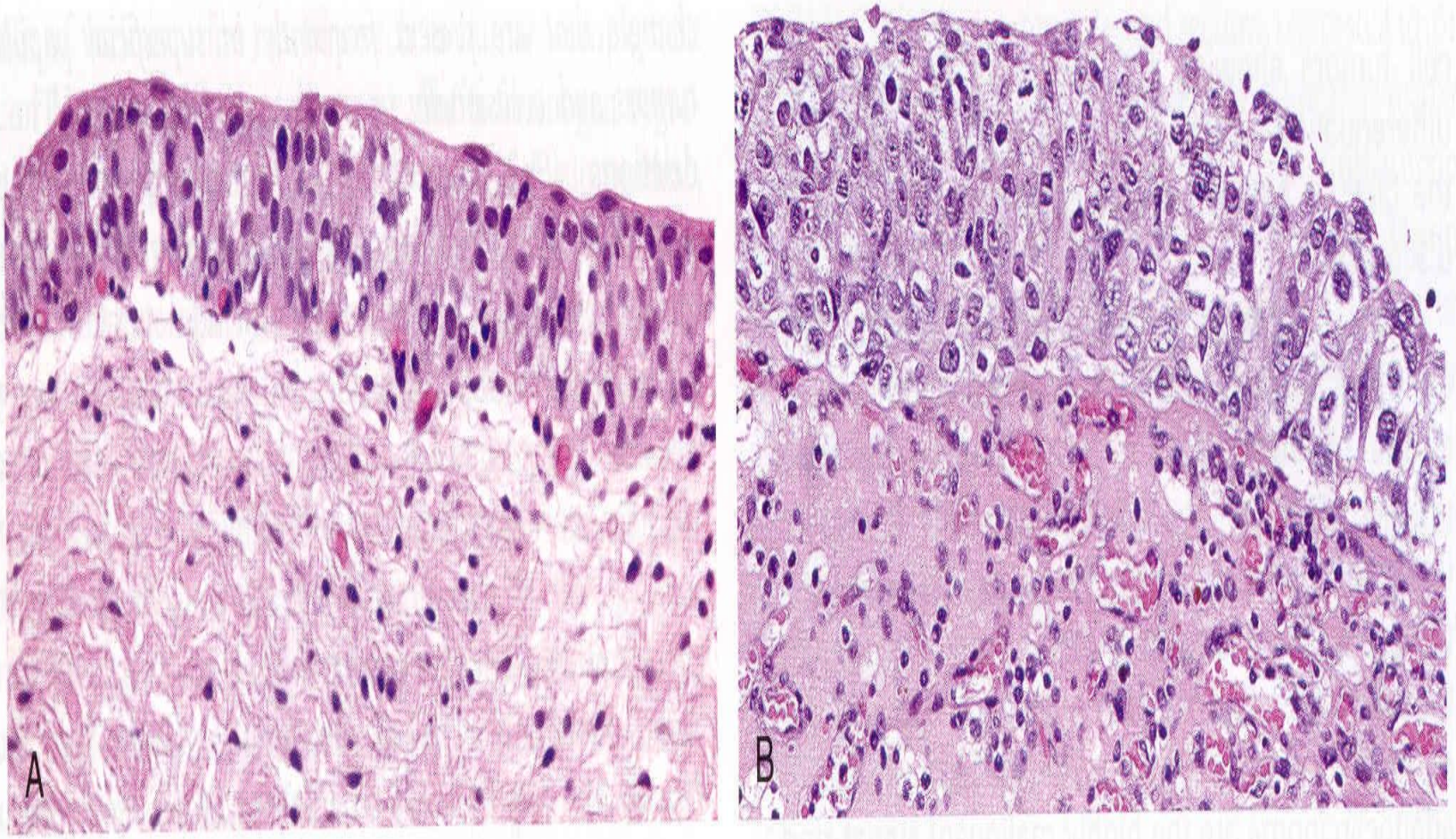


FIGURE 21–11 *A*, Normal urothelium with uniform nuclei and well-developed umbrella cell layer. *B*, Flat carcinoma in situ with numerous cells having enlarged and pleomorphic nuclei.

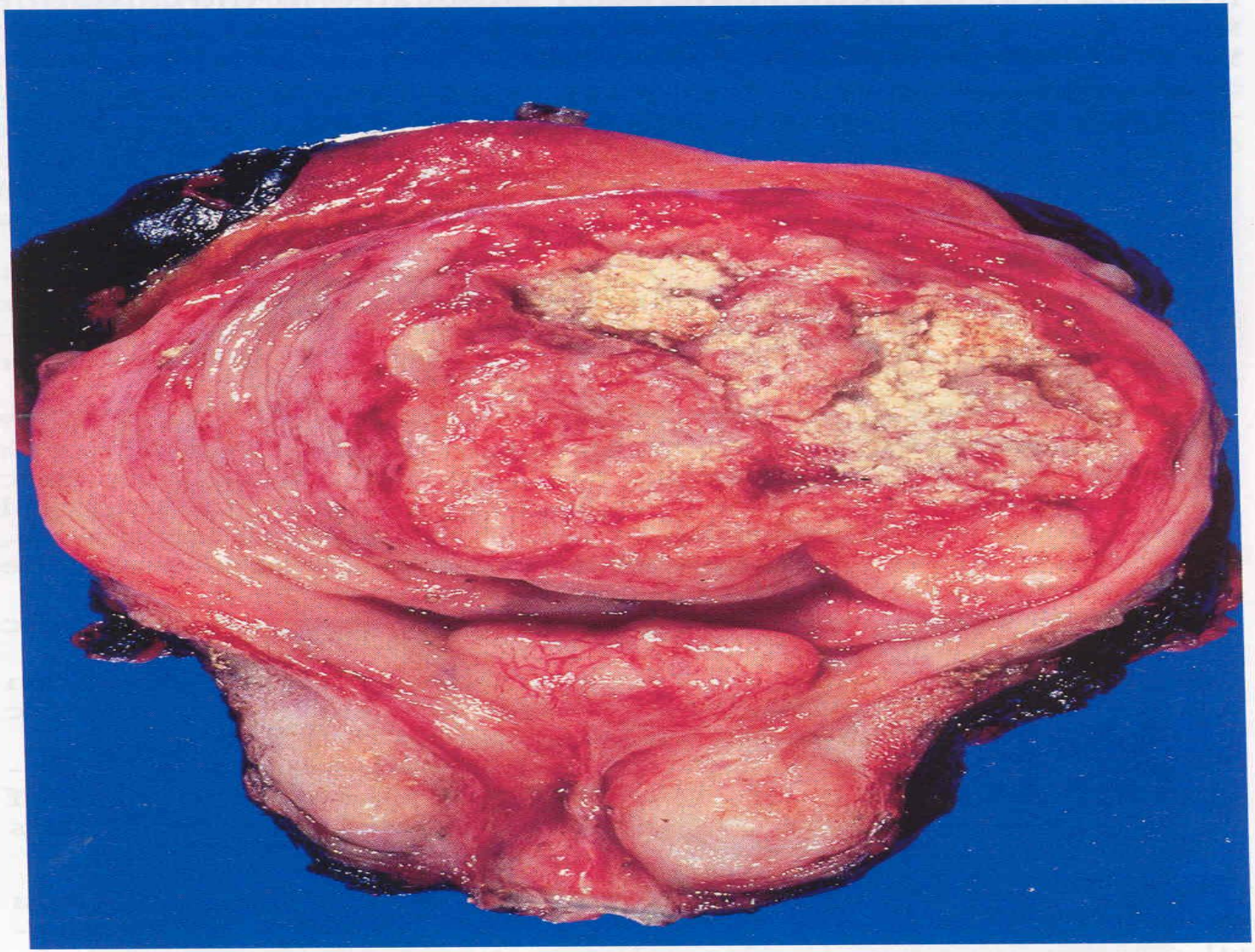


FIGURE 21–12 Opened bladder showing a high-grade invasive urothelial cell carcinoma at an advanced stage. The aggressive multinodular neoplasm has fungated into the bladder lumen and spread over a wide area. The yellow areas represent areas of ulceration and necrosis.

b) - Cancer of ureters is very rare
i) 5 yr survival <10%