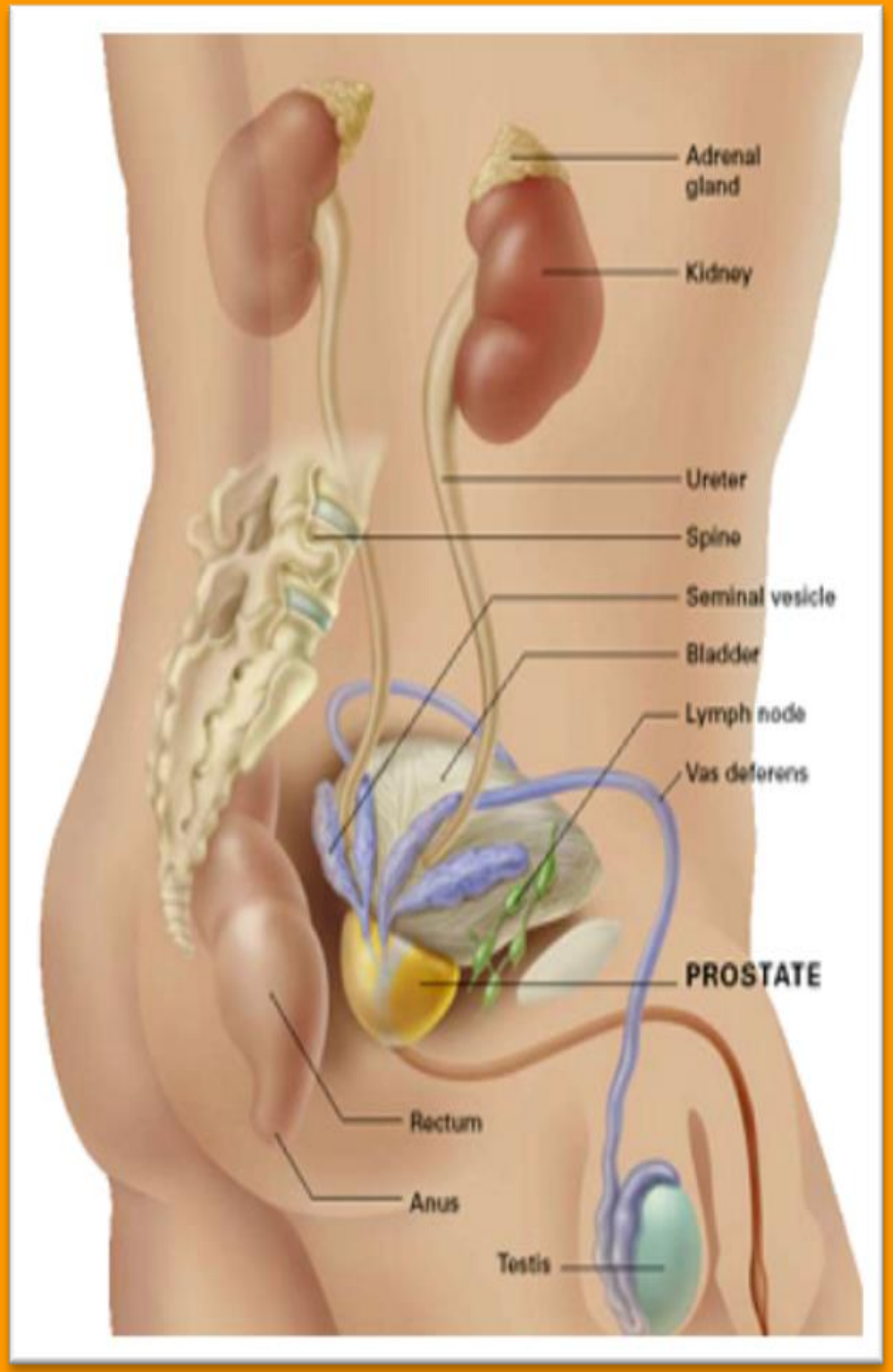
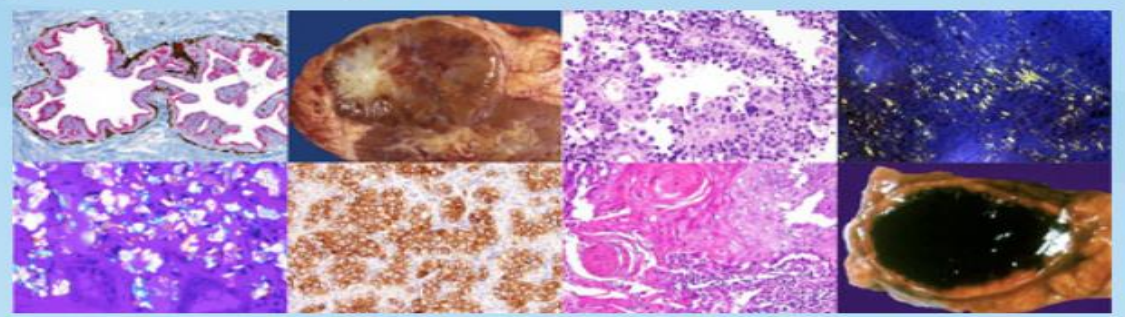



# Urological Pathology and Embryology

林威宇
嘉義長庚醫院

# Pathology for Urologists



This program was designed to help Urology residents and fellows familiarize themselves with the pathologic features of common urologic entities. This will serve not only as a resource tool for your review but also as a quick reference guide to urologic pathology.

This tutorial covers >250 different entities, encompassing pertinent histoanatomic structures to recent innovations and advances in the field. These include among others, newly recognized tumors and terminologies, latest classification schemes, current grading approaches (e.g. recent WHO grading for urothelial neoplasms, ISUP modified Gleason grading, etc.), molecular alterations, and commonly used ancillary diagnostic techniques particularly immunohistochemistry. Main differential diagnoses and their distinguishing features are also presented. There are >650 high-quality images which include gross pictures, histologies, cytologies, special stains, other ancillaries, drawings and illustrations. A self-test is provided at the end for your own assessment.

Descriptions are made short and concise (not >1 page per entity) but enough to cover the basics that urologists should know about pathology. The text is bulleted, key terms and messages are bolded or italicized, and some pathology lexicons are clarified. The images have labels in place and can be enlarged for ease of use in your laptops, tablets and even smartphones.

# Urinary Bladder: Normal Urothelium

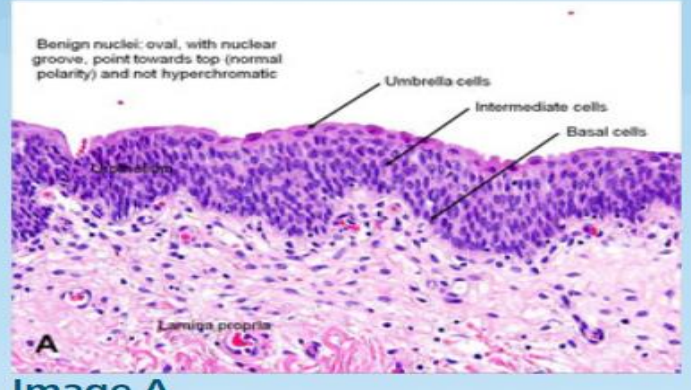



Image A

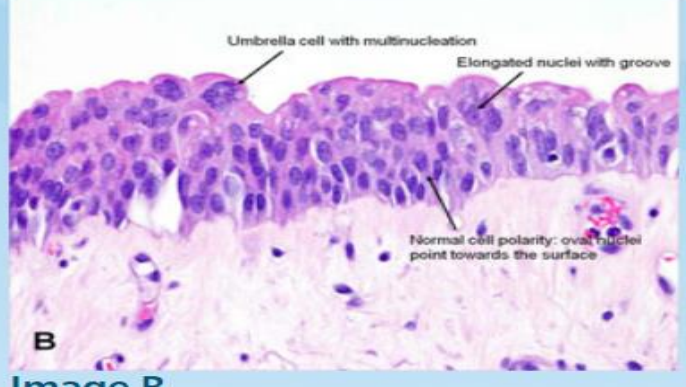



Image B

- Consists of several layers of polyhedral (transitional) cells.
  - 5-7 cells in contracted and 2-4 cells in dilated bladder.
- Top to base, divided into **umbrella, intermediate** and **basal cells (image A)**.
  - Basal cells are smaller cells next to basement membrane.
  - Basal and intermediate cells contain oval or **elongated** nuclei oriented perpendicularly to basement

# Urinary Bladder: Lamina Propria

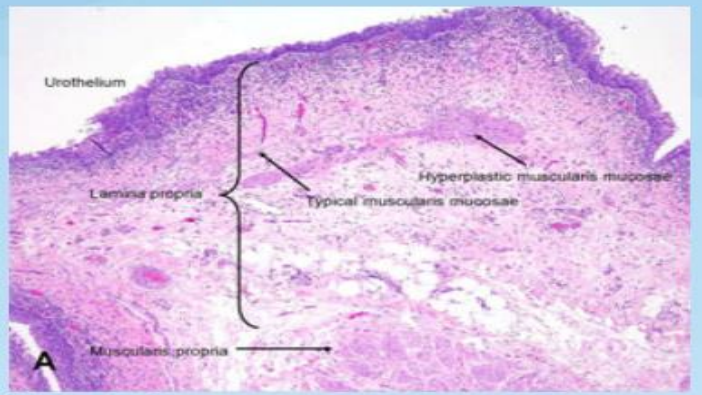



Image A

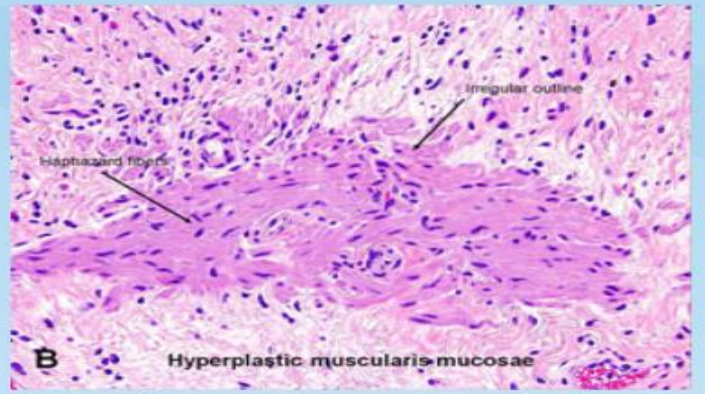



Image B

- Extends from suburothelium to upper boundary of muscularis propria (MP) layer and contains predominantly loose connective tissue, nerves, vasculatures and lymphatics **(image A)**.
- Thickness of LP varies at different bladder subsites.
  - Thickest at dome (1.0-3.1 μm) and thinnest at trigone (0.5-1.6 μm).

LP contains an inconsistent layer of typically veins of smooth muscle fibers known as muscularis mucosae (MM)

American Urological Association



# Urinary Bladder: Muscularis Propria

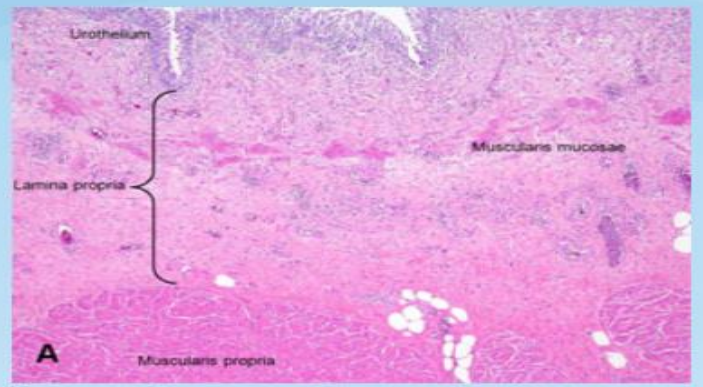



Image A

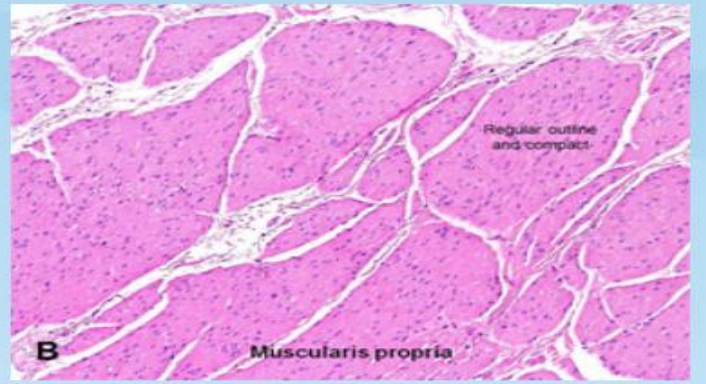



Image B

- Also known as "deep muscle" or "detrusor muscle" **(image A)**.
- Forms the bulk of bladder wall and consists of 3 differently oriented layers of smooth muscles that contract during micturition.
- An important histo-anatomic landmark in staging invasive bladder cancer.
  - Identification and status of involvement of MP is essential in TURBT containing high grade or invasive carcinoma for staging adequacy.
  - Muscularis mucosae (MM) when hyperplastic can mimic MP (tumor in MM is pT1 and tumor in MP is pT2*).
- MP consists of large bundles of regularly oriented muscle fibers with regular outline that are typically closely

# Cystitis Cystica

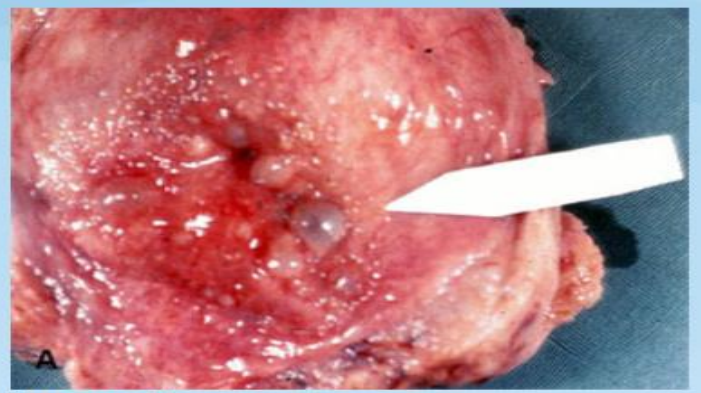



Image A

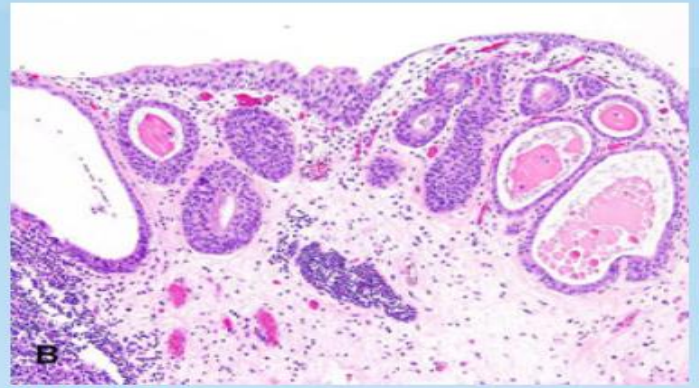
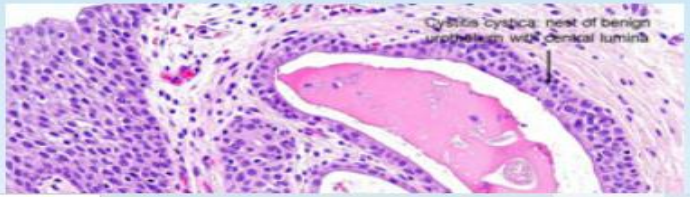
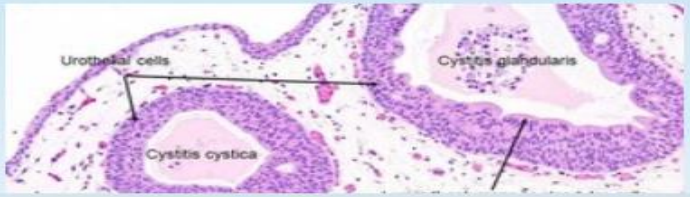



Image B

- Nests of benign urothelium in lamina propria with cystic dilatation.
- Encountered as incidental finding, most often in the region of trigone.
- May appear grossly as pearly or luminescent cysts with intact surface urothelium **(image A)**.



# Hemorrhagic Cystitis

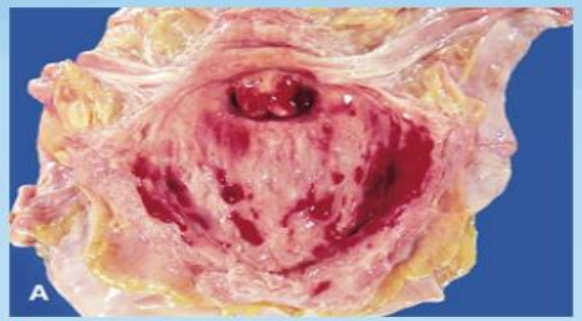


Image A

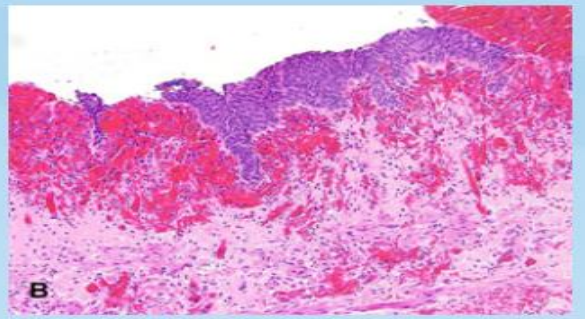


Image B

- Often found in patients receiving chemotherapy (e.g. cyclophosphamide, busulfan, thiotepa) and also can be seen in insecticide or aniline dye exposure, radiation, viral infections (adenovirus, types 11 and 21, polyomavirus, herpes simplex type 2), and idiopathic situations **(image A)**.
- Histology:
  - Congested vasculatures and extensive lamina propria hemorrhage **(image B)**.
  - Can be accompanied by sloughing of surface urothelium, ulceration or cytologic atypia depending on the cause of hemorrhagic cystitis *(radiation-induced or chemotherapy-induced atypia)*.

# Interstitial Cystitis

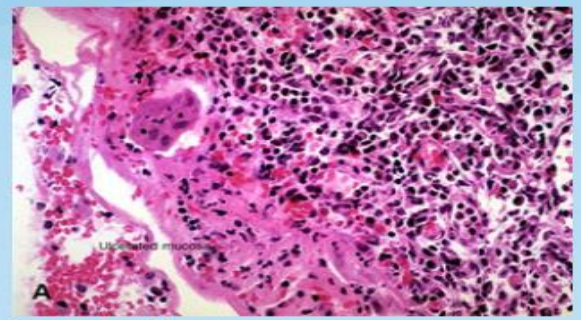



Image A

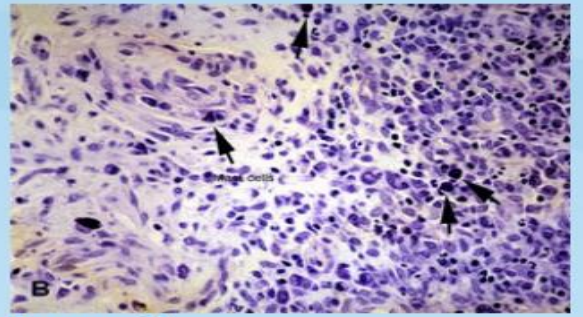



Image B

- Chronic inflammatory process of the bladder of unknown etiology with protracted exacerbations.
- Much more common in women (90%) between 30's to 50's.
- Presents with constellation of symptoms including urinary frequency, urgency, suprapubic pressure, and bladder or pelvic pains.
- Clinical diagnosis of exclusion: must have negative culture studies, no inciting irritating agents to bladder and without bladder neoplasia.
- Cystoscopy:
  - Reddened mucosa with ulcer containing blood vessels radiating towards a central scar **(Hunner ulcer)**.
  - In non-ulcerative form, exhibits petechia and submucosal hemorrhages (glomerulations) or linear cracks after bladder distention.

# Radiation Cystitis

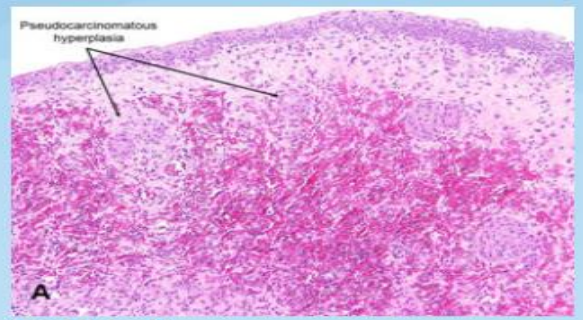



Image A

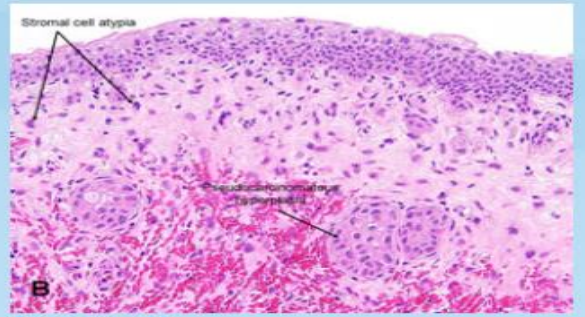
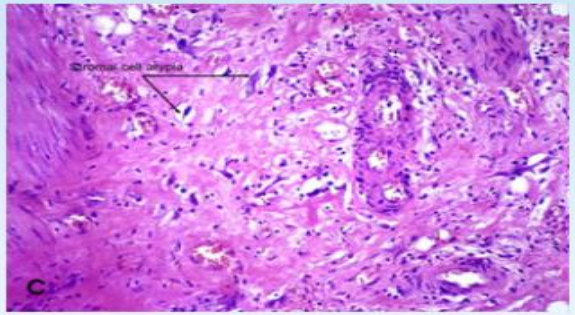
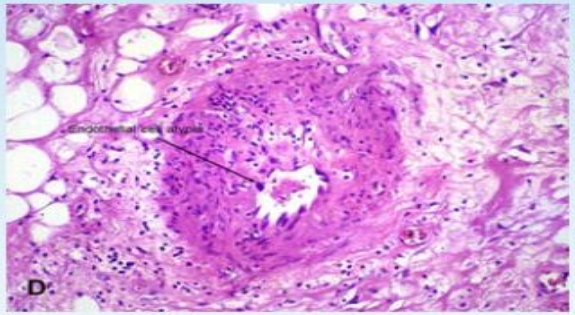



Image B

- Typically occurs ~3 to 6 weeks after radiation of pelvic tumors.
- Histology:
  - Urothelium exhibits marked cytologic atypia characterized by nuclear pleomorphism, smudgy chromatin and cytoplasmic vacuolations, but with normal or maintained nuclear to cytoplasmic ratio **(image A)** & **(image B)**.



# Urothelial Carcinoma in Situ

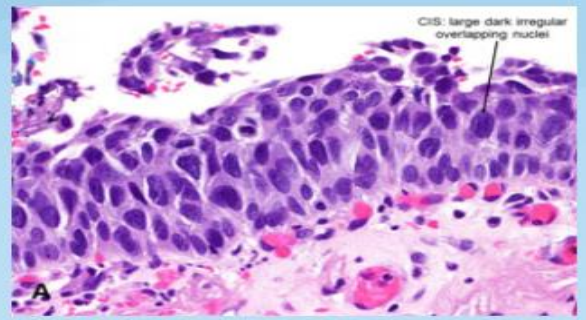



Image A

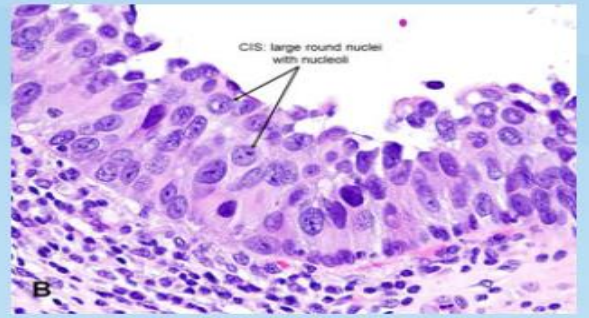



Image B

- Flat lesion composed of malignant urothelial cells confined to the basement membrane, either with full or partial thickness involvement of urothelium.
- Most commonly in men in 50's to 70's.
- Three clinical forms:
  - **Primary (de novo) CIS:** Isolated CIS without prior or concurrent papillary neoplasm (rare).
  - **Secondary CIS:** In patients with prior papillary neoplasm.
  - **Concurrent CIS:** Identified on bladder mucosa with concomitant papillary neoplasm or invasive carcinoma.
- Multifocality is common.
- Associated with amplification/mutation of *p53* and *RB* genes.
- Histology:
  - Diagnosis requires **unequivocal high-grade cytology (image A)** & **(image B)**.
  - Cellular crowding and loss of polarity (see normal urothelium for comparison).

# Urothelial Dysplasia

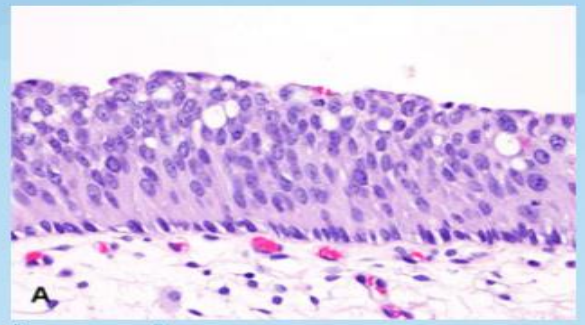



Image A

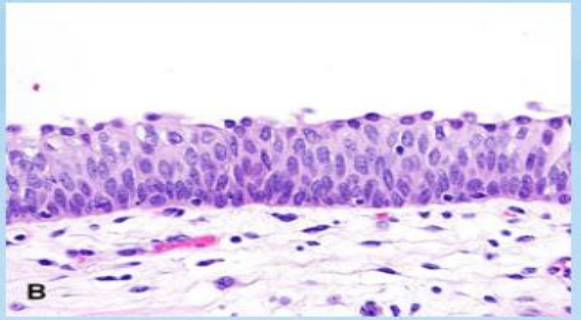



Image B

- Atypical cytologic and architectural features felt to be neoplastic that fall below the threshold for CIS.
- Suffers from poor diagnostic reproducibility.
- Histology:
  - Nuclear abnormalities in the absence of inflammation, or disproportionate in the presence of inflammation, but not severe enough to merit CIS **(image A)** & **(image B)**.
  - Usually normal urothelial thickness.
  - Mild loss of polarity and nuclear crowding.
- Immunohistochemistry: may aberrantly express CK20 and have higher p53+.
- On follow-up, 5-19% progress to bladder neoplasia including CIS.

# Papillary Urothelial Carcinoma, Low Grade

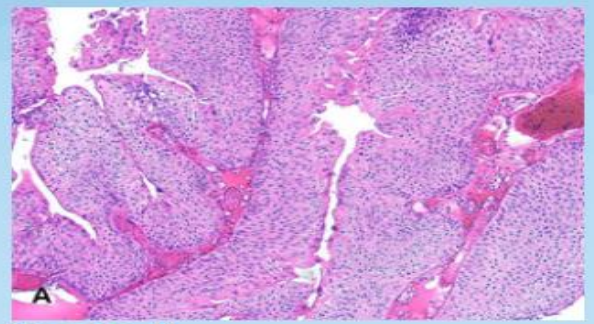



Image A

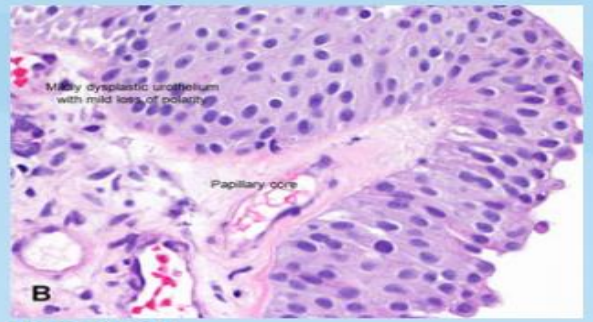



Image B

- Papillary urothelial neoplasm with distinct low-grade dysplastic features.
- More common in men, at trigone or bladder neck region and presents with hematuria *(so as all other papillary neoplasms)*.
- Not synonymous with older 1973 WHO grade 1 transitional cell carcinoma (TCC) category.
  - LGPUC includes mostly former TCC grade 1 and some grade 2.
  - Some former TCC grade 1 also became PUNLMP.
- Associated with mutations in *EGFR* and *HRAS*.
- Size varies, but generally is visualized as smaller lesions.
- Histology:
  - Papillae (with fibrovascular core) may variably exhibit branching and fusion.
  - Mild loss of cellular polarity.
  - Nuclear rounding, slight size variation and mildly abnormal chromatin **(image A)** & **(image B)**.
  - Mitosis is occasional and when present is usually closer to base.

# Papillary Urothelial Carcinoma, High Grade

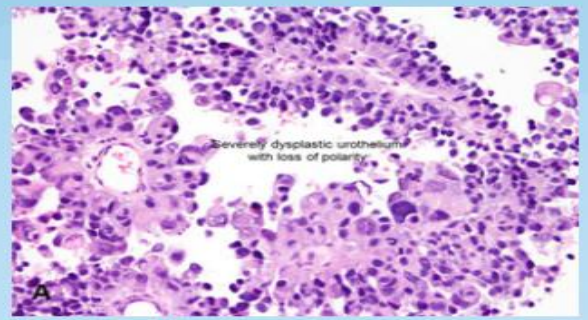



Image A

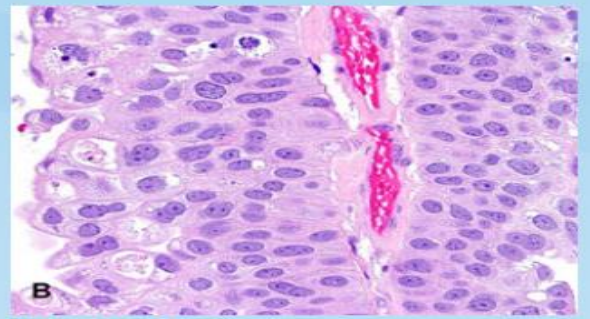



Image B

- Papillary urothelial neoplasm with moderate to high-grade cytology.
- Includes some former 1973 WHO TCC grade 2 and all grade 3.
- Histology:
  - Papillae more complex with fusion or confluence.
  - Loss of cellular polarity, often crowded and overlapping.
  - Moderate to marked pleomorphism, prominent nucleoli and abundant mitosis, at any level **(image A)** & **(image B)**.
- In cases of tumors with mixed low-grade and high-grade (should be at least 5%) areas, the overall grade is assigned as high-grade.
- Presence of invasion should always be thoroughly excluded.
- Recurrence rate of 34-74% and progression rate to invasive cancer of 15-40%.

# Invasive Urothelial Carcinoma

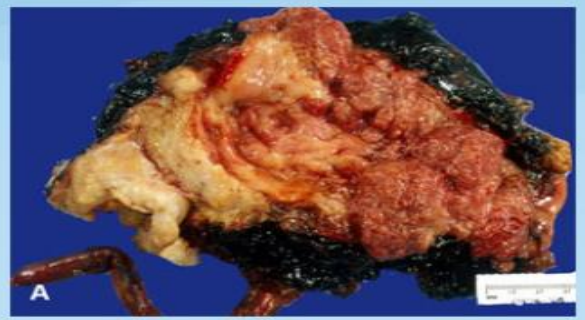



Image A

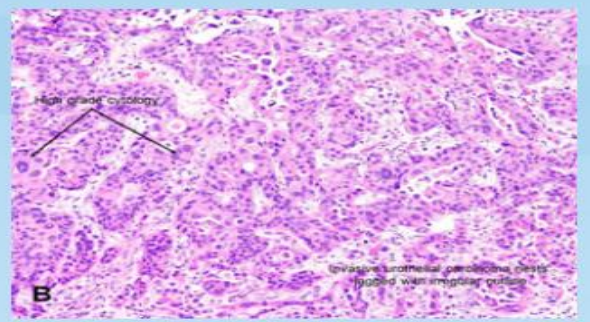
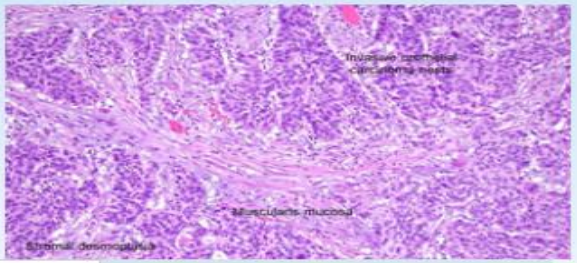
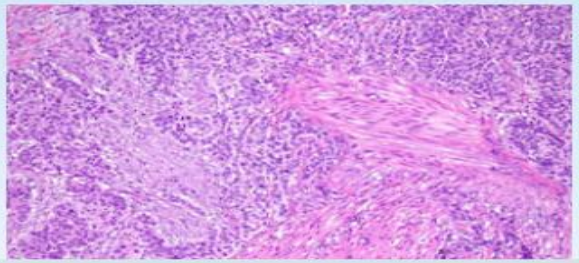



Image B

- Progression to invasive urothelial cancer is believed to occur via 2 molecular pathways: **hyperplasia/papillary** (70-80%) and **flat/dysplasia** (20-30%) pathways, both are associated with chr. 9 losses at initiation.
  - Majority in flat pathway progress to invasive carcinoma **(image A)**, and is associated with abnormalities in p53 and Rb genes.
  - Hyperplasia pathway is associated with HRAS and EGFR mutations, and although has high recurrence (~70%), only few (~15%) progress to invasive cancer.





# Primary Bladder Adenocarcinoma

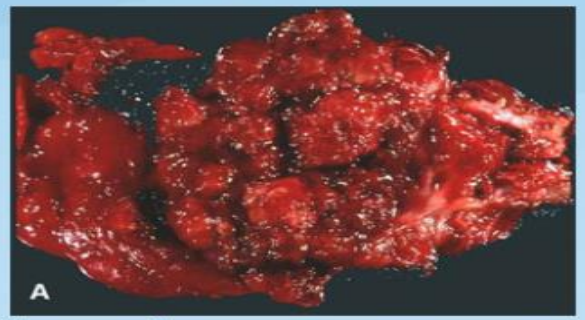



Image A

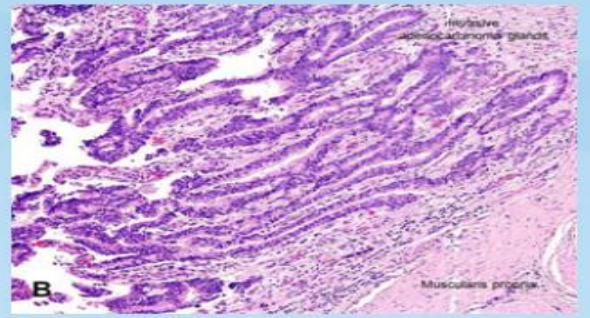
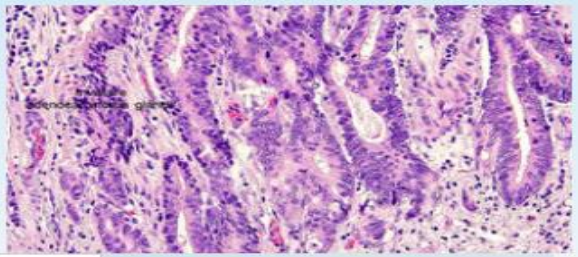
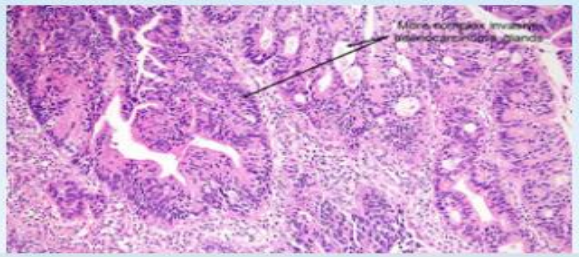



Image B

- There are 2 general types of adenocarcinomas in the bladder:
  - Those arising from the urachus (**urachal adenocarcinoma**, ~1/3), and those arising from the bladder itself (~2/3) **(image A)**.
- Primary adenocarcinoma of the bladder overall is rare, and accounts for only 1% of bladder carcinomas.
- Suggested to arise from intestinal metaplasia of the urothelium.
- Nonfunctioning bladder, chronic irritation, obstruction, exstrophy are risks.





# Small Cell Carcinoma

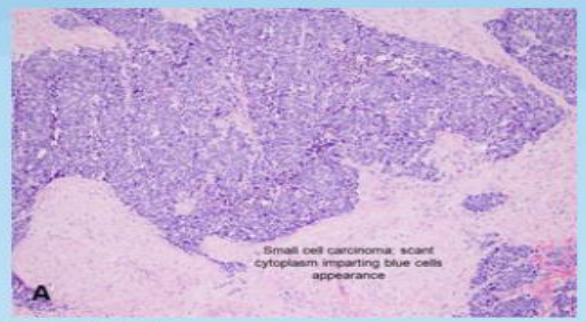



Image A

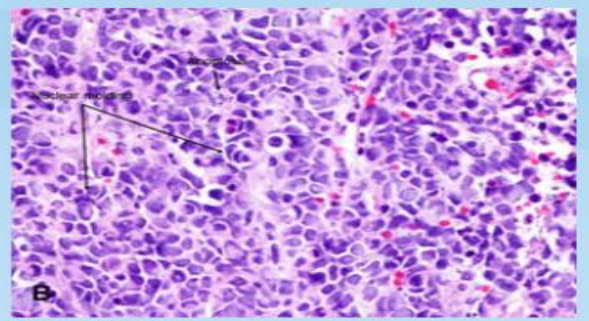



Image B

- Rare, represents <1% of bladder tumors.
- Hematuria is a common presenting complaint and may have paraneoplastic syndromes (e.g. hypercalcemia, hyperphosphatemia, ACTH secretion).
- Usually a large polypoid tumor with extensive bladder infiltration.
- Histology:
  - *Indistinguishable from small cell carcinoma of other organs such as lung and prostate* **(image A)**, **(image B)**, & **(image C)**.
  - Sheets of small round blue cells that infiltrate in a diffuse pattern.
  - Cells have nuclei with "salt and pepper" chromatin (dusty appearance with inconspicuous nucleoli).
  - Crush artifact (smearing of cells) and nuclear molding is common.
  - High mitotic activity, apoptosis and necrosis common.
  - About half occur mixed with urothelial carcinoma.

# Prostate

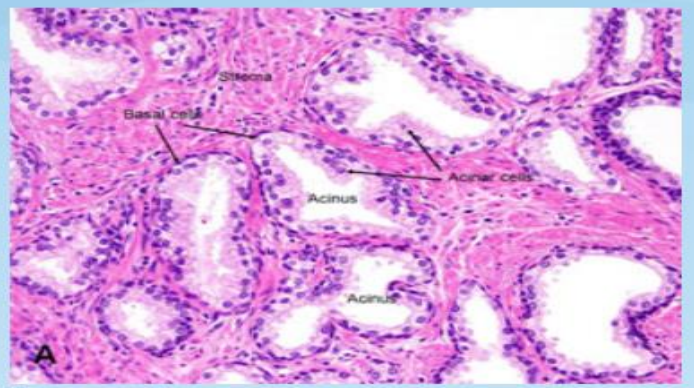



Image A

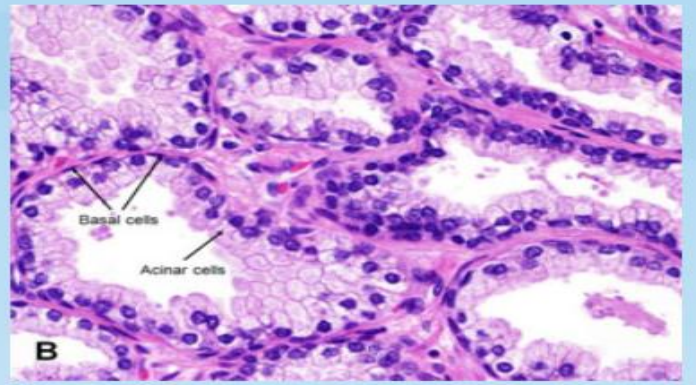
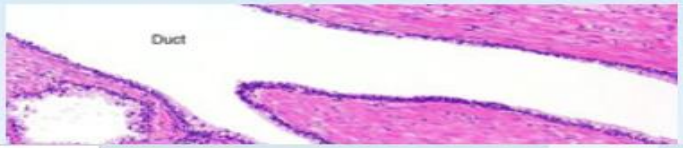
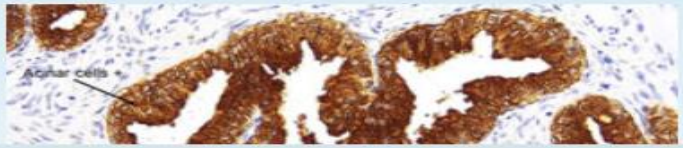



Image B

- Secretes a thin milky fluid that comprises ~1/3 of seminal fluid.
- Microanatomy: divided into **glandular** *(the bulk)* and **non-glandular** parts.
  - Glandular prostate divided into **peripheral zone** (PZ, 70%), **central zone** (CZ, 25%), **transition zone** (TZ, 5%)*, and periurethral gland region.
  - Most common cancer are in PZ (~75%), followed by TZ (~15%).
  - Non-glandular part is mainly the anterior fibromuscular stroma and sphincters.



# Prostatic "Capsule" and Periprostatic Tissues

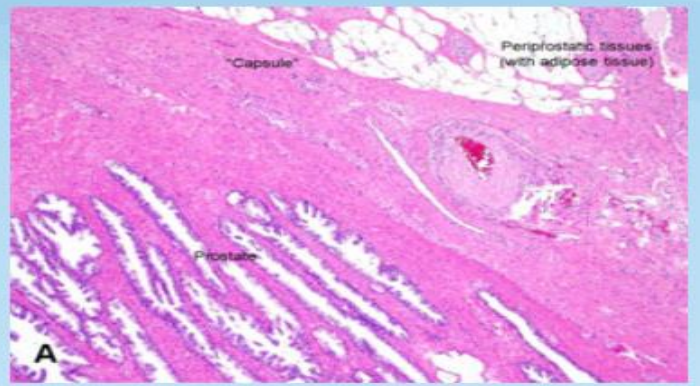



Image A

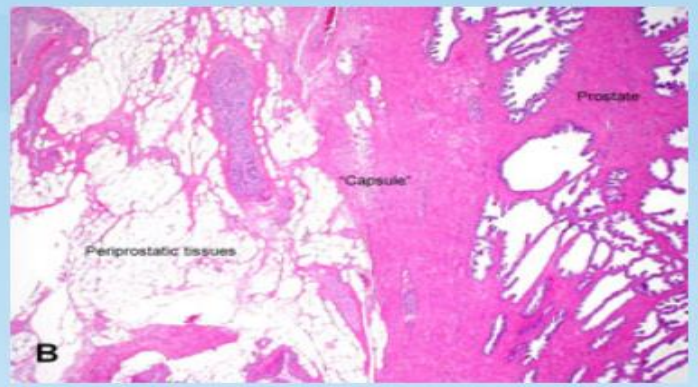



Image B

- Prostate does NOT have a true capsule but an outer condensed fibromuscular band, which is an inseparable component of prostatic stroma **(image A)** & **(image B)**.
  - For convenience is referred to in the literature as prostate "capsule".
    - Important boundary for staging locally aggressive prostate cancer (i.e. extraprostatic extension [EPE]).
  - This capsule is absent at prostate base and is not clearly defined at the apex, thus assessment of EPE is not amenable at these 2 sites.
- **Adipose tissue** is not present within the prostate parenchyma, and involvement by prostate cancer is thus considered as EPE, including in needle biopsy.
  - Adipose tissue may be absent over large areas of radical prostatectomy specimen making pathologic evaluation of EPE difficult.

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# Prostatic Urethra


Image A

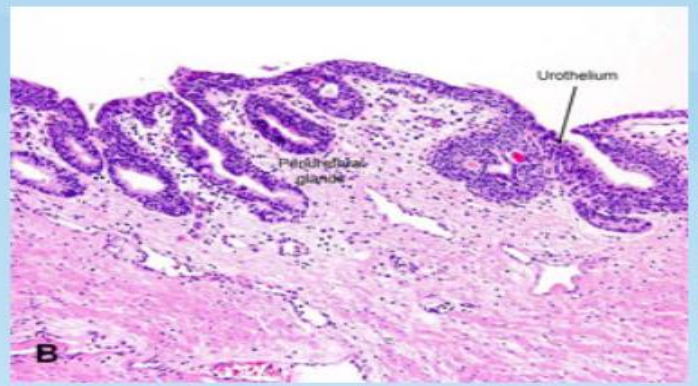


Image B

- Prostatic urethra **(image A)** & **(image B)** and **proximal portion of prostatic ducts (image C)** & **(image D)** are lined by urothelial cells.
  - Thus, prostate can also have *primary urothelial carcinoma.*
  - More often, urothelial carcinoma arises from prostatic urethra and extends into the prostate via prostatic ducts or directly from suburothelium.

# Prostatitis

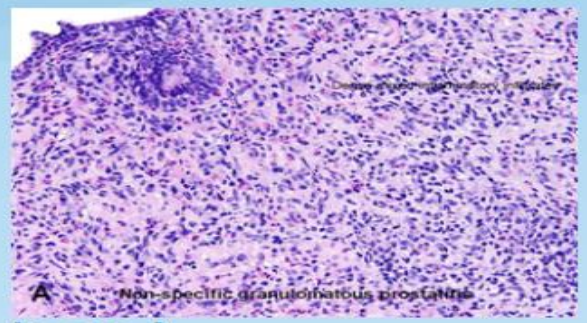


**Image A**

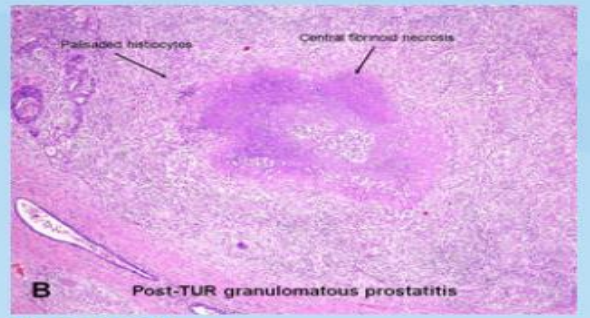


**Image B**

Granulomatous prostatitis (GP)

- Inflammation of prostate with granulomas (seen in <1% of prostate).
- Includes **non-specific GP** (most common), **post-procedural GP** (post-TUR), **infectious GP** (includes **BCG-related**, mycobacterial, fungal) and **systemic GP** (such as Churg-Strauss syndrome, Wegener granulomatosis).
- May present with irritative voiding symptoms, fever or chills.
- May present with palpable nodule (60%), raising suspicion for a carcinoma.
- Histology:
  - *Granuloma is characterized by central clusters of epithelioid histiocytes and surrounded by lymphocytic infiltrates.*
  - Non-specific GP shows expansile nodular mixed inflammatory infiltrates with rare discrete granulomas **(image A)**.
  - Post-resection GP shows central fibrinoid necrosis surrounded by palisaded histiocytes (looks like rheumatoid nodule) **(image B)**.
  - BCG-related granulomas have may have central caseation in larger granulomas, surrounded by

# Benign Prostatic Hyperplasia

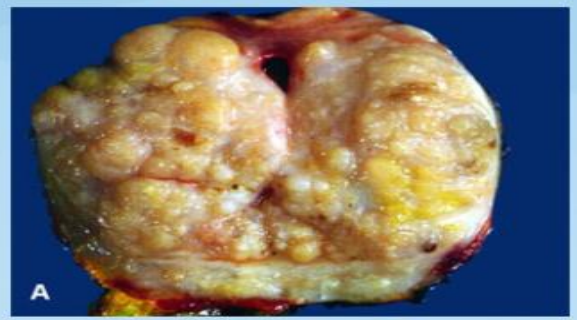


Image A

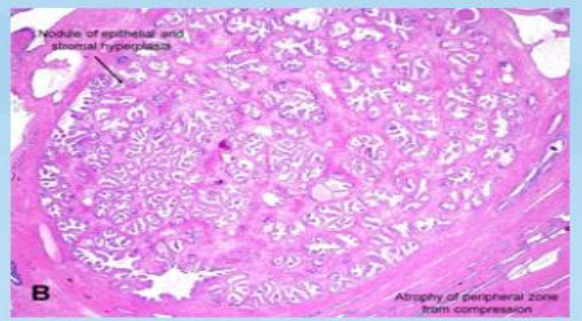


Image B

- Most common urologic disease of men; incidence increase with age (50% in 50s and 80-90% in 70s and 80s).
- Pathophysiology remains poorly understood; hormone alteration plays a central role – cellular accumulation of testosterone, particularly the active metabolite dihydrotestosterone (DHT).
- Almost exclusively involves the area of transition zone (TZ).
- Presents with lower urinary tract symptoms (LUTS).
- Most common non-cancerous cause of serum PSA elevation.
- Gross:
  - *Hallmark is nodular prostatic enlargement* **(image A)**.
  - Hyperplastic nodules are often multiple, mainly centered on proximal prostatic urethra involving submucosal compartment and TZ.

# Targeting phenotypic heterogeneity in benign prostatic hyperplasia

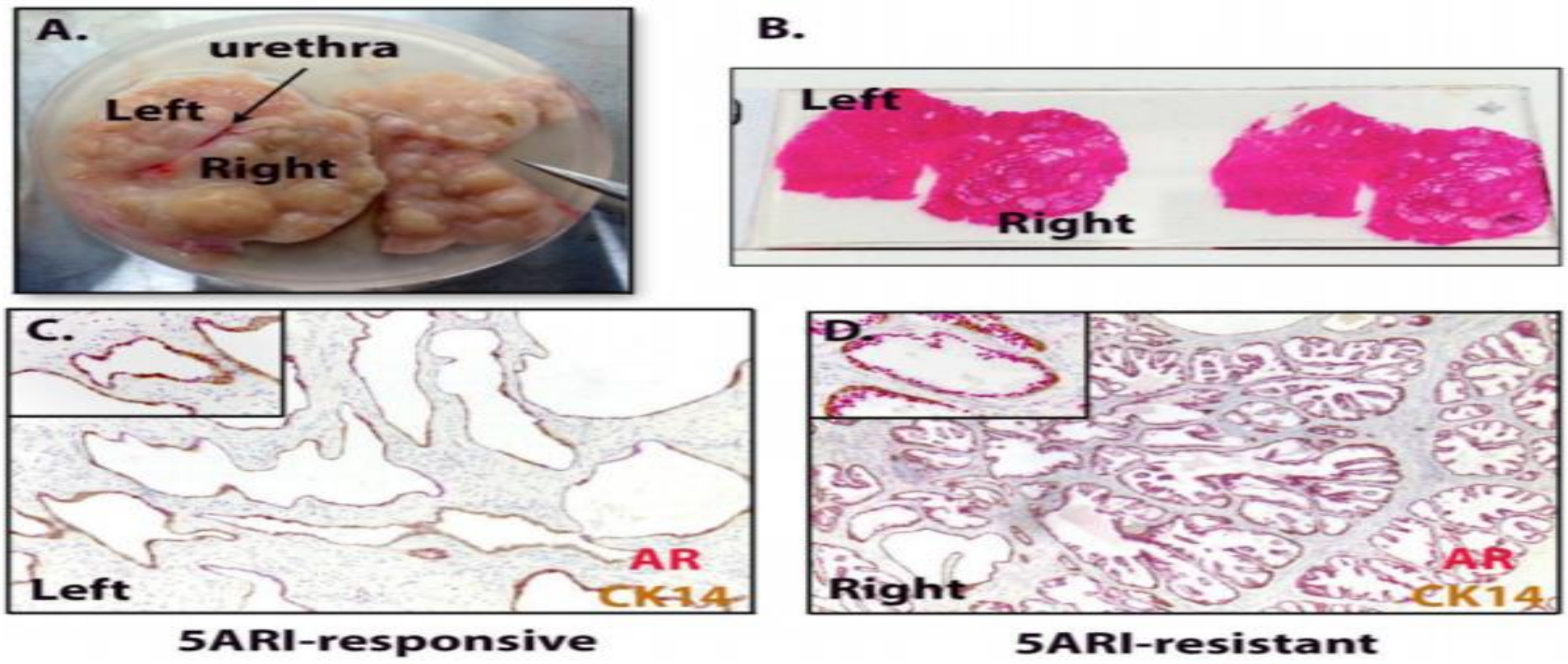


**Figure 1. Regional 5ARI resistance in BPH**
**A**, Coronal section of a 130g prostate from a BPH patient on 5mg/day finasteride for 5 years. **B**, H&E stained glass slide with serial sections showing morphological differences between atrophied left side and nodular right side. **C**, AR/CK14 dual IHC of atrophied left side shows loss of luminal epithelia. **D**, AR/CK14 IHC of right side shows strong AR staining of luminal epithelia in non-atrophied glands.

# Targeting phenotypic heterogeneity in benign prostatic hyperplasia

Differentiation. 2017

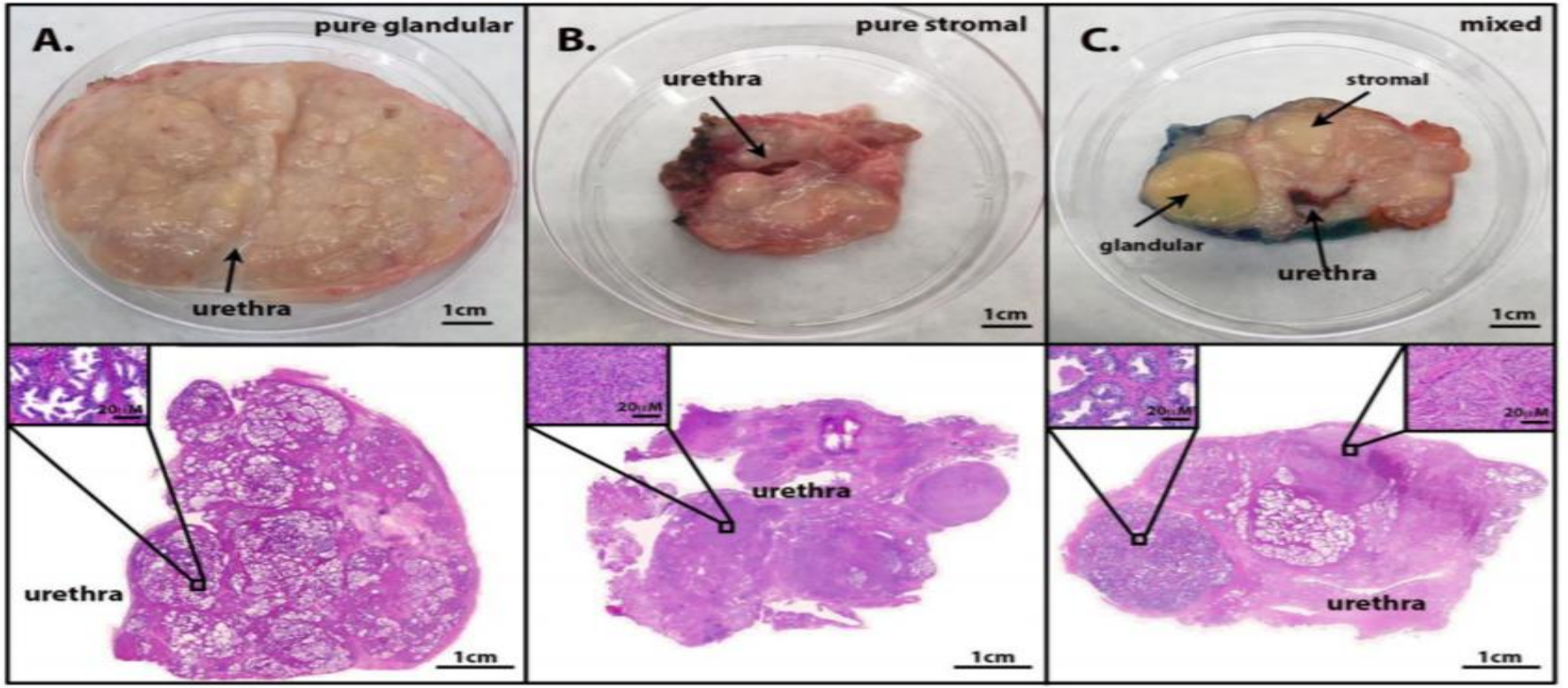


**Figure 4. Examples of pure and mixed phenotypes in BPH**

**A,** A coronal section of a purely glandular 250cc BPH specimen is shown in a 10cm dish. Only one hemisphere of the specimen fit onto a 2″×3″ glass slide subjected to high resolution scanning. **B,** A 100cc BPH specimen with a purely stromal composition. **C,** A 130cc specimen with both stromal and glandular hyperplasia.

# Prostatic Adenocarcinoma: General Features

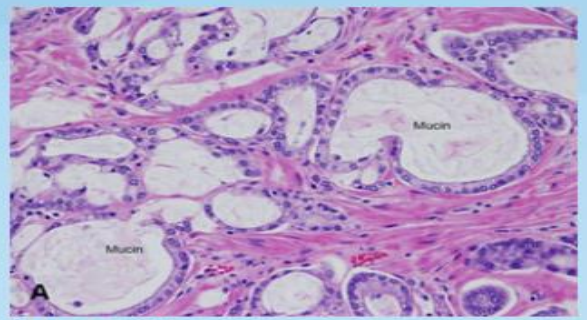


Image A

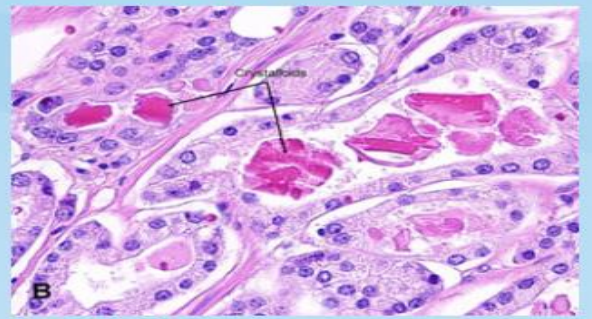


Image B

- Most common cancer and 2nd leading cause of cancer-related death in men.
- Common in elderly, incidence increases with age, 70% affected by 70 years.
- ~50% harbor TMPRSS2 and ETS gene fusion; *TMPRSS2:ERG* (~90%).
- 75-80% occurs in peripheral zone, 15-25% in transition zone.
- Gross: solid yellow or gray-white areas, although often tumor is not grossly discernible.
- Histology:
  - Spectrum of architectures *(that is why we have the unique Gleason grading system, see later).*
  - *Diagnosis of well-differentiated tumors (well formed glands or grade 3) is most difficult due to overlap with benign glands and lesions.*
  - Diagnosed by architectural, nuclear, cytoplasmic, and intraluminal features; some may be seen in benign glands *(except pathognomonic features listed below).*
  - Malignant gland should lack basal cells!

- Diagnosed by architectural, nuclear, cytoplasmic, and intraluminal features; some may be seen in benign glands *(except pathognomonic features listed below)*.
- **Malignant gland should lack basal cells!**
- Large nuclei with prominent nucleoli that can be multiple.
- Cytoplasmic tincture different to adjacent benign glands.
- Lumen may have blue mucin **(image A)**, crystalloids (bright eosinophilic rhomboid to prismatic structures, seen in ~40% cancer) **(image B)** and amorphous eosinophilic secretions.

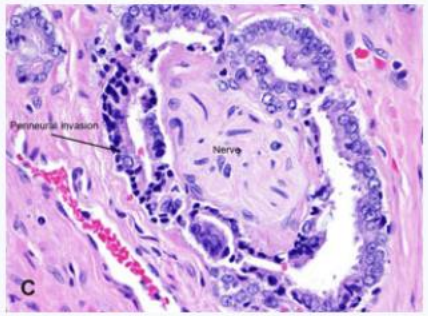


Image C

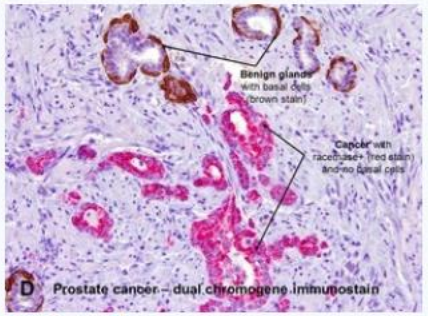


Image D

- Pathognomonic features: **glomerulation** *(looks like glomerulus)*, **collagenous micronodules** (mucinous fibroplasia) and **circumferential perineural (image C)** or **intraneural invasion** *(benign glands can next to nerve)*.

- Immunohistochemistry: NO basal cells (HMWK- and p63-) and over expresses AMACR, in contrast to benign glands **(image D)**.
- Metastasis often to bone (osteoblastic), lung and pelvic (obturator) lymph nodes.
  - PSA or PSAP immunostain helpful to confirm prostatic origin.

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# (Modified Grading by ISUP)


Image A

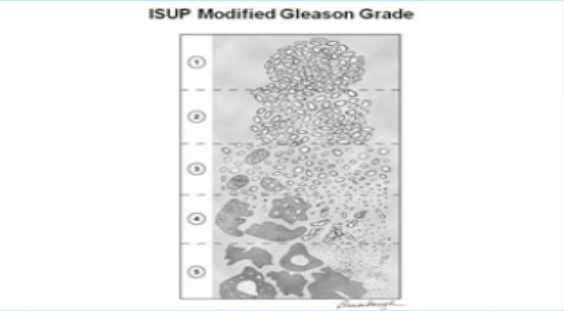



Image B

- Based purely on **architecture**, classified into 5 patterns or grades (1 to 5) representing a spectrum from better-differentiated well-formed glands to poorly differentiated cancer incapable of forming glands.
- After its development by Dr. Donald Gleason in 1966, underwent refinements in 1974 and 1977 (image A), and had its latest modification in 2005 by ISUP (image B).
- **Gleason Score (GS) = primary + secondary grades** (scores of 2-10).
  - In **prostatectomy:**
    - Primary grade: most predominant pattern.
    - Secondary grade: second most predominant pattern.
    - In case there are 3 different grades, a tertiary pattern is included if it is higher than the secondary grade.
  - **In biopsy:**
    - Primary grade: most predominant.
    - Secondary grade: highest non-predominant pattern.

# Prostatic Adenocarcinoma: Gleason Pattern 5

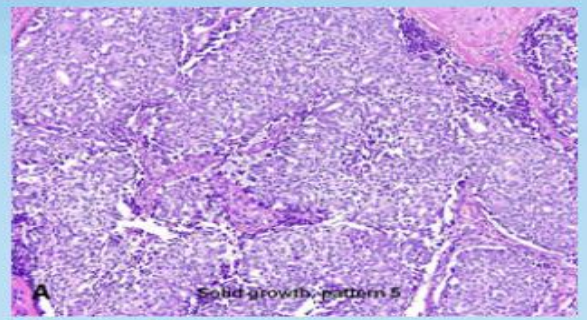



Image A

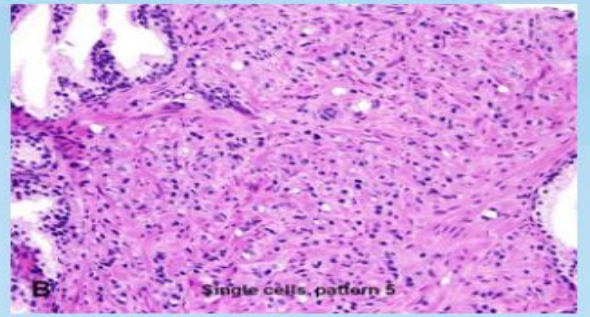



Image B

- No gland formation is evident.
- **Solid sheets (image A).**
- **Single cell infiltration (image B).**

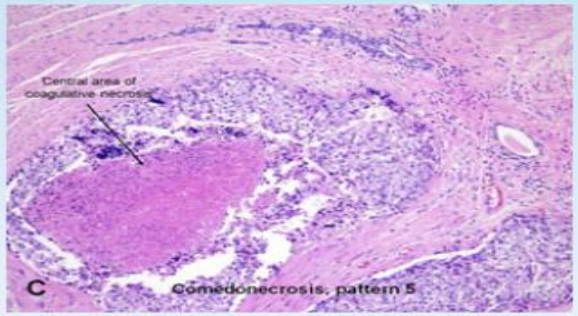



Image C

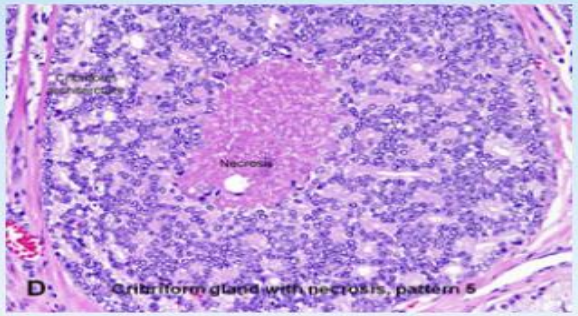



Image D

- **Comedonecrosis** – glands with central necrosis **(image C).**

# Small Cell Carcinoma

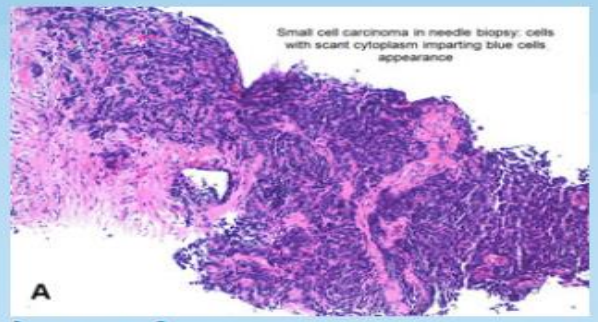



Image A

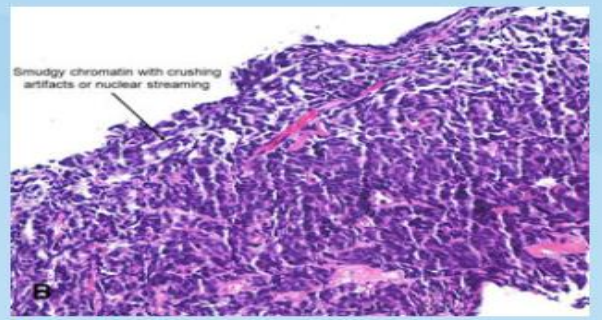



Image B

- Rare, comprises 1% of all prostate cancer.
- May occur pure or mixed with acinar adenocarcinoma.
- ~1/2 of patients have history of acinar adenocarcinoma, and some with prior hormonal treatment.
  - Neuroendocrine cells are devoid of androgen receptors; ADT may lead to clonal progression.
- Presents with rapid onset urinary tract obstruction, dysuria, nocturia, or urgency and some may present with paraneoplastic syndromes.
- Serum PSA level variable, may be normal.
- Histology:
  - Indistinguishable from small cell carcinoma of other organs such as lung and bladder.
  - Sheets of small round blue cells that infiltrate in a diffuse pattern **(image A)**, **(image B)**, **(image C)**.


# Urothelial Carcinoma of the Prostate


Image A

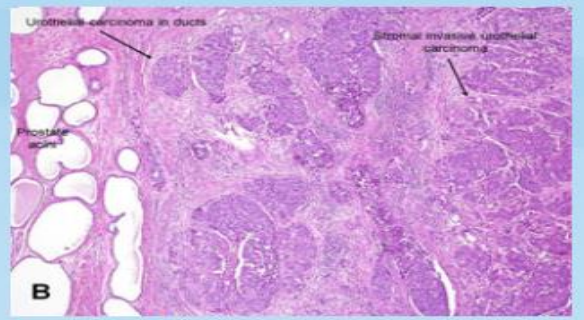
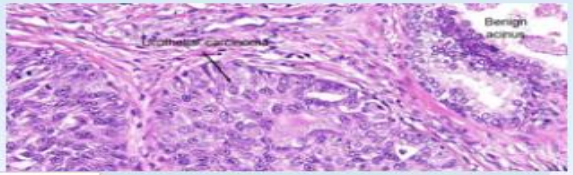
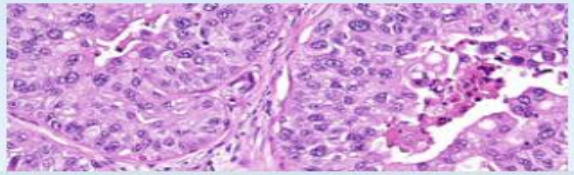



Image B

- UCa involving the prostate that originates from prostatic urethra, periurethral glands and proximal prostatic ducts **(image A)** & **(image B)**.
- Strictly speaking, *primary prostatic* UCa are those arising within proximal prostatic duct urothelium, however, urethral and duct involvement often goes hand in hand and its difficult, if not impossible, to identify if the invasive UCa arose only from the ducts.
- But must be distinguished from secondary bladder UCa that invades into the prostate. *(pT4 bladder cancer, which has poorer prognosis)*
- Rare, 1-4% of prostate cancers in adults; secondary involvement by bladder UCa is more common (12% to 58%).



# Xanthogranulomatous Pyelonephritis

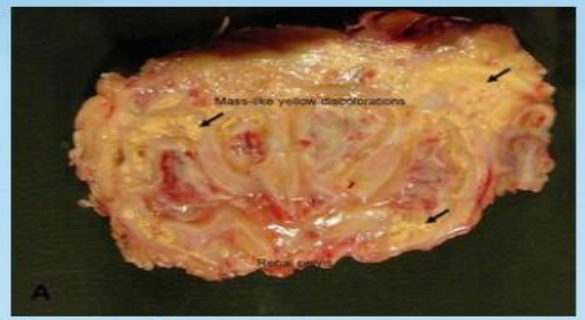



Image A

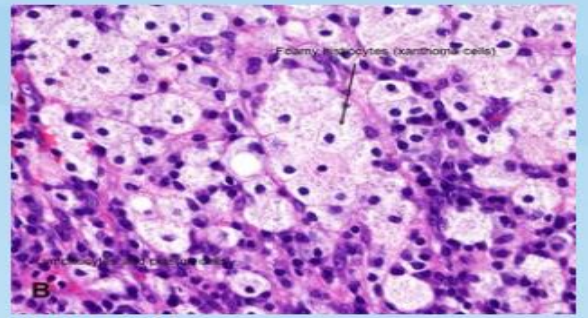



Image B

- Destructive chronic histiocytic inflammation (xanthoma cells) of pelvicaliceal and renal parenchyma forming a mass or pseudotumorous lesion.
- Often associated with gram-negative bacteria.
- Occurrence associated with obstruction, stones or staghorn calculus and recurrent urinary tract infections.
- Begins with obstruction, followed by suppurative inflammation at pelvis then extends into kidney medulla, resulting to a "destructive" appearing inflammation and necrosis.
- More common in females (70%).
- Presents with renal mass, pain and fever; renal mass raises concern for a neoplasm.

# Autosomal Recessive Polycystic Kidney Disease

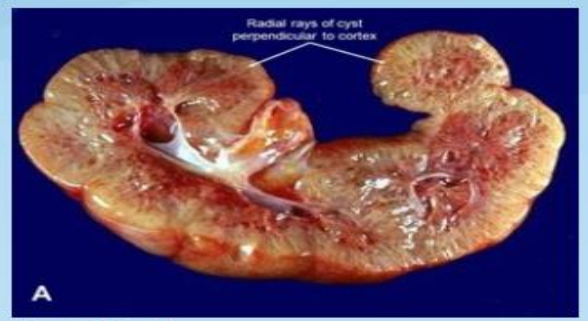



Image A

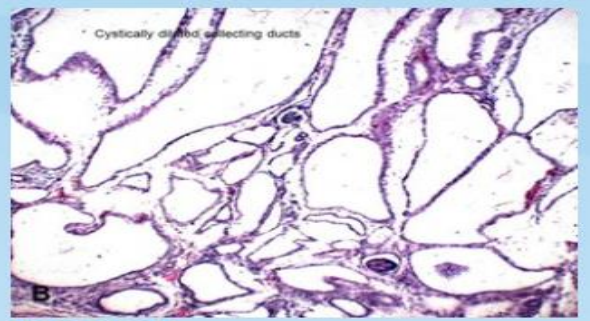



Image B

- Most cases result in stillbirth or early neonatal death (40%); encountered in 1:20,000 live births.
- Associated with gene *PKHD1* that maps to chr region 6p21-p12 and encodes for protein fibrocystin located in cilium; >300 mutations in PKHD1 identified.
- Mutations in PKHD1 are detected in 80-85% of cases.
- Enlarged cystic kidney at birth.
- Gross:
  - Bilaterally enlarged kidneys with "radial rays" of cysts oriented perpendicular to the cortex **(image A)**.
  - Reniform shape is generally maintained.
  - Ureters are normal.
- Histology:
  - Cystic dilatation of cortical and medullary *collecting ducts* +/- involvement of PCT and Bowman's capsule **(image B)**.
  - Nephrons between dilated ducts are normal *(vs. renal dysplasia)*.

# Clear Cell Renal Cell Carcinoma


Image A

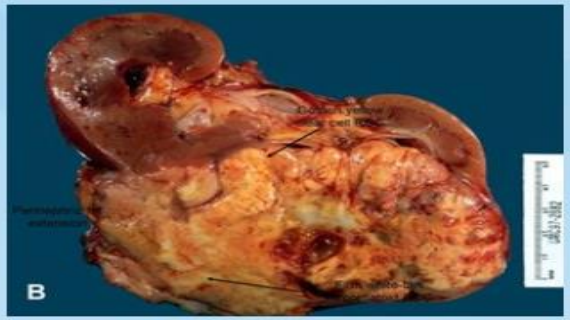



Image B

- Most common type of RCC.
- Cytogenetically characterized by 3p- and inactivating mutations in *VHL* gene (a tumor suppressor gene at 3p25-26).
- Also has inactivating mutation in *PBRM1* at chr 3p21 (41%).
- Almost all von Hippel-Lindau syndrome patients will develop clear cell RCC.
- Mostly asymptomatic; classic triad of abdominal mass, flan pain and hematuria detected in only ~1/3 of patients.
- Gross:
  - Golden yellow tumor *(due to lipid content)* with hemorrhages and necrosis **(image A)**.
  - +/- cystic changes; more solid fleshy (non golden-yellow) area may represent sarcomatoid change **(image B)**.

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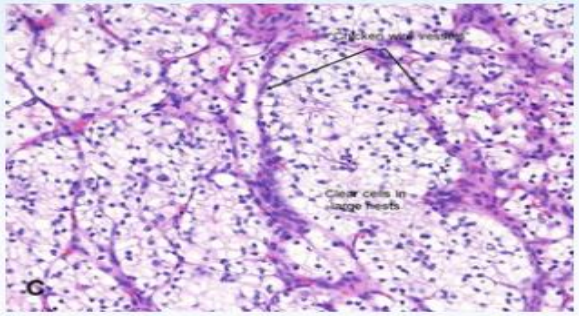



**Image C**

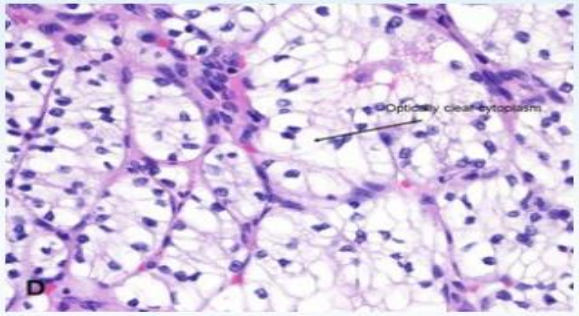
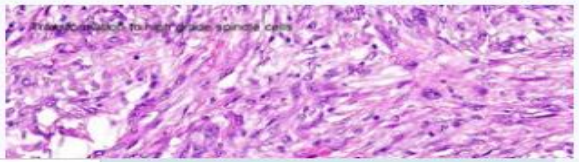
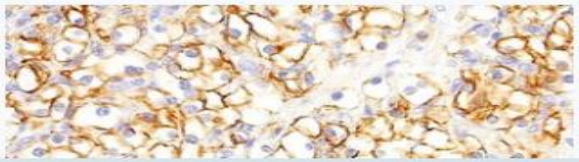



**Image D**

- Microscopic:
  - Water-clear or optically-clear cells *(due to glycogen content)* arranged in nests in "chicken wire" vasculatures **(image C)** & **(image D)**.
  - Delicate capillary often ruptures during surgical manipulation, resulting in formation of "blood lakes" within tumor cell nests.
  - Some cells may have granular eosinophilic cytoplasm *(not all clear cell RCC have clear cytoplasm! – in the past was called "granular cell RCC")*.
  - May develop sarcomatoid change (like all other RCC) and most often shows high-grade spindle cell morphology **(images E)**; more aggressive behavior.
  - Nuclear grading based on Fuhrman classification (grades 1-4).





# Chromophobe Renal Cell Carcinoma


Image A

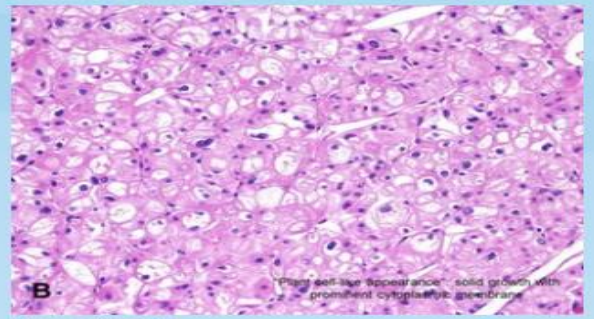



Image B

- 3rd most common subtype of RCC.
- Morphologically has "classic" and eosinophilic types, the later has significant overlap with oncocytoma and often poses a diagnostic problem.
- Cytogenetics: multiple chromosomal losses involving 1, 6, 10, 13, 17, 21 and Y *(more than in oncocytoma)*.
- Gross:
  - Well-circumscribed, solid, beige or light brown **(image A)**.
  - Eosinophilic type can be mahogany-brown and ~1/5 has central scar *(similar to oncocytoma)*.
- Histology:
  - Classic chromophobe RCC cells have flocculent cytoplasm *(pale or reticulated, not-optically clear as in clear cell RCC)* that condenses around the edges, giving the appearance of thick prominent cell borders *("plant cell-like")* **(image B)**.
  - Cells grow in larger nests *(larger than in renal oncocytoma and without the "chicken wire" vessels of clear cell RCC)*.

*cell RCC).*

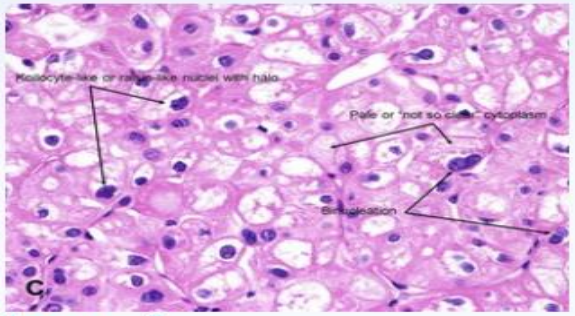



**Image C**

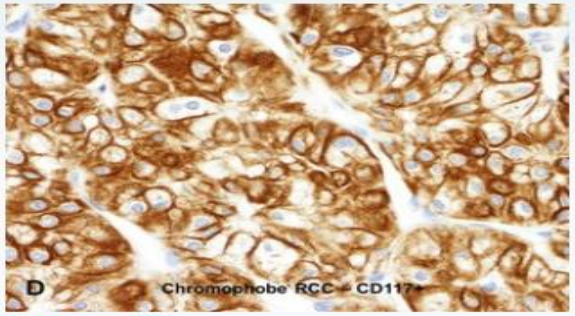



**Image D**

- Nuclei tend to be much more pleomorphic than in clear cell RCC or oncocytoma. *(Fuhrman grading not used because of this innate "high-grade" appearance in this mostly low-grade tumor).*
  - Other grading approaches being introduced.
- Characteristic nuclei have koilocyte-like or raisin-like appearance, sometimes binucleated and with perinuclear halo **(image C)**.
- Eosinophilic type cells have abundant eosinophilic cytoplasm like oncocytoma, but in contrast have larger nests.

- Immunohistochemistry: CD117 (c-kit)+ **(image D)**, Ksp-cadherin+, and CK7+ (diffuse).
- Relatively higher proportion of high-grade sarcomatoid change (2-9%).
- Better survival than clear cell and papillary RCCs (5 year survival of >90%).
- DDX: *(Morphologic differences as above)*
  - Clear cell RCC: CAIX+, CD117- or KSP-cadherin-
  - Renal oncocytoma: CK7– or focal+

American Urological Association









# Multilocular Cystic Renal Cell Carcinoma

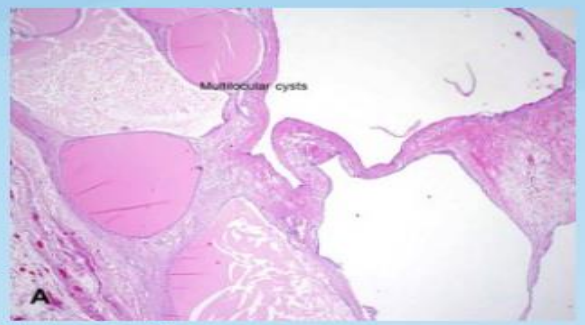



Image A

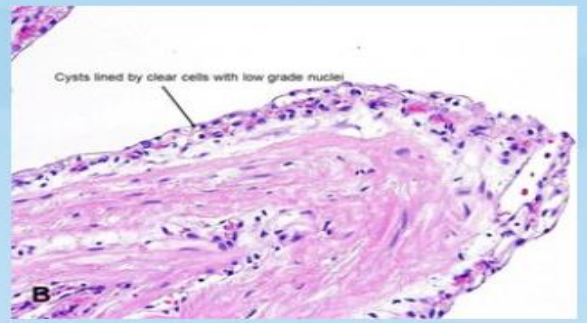



Image B

- Purely cystic tumor lined by clear cells of same cytology to clear cell RCC; *additional presence of solid area qualifies the tumor as clear cell RCC.*
- Alteration in *VHL* also present.
- Occurs in adult patients, mean in their 50s.
- Vast majority discovered incidentally.
- Gross: Multicystic tumor of varying sizes with thin septae and contains clear or bloody fluid. *(Should have no solid area).*
- Histology:
  - Cysts are separated by thin septae and lined by single or few layers of clear cells with low-grade nuclei (Fuhrman grade 1 or 2) **(image A)**, **(image B)**, **(image C)**, & **(image D)**.
  - Few clears cells may be seen within the septa, but there should be no sheet or solid area of clear cells.

(Fuhrman grade 1 or 2) (image A), (image B), (image C), & (image D).

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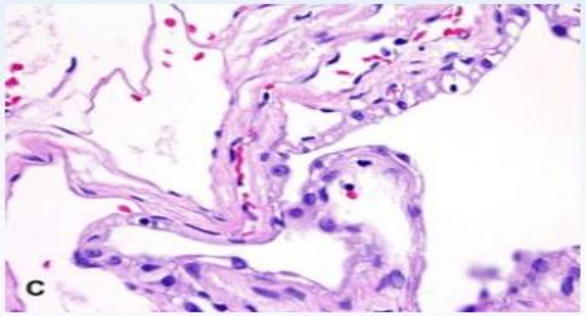



Image C

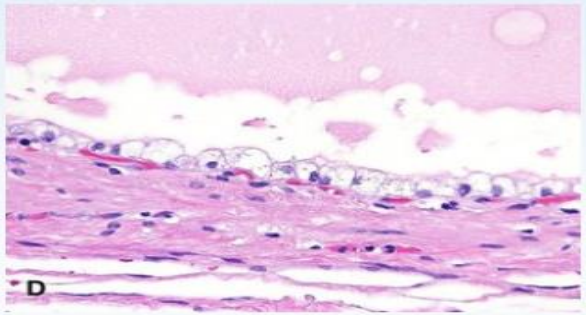



Image D

- No recurrence or metastasis reported, including in those few cases with extrarenal extension (pT3).
- DDX:
  - Non-neoplastic cystic diseases of the kidney: no clear cell lining.
  - Cystic nephroma: lined by "hobnailed cells" and may have "ovarian-type stroma".
  - Cystic partially differentiated Wilms tumor: cells are primitive appearing (small blue cells) and seen in children.

# Adrenocortical Adenoma

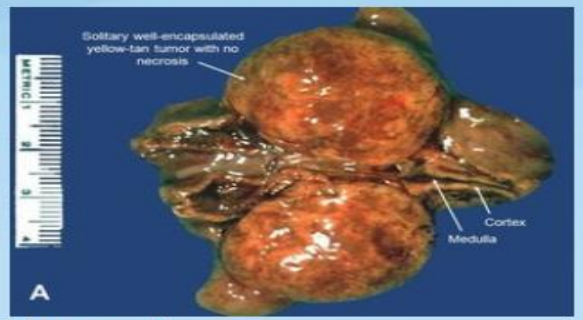



Image A

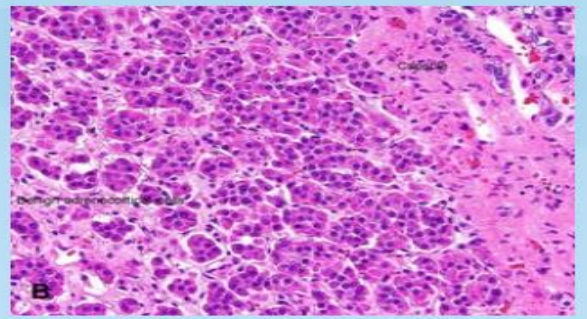
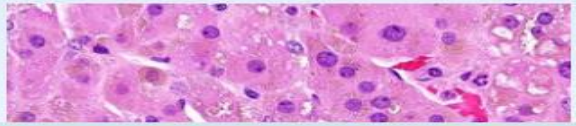



Image B

- Functional and can differentiate to any of the three layers of cortex
- Non-functional also common, seen in 25% autopsy
- Results to overproduction of corticosteroids (Cushing syndrome), aldosterone (Conn syndrome), and sex hormones (adrenogenital syndrome)
- Often unilateral
- Gross:
  - Usually solitary lesions, well-encapsulated, cut surface is yellow-tan **(image A)**
  - Can be black heavily pigmented, for black adenomas **(image B)**
- Adenomas generally measure <5 cm and weigh <50 g; tumors >100gm should be examined for malignancy

# Pheochromocytoma (Adrenal Paraganglioma)

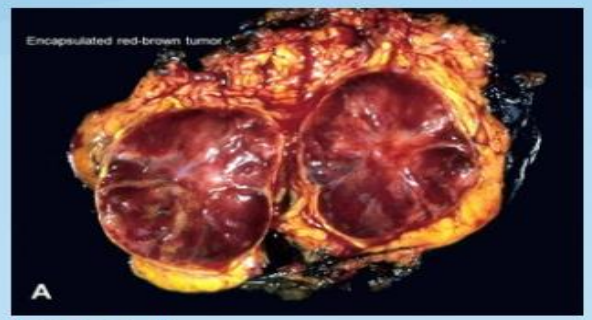



Image A

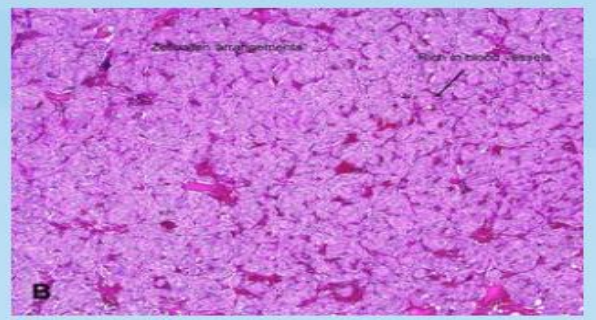
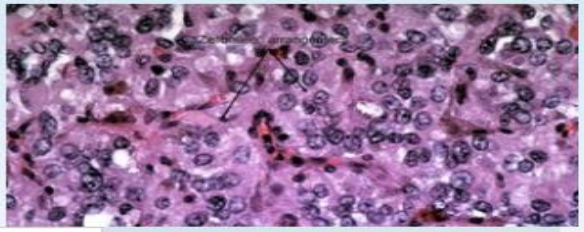
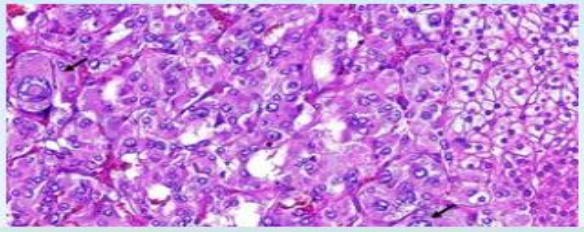



Image B

- Occurs 70% in adrenal gland and 30% are extra-adrenal in location.
- 10% are familial and usually bilateral and multifocal.
- Occurs mostly in adults; rare in children.
- Clinical: Classically associated with paroxysmal sweating attacks, headaches, and tachycardia; hypertension may be intermittent or sustained; these tumors may secrete epinephrine and/ or norepinephrine, ACTH, or parathormone; urinary vanillylmandelic acid (VMA) is elevated in up to 90% of cases.
- Gross: encapsulated yellow-white to red-brown, soft, fleshy tumor **(image A)**.





Urological Embryology, Anatomy, Physiology and Pathophysiology

# Embryology

Campbell 12th ed

Incomplete duplication

Complete duplication

Upper moiety
Lower moiety

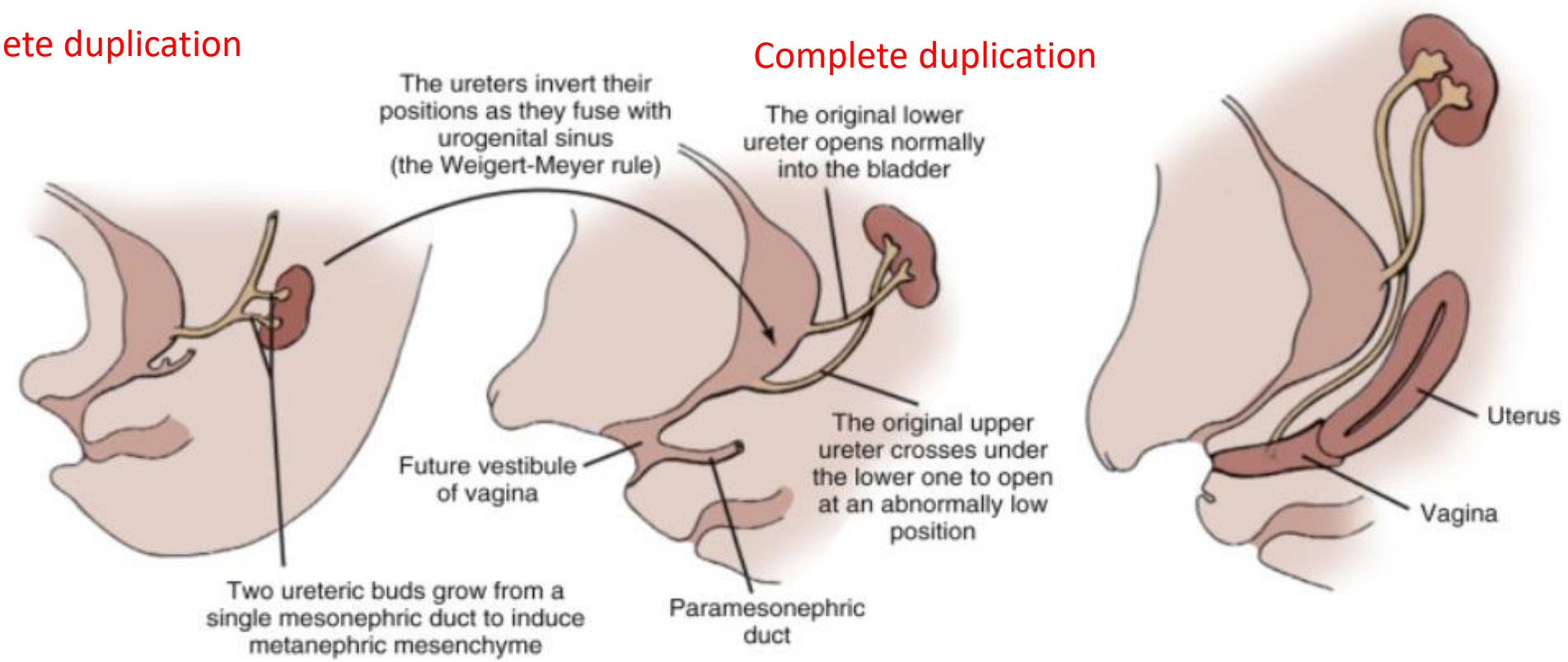
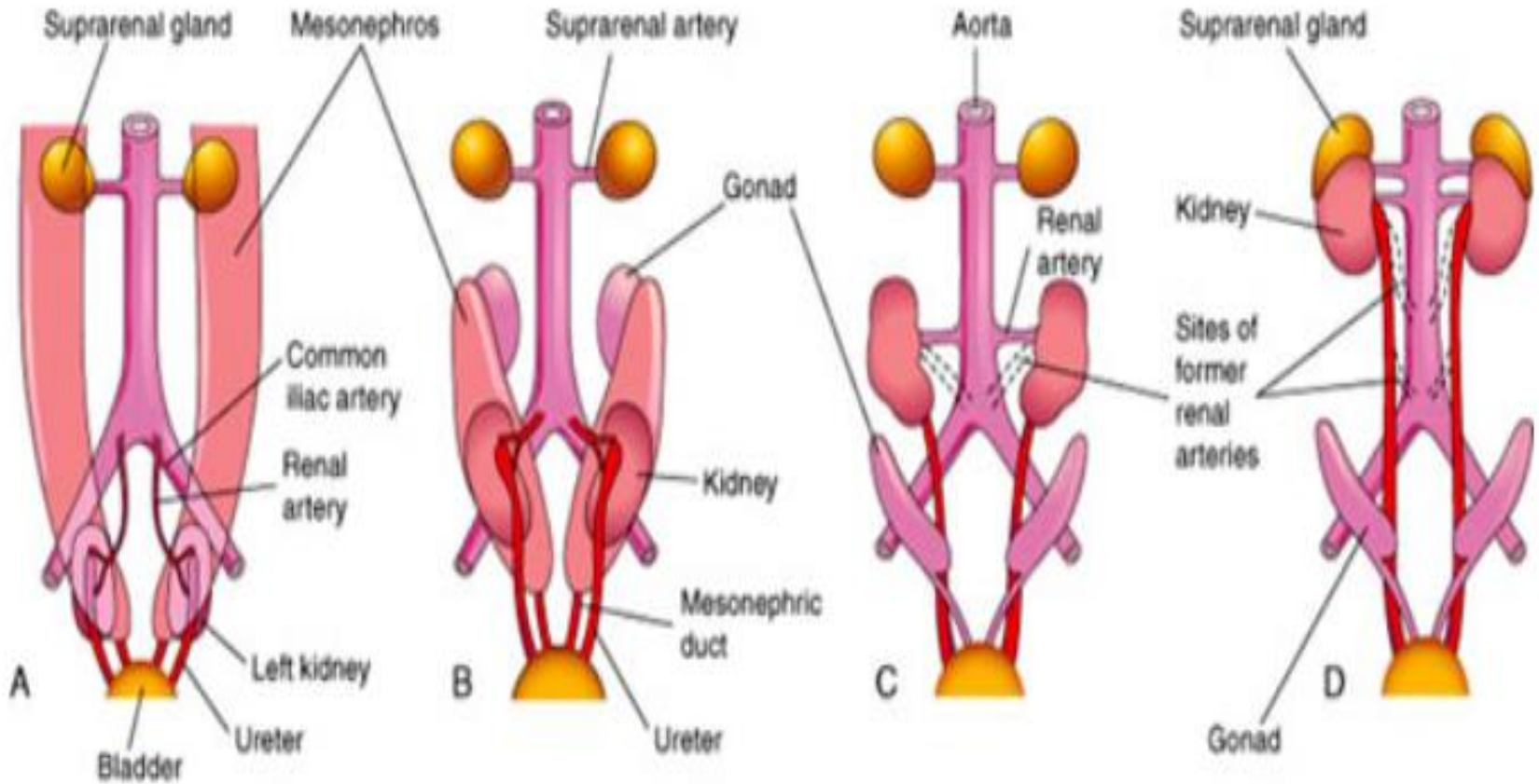



Fig. 20.43

Embryologic schematic of the Weigert-Meyer rule, in which two ureteric buds grow from a single mesonephric duct to induce the metanephric mesenchyme. The ureters invert their positions as they fuse with the urogenital sinus. The upper-pole ureter crosses under the lower ureter and when ectopic can open into an abnormally low position such as draining into the vagina as illustrated.

## V. Ascent of the kidneys

- The kidneys initially form near the tail of the embryo.
- Vascular buds from the kidneys grow toward and invade the common iliac arteries.
- Growth of the embryo in length causes the kidneys to "ascend" to their final position in the lumbar region.
- Rather than "drag" their blood supply with them as they ascend, the kidneys send out new and slightly more cranial branches and then induce the regression of the more caudal branches.



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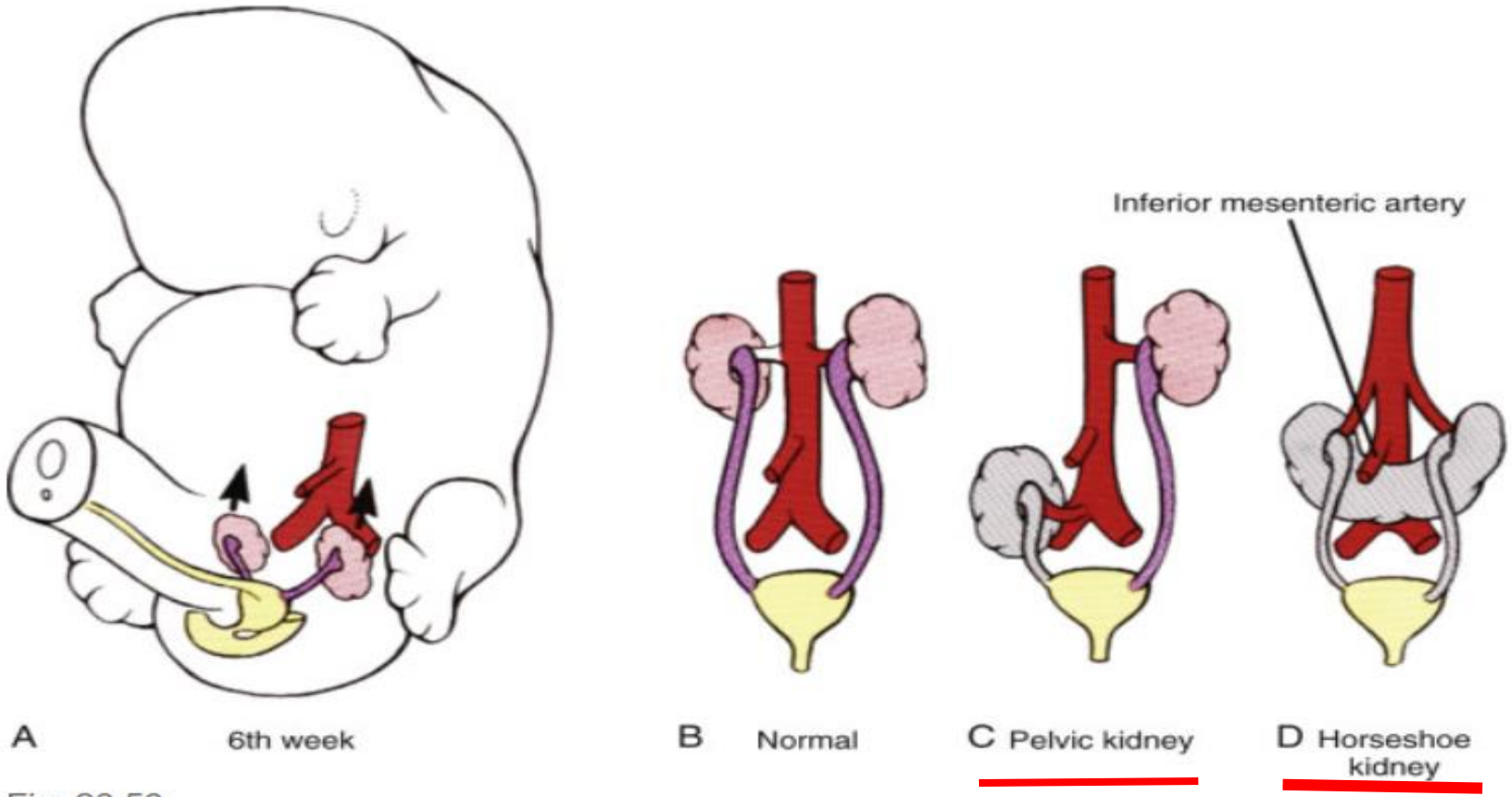


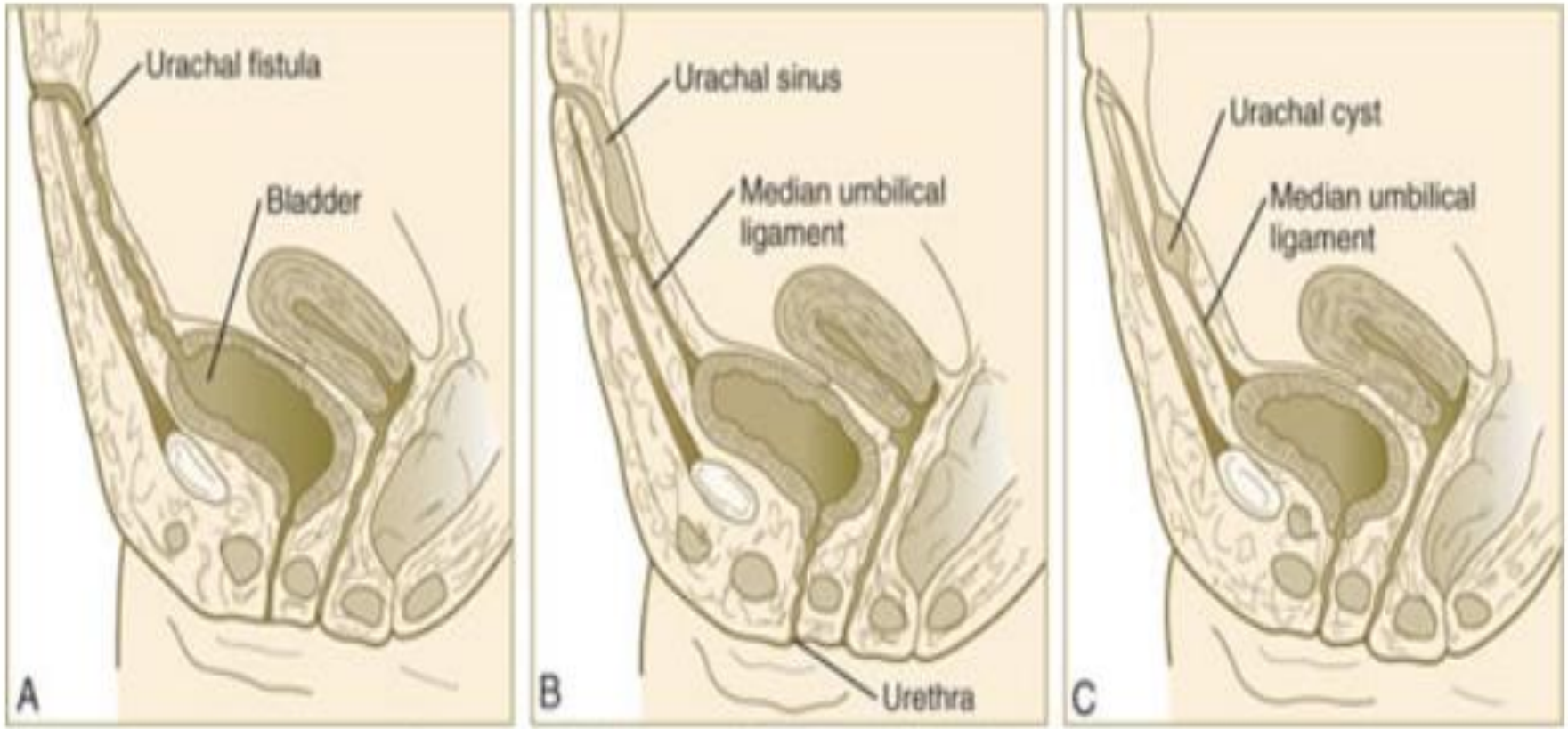

Fig. 20.50

Normal and abnormal ascent of the kidneys. (A and B) The metanephros normally ascends from the sacral region to its definitive lumbar location between the sixth and ninth weeks. (C) Rarely, a kidney may fail to ascend, resulting in a pelvic kidney. (D) If the inferior poles of the kidneys fuse before ascent, the resulting horseshoe kidney does not ascend to a normal position because of entrapment by the inferior mesenteric artery.

(Modified from Larsen WJ. *Human embryology.* New York: Churchill Livingstone; 1997.)

## VIII. Malformations related to the development of the bladder

- **Trigonitis:** As a MESONEPHRIC DUCT derivative, the trigone is sensitive to sex hormones and can undergo hormone-induced epithelial metaplasia (usually transformation from a transitional type to squamous type epithelium which can overproliferate and lead to urinary blockages).
- **Abnormal attachment of the ureters**: the ureters can sometimes be attached to either to the urethra or parts of the reproductive tracts.
- **Urachal fistulas, sinuses, and cysts**: occur when a **remnant of the allantois persists** and are found in the midline along the path from the umbilicus to the apex of the bladder (i.e. along the median umbilical ligament).




Carlson: Human Embryology and Developmental Biology, 4th Edition.

# Urological Embryology, Anatomy, Physiology and Pathophysiology

# Embryology

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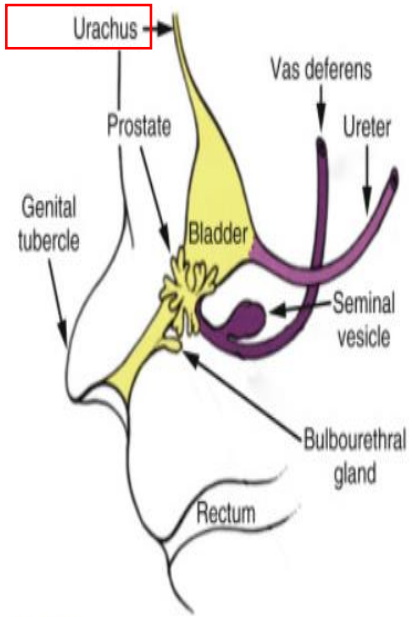
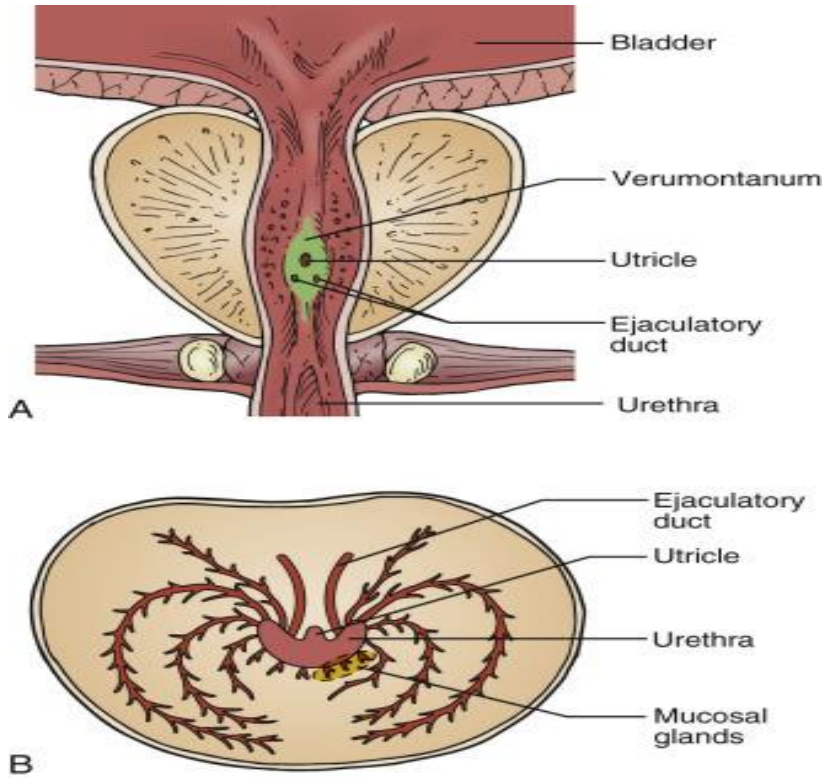



Fig. 20.16

Diagram of developing male urogenital organs. The bladder, urachus, prostate, urethra, and bulbourethral glands are derived from endodermal urogenital sinus epithelium *(yellow)*. The ureter, vas deferens, and seminal vesicle are derived from the mesodermal mesonephric (Wolffian) ducts *(purple)*.

(Modified from Shen J, Cunha G, Sinclair A, et al. (2018). Macroscopic whole-mounts of the developing human fetal urogenital-genital tract: indifferent stage to male and female differentiation. *Differentiation* . pii: S0301-4681(18)30098-7. [Epub ahead of print].)




Drawings of adult human prostate. (A) Anterior wall of the urethra has been removed to visualize the verumontanum *(green)* and the posterior and lateral walls of the prostatic urethra.
Note the distribution of openings of the prostatic ducts in the "gutters" lateral to the verumontanum as described previously ( ).
(B) Drawing of a transverse section through the verumontanum of an adult human prostate showing the prostatic utricle and ejaculatory ducts joining the prostatic urethra.
The prostatic ducts emerge from the urethra in the gutters lateral to the verumontanum. Mucosal glands emerge from the ventral aspect of the urethra.
(From Cunha GR, Vezina CM, Isaacson D, et al. New insights in the development of the human prostate. *Differentiation*

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# Embryology

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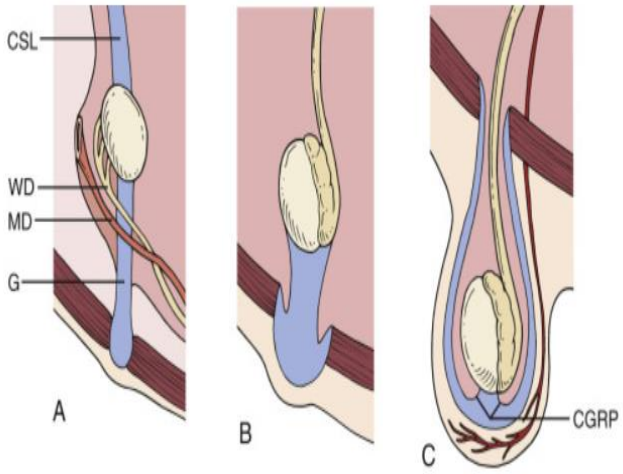



Fig. 20.25

The two stages of testicular descent. (A) Before descent, the developing testis is held in the urogenital ridge by the cranial suspensory ligament *(CSL)* cranially and the gubernaculum *(G)* caudally. The adjacent Wolffian duct *(WD)* forms the epididymis and vas deferens in the male, and the Müllerian duct *(MD)* forms the uterus and tubes in the female. (B) At the end of the transabdominal phase (*15 weeks), the testis is held near the future inguinal ring by the swelling reaction in the gubernaculum. The skin just beyond the gubernaculum is over the future external inguinal ring, as the scrotum is remote in the perineum of humans. (C) The inguinoscrotal phase requires the gubernaculum to elongate to the scrotum, under control of androgens and calcitonin gene–related peptide *(CGRP)* released from the genitofemoral nerve (GFN). After migration is complete, the peritoneum of the processus vaginalis (PV) closes and then completely involutes and disappears.

Gubernaculum
睾丸引帯

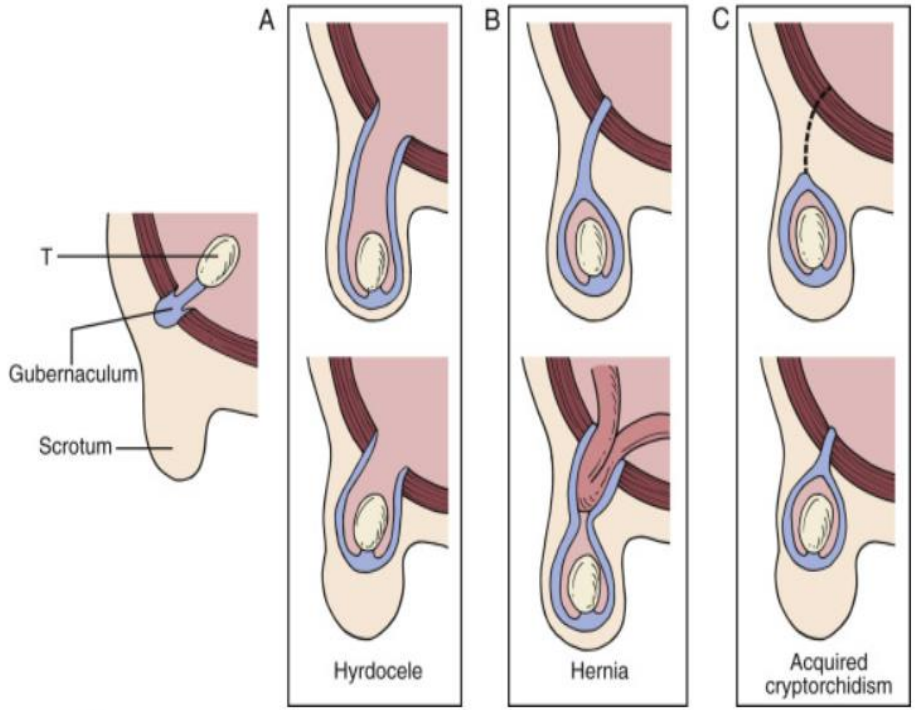
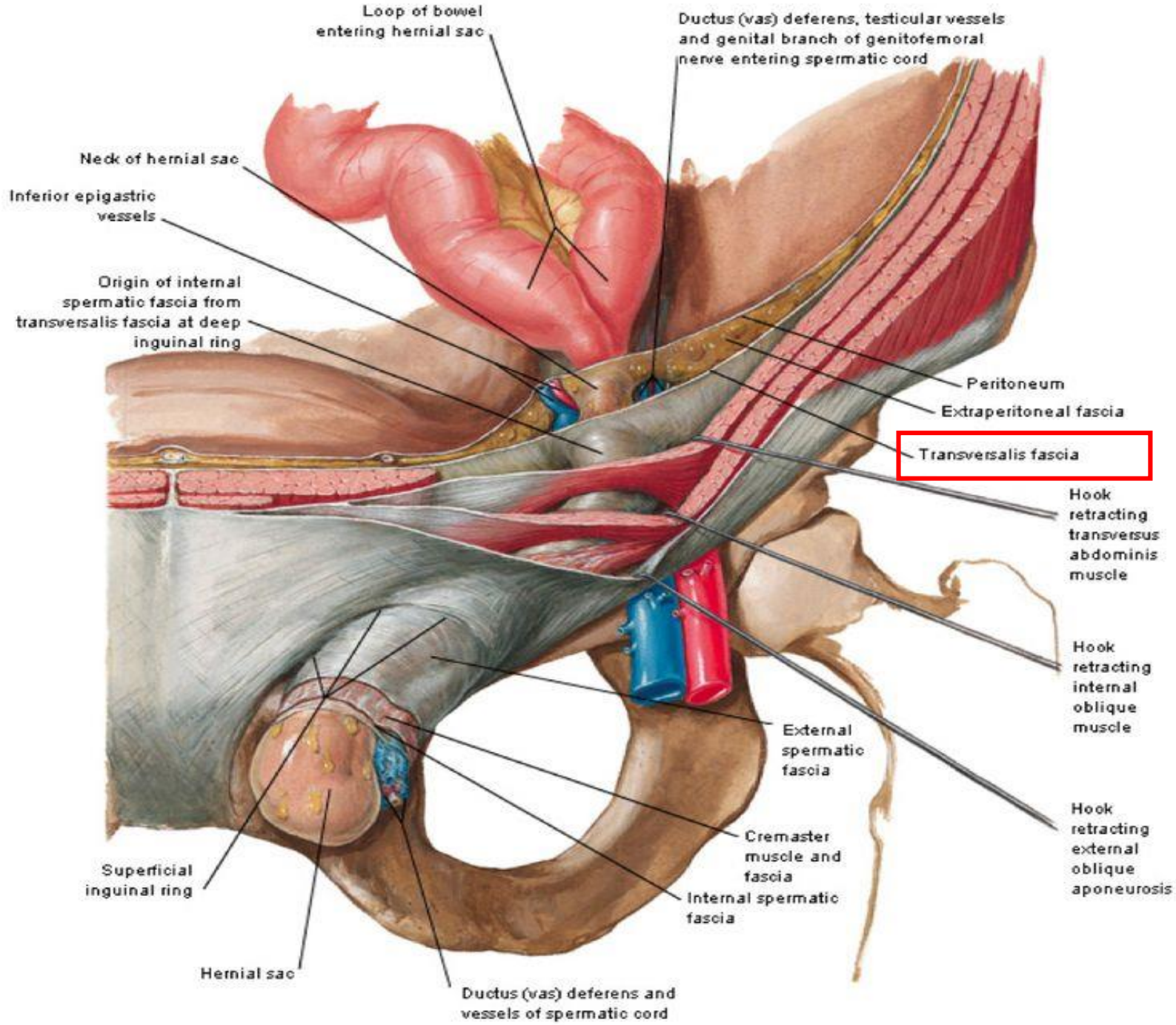



Fig. 20.26

Schematic depicting inguinoscrotal testicular descent and embryology explanation for congenital cryptorchidism, hydrocele, hernia, and acquired cryptorchidism (ascending testis [ *T* ]). At the end of the transabdominal phase, the enlarged gubernaculum occupies the future inguinal canal, and must migrate 3 to 5 cm to the scrotum (A, step 1), taking the testis inside the processus vaginalis, which elongates inside the gubernaculum. Failure of this first step causes congenital cryptorchidism. After migration is complete, the processus vaginalis closes (B, step 2), and failure of this


Loop of bowel entering hernial sac
Ductus (vas) deferens, testicular vessels and genital branch of genitofemoral nerve entering spermatic cord
Neck of hernial sac
Inferior epigastric vessels
Origin of internal spermatic fascia from transversalis fascia at deep inguinal ring
Peritoneum
Extraperitoneal fascia
Transversalis fascia
Hook retracting transversus abdominis muscle
Hook retracting internal oblique muscle
External spermatic fascia
Hook retracting external oblique aponeurosis
Cremaster muscle and fascia
Internal spermatic fascia
Superficial inguinal ring
Hernial sac
Ductus (vas) deferens and vessels of spermatic cord