Female Genital tract Pathology 2024

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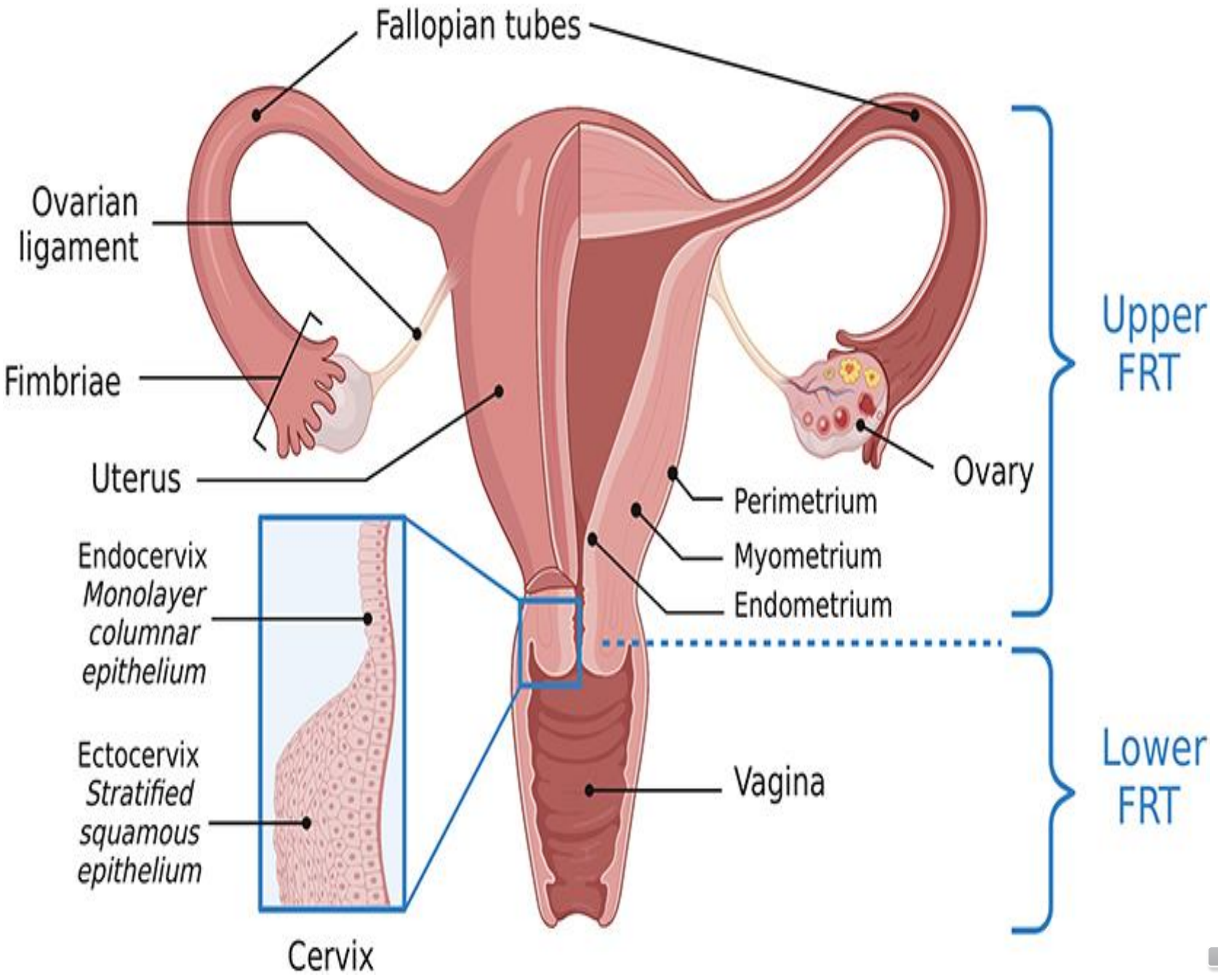

Fallopian tubes
Ovarian ligament
Fimbriae
Uterus
Ovary
Perimetrium
Myometrium
Endometrium
Upper FRT
Endocervix
Monolayer columnar epithelium
Ectocervix
Stratified squamous epithelium
Cervix
Vagina
Lower FRT

Pathology of the lower female genital tract

- **Vulvar Diseases:**
- Include non-neoplastic and neoplastic diseases.
- The neoplastic diseases are much less common. Of those, **squamous cell carcinoma is the most common.**

- The moist, hair-bearing skin & delicate membrane of the vulva are vulnerable to many nonspecific microbe-induced inflammations & dermatologic disorders.
- Intense itching (**pruritus**) & subsequent scratching often exacerbate the primary condition.

The 5 most important specific forms of vulvar infection related to

- **Sexually Transmitted Diseases** in North America are:

(1) human papillomavirus (**HPV**), producing condylomata acuminata & vulvar intraepithelial neoplasia;

(2) herpes genitalis {herpes simplex virus [**HSV**1 or 2]} causing a vesicular eruption;

(3) Gonococcal suppurative infection of the vulvovaginal glands;

(4) syphilis, with its primary chancre at the site of inoculation;

(5) candida vulvitis.

Contact Dermatitis

- One of the **most common causes of vulvar pruritus** is a reactive inflammation to exogenous stimulus, whether

(I) **Irritant contact dermatitis** to an irritant e.g., urine, soaps, detergents, antiseptics, deodorants, or alcohol; or

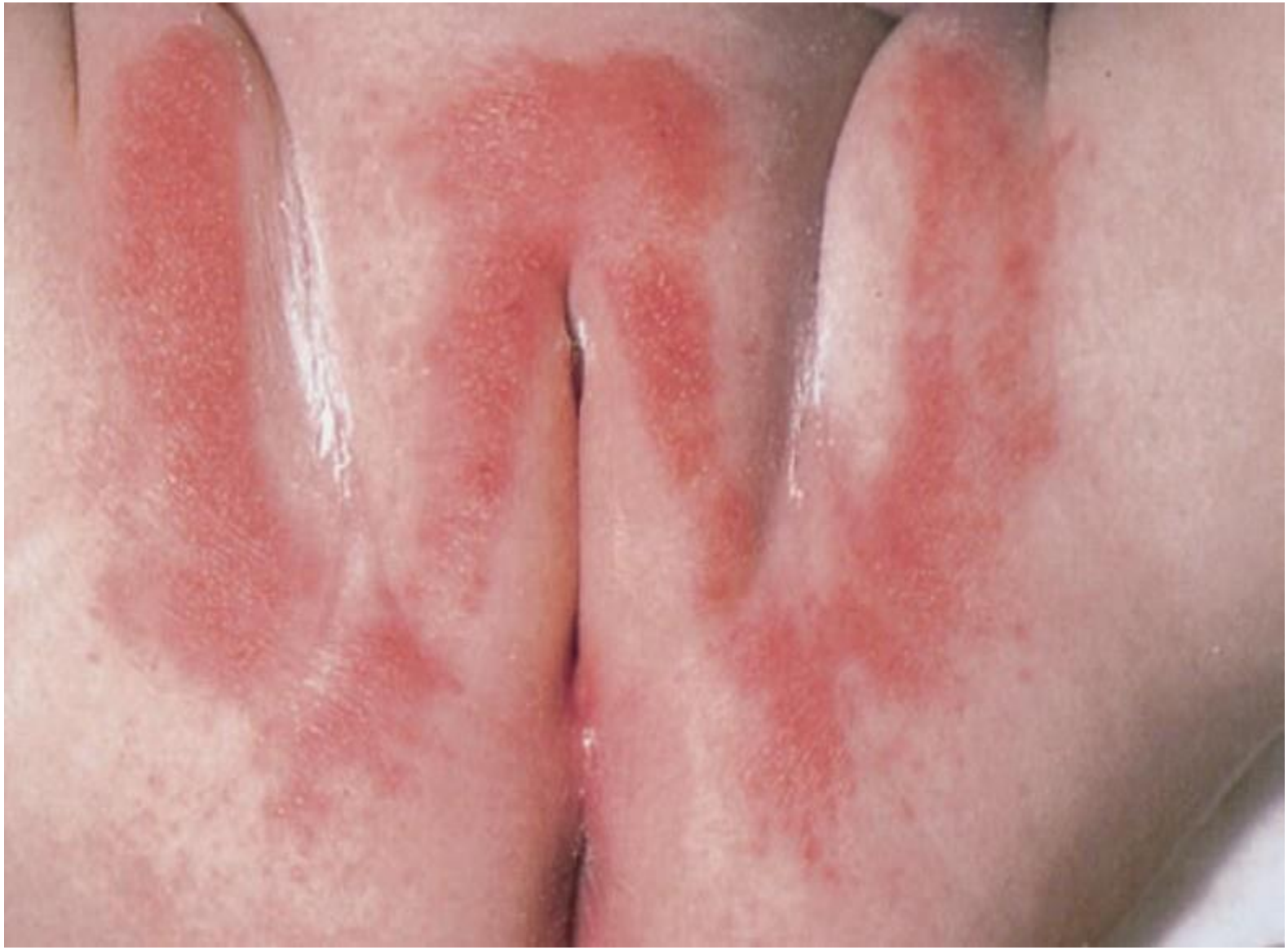
(II) **Allergic contact dermatitis** to an allergen e.g., allergy to perfumes & other additives in creams, lotions, & soaps, chemical treatments on clothing & other antigens.

- Grossly, Both irritant & allergic contact dermatitis may present as well-defined erythematous weeping & crusting papules & plaques, either as an

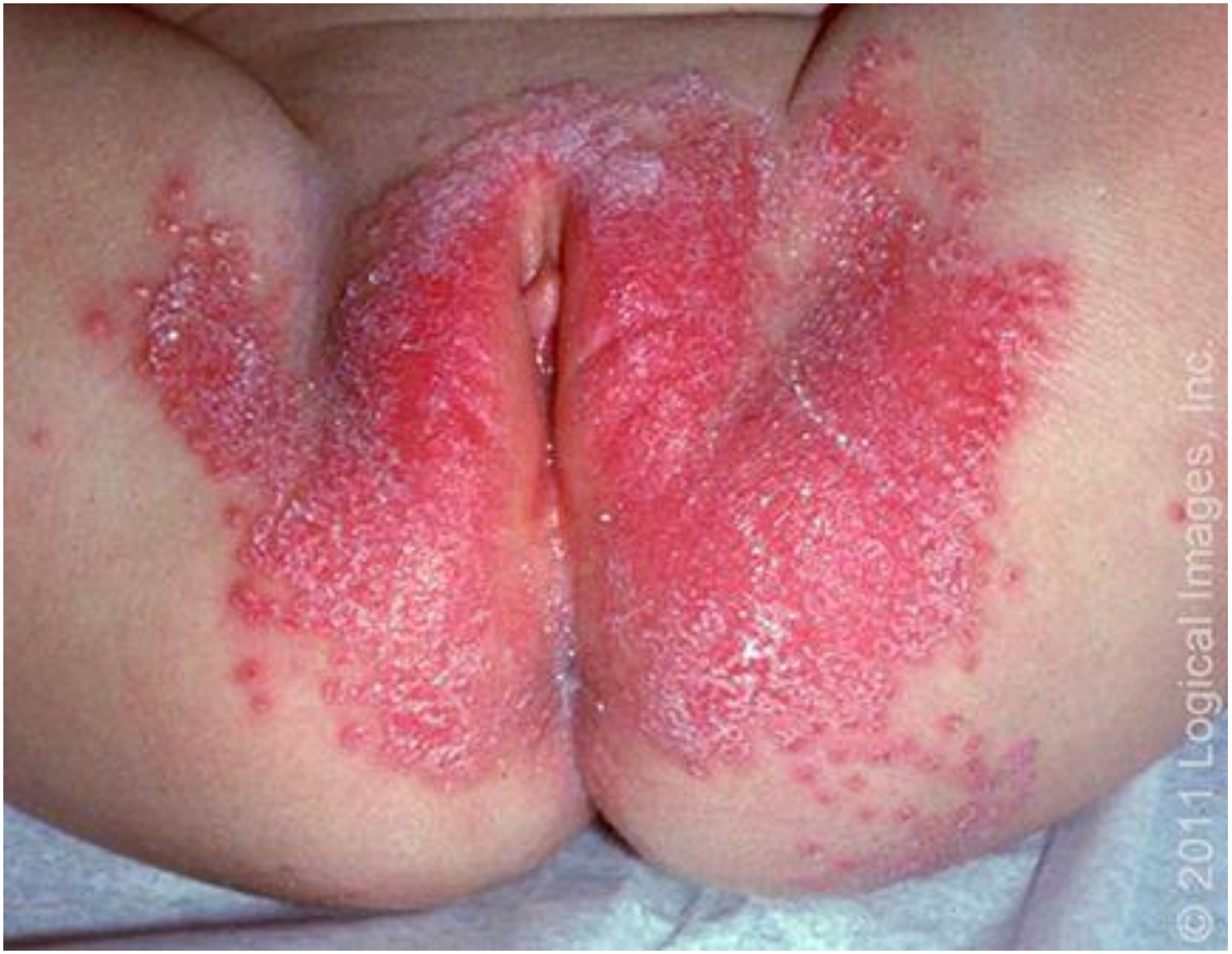
(1) acute spongiotic dermatitis or as

(2) subacute dermatitis with epithelial hyperplasia

Contact dermatitis in the vulva



Diaper Dermatitis



Non-neoplastic vulvar diseases

- Lichen sclerosus
- Lichen Simplex Chronicus
- Condyloma accuminatum

The vulvar mucosal epithelium may undergo atrophic thinning or hyperplastic thickening of two forms:

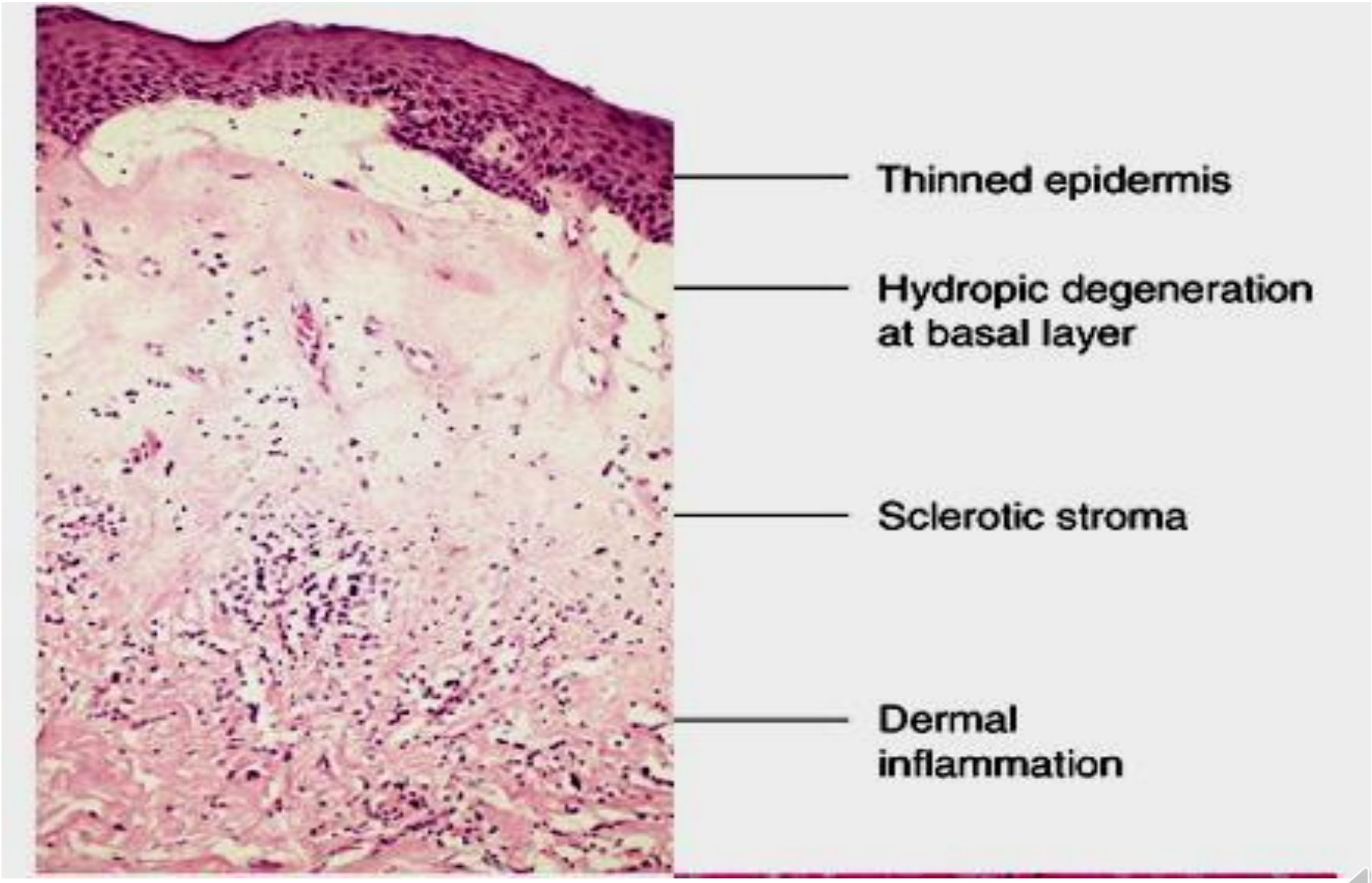
(1) **lichen sclerosis & (2) lichen simplex chronicus** , both are simply referred to as non-neoplastic epithelial disorders (to differentiate them from the premalignant lesions).

- Both may coexist in different areas in the same female & both may appear grossly as depigmented white patches (leukoplakia).

Lichen sclerosis

•postmenopausal women.
•smooth, white plaques; thinned out skin
•Microscopically: thinning of epidermis, disappearance of rete pegs, hydropic degeneration of basal cells
•pathogenesis: uncertain, (?)autoimmune
•Although the lesion in lichen sclerosis is **not pre-malignant** by itself, women with symptomatic lichen sclerosis have 15% chance of developing SCCa in their lifetime.

Lichen sclerosus



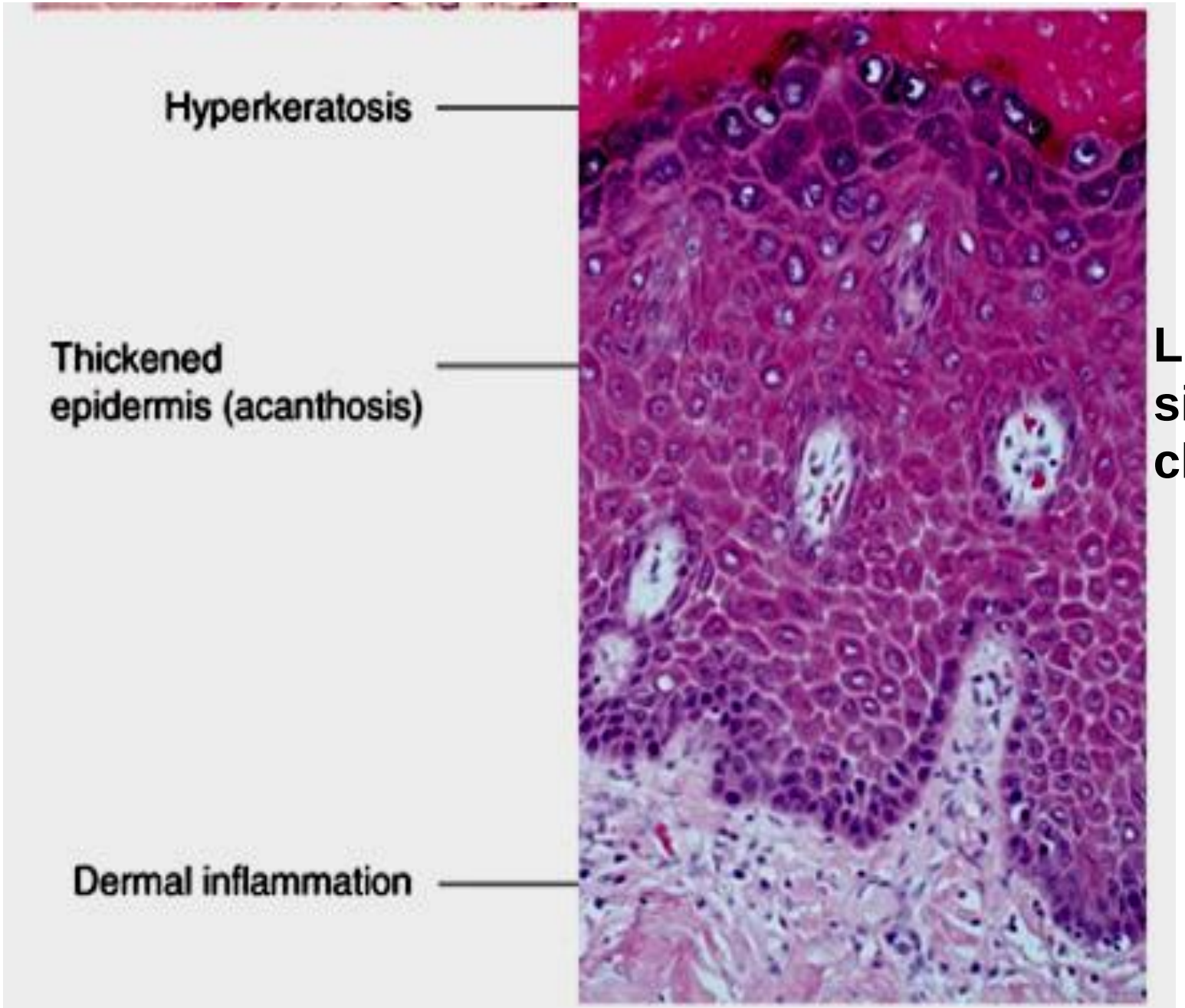
Lichen Simplex Chronicus

- End result of many inflammatory conditions.
- Clinically appears as an area of leukoplakia.

- Microscopically :

hyperkeratosis + hypergranulosis + acanthosis + epithelium shows no atypia with pronounced leukocytic infiltration of the dermis

- **no increased predisposition to cancer**, however, maybe present at margins of adjacent cancer.



Lichen simplex chronicus

Tumors

Condylomas

- Condylomas fall into 2 distinctive biologic forms:
  (**I)Condylomata lata** that occur in **secondary syphilis as** moist, flat or minimally elevated, highly infectious syphilitic lesions, not commonly seen today,

- (2)The more common **condylomata acuminate** may be papillary & distinctly elevated or flat & rugose.

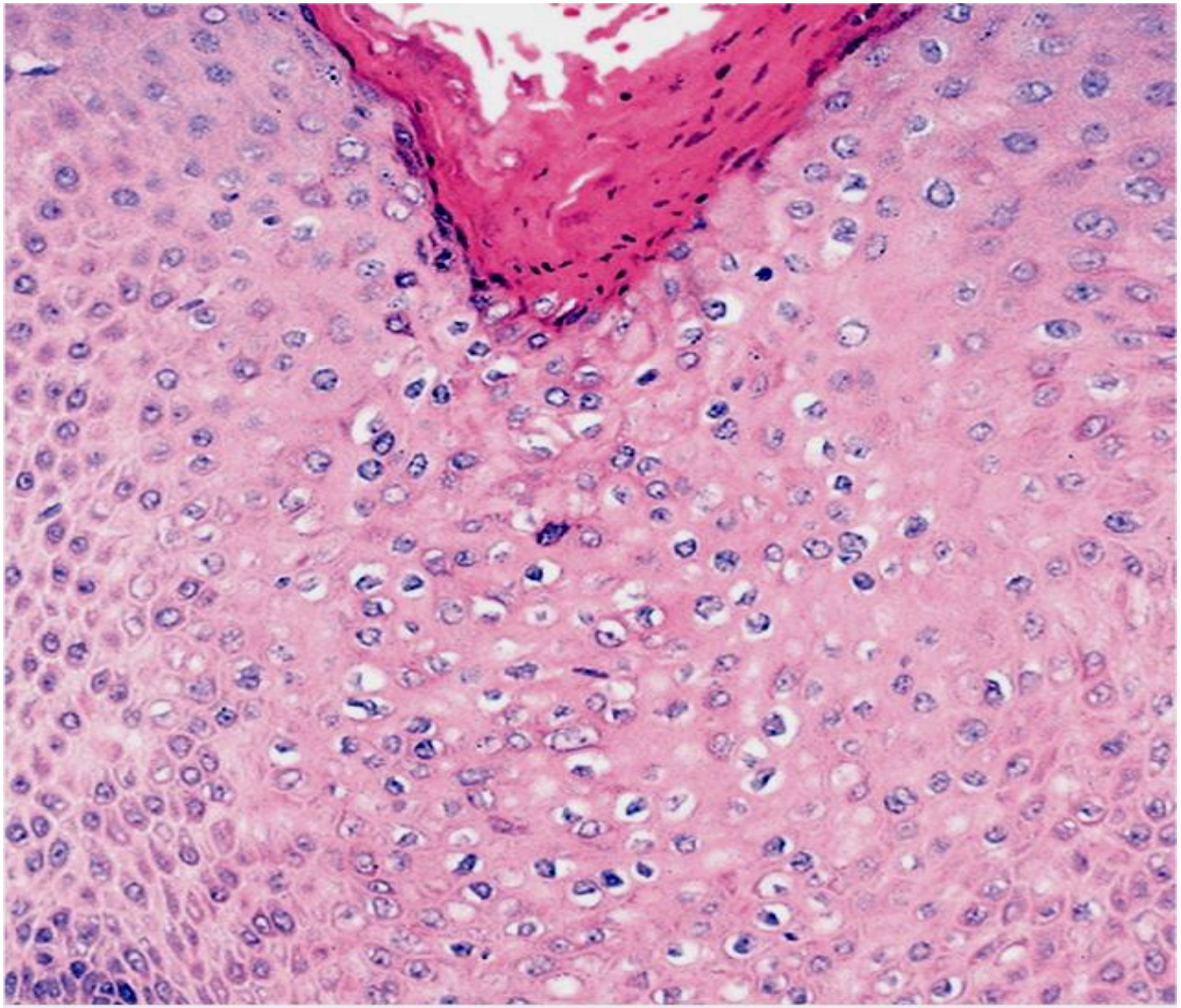
- They occur anywhere on the anogenital surface, usually **single**, but more often **multiple.**
- On the vulva, they range from a few mm to many cm in Ø& are red-pink to pink-brown

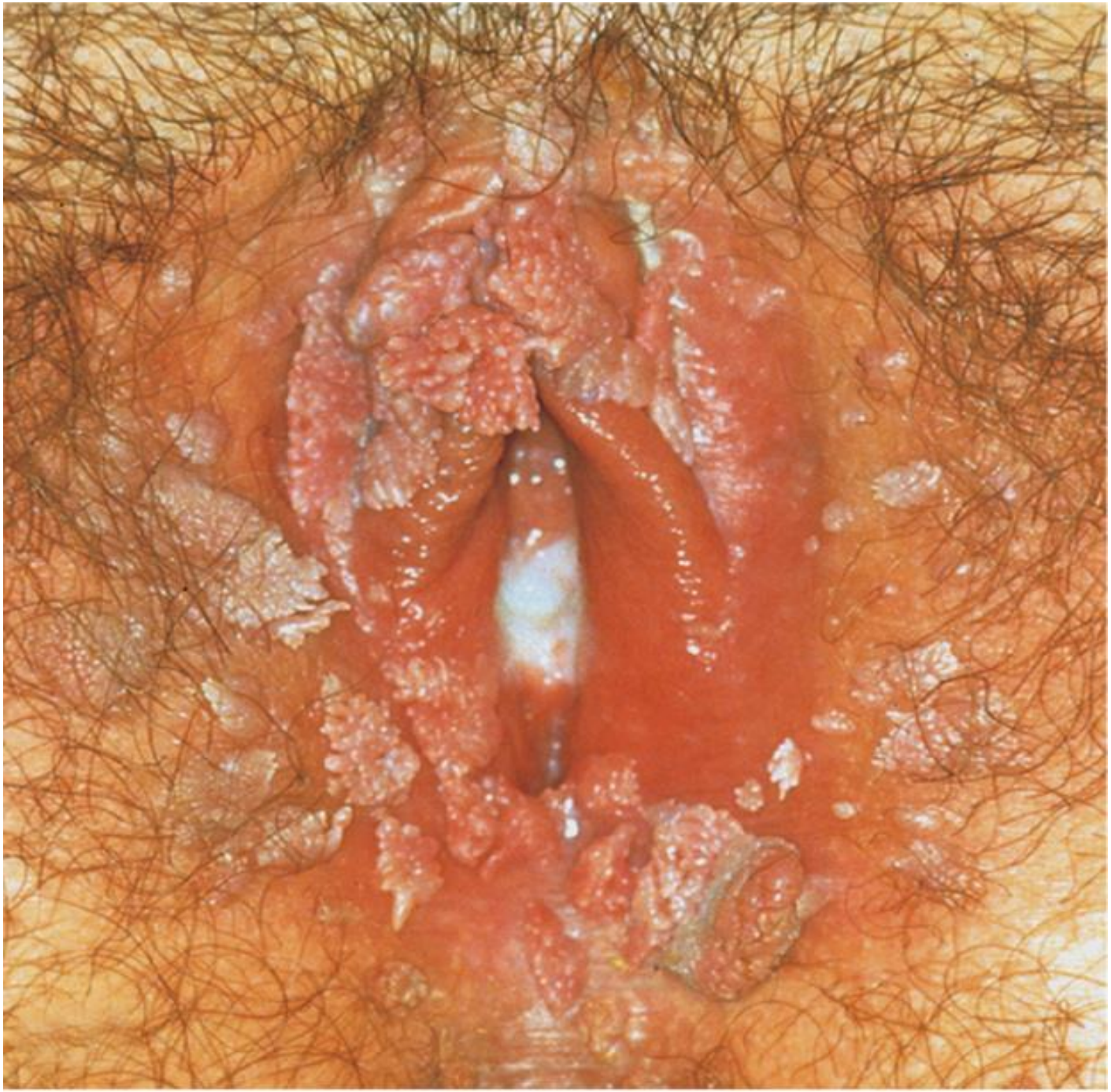
- **Anogenital warts (HPV type 6 and HPV type11)**
- They occur anywhere on the anogenital surface, usually **single**, but more often **multiple. On** the vulva, they range from a few mm to many cm in Ø& are red-pink to pink-brown.
- **Hallmark= koilocytosis(perinuclear cytoplasmic vacuolization + nuclear pleomorphism).**

•HPV types isolated from cancers differ from those found in condylomas.

•Condyloma is not precancerous by itself.

Condyloma acuminatum





Numerous **condylomata acuminate** of the vulva.

Neoplastic vulvar diseases

1-Vulvar Intraepithelial Neoplasia(VIN)

2-Invasive Carcinoma of Vulva:

Squamous Cell Carcinoma (most common);adenocarcinomas, melanomas, or basal cell carcinomas

High-Grade Vulvar Intraepithelial Neoplasia and Carcinoma of the Vulva

- high grade VIN= VIN II or VIN III.
- VIN III = carcinoma in situ.
- may be multiple foci, or it may coexist with an invasive lesion.
- VIN may be present for many years before progression to cancer.
- genetic, immunologic, or environmental influences (e.g., cigarette smoking or super infection with new strains of HPV) determine the course.

Carcinoma of the Vulva

- 3% of all genital tract cancers in women.
- > 60 years.
- 90% →squamous cell carcinomas;

- **Squamous cell carcinoma SCC:** there are two biologic forms of vulvar SCC:

First type of SCC (basaloid or poorly differentiated SCC):

- ❖most common (75% to 90%)
- ❖relatively younger
- ❖HPV-related (types 16 & 18)
- ❖HPV lesions also in vagina and cervix.
- ❖Poorly differentiated cells

The second form of SCC (well-differentiated SCC):

- ❑ older women (60-70s).
- ❑ **Not** HPV-related
- ❑ Less common
- ❑ well to moderately differentiated
- ❑ Maybe found adjacent to lichen simplex or sclerosus
- ❑ The overlying epithelium **lacks** the typical cytologic changes of VIN &T tend to be well differentiated SCC

Extramammary Paget Disease

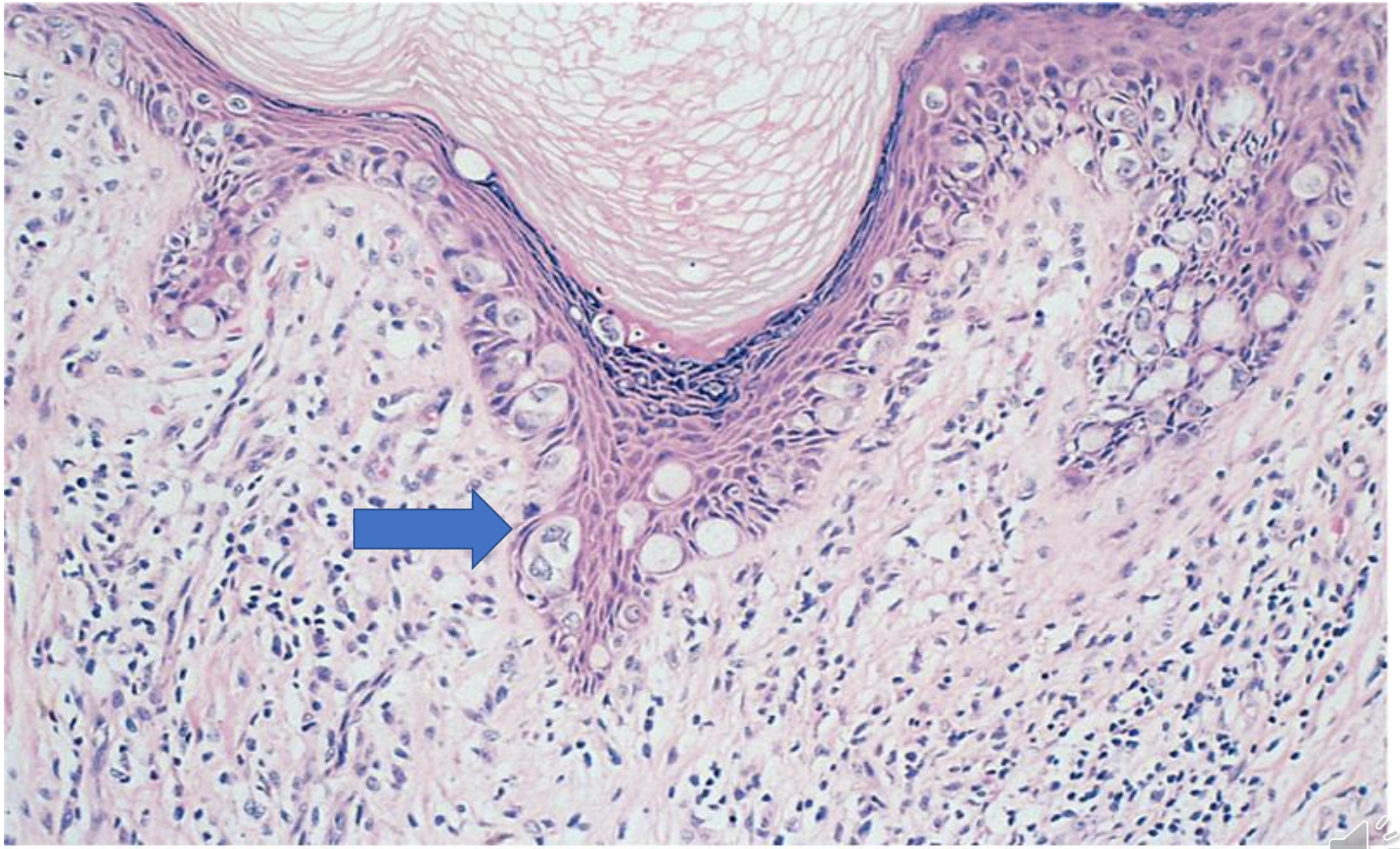
★Vulvar Paget disease like that of the breast, is essentially a form of **intraepithelial carcinoma**.

★Unlike the breast, where Paget disease is always associated with an underlying ca, the majority of cases of vulvar Paget disease have no demonstrable underlying ca.

★Vulvar Paget disease presents as a red, scaly, crusted plaque or as an inflammatory dermatosis.

Micro: Show large malignant epithelioid cells infiltrate the epidermis, singly & in groups, with abundant granular cytoplasm & occasional cytoplasmic vacuoles containing mucin that stains positive for PAS. When the Paget cells are confined to the epidermis, the lesion may persist for years or decades without evidence of invasion.

Paget disease of the vulva. Scattered large, clear tumor cells within the squamous epithelium.



VAGINA

VAGINITIS

- Vaginitis is a relatively common transient clinical problem produces a **vaginal discharge(leukorrhea).**
- A large variety of organisms have been implicated, including bacteria, fungi, & parasites and …..
- Many represent **normal commensals** that become pathogenic in conditions such as

(1) DM,

(2) systemic antibiotic therapy that disrupts the normal microbial flora,

(3) after abortion or pregnancy, or

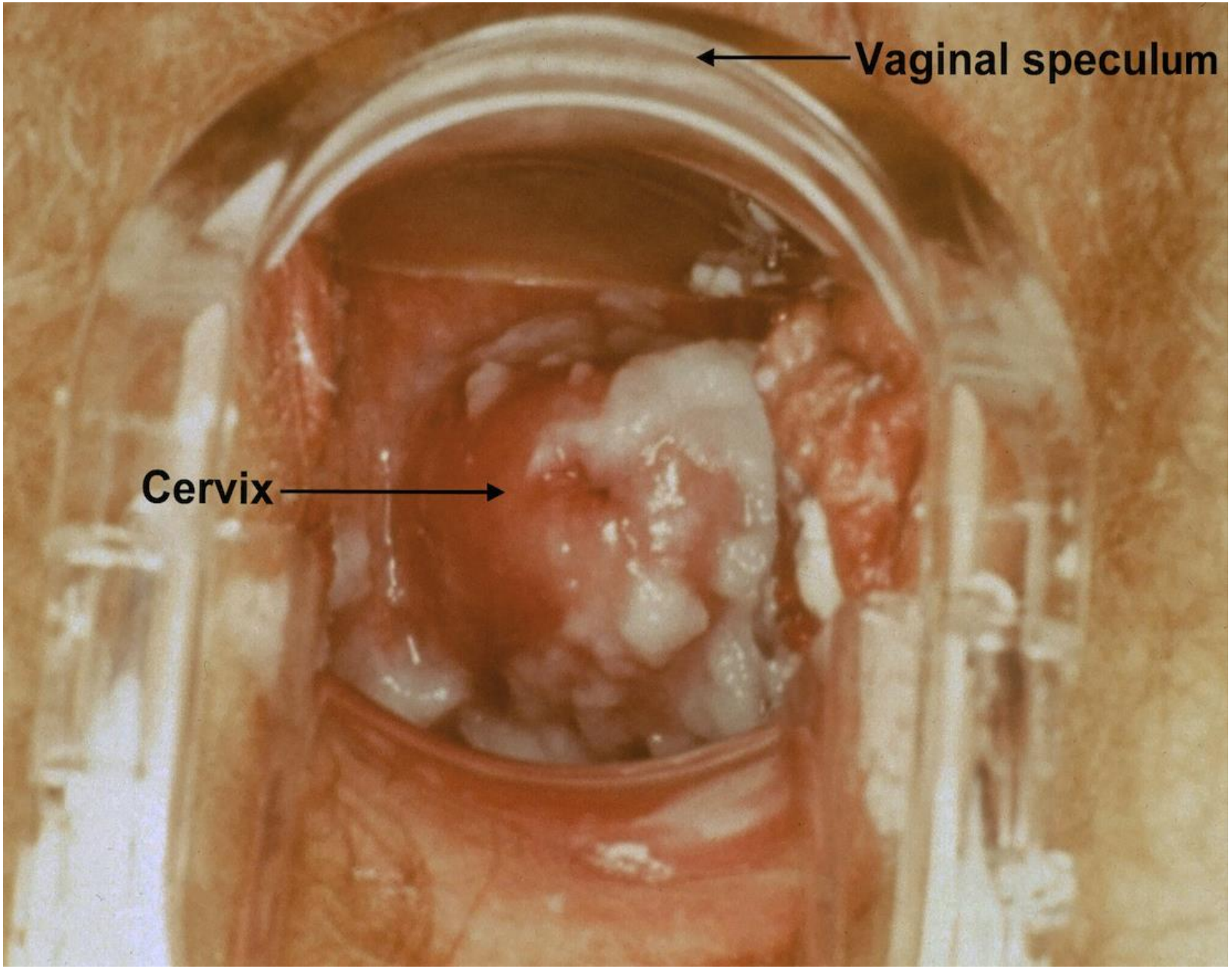
(4) in elderly persons with compromised immune function,

(5) in patients with AIDS.

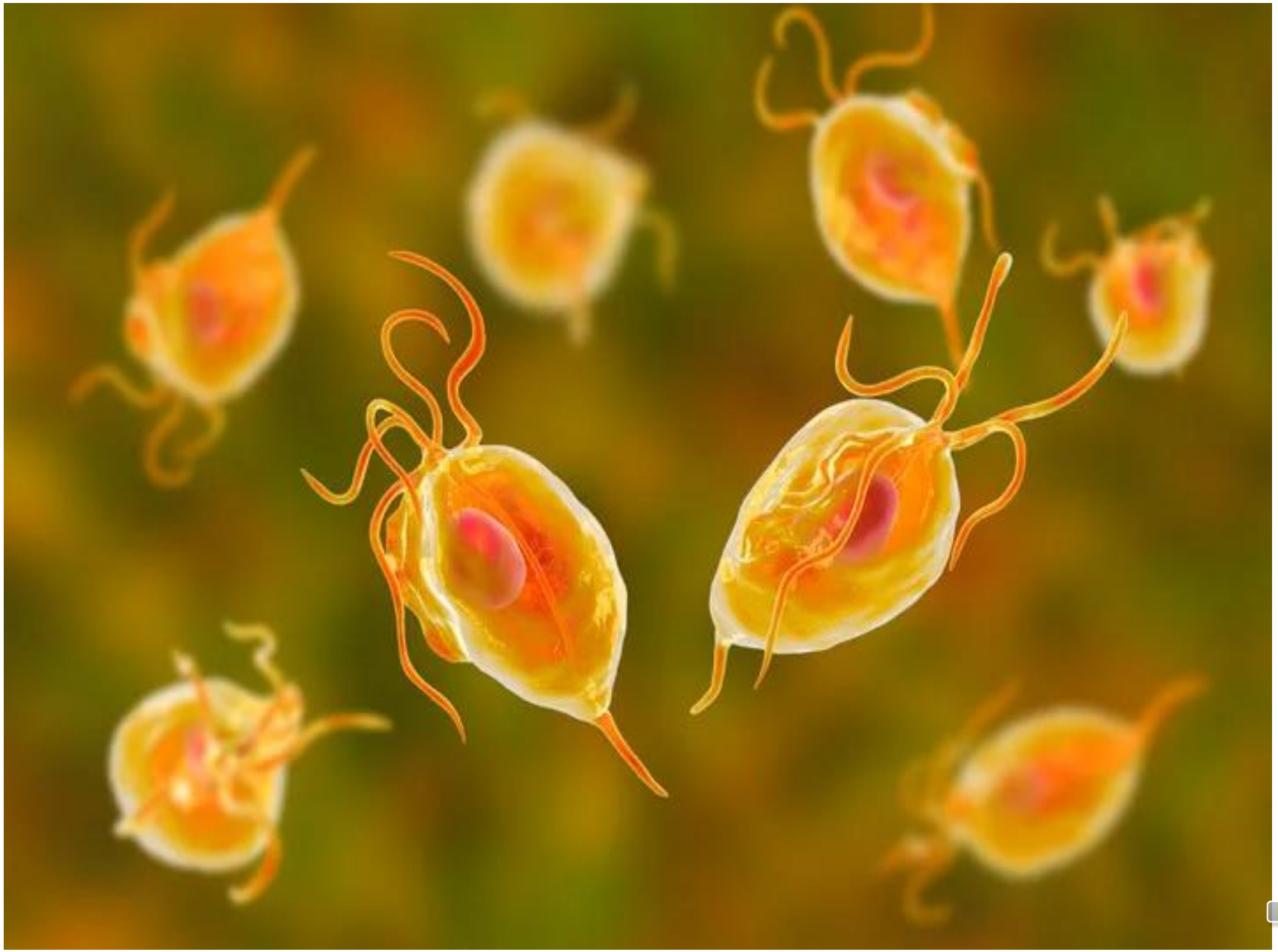
- **Candidal (monilial) vaginitis** produces a curdy white discharge.
- This organism is present in about 5% of normal adults, & so the appearance of symptomatic infection almost always involves predisposing influences or sexual transmission of a new, more aggressive strain.
- **T. vaginalis** produces a watery copious gray-green discharge in which parasites can be identified microscopically.
- **Nonspecific atrophic vaginitis** may be encountered in postmenopausal women with preexisting mucosal atrophy.

Types of candidal vulvovaginitis

- **Uncomplicated thrush**
  - single episode/less than four episodes in a year.
  - mild or moderate symptoms
  - caused by the Candida albicans .
- **Complicated thrush**
  - four or more episodes in a year.
  - severe symptoms.
  - Pregnancy
  - poorly controlled diabetes/immune deficiency.
  - not caused by the Candida albicans


Vaginal speculum
Cervix

Trichomonus vaginalis



Vaginal Neoplastic Diseases: vaginal clear cell adenocarcinoma

- are usually encountered in young women in their late teens to early 20s whose mothers took **diethylstilbestrol during pregnancy**.

- Sometimes these cancers do not appear until the 3rd or 4th decade of life. The **risk for ca is less than 1 per 1000** of those exposed in utero.

- In about one-third of instances these **clear cell adenocarcinoma** arise in the **cervix**.

CERVIX

- The cervix serves as a **barrier** to the entrance of air & the microflora of the normal vagina, yet **it must permit** the escape of menstrual flow & be capable of dilating to accommodate childbirth.

CERVICITIS

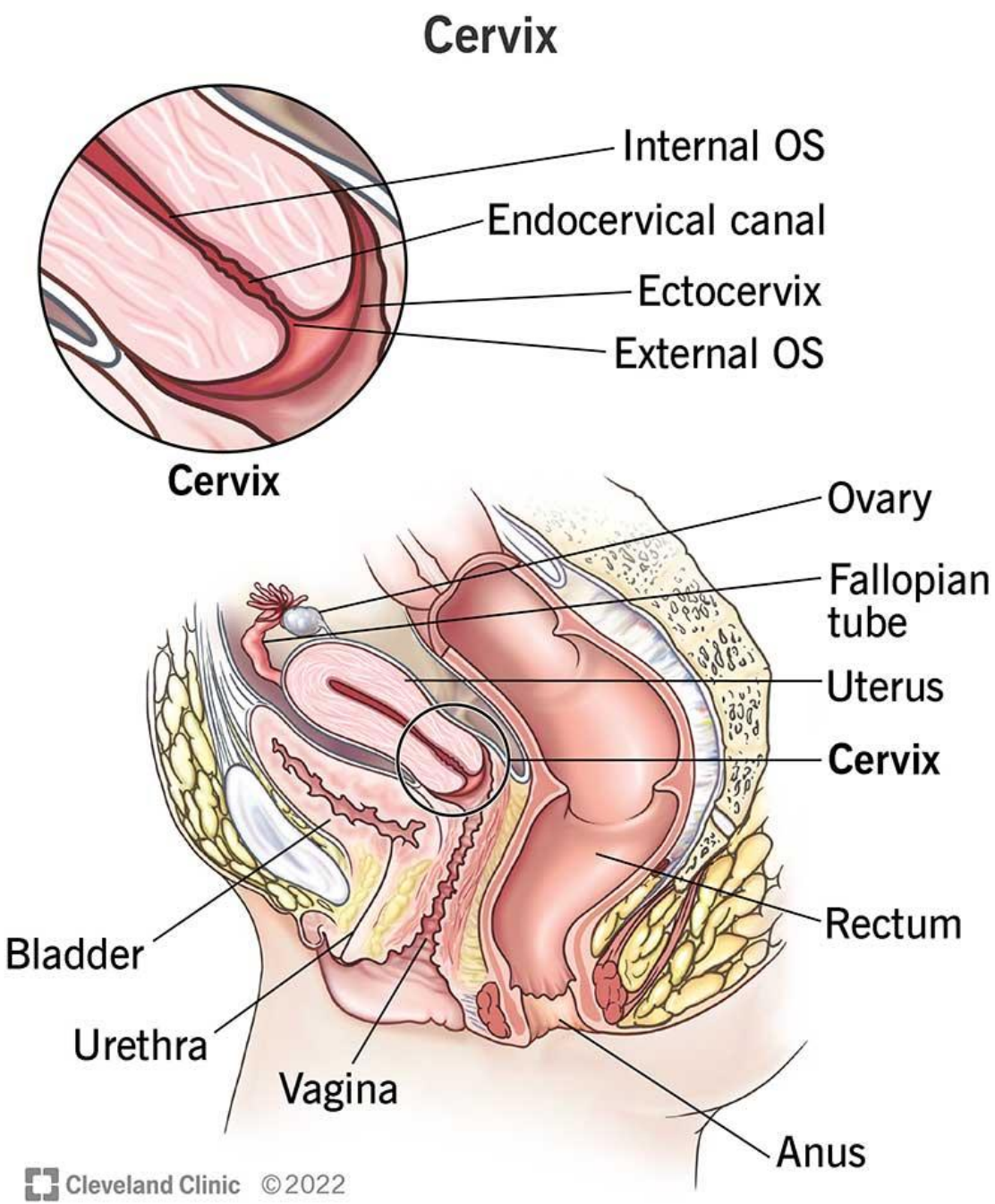
Predisposing factor :

1-trauma (child birth m instrumentation during vaginal examination 0

2-High and low level of estrogen

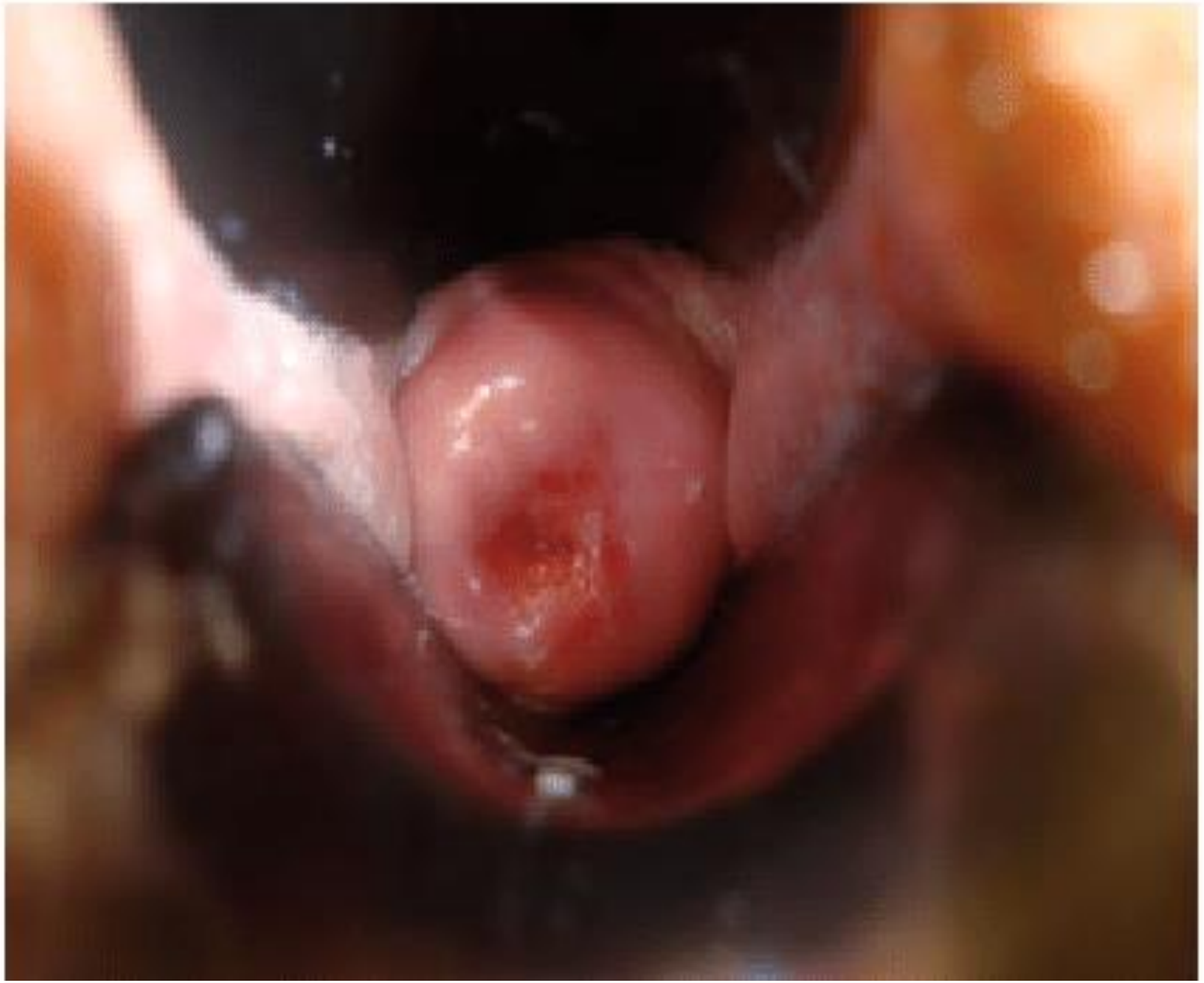
3-Excessive secretion

4- Alkaline media of cervical canal during ovulation


Cervix
Internal OS
Endocervical canal
Ectocervix
External OS
Cervix
Ovary
Fallopian tube
Uterus
Cervix
Rectum
Bladder
Urethra
Vagina
Anus
Cleveland Clinic ©2022

Cervicitis

- Cervicitis are extremely common & are associated with a mucopurulent to purulent vaginal discharge.
- Cytologic examination of the discharge reveals WBC & inflammatory atypia of shed epithelial cells, as well as possible microorganisms.
- may be acute cervicitis (child birth and sexually transmitted disease (gonorrhea), Chlamydia,Herpes,Trichomoniasis,It is often confused with vaginitis.
- chronic cervicitis , more common is used for women with persistent discharge for three months despite the resolution/exclusion of infection.



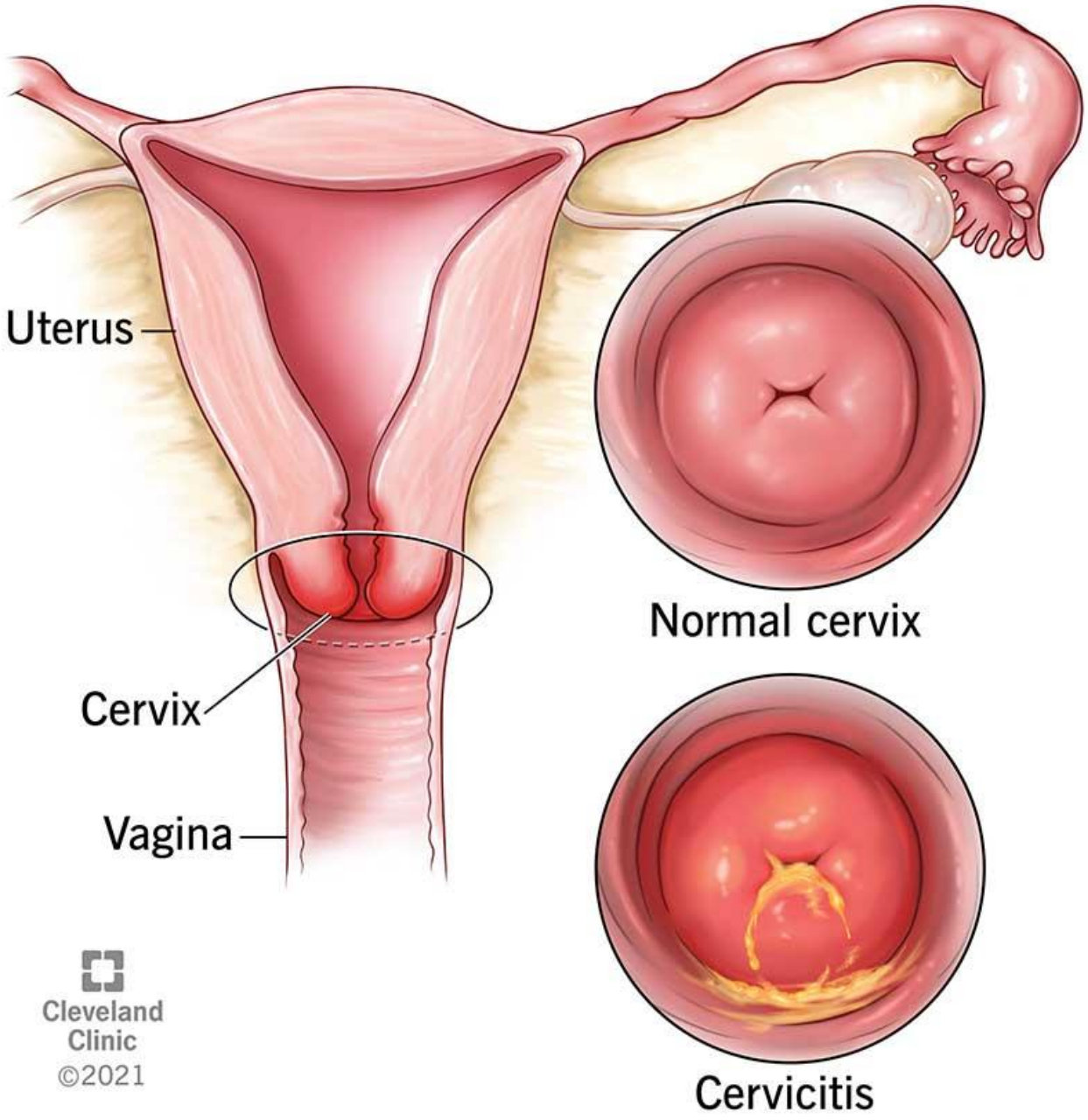
- Chronic Cervicitis is associated with
- Leukorrhea (vaginal discharge)
- Destruction of stratified squamous epithelium of ectopic Cx
- Growth of columnar epithelial of endocervix causing cervical erosion (reddening of ectocevix)
- Granularity of ectocervix
- Development of nabothian cyst
- Endocervical polyp
- Cervicitis is caused by organisms that can move up into the uterus and fallopian tubes if not treated. This can cause pelvic inflammatory disease (PID). PID can lead to infertility and peritonitis, a life-threatening infection. The organisms can also be passed to sexual partners who can develop serious complications.

Grossly, nonspecific cervicitis may be either:

- (1) the relatively uncommon **acute nonspecific form** limited to postpartum women& is usually caused by staphylococci or streptococci, or

- (2) the common, nearly ubiquitous,ever-present entity usually referred to as chronic **nonspecific cervicitis.**

- Frequently, overgrowth of the regenerating squamous epithelium blocks the orifices of endocervical glands in the transformation zone to produce small Nabothian cysts lined by columnar mucus-secreting epithelium.


Uterus
Cervix
Vagina
Normal cervix
Cervicitis
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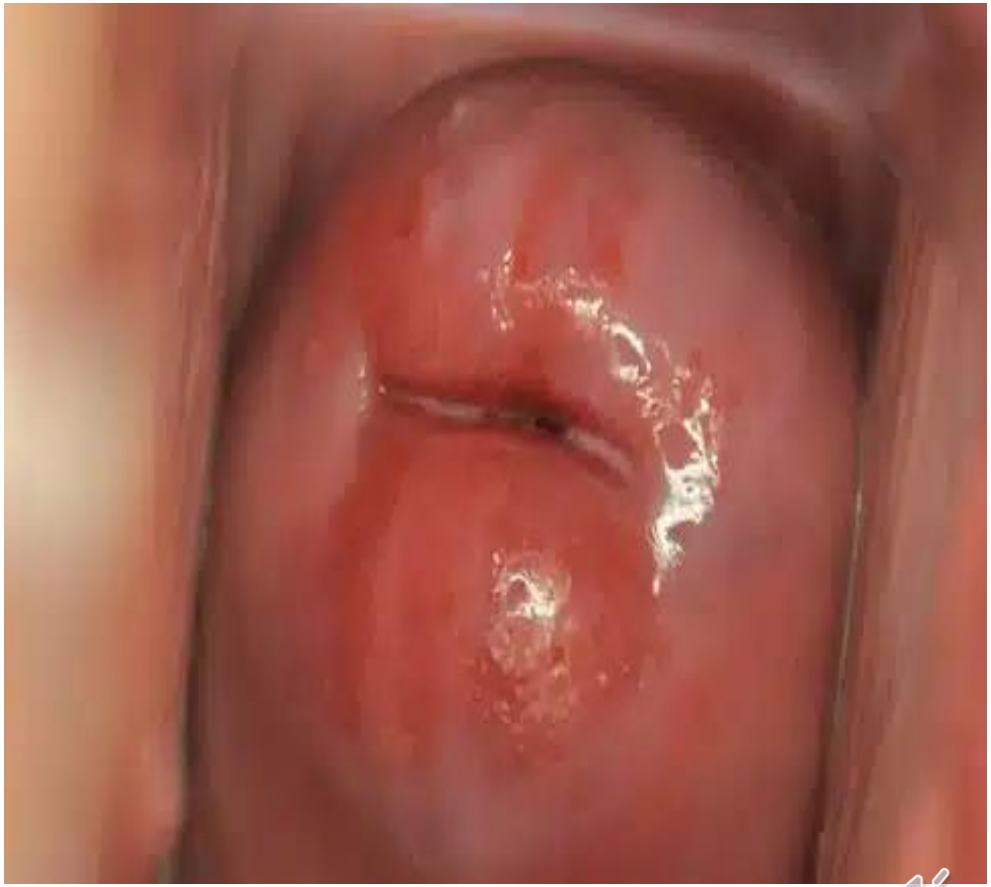
Cervical ectropion

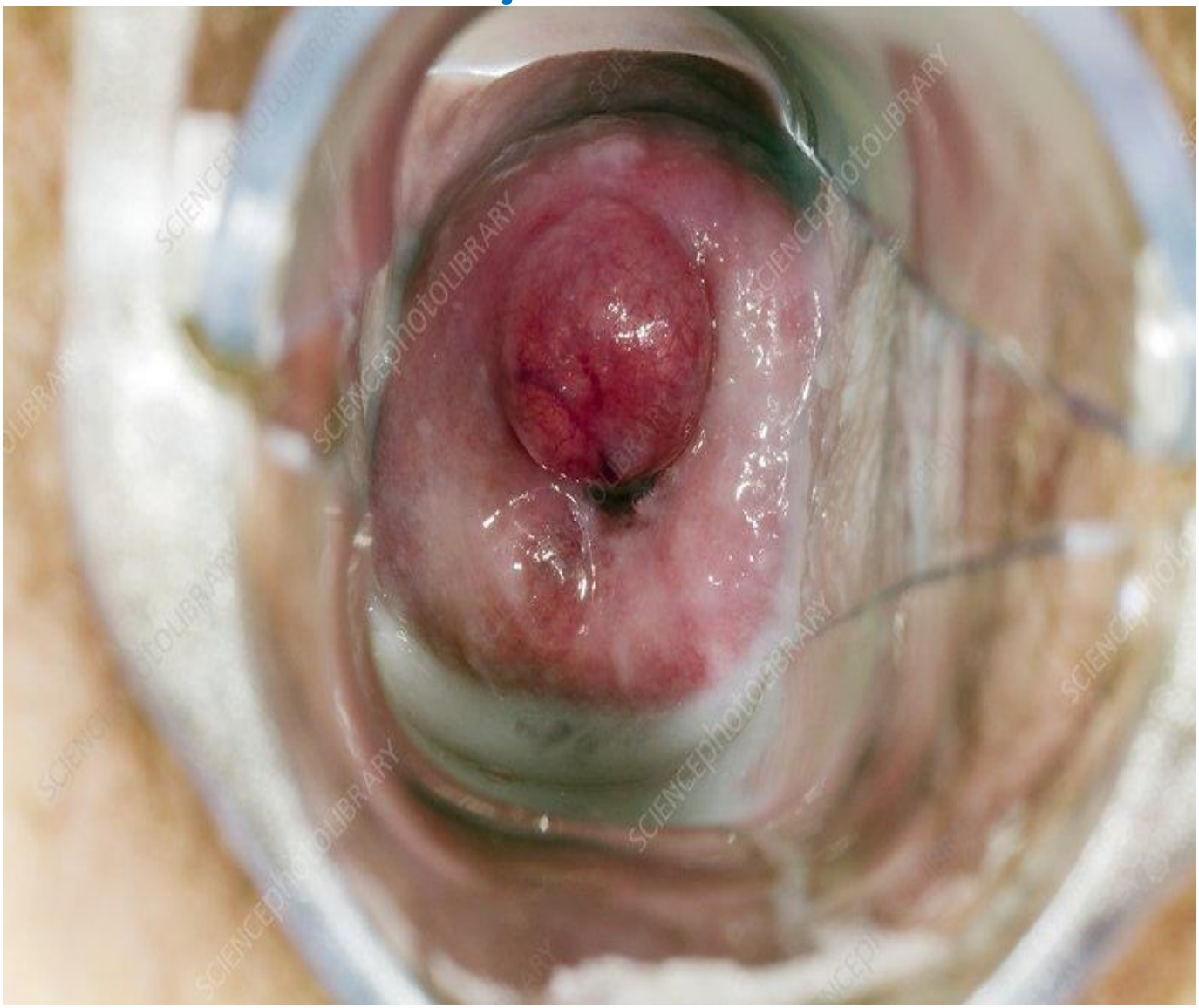
- occurs when there is eversion of the endocervix, exposing the columnar epithelium to the vaginal milieu. It is also known as a cervical erosion, although no “erosion” of cells actually occurs.
- It is a normal physiological condition, which is commonly seen on examination of the cervix in adolescents, in pregnancy, and in women taking oestrogen containing contraceptives.
- This change is thought to be induced by high levels of estrogen, and does not represent metaplasia.

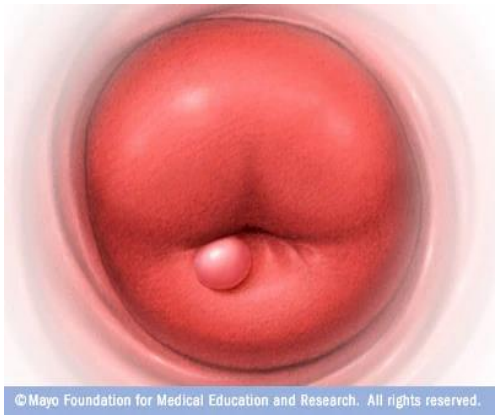


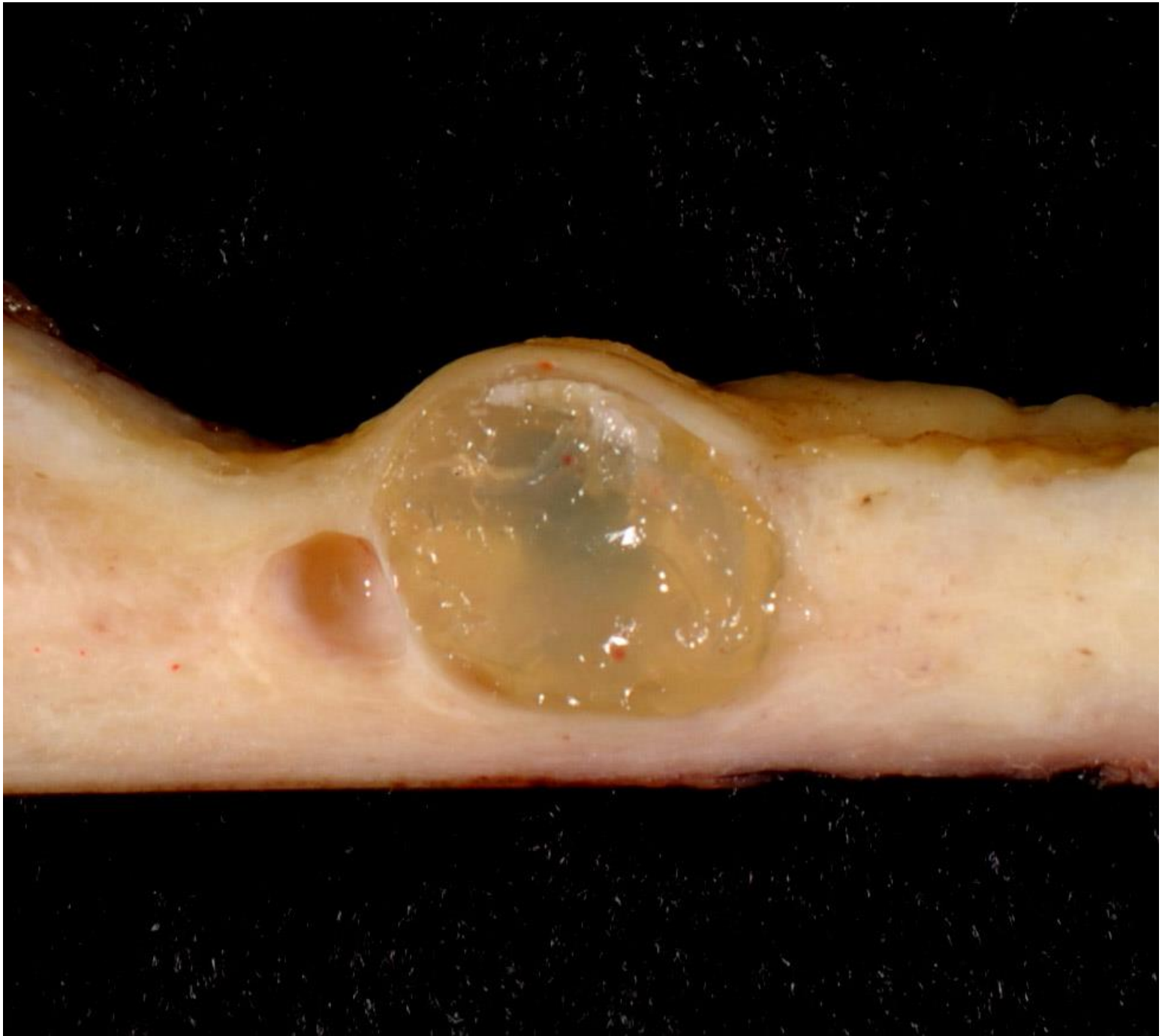
Nabothian cyst

- is a mucus-filled cyst on the surface of the cervix.
- They are most often caused when stratified squamous epithelium of the ectocervix (portion nearest to the vagina) grows over the simple columnar epithelium of the endocervix (portion nearest to the uterus).
- This tissue growth can block the cervical crypts trapping cervical mucus inside the crypts.
- Nabothian cysts appear most often as firm bumps on the cervix's surface
- Nabothian cysts usually require no treatment and frequently resolve on their own if nabothian cysts occur with chronic cervicitis (inflammation of the cervix) then the underlying cause of the inflammation must be treated

Nabothian cyst



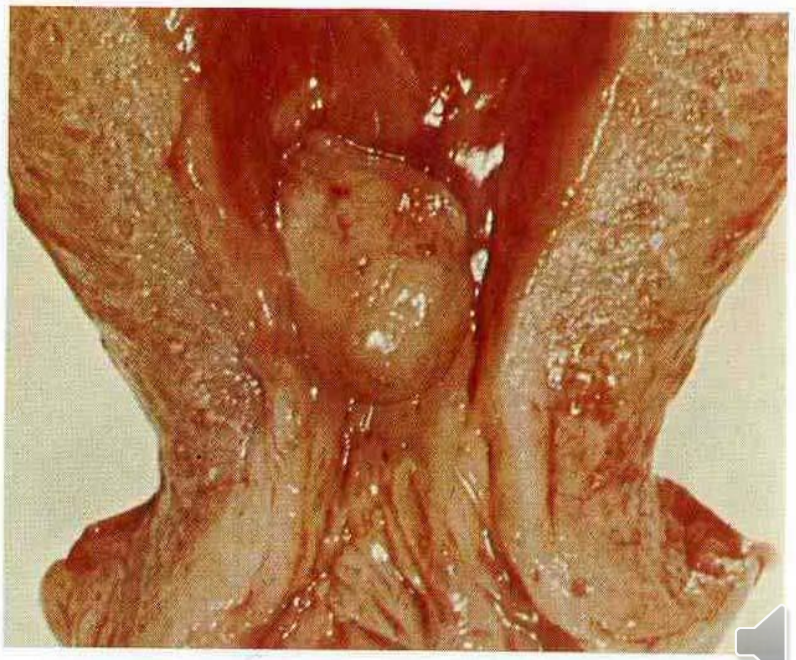




Endocervical Polyp

- Is inflammatory lesion which may protrude as polypoid mass through the exocervix.
- It can be large (few cm), soft & smooth with glistening surface & underlying cystically dilated spaces filled with mucinous secretion.
- they have **no malignant potential**.

- A rounded, soft, sessile gelatinous polyp fills the endocervical canal



12.30 Endocervical polyp: uterus

Cervical Intraepithelial Neoplasia (CIN)

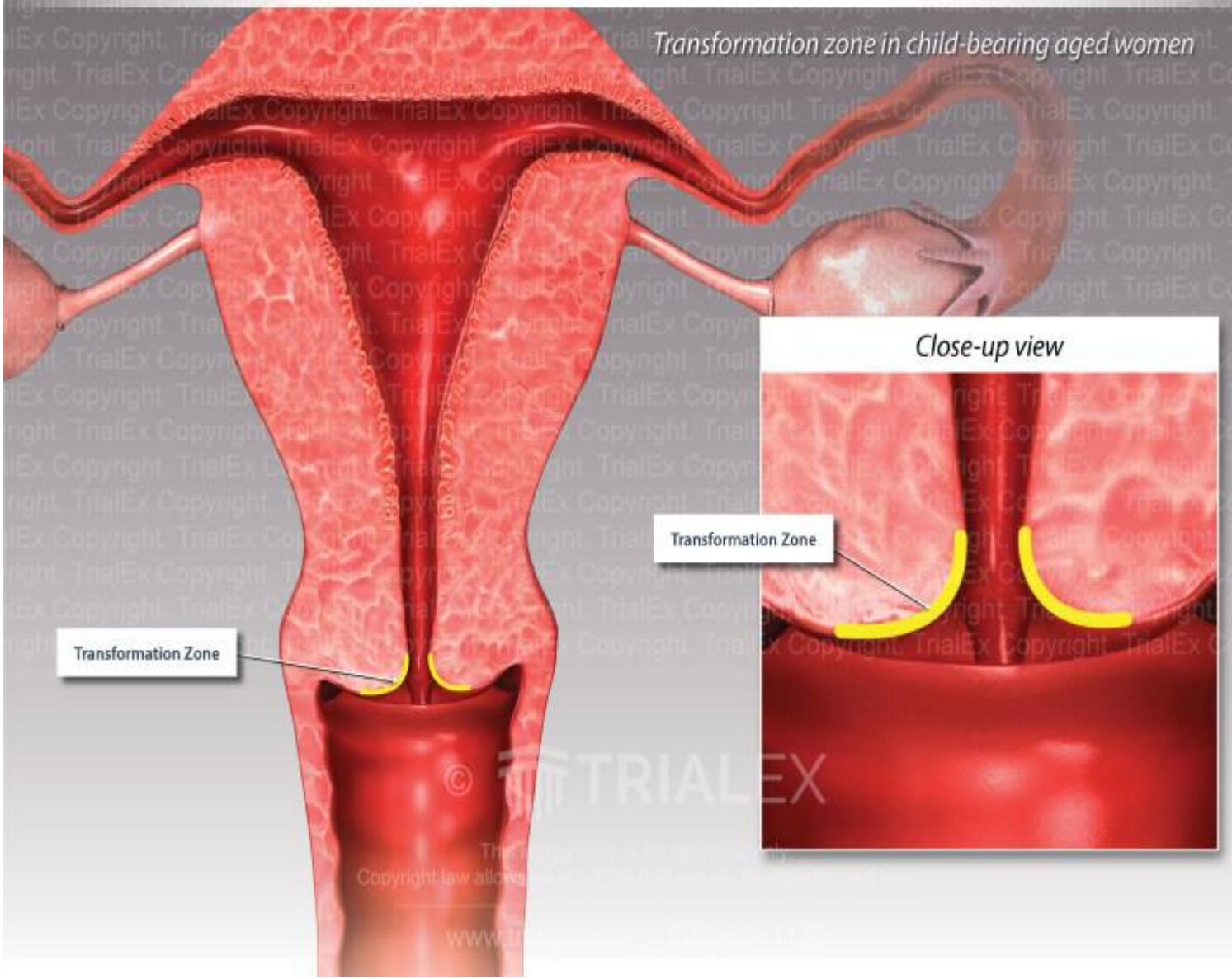
Dysplasia graded depending on the extent of epithelial involvement:

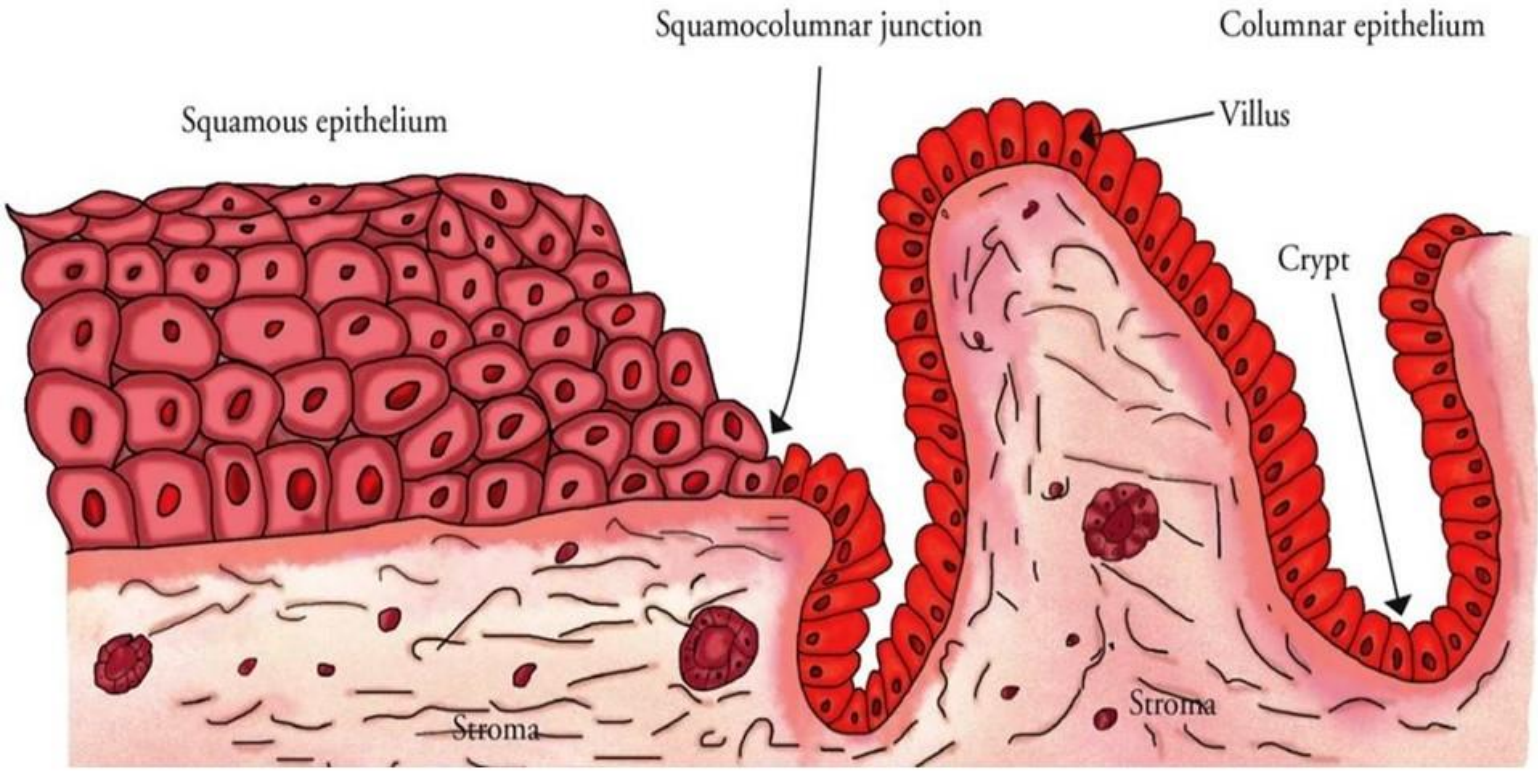
*__CIN I__: Mild dysplasia (<third of full epithelial thickness)

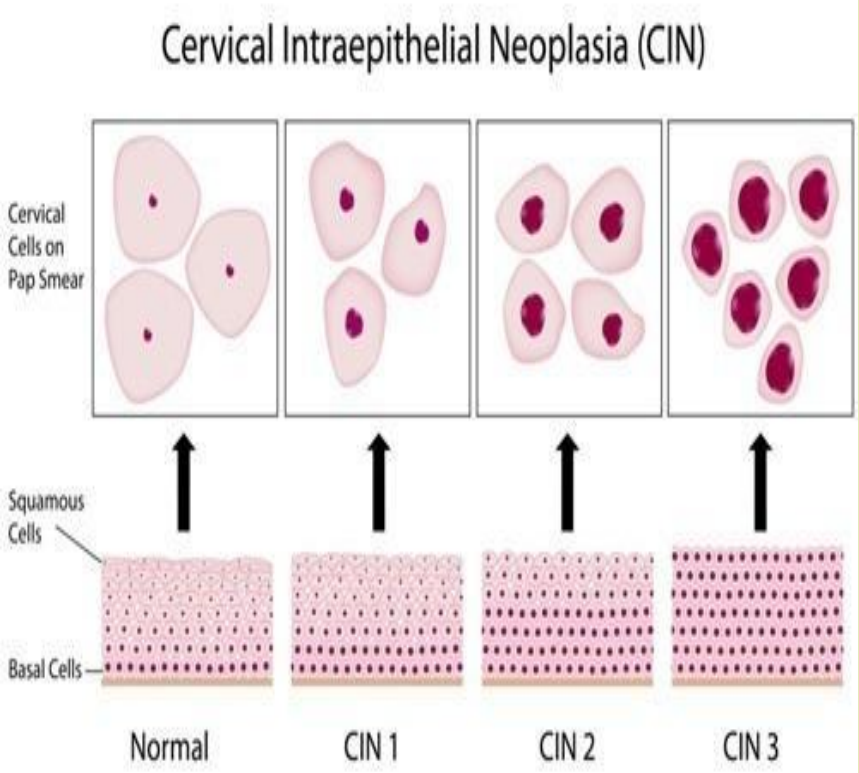
*__CIN II__: Moderate dysplasia (up to 2/3 of full epithelial thickness)

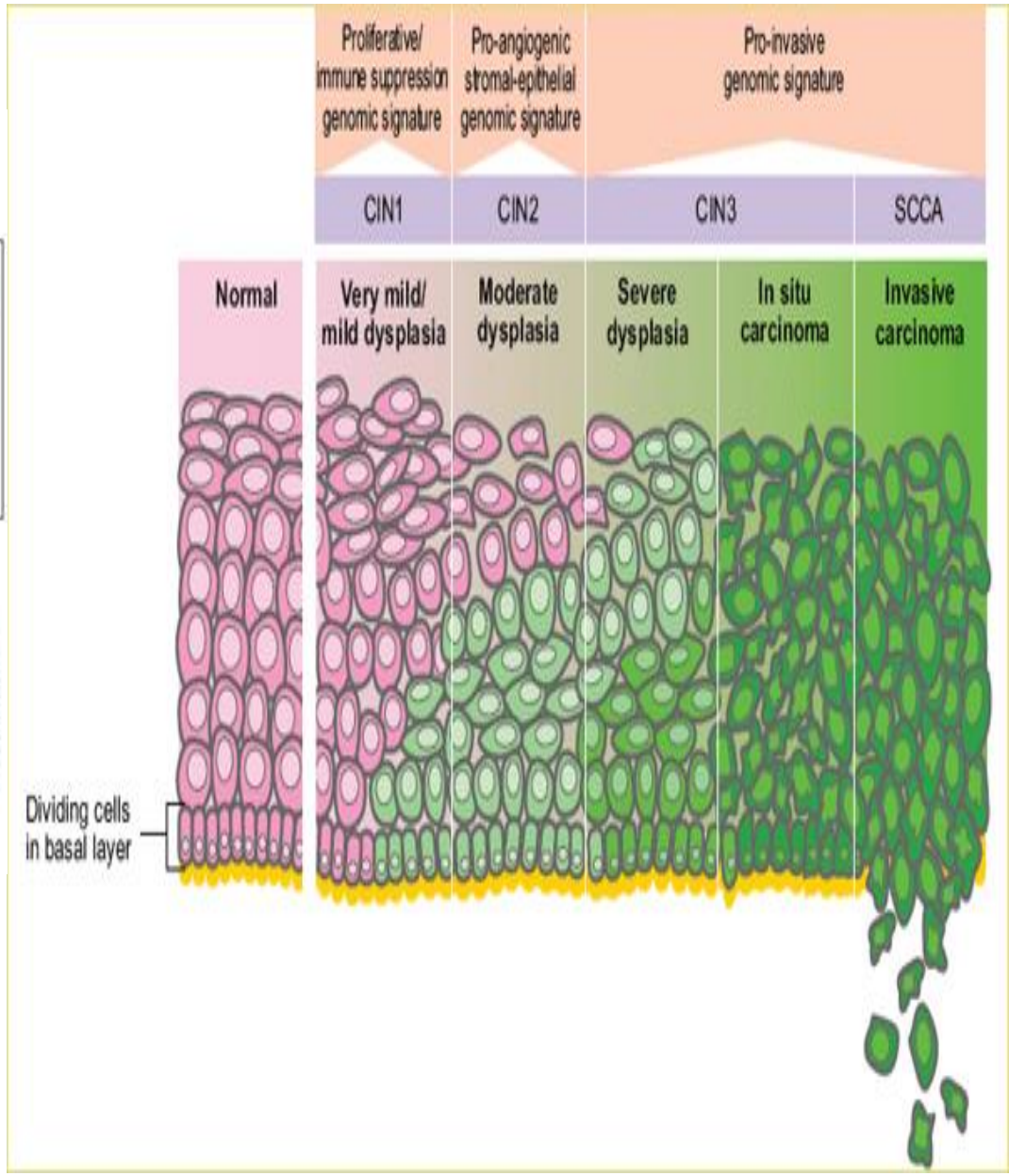
*__CIN III__: Severe dysplasia in full epithelial thickness (carcinoma in situ)

Cervical Squamocolumnar Junction (SCJ) and Transformation Zone




Squamocolumnar junction
Columnar epithelium
Squamous epithelium
Villus
Crypt
Stroma
Stroma


Cervical Intraepithelial Neoplasia (CIN)
Cervical Cells on Pap Smear
Squamous Cells
Basal Cells
Normal
CIN 1
CIN 2
CIN 3


Proliferative/ immune suppression genomic signature
Pro-angiogenic stromal-epithelial genomic signature
Pro-invasive genomic signature
CIN1
CIN2
CIN3
SCCA
Normal
Very mild/ mild dysplasia
Moderate dysplasia
Severe dysplasia
In situ carcinoma
Invasive carcinoma
Dividing cells in basal layer

CIN-Epidemiology and Pathogenesis

- peak age of CIN is 30 years, whereas invasive cancer is about 45 years.
- HPV can be detected by molecular methods in nearly all precancerous lesions and invasive neoplasms.
- high-risk HPV types (16, 18, 45, and 31), account for majority of cervical ca
- It is important to emphasize here that: nearly all invasive cervical SCC arise from precursor CIN.
- However, Not all cases of CIN progress to invasive ca& indeed many persist without change or even regress!

- HPV 16 and 18 usually integrate into the host genome and express large amounts of **E6 and E7 proteins, which block or inactivate tumor suppressor genes p53 and RB, respectively**.
- Recently introduced **HPV vaccine** used in USA and Europe is effective in preventing HPV infections and hence cervical cancers.
- Cytological examination can detect CIN long before any abnormality can be seen grossly.

- The follow-up of such women has revealed that:
  - (I) Precancerous CIN may precede the development of an overt ca by many years, or in some cases even decades. However, (II) **a fraction of cases of CIN progress to invasive ca.**

❖ The precancerous CIN may begin as:

- (I) low-grade & progress to higher CIN grade, or
- (II) high-grade CIN arise de novo, depending on:
- the **location of the HPV infection** in the transformation zone.
- **type of HPV** infection(high or low risk)
- **other** contributing host factors.

❖**Important risk factors** for the development of CIN & invasive cervical ca are:

(1) Early age at first intercourse.
(2) Multiple sexual partners.
(3) A male partner with multiple previous sexual partners.
(4)Persistent infection by "high-risk" **HPV** papilloma viruses. Many other risk factors can be related to these 4, including the higher incidence in lower socioeconomic groups & the association with multiple pregnancies,& rarity among virgins,.

➔They point to the likelihood of sexual transmission of a causative agent, in this case ➔**HPV**.

Morphology

The cervical epithelial changes included within the term

(I) In **CIN I,**begin with **mild dysplasia**, **characterized** by **Koilocytosis {**produced by cytopathic effect of HPV} seen mostly in the superficial layers of the epithelium, **composed** of **nuclear hyperchromasia & angulation with perinuclear vacuolization**

(II) **In CIN II the dysplasia is more severe**,

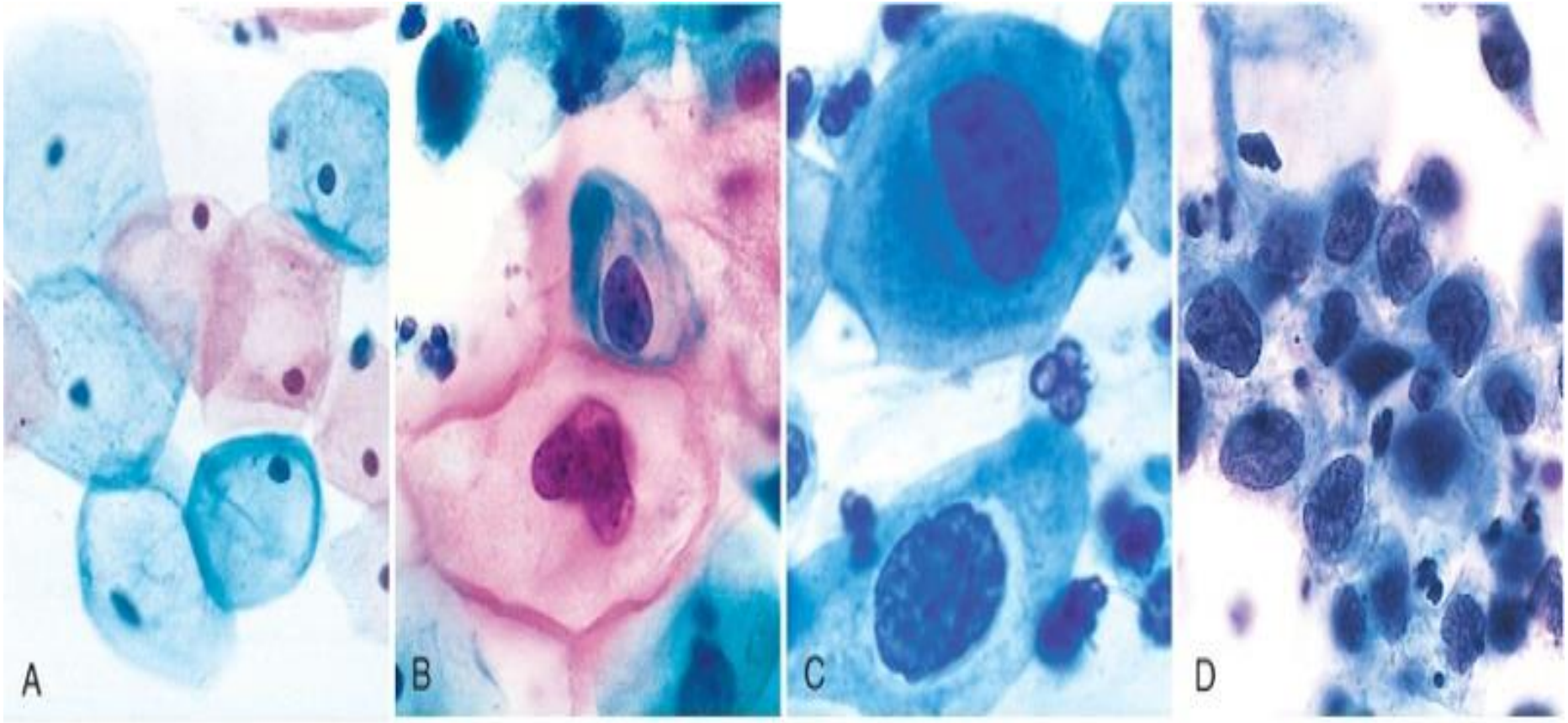
- with (1) maturation of keratinocytes delayed into the middle third of the epithelium, (2) cell & nuclear size pleomorphism, heterogeneity of nuclear chromatin & (3) **mitoses** above the basal layer, extending in to the middle third of the epithelium. The superficial layer of cells shows some differentiation.

(III) **CIN III** shows **greater pleomorphism in cell & nuclear size, marked hyperchromasia, &, disorderly orientation of the cells,** & normal or abnormal mitoses; **these changes affect virtually all layers of the epithelium & are characterized by loss of maturation ;** i.e., the differentiation of surface cells & koilocytotic changes have usually disappeared

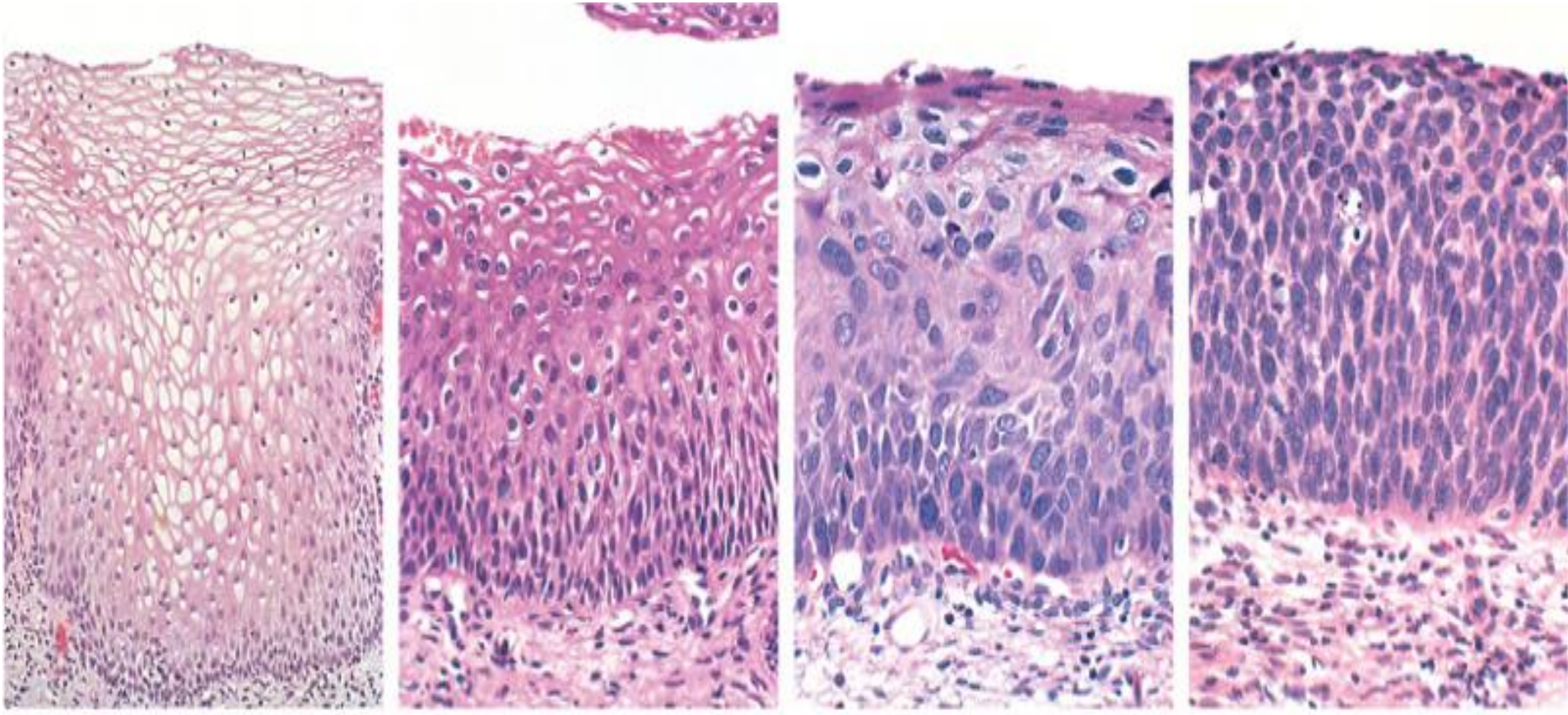
(IV) In time, dysplastic changes become more atypical & may extend into the end cervical glands, but **the alterations are confined to the epithelial layer & its glands. These** changes constitute **carcinoma in situ.**

➡ The next stage, if it is to appear, is **invasive ca,** however, as emphasized, there is no inevitability to this progression.

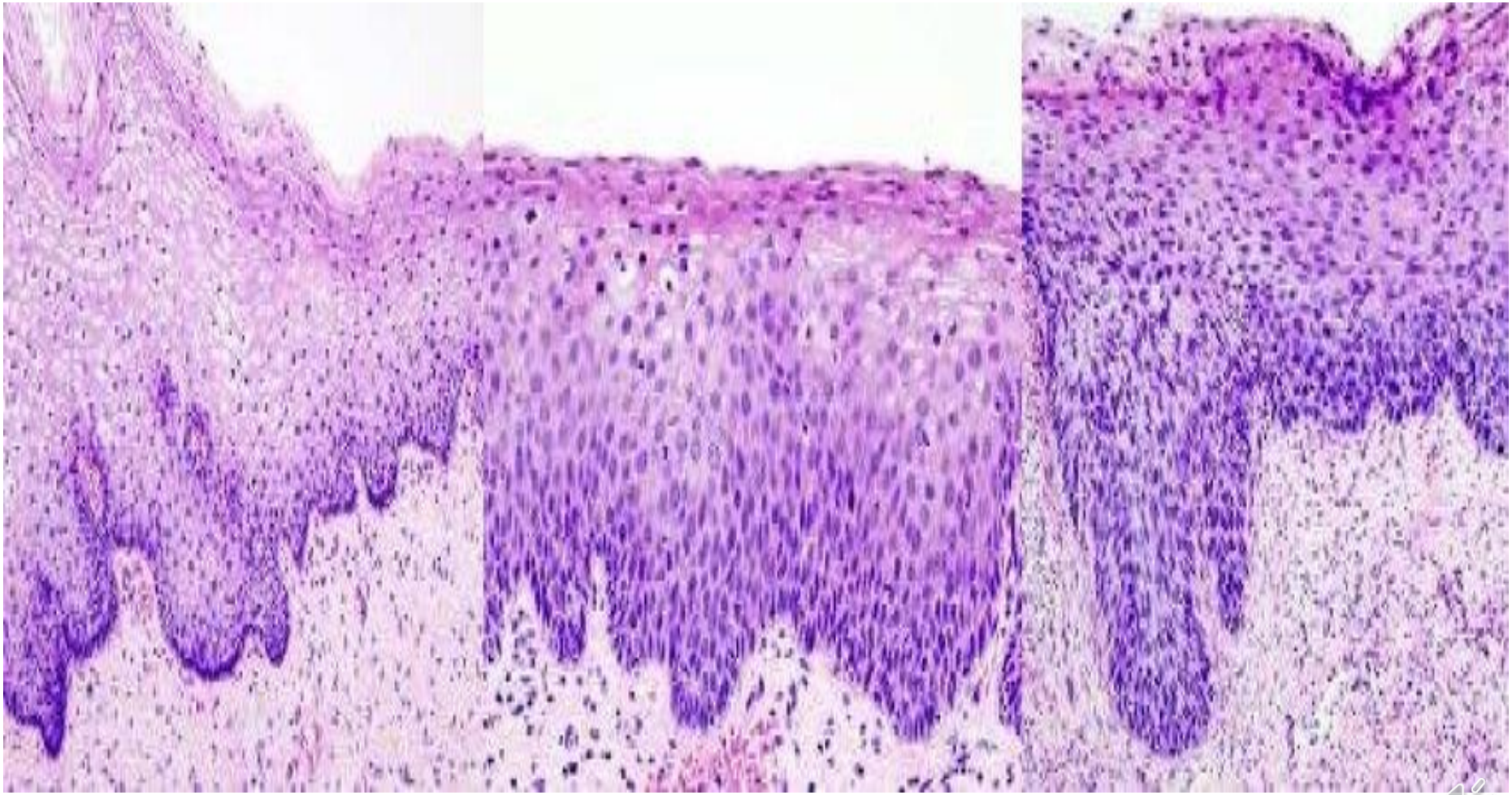
Papanicolaou smear:A, Normal exfoliative superficial squamous epithelial cells. **B**, CIN I. C, CIN II. D, CIN III. ★Note (1) the reduction in cytoplasm & (2) the increase in the nucleus-to-cytoplasm ratio as the grade of the lesion increases. ★This reflects the progressive loss of cellular differentiation ofthe cervical surface lesions from which these cells are exfoliated .



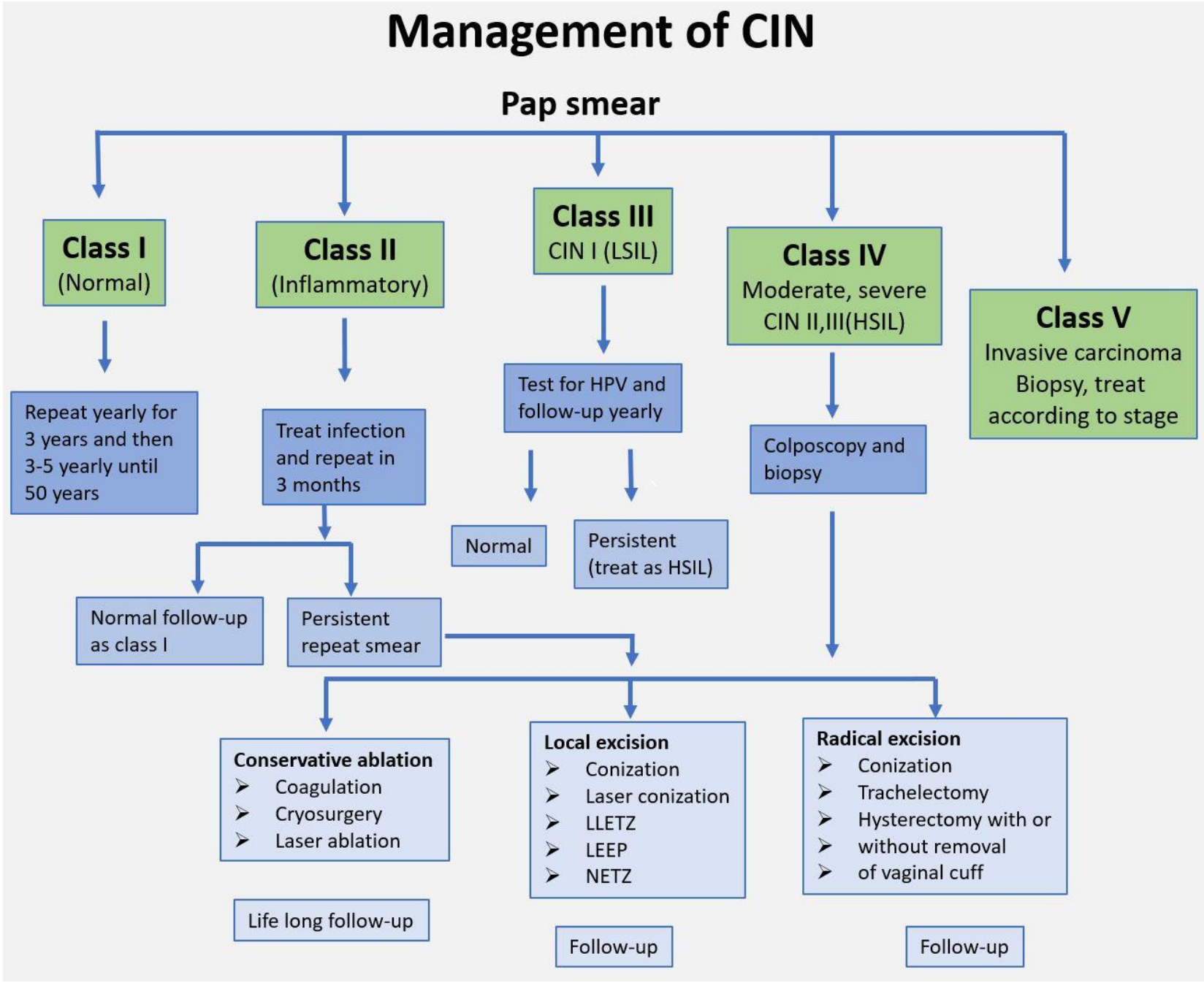
Spectrum of CIN: Normal cervical squamous epithelium for comparison. CIN I with koilocytotic atypia; CIN II with progressive atypia in all epithelial layers CIN III (ca in situ) with full thickness diffuse atypia & loss of maturation.



Cervical Intraepithelial neoplasia (CIN). A) CIN grade I showing dysplastic squamous cells in the lower one-third of the epithelium. B) CIN grade II showing dysplastic squamous cells in the basal two-thirds of the epithelium. C) CIN grade III showing dysplastic squamous cells marked throughout the full thickness of the epithelium.



Management of CIN



HPV Related Disease

- Genital warts
- CIN→Cervical Cancer
- VIN → Vulvar Cancer
- VaIN → Vaginal Cancer
- AIN → Anal Cancer
- PIN → Penile Cancer
- Recurrent Laryngeal Papillomatosis
- Head&Neck Cancers

1. Walboomers JM et al. *J Pathol*. 1999
2. WHO 1999
3. Herrero R et al. *J Natl Cancer Inst*. 2003;95:1772–1783.

Cervical cancer

- most common are **SCC (75%),** followed by adenocarcinomas and adenosquamous carcinomas (20%), and neuroendocrine carcinomas (<5%).
- SCC now has peak incidence at 45 years, almost **10 to 15 years after detection of their precursors: cervical intraepithelial neoplasia(CIN).**

- The only reliable way to monitor the course of the disease is with careful follow-up & repeat biopsies.

Grossly

- invasive cervical ca develop in the region of the **transformation zone** & range from **invisible** microscopic foci of early stromal invasion to grossly **visible exophytic** cancers encircling the os Ca encircling the cervix & penetrating into the underlying stroma produce a "barrel cervix," which can be identified by direct palpation.

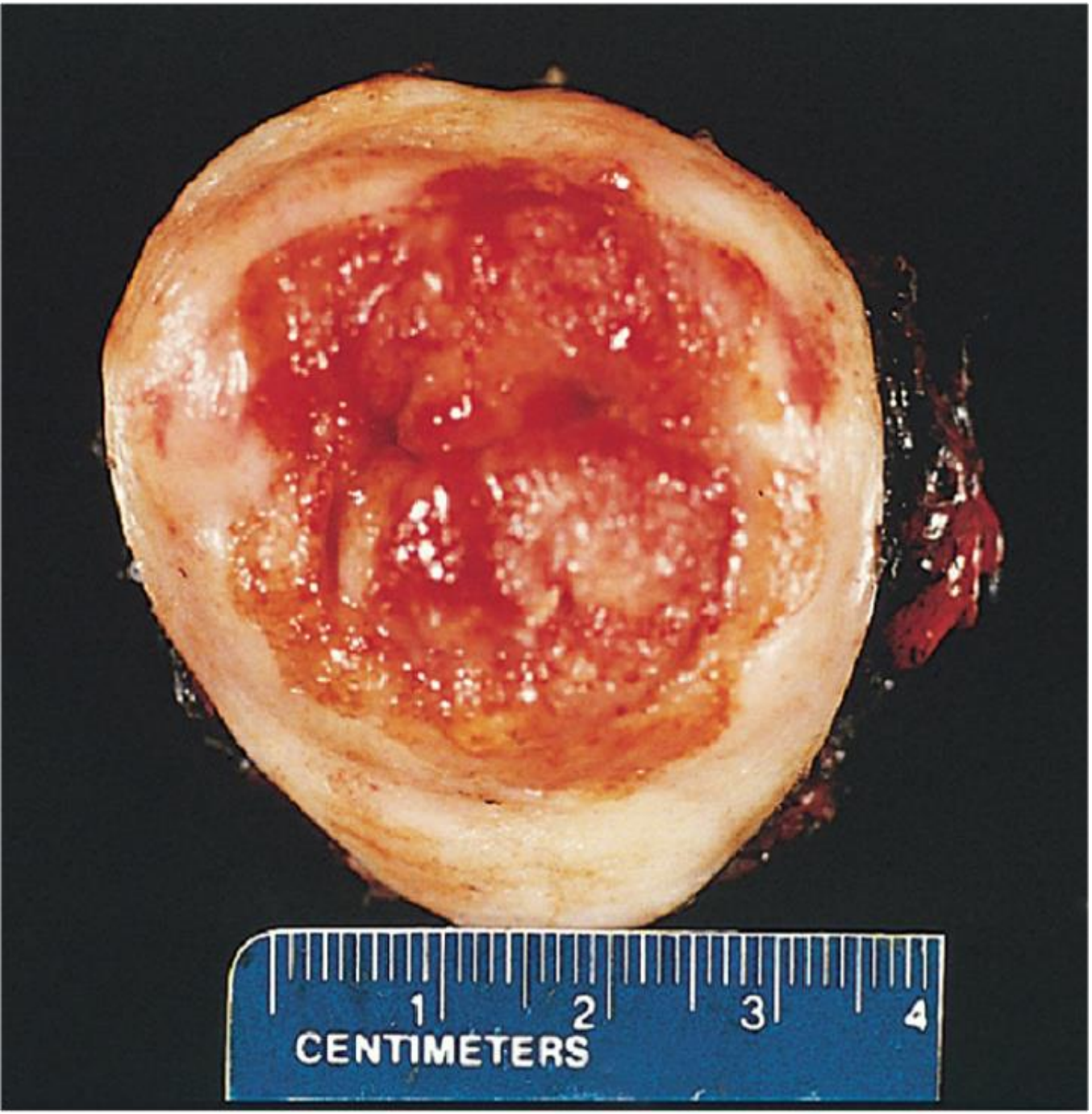
- Extension into the **parametrial** soft tissues can fix the uterus to the pelvic structures.

- Spread to **pelvic LNs** is determined by (1) T depth (ranging from < 1% for T < 3 mm in depth to more than 10% once invasion is more than 5 mm), & (2) the presence of capillary-lymphatic invasion,

- Invasion of **adjacent** structures {vagina, ureters, bladder or rectum} &**distant metastases {**including para-aortic LN & remote organs} occur late in the course of disease.

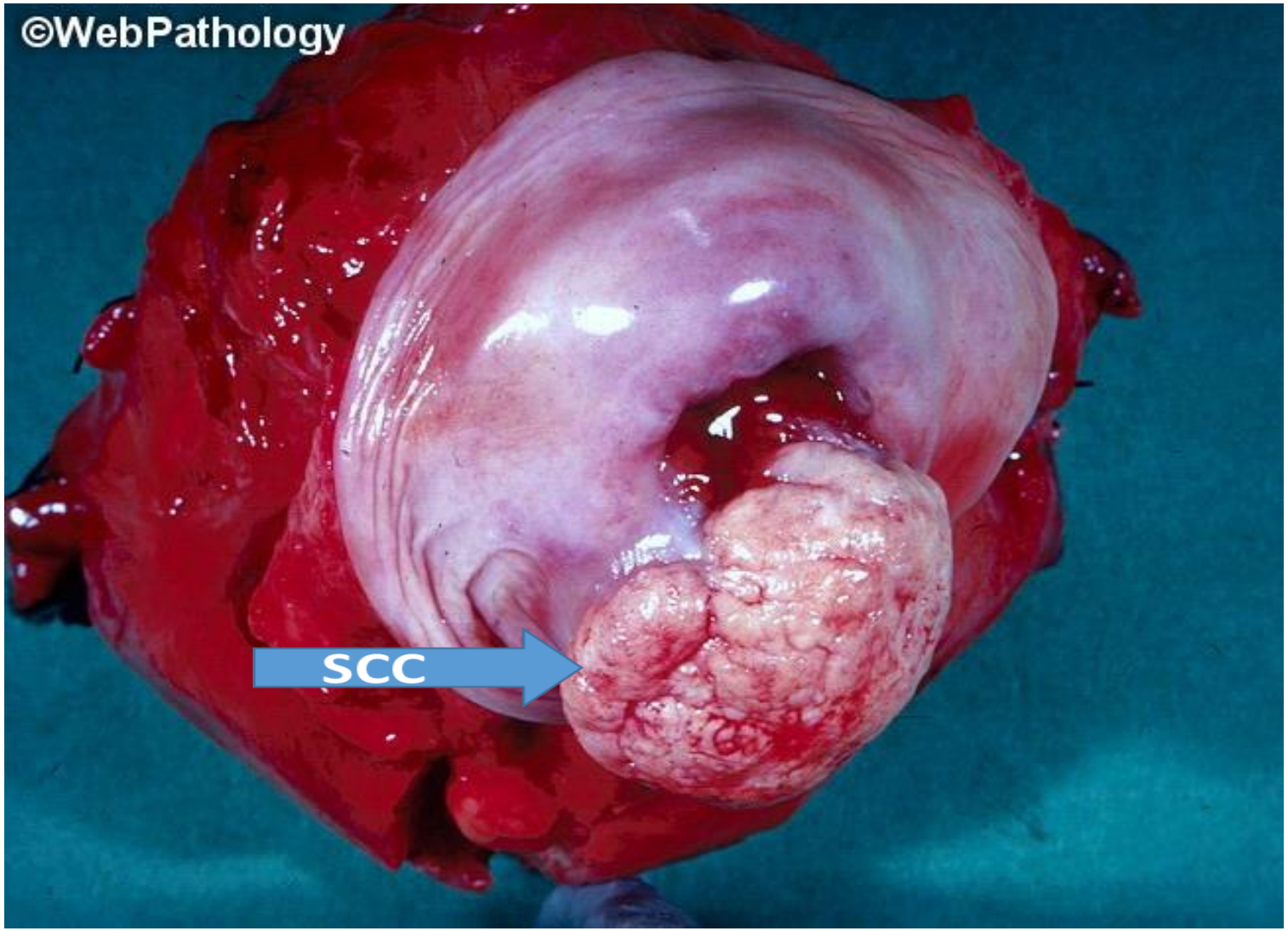
- With the exception of neuroendocrine T, which are uniformly aggressive in their behavior, the cervical ca are: ★graded from 1 to 3 based on cellular differentiation &

- staged from 1 to 4 depending on clinical spread.



Advanced Carcinoma of the cervix.

Squamous carcinoma: cervix. Irregular, polypoid tumor involving the ectocervix protruding from the cervix .



This is a larger cervical squamous cell carcinoma which spread to the vagina. A total abdominal hysterectomy with bilateral salpingo-oopherectomy (TAH-BSO) was performed.

Clinical Aspects Of Cervical Cancers

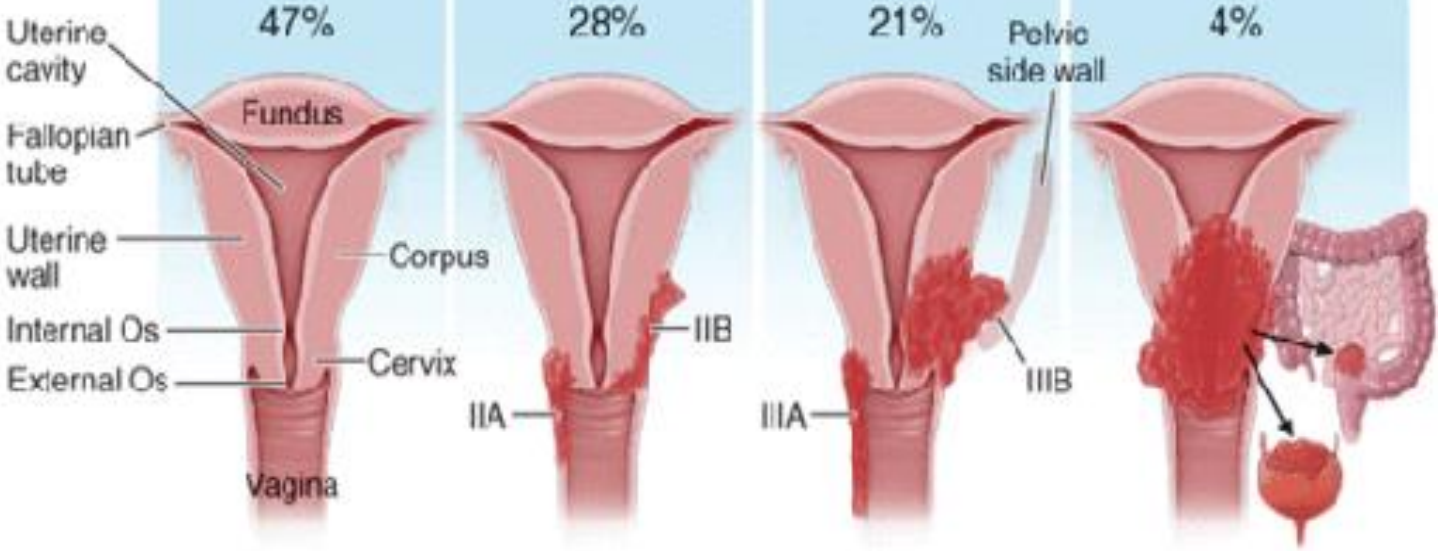
- With the advent of the Pap smear, an ↑proportion of cervical ca are diagnosed early in their course (stage 1).
- The vast majorities of cervical T are diagnosed in the preinvasive phase & appear as white areas on colposcopy examination after application of dilute acetic acid.
- **More advanced** cervical ca are invariably seen in:-

- (1) women who either have never had a Pap smear, or
- (2) have waited many years since the prior smear.
- Clinically :such tumors may cause unexpected

vaginal bleeding, leukorrhea, painful coitus (dyspareunia), & dysuria,and post coital bleeding

Staging of cervix cancer

Stage	0	I	II	III	IV
Extent of tumor	Carcinoma in-situ	Confined to cervix	Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina	Disease to pelvic wall or lower 1/3 vagina	Invades bladder, rectum or metastasis
5-year survival	100%	85%	65%	35%	7%
Stage at presentation		47%	28%	21%	4%



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

- CIN: treatment by **laser or cone biopsy**
- Invasive cancer: surgical excision

❑**Prognosis**: the 5-year survival is as follows: Stage 0 (preinvasive), **100%**; stage 1, **85%**; stage 2, **65%**; stage 3, **35%**; & stage 4, **7%.**

❑ Prevention:

- HPV vaccine can prevent the occurrence of cervical ca.
- Detection of precursors by cytologic examination & their eradication by **laser vaporization** or **cone biopsy** is the most effective method of cancer prevention.

Disease of Uterus

- **1-Purperal sepsis :** acute suppurative inflammation of uterus following labour or abortion
- Any fever during 2 weeks post labour or abortion consider Purperal sepsis till proved otherwise
- Caused by pyogenic bacteria ,E.Coli or Streptococcus (endogenous route of infection or exogenous)
- Complication

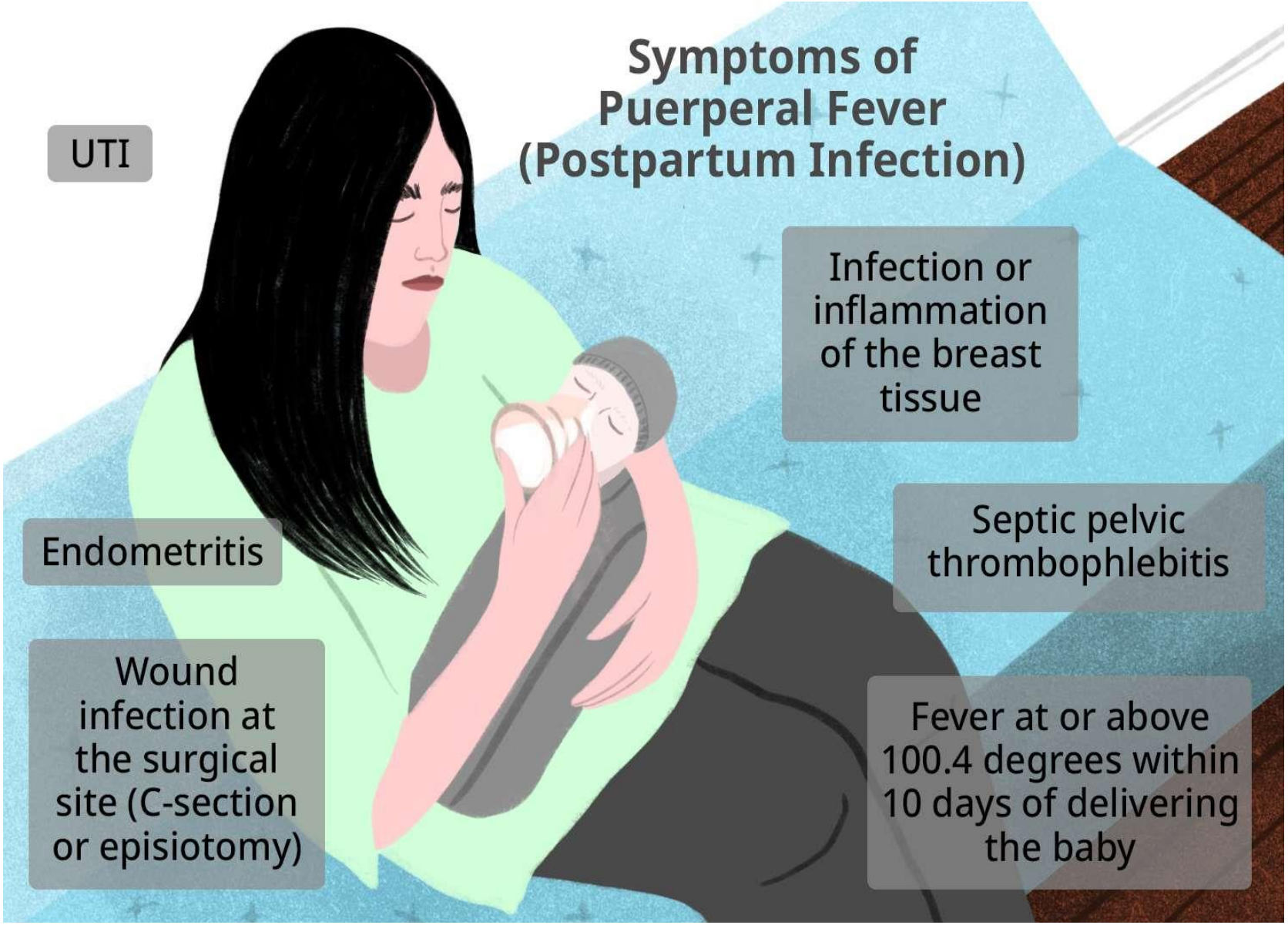
1- Toxemia

2-Septicemia

3-Peritonitis

4- Pyemia

5- Septic Thrombophlebitis


Symptoms of Puerperal Fever (Postpartum Infection)
UTI
Infection or inflammation of the breast tissue
Endometritis
Septic pelvic thrombophlebitis
Wound infection at the surgical site (C-section or episiotomy)
Fever at or above 100.4 degrees within 10 days of delivering the baby

Uterine Pathology

2-ENDOMETRITIS

❑ Inflammation of the endometrium.

•Causes:

1-Pelvic inflammatory disease (PID)

2-Miscarriage or delivery

3-Intrauterine device (IUCD).

Clinically:

Fever, abdominal pain, menstrual abnormalities, infertility and ectopic pregnancy due to damage to the fallopian tubes.

- **Acute or Chronic**
- Acute :due to N. gonorrhoeae or C. trachomatis with predominant neutrophilic cell respond
- Chronic endometritis**,** frequently due to chlamydial & Mycoplasma, with predominant lympho-plasmacytic cell response; **the diagnosis of which requires the presence of plasma cells in the endometrium..**
- Occasionally TB endometritis may present, frequently with TB salpingitis & peritonitis
- Rx: removal of cause, antibiotics, D&C.

3-ADENOMYOSIS

- Is the growth of the basal layer of the endometrium down into the myometrium.
- Endometrial stroma, glands, or both embedded in myometrium.
- Thick uterine wall, enlarged uterus.
- Derived from **stratum basalis**, **no** cyclical bleeding.

- Marked adenomyosis may produce premenstrual menorrhagia, dysmenorrhea (painful menses), (due to enlarged uterus, uterine contractions are exaggerated) & pelvic pain

BACKGROUND

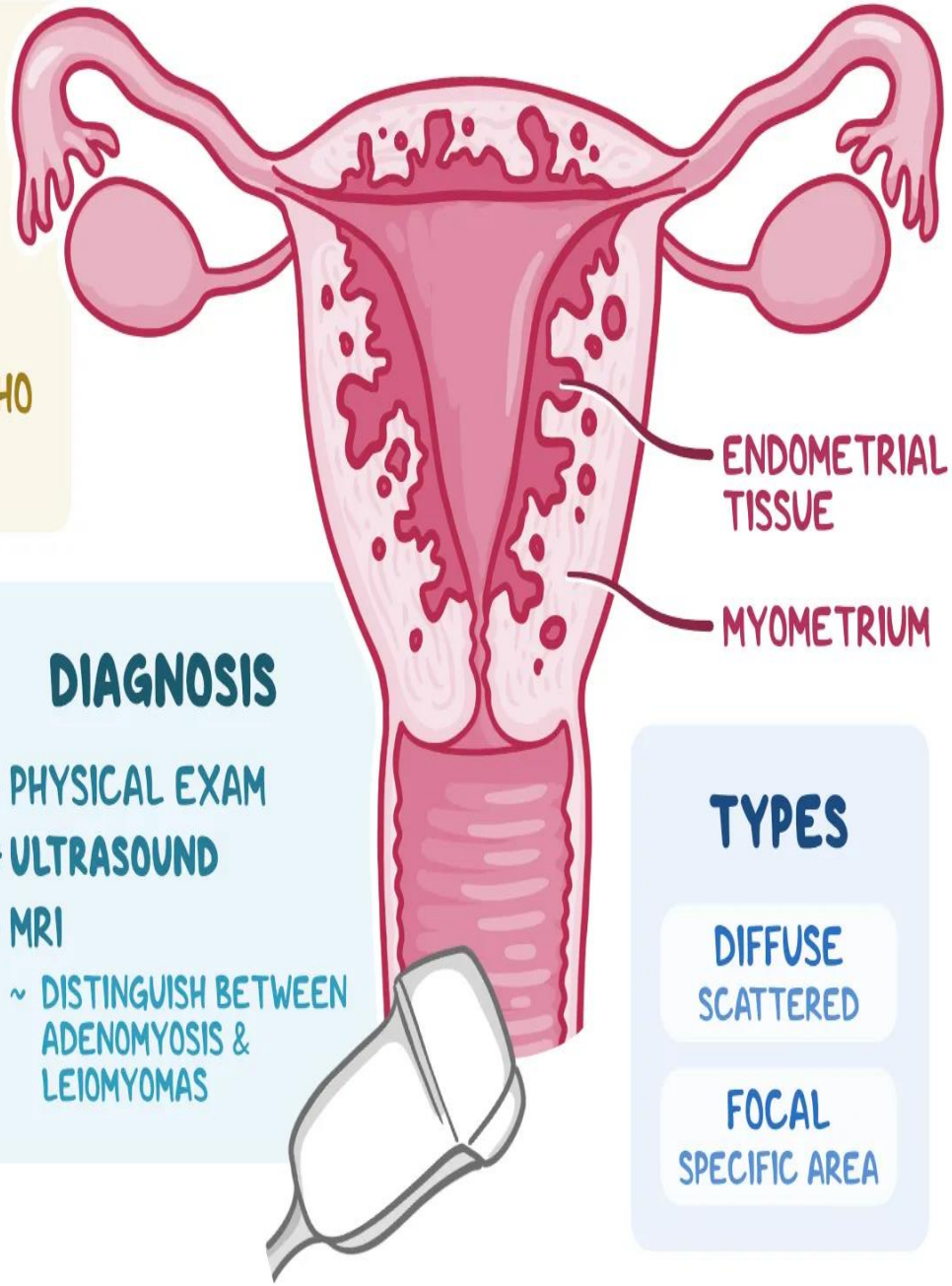
* ECTOPIC ENDOMETRIAL TISSUE FOUND WITHIN MYOMETRIUM
  ↳ HYPERPLASIA of MYOMETRIUM
* COMMON AMONG INDIVIDUALS WHO HAVE GIVEN BIRTH

SYMPTOMS

* MENORRHAGIA
* DYSMENORRHEA
* DYSPAREUNIA
* CHRONIC PELVIC PAIN
* UTERINE ENLARGEMENT & DISCOMFORT

DIAGNOSIS

* PHYSICAL EXAM
* **ULTRASOUND**
* MRI
  ~ DISTINGUISH BETWEEN ADENOMYOSIS & LEIOMYOMAS

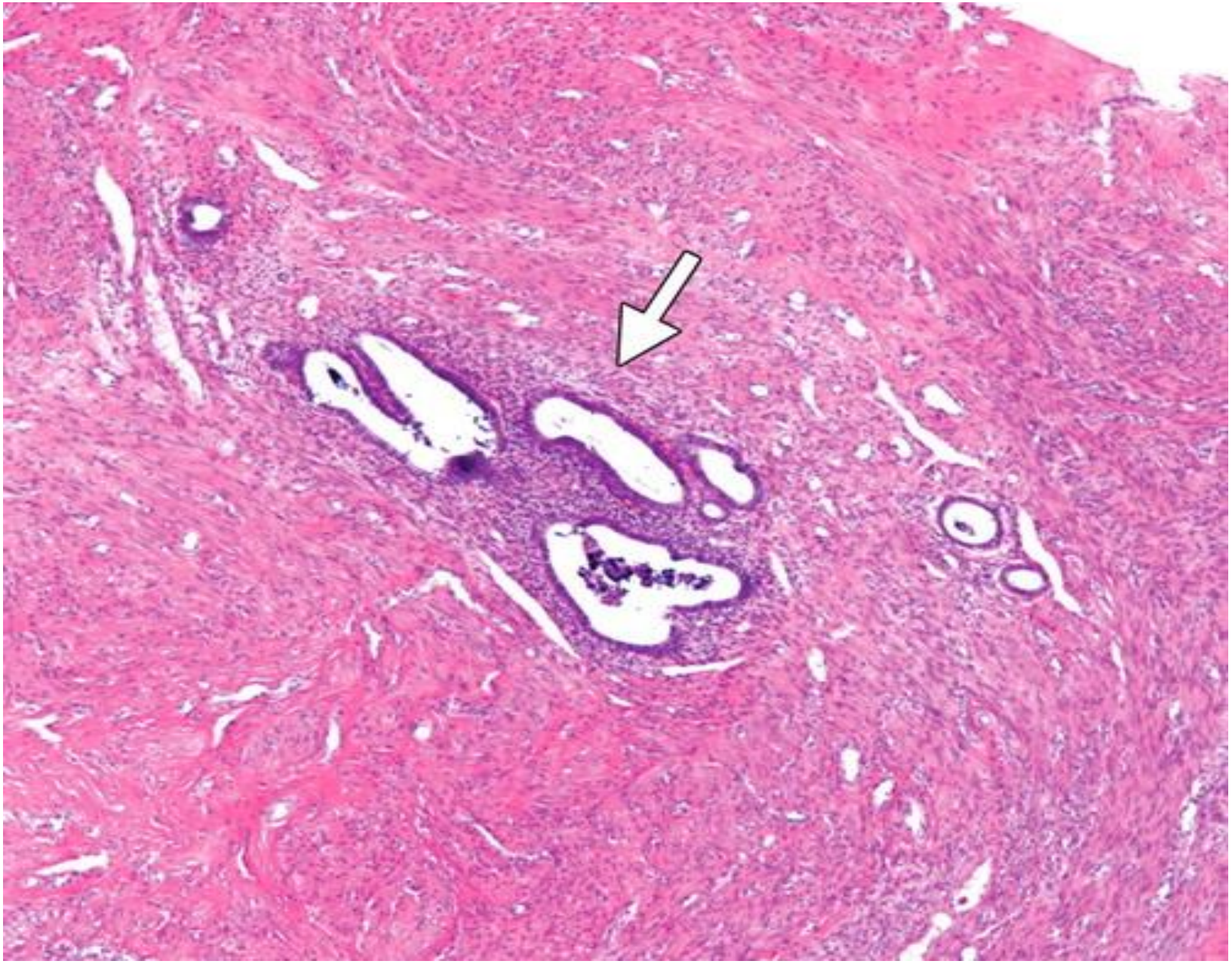


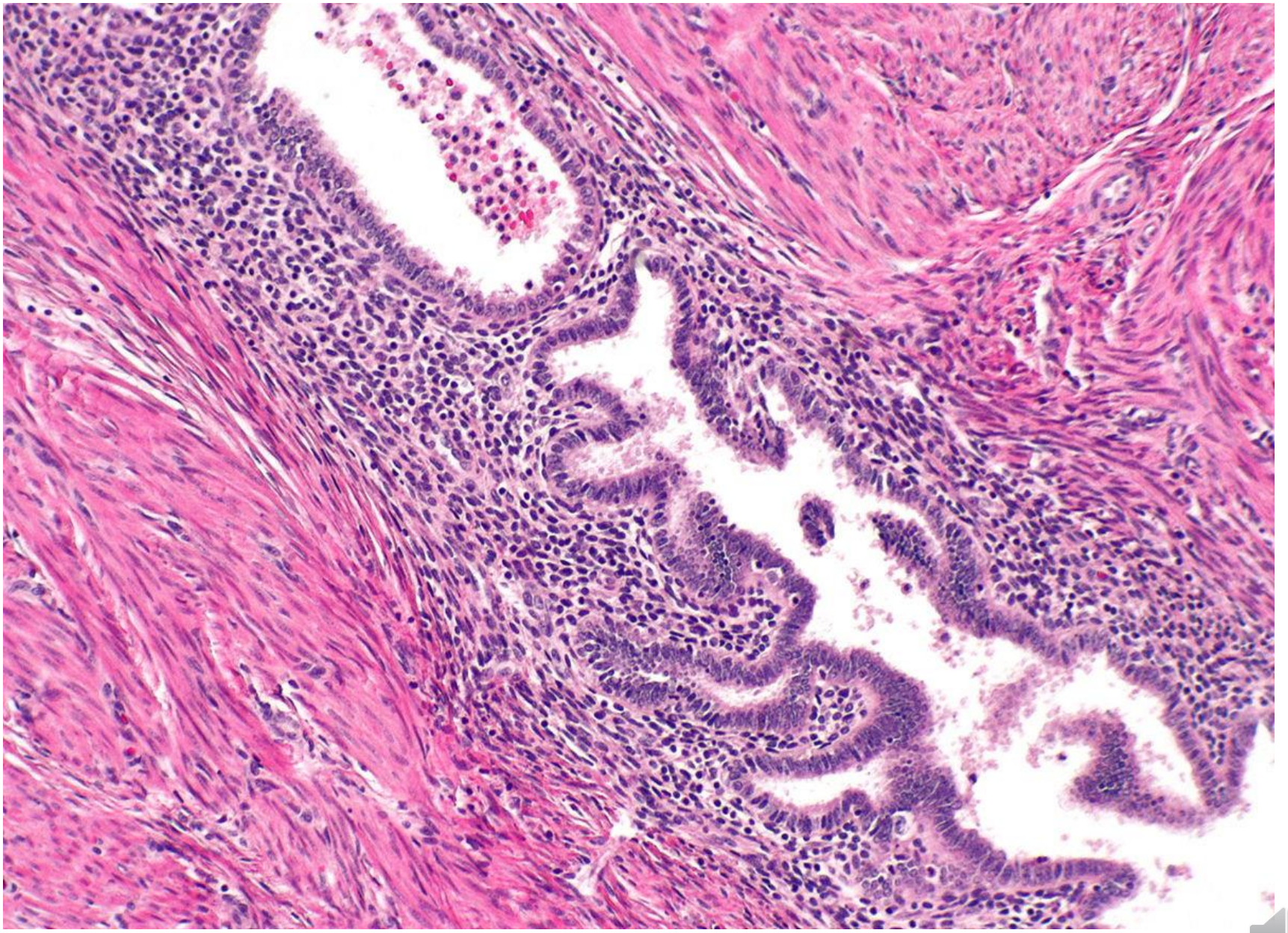
TYPES

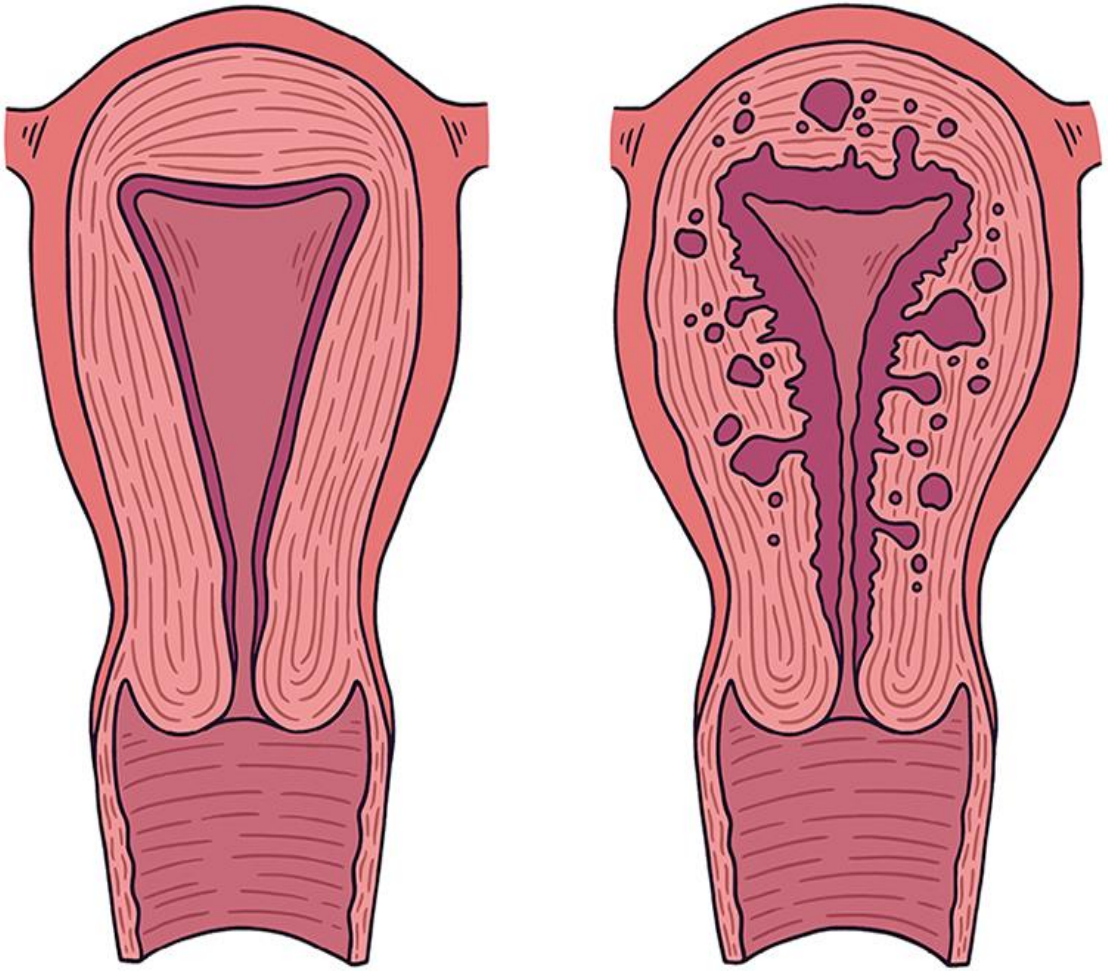
DIFFUSE
SCATTERED

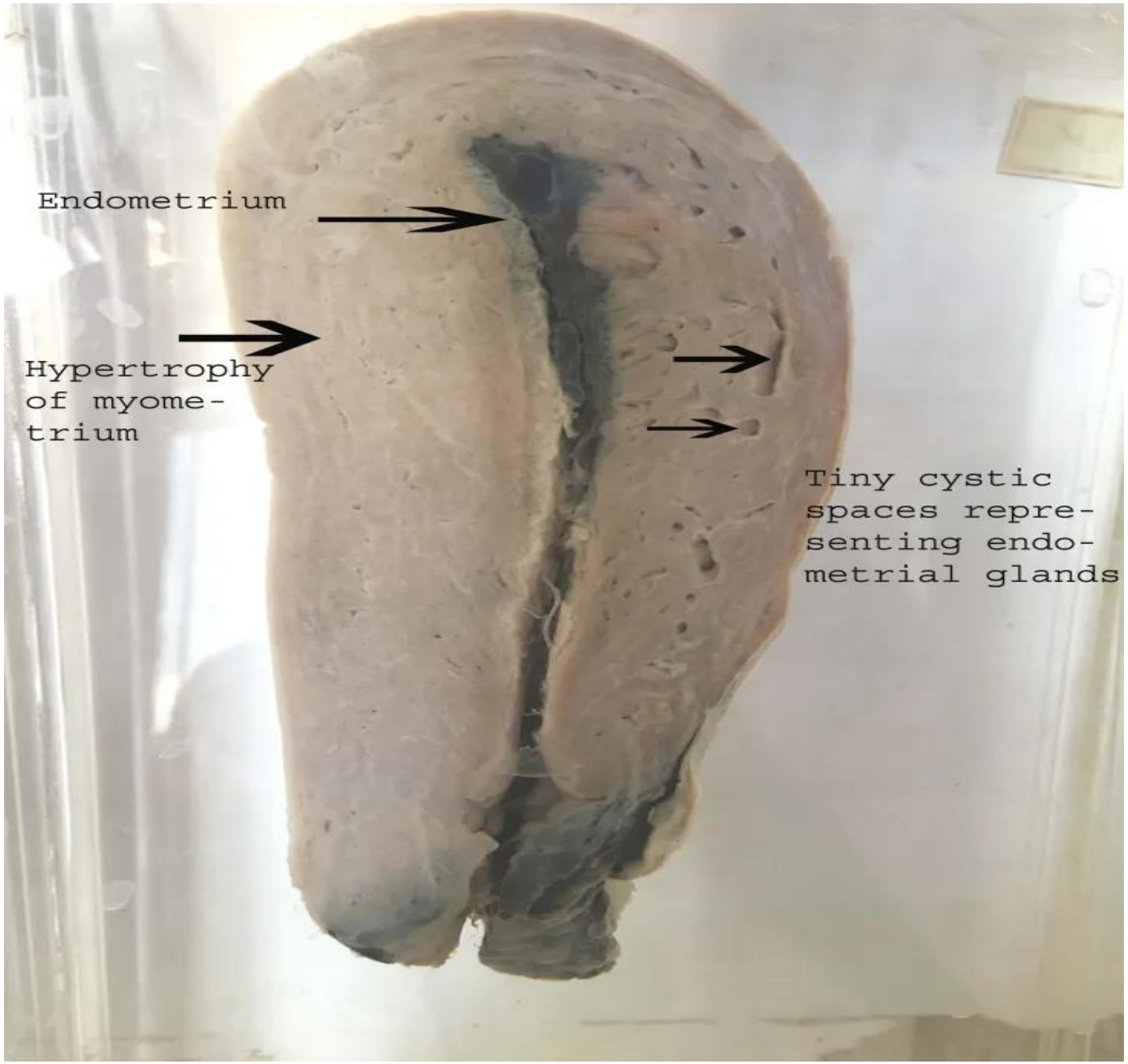
FOCAL
SPECIFIC AREA

Adenomyosis








Endometrium
Hypertrophy of myome-trium
Tiny cystic spaces repre-senting endo-metrial glands

4-ENDOMETRIOSIS

• Is the presence of endometrial glands and stroma **outside the uterus**.

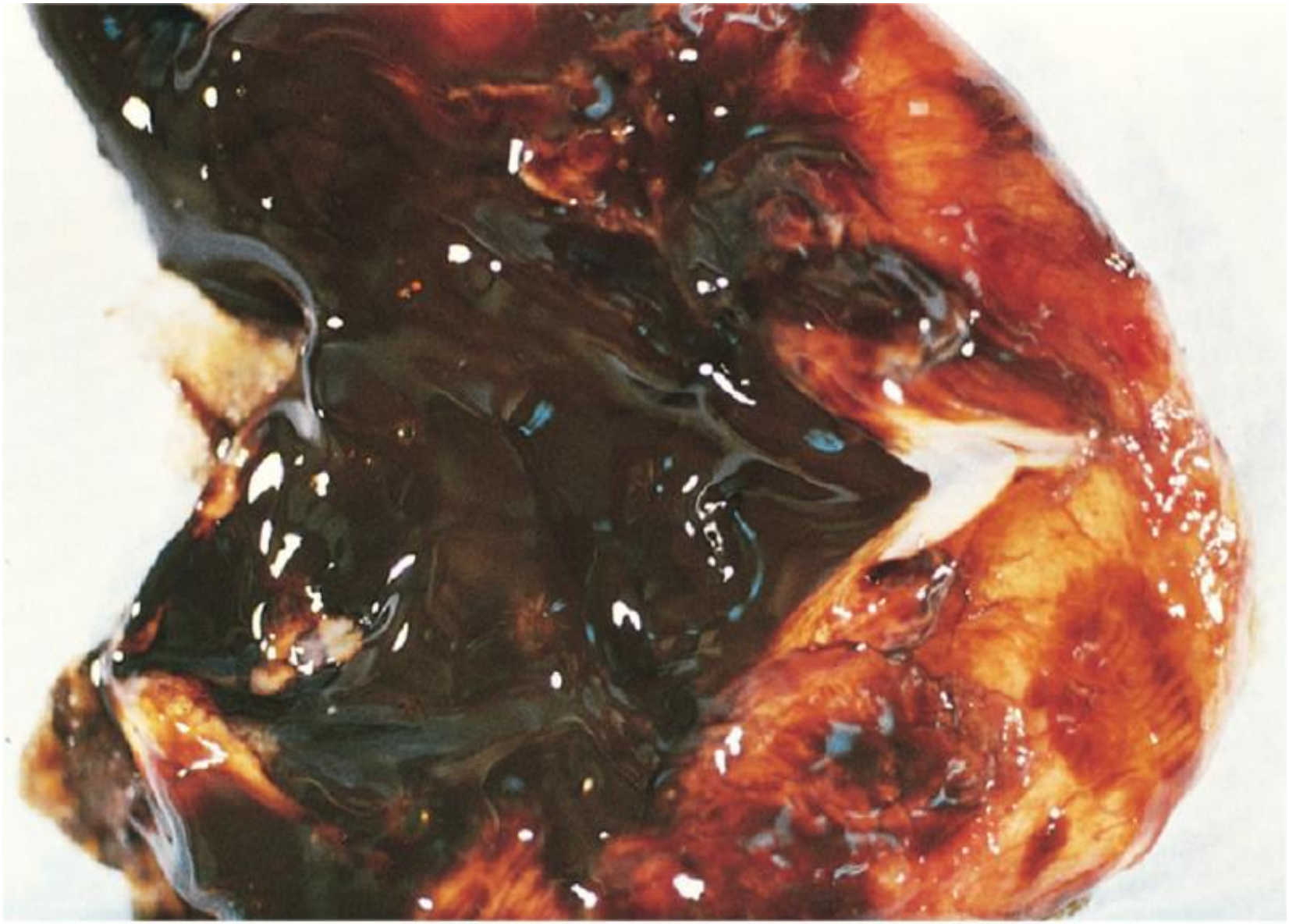
• It occurs in **10% of women in their reproductive years &** in **50% of women with infertility**

•Dysmenorrhea, and pelvic pain, pelvic mass filled with blood (chocolate cyst).

•Multifocal, multiple tissues in pelvis (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum).

•Sometimes distant sites e.g. umbilicus, lymph nodes, lungs, etc

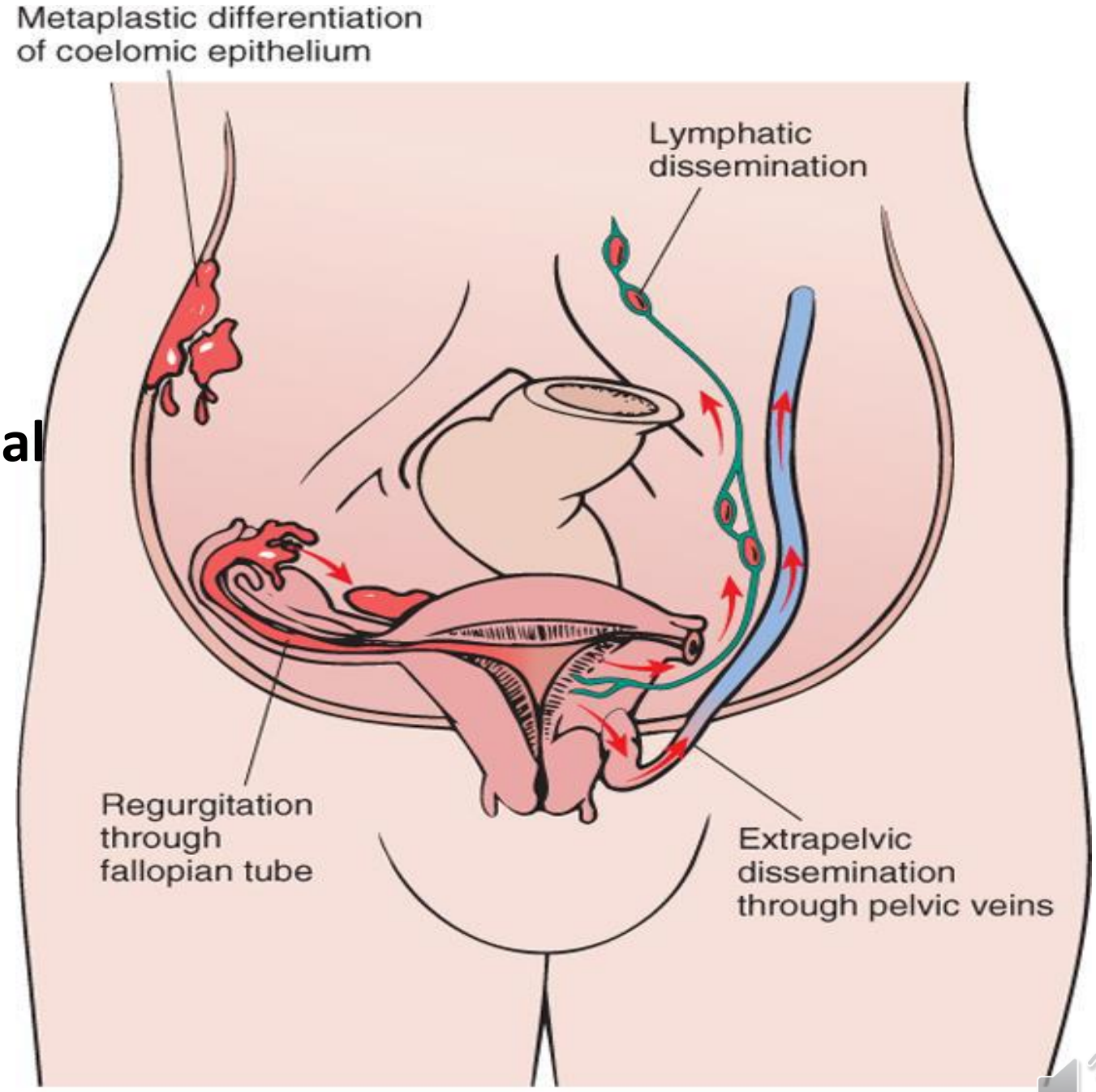
“Chocolate“ cyst in an ovary



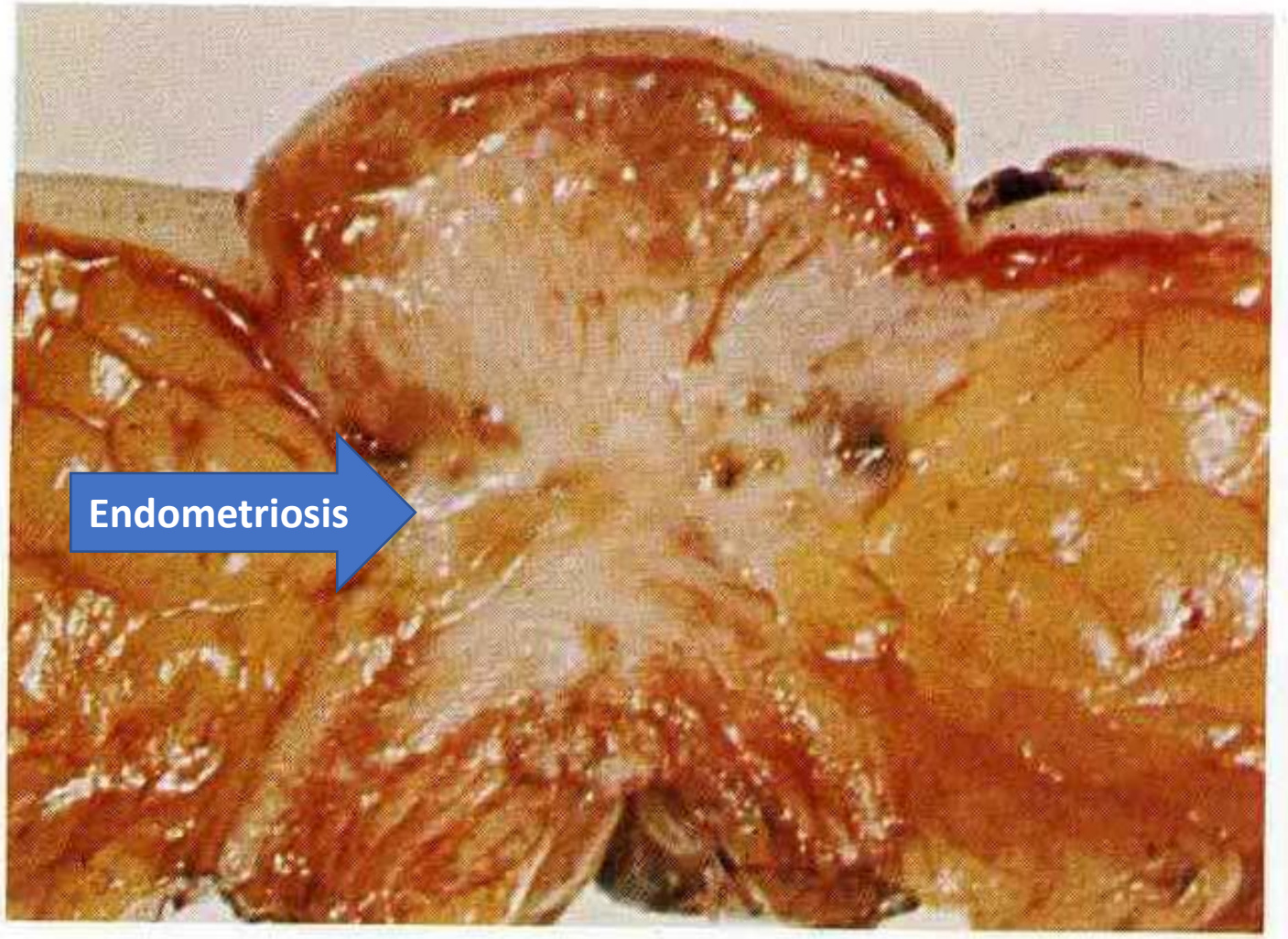
ENDOMETRIOSIS-Pathogenesis

- Three theories:
  - ***regurgitation theory.*** ***(***most accepted). Menstrual backflow through tubes and implantation..
  - ***metaplastic theory***. Endometrial differentiation of coelomic epithelium.
  - ***vascular*** **or** ***lymphatic dissemination theory.*** ***May*** explain extrapelvic or intranodal implants.

Conceivably, all pathways are valid in individual instances.



- **Endometriosis: umbilicus.** Accidental implantation of endometrial tissue during previous caesarean section in the abdominal wound caused the formation of a raised greyish-white mass of endometriotic tissue mass in the umbilicus within which there are several small blood-filled cysts.



12.28 Endometriosis: umbilicus

Grossly:

- in contrast to adenomyosis, **endometriosis** almost always contains **functioning endometrium,**which undergoes cyclic bleeding.
- Because blood collects in these abnormal foci, they usually appear grossly as **red-blue to yellow-brown nodules or implants**. contains **functionalis endometrium,**so undergoes **cyclic bleeding**.

- In the affected ovaries, large blood-filled cysts may form **chocolate cysts** as the blood ages **.**Seepage(leakage) & organization of the blood leads to widespread fibrosis.
- Consequences: fibrosis, sealing of tubal fimbriated ends, and distortion of the ovaries,and infertility

- In all sites, the histologic diagnosis of endometriosis depends on finding 2 of the following 3 features within the lesions:

(1)endometrial gland,(2) endometrial stroma (Positive CD10 immuno-stain) or (3) hemosiderin pigment.

Clinical manifestations of endometriosis depend on its site:

►Endometriosis is a common cause of d**ysmenorrhea** (painful menses) **& pelvic pain; both** of which are present in almost all cases of endometriosis as a result of intrapelvic bleeding & peri-uterine adhesions.

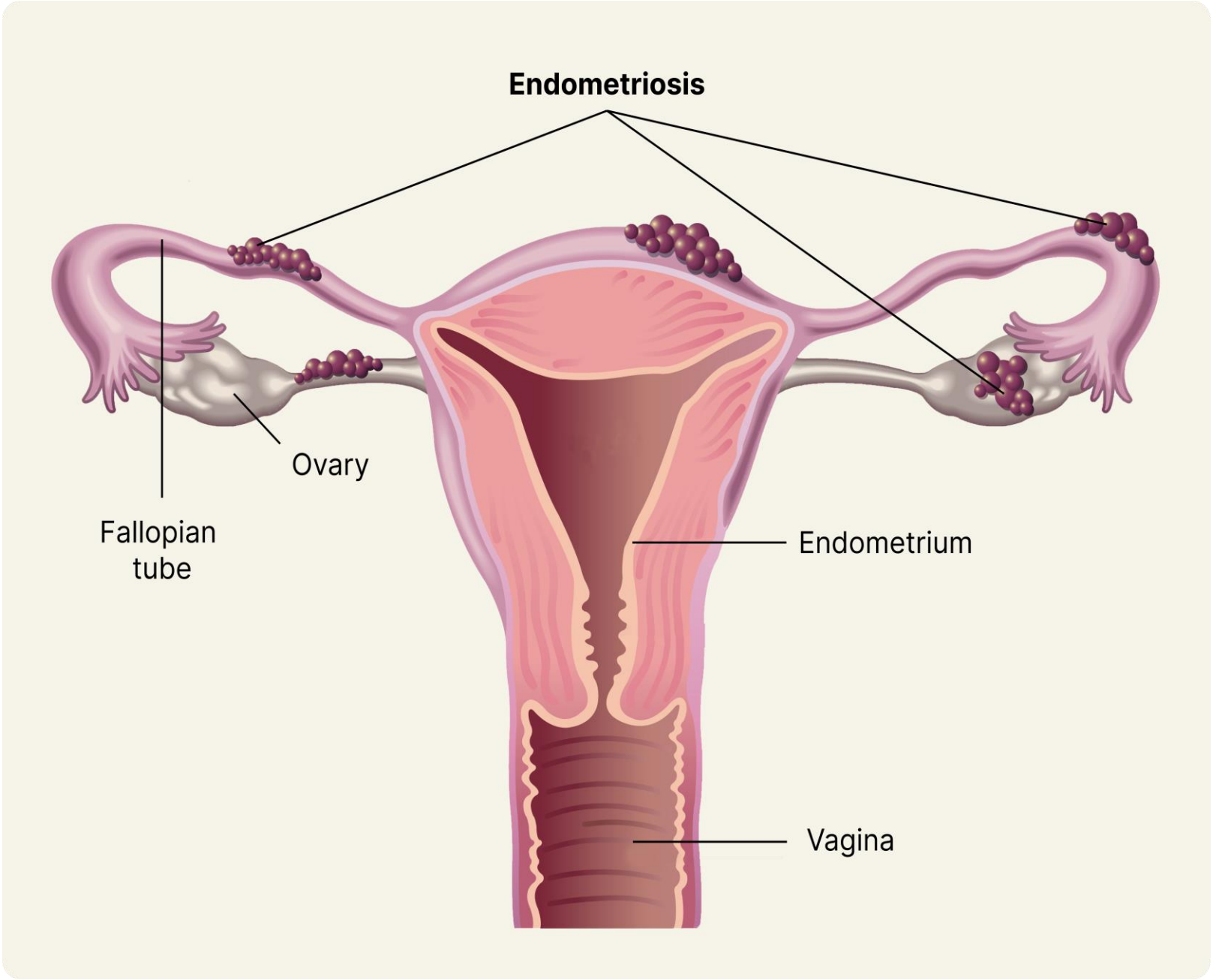
►Extensive scarring of the **oviducts & ovaries** produces lower abdominal **discomfort** & eventually causes **sterility.**

►**Pain on defecation** reflects rectal wall involvement, &

►**Dyspareunia (painful intercourse) &dysuria** reflect involvement of the uterine & bladder serosa, respectively.

►Ovarian endometriosis may present as a pelvic mass **(chocolate cyst).**


ENDOMETRIOSIS:
CLINICAL MANIFESTATIONS
Infertility
Dyspareunia
Painful Sex
Dysuria
Painful
Urination
Dyschezia
Painful Bowel
Movements
Dysmenorrhea
Painful Periods

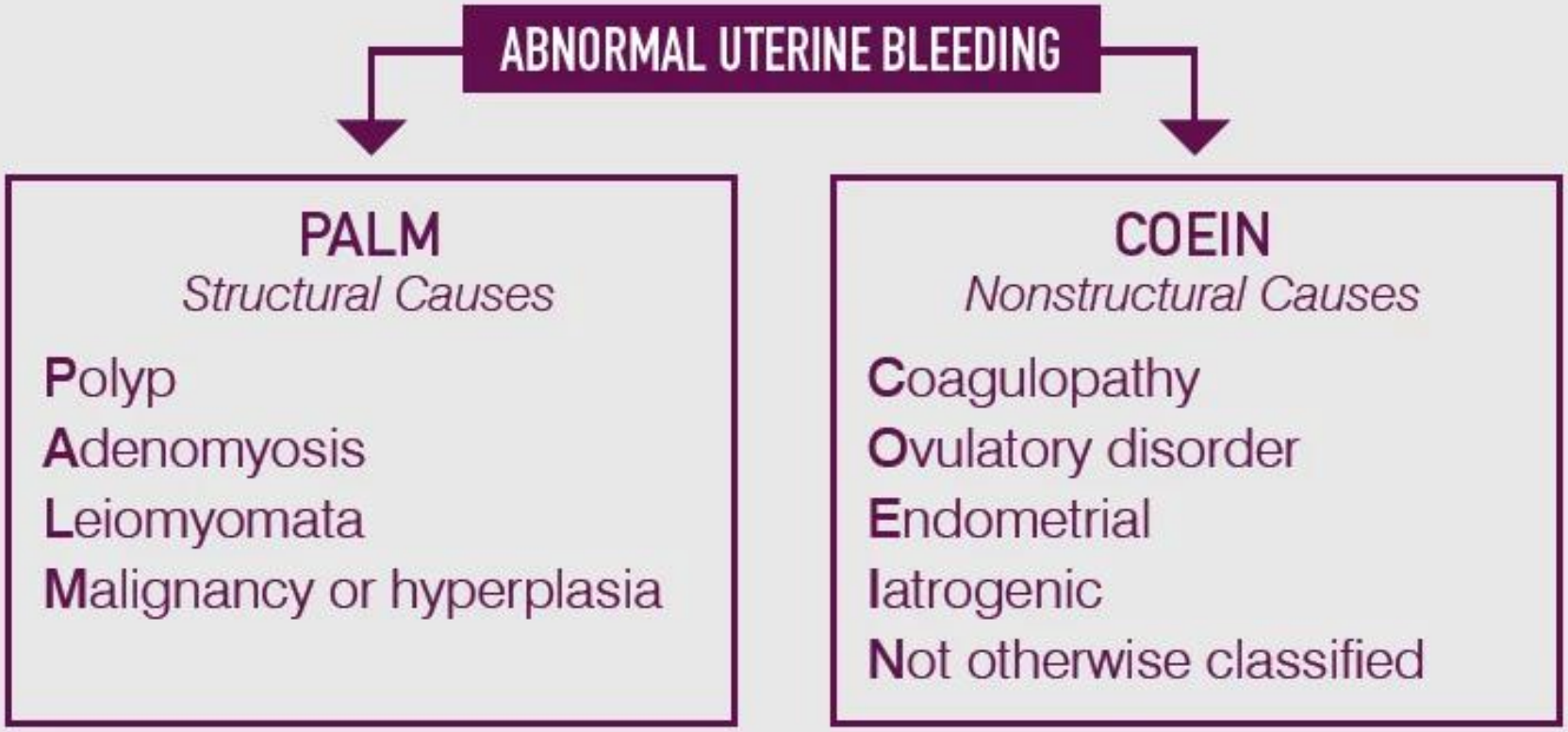

Endometriosis
Ovary
Fallopian tube
Endometrium
Vagina

Vaginal bleeding (Blood passes per vagina)

- The most common problem for which women seek medical attention is some disturbance in menstrual function:

(1) Menorrhagia=profuse or prolonged menstrual bleeding
(2) Metrorrhagia= irregular bleeding between the periods,
(3) Ovulatory(intermenstrual) bleeding
(4) Postmenopausal bleeding.
(5) Common causes include endometrial polyps, hyperplasia, ca, leiomyomas, & endometritis.
(6) Vaginal bleeding may also be due to cervical & vagina lesions, such as polyps, cervicitis, or ca.

Figure 1. The PALM-COEIN system is used to classify causes of abnormal bleeding in nonpregnant premenopausal women.



First described in FIGO Working Group on Menstrual Disorders. Int J Gynaecol Obstet 2011; 113:3-13.

5-Dysfunctional Uterine Bleeding.

- Is the abnormal uterine bleeding in the absence of a well-defined organic lesion in the uterus.

- **The 4 causes of dysfunctional bleeding are :**

❖ (I) Failure of ovulation . An ovulatory cycles are very common at both ends of reproductive life.

- with any dysfunction of the hypothalamic-pituitary axis.
- adrenal,
- thyroid;
- with a functioning ovarian lesion producing an excess of estrogen.
- with malnutrition
- debilitating disease •obesity •severe physical or emotional stress.

Whatever the cause…

- failure of ovulation leads to an excess of estrogen relative to progesterone, with the endometrium (E) going through a proliferative phase that is not followed by the normal secretory phase.
- The E shows relatively scant stroma, which requires progesterone for its support.
- The poorly supported E partially collapses, rupturing the spiral arteries, causes the bleeding.

(II) Inadequate luteal phase. The corpus luteum may fail to mature normally or may regress prematurely, leading to a relative lack of progesterone.

(III) Contraceptive-induced bleeding

Older oral contraceptives containing synthetic estrogens & progestin induced a variety of E responses e.g., inactive, non-secretory glands with decidual-like stroma. The pills in current use have corrected these abnormalities.

(IV) Endomyometrial disorders,including **E** polyps, chronic endometritis & submucosal leiomyomas.

Endometrial Hyperplasia

- **Endometrial hyperplasia is a condition of the female reproductive system. The lining of the uterus (endometrium) becomes unusually thick because of having too many cells (hyperplasia). It's not cancer, but in certain women, it raises the risk of developing endometrial cancer, a type of uterine cancer.**
- Prolonged or marked excess of **estrogen** relative to progestin →exaggerated proliferation →may progress to cancer
- severity is based on architectural crowding and cytological atypia, they 4 types ranging from:

- simple endometrial hyperplasia,
- complex endometrial hyperplasia,
- simple atypical endometrial hyperplasia,
- complex atypical endometrial hyperplasia

- These types represent a continuum based on the level & duration of the estrogen excess.
- Not surprisingly, in time, the **EH** may become autonomous proliferation, no longer needing estrogenic influence, eventually giving rise to **carcinoma**.

Causes : any estrogen excess may lead to **EH ,**Including

❖ **Endogenous:**

(1)failure of ovulation, such as is seen around the menopause;

(2)estrogen-producing **ovarian lesions** such as:

★polycystic ovaries (including Stein-Leventhal syndrome);

★cortical stromal hyperplasia;

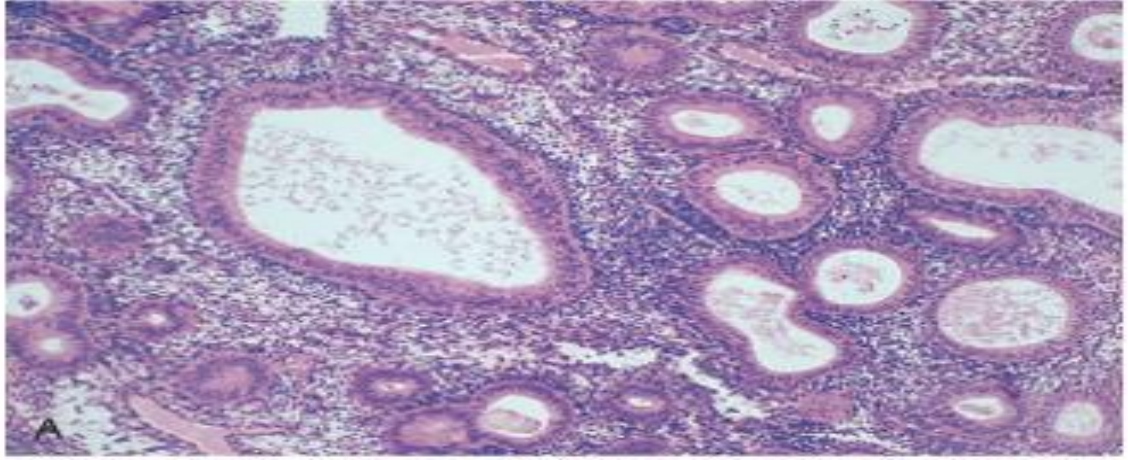
★**granulosa-theca cell tumors of the ovary**.

★common risk factor is **obesity, because** adipose tissue processes steroid precursors into estrogens.

❖ **Exogenous:**→prolonged **administration** of estrogenic steroids without counter balancing progestin.

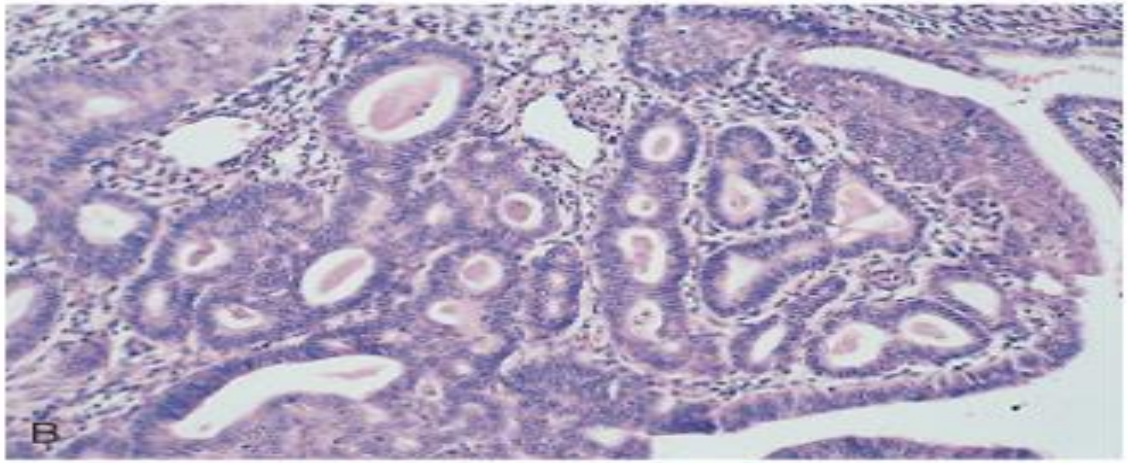
Simple hyperplasia

A, **An unovulatory** or "disordered" endometrium with dilatation of glands.



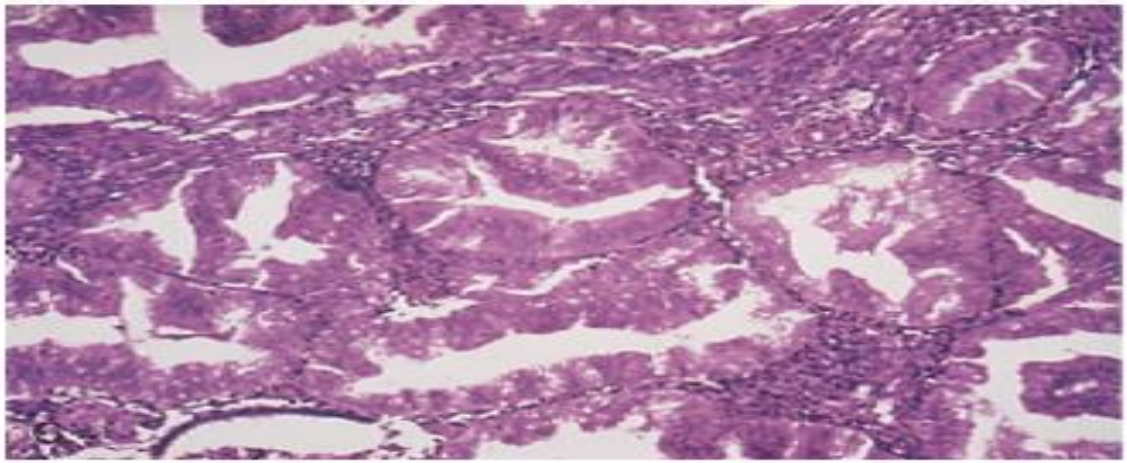
Complex Hyperplasia

displaying a nest of closely packed glands



Atypical Hyperplasia

endometrial hyperplasia with "back to back" crowding of glands & some loss of polarity.



er. Kumar et al: Robbins Basic Pathology 8e - www.studentco

TUMORS OF THE ENDOMETRIUM

❖Benign Endometrial Polyps

- Sessile or pedunculated.
- Cystically dilated Endometrial glands, with small muscular arteries and Fibrotic stroma.
- in most E polyps, the stromal cells are monoclonal& have a cytogenetic rearrangement at 6p21, making it clear that they are the neoplastic component of the polyp.
- no risk of endometrial cancer.

Endometrial Carcinoma

- It is **The most common cancer in female genital tract.**
- Common in 50s and 60s and is **distinctly uncommon** in women younger than 40 years of age
- Arise in one of two clinical settings:

1)Perimenopausal women with estrogen excess

2)older women with endometrial atrophy.

- These scenarios are correlated with differences in histology:
- 1-**endometrioid**
- 2-**serous carcinoma**, respectively.

Endometrioid carcinoma:

- Termed because similar to normal endometrium.

- Risk factors point to increase estrogen stimulation include:
- **Obesity;** (mostly an association and not a true risk factor);
- **Infertility**(nulliparous, often with non-ovulatory cycles)**;**
- **Prolonged estrogen replacement therapy;**
- **Estrogen-secreting ovarian tumors**.

Other risk factors **Diabetes and Hypertension**

- **Precancerous** lesion is atypical endometrial hyperplasia.
- **Breast ca occurs in women with E ca (& vice versa) more frequently than by chance alone.**

Pathogenesis

- Endometrial ca is the 2nd most common cancer associated with hereditary nonpolyposis colon cancer syndrome ,an inherited genetic defect in a DNA mismatch repair gene, resulting in (microsatellite instability).

- Mutations in DNA **mismatch repair genes** and **PTEN.**

- **Both mismatch repair gene &** PTEN **mutations** are **early events** in endometrial carcinogenesis, occurring in the progression from abnormal proliferation to atypical hyperplasia.

Serous carcinoma

- **No relation with endometrial hyperplasia.**
- **Not hormone-dependent.**

- (1) it typically arises in a background of **atrophy**, sometimes in the setting of an **endometrial polyp**
- (2) Mutations in DNA mismatch repair genes & PTEN are **rare** in serous ca; however,
- (3) **all cases have mutations in the** p53 **tumor suppressor gene.**

❑ **Grossly,**

❖ **Endometrioid ca** may be **fungating or infiltrative**, infiltrating the myometrium.

❑ H, T closely resemble normal **E,** ranging from mucinous to tubal (ciliated) to squamous or adenosquamous differentiation.

For **Endometrioid ca**, the grading (grades I-III) & the staging closely parallel outcome:

stage I, confined to the **corpus**; stage II, involvement of the **cervix**; stage III, beyond the uterus but **within the true pelvis**; stage IV, distant **metastases** or involvement of other viscera.

❖ **Serous carcinoma** forms small papillae (rather than the glands seen in endometrioid ca) & has much greater cytological atypia. They behave as poorly differentiated cancers **are not graded**, & are particularly **aggressive.**

❑ **Clinically**, **irregular bleeding is** the first clinical indication of all E ca, caused by erosion & ulceration of the T surface.

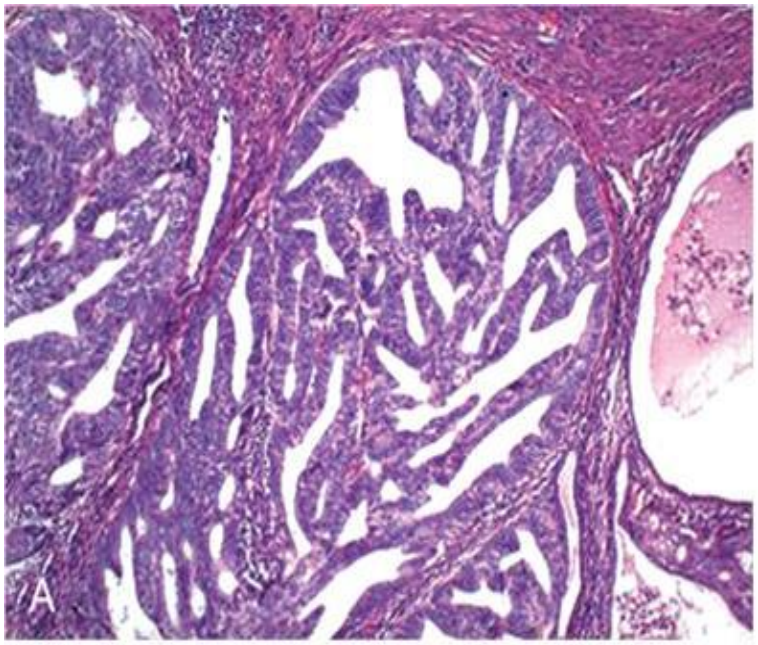
- With progression, the uterus may be palpably **enlarged**, &in time, extension of the E ca beyond the uterus **fixed** it to surrounding structures.

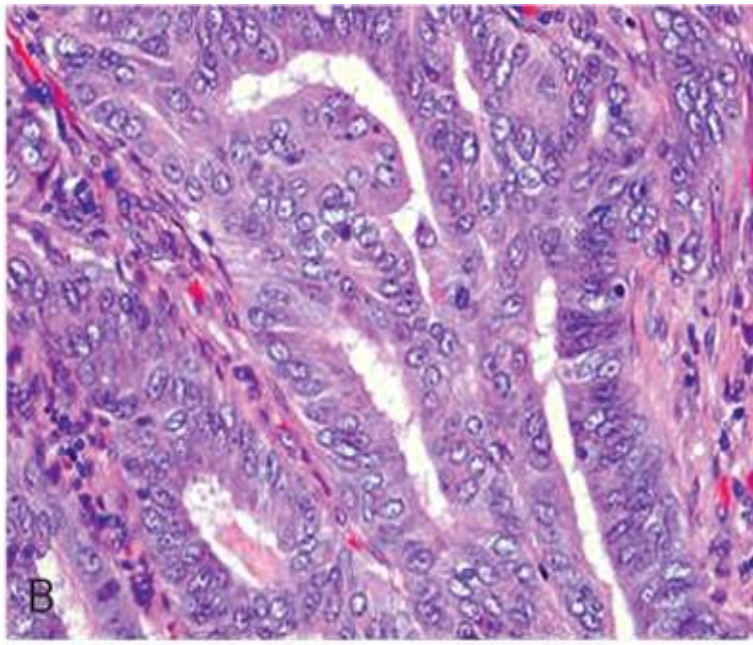
- Fortunately, E ca is usually **late-metastasizing cancer**, but dissemination eventually occurs, with involvement of ovary **,**LN & distant sites.
- **Papillary serous ca** prognosis is strongly dependent on the extent of tumor, as determined by operative staging with peritoneal cytology; since even very small or superficial serous T may spread via the fallopian tube to the peritoneal cavity.

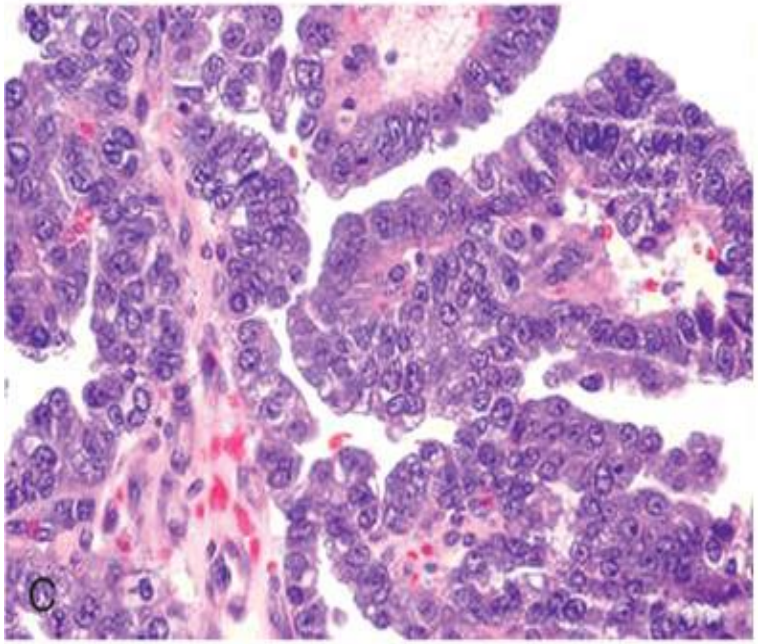
- **Prognosis: depends on stage.** 5-year survival in stage I= 90%; drops to 20% in stages III and IV.

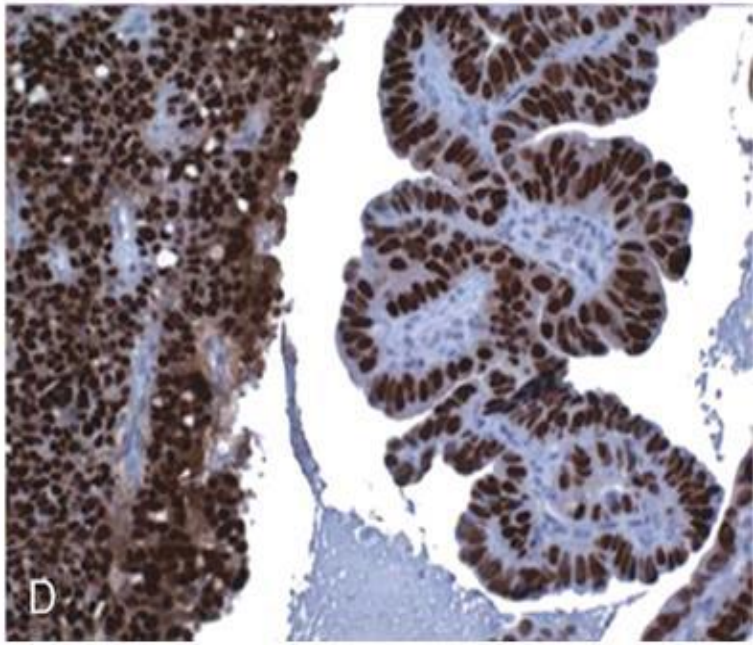
Endometrioid carcinoma

Serous carcinoma

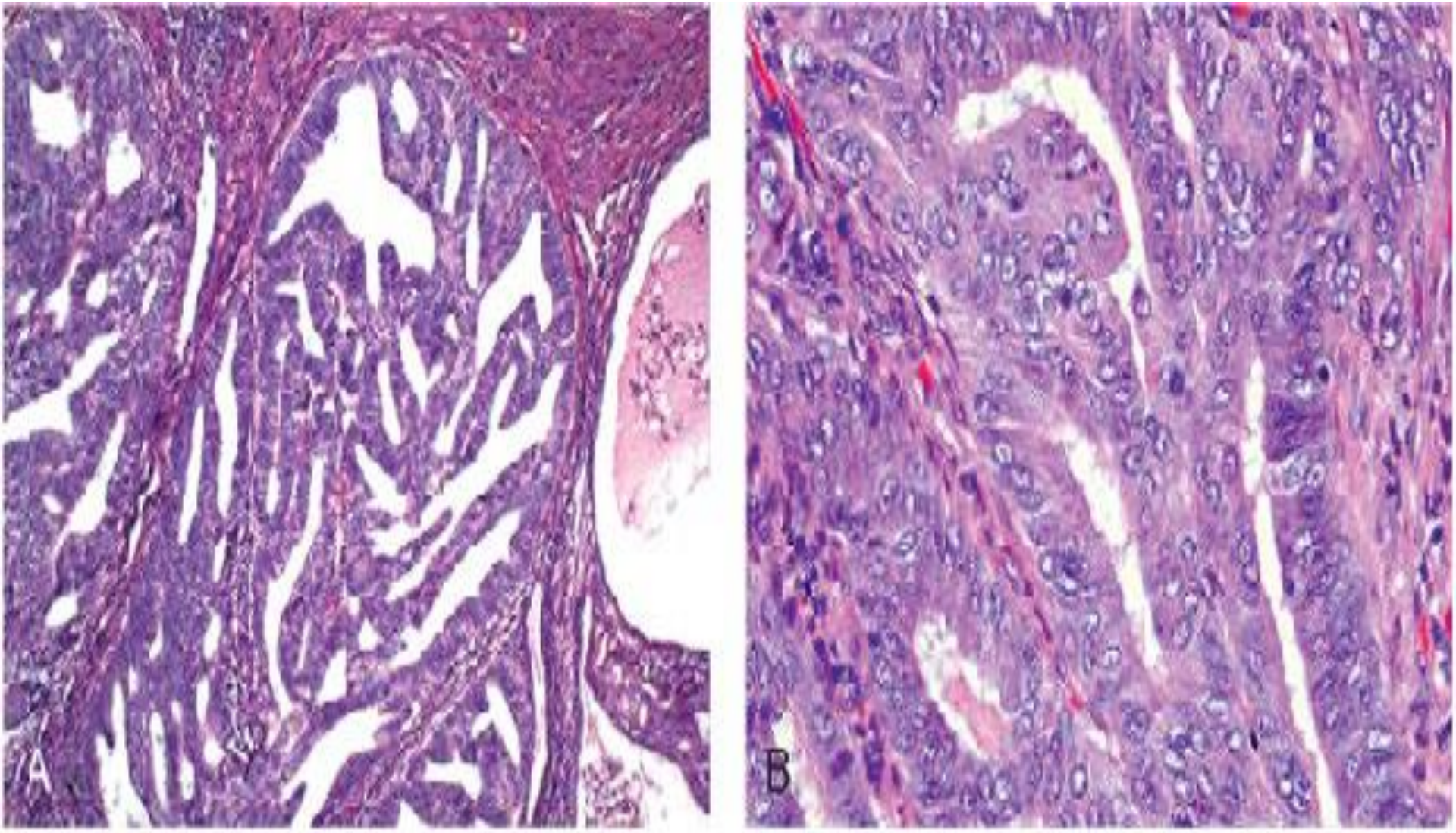




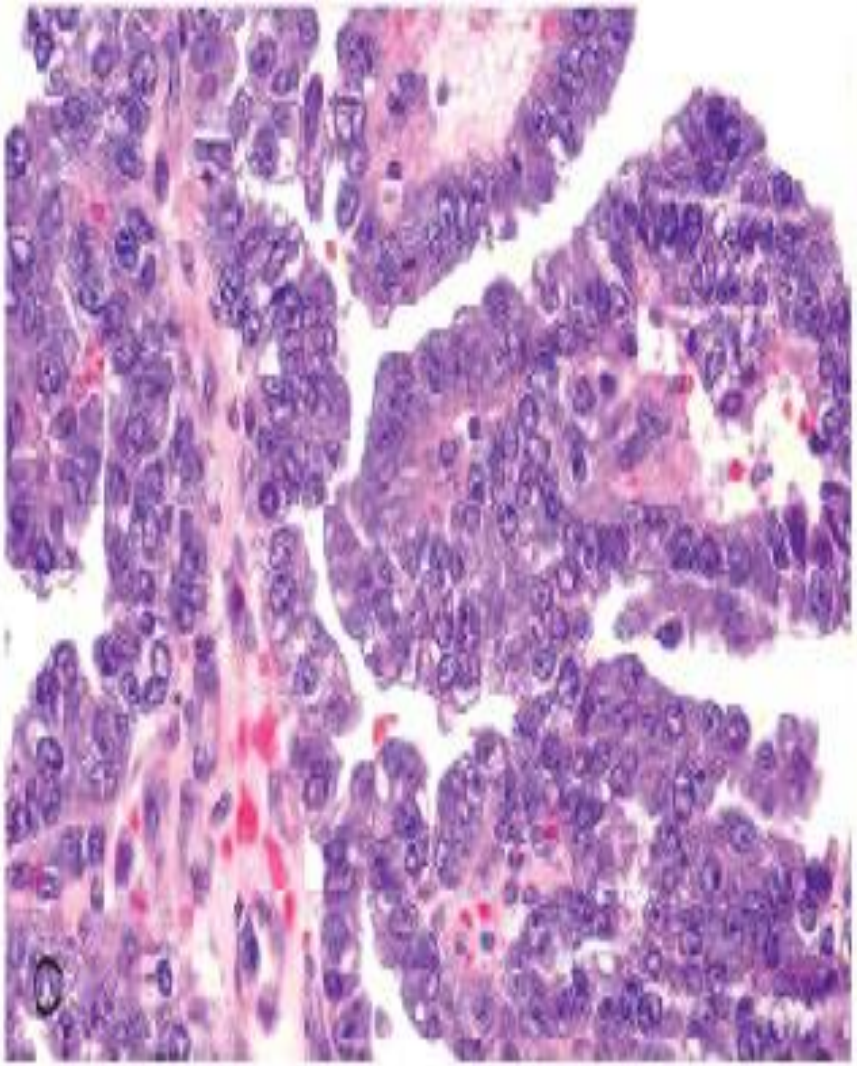


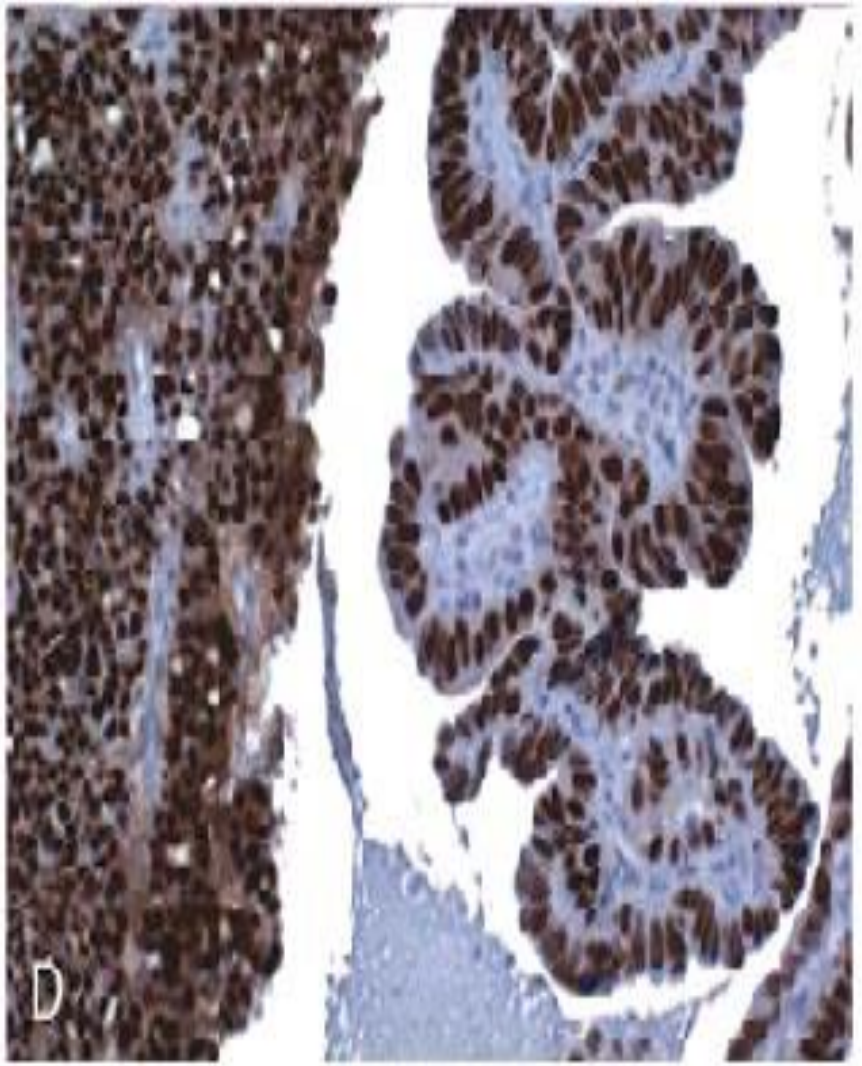


Endometrioid type of endometrial carcinoma:A,Displaying cribriform architecture & infiltrating the myometrium . **B,**Reveals back to back glands, loss of polarity & nuclear atypia.

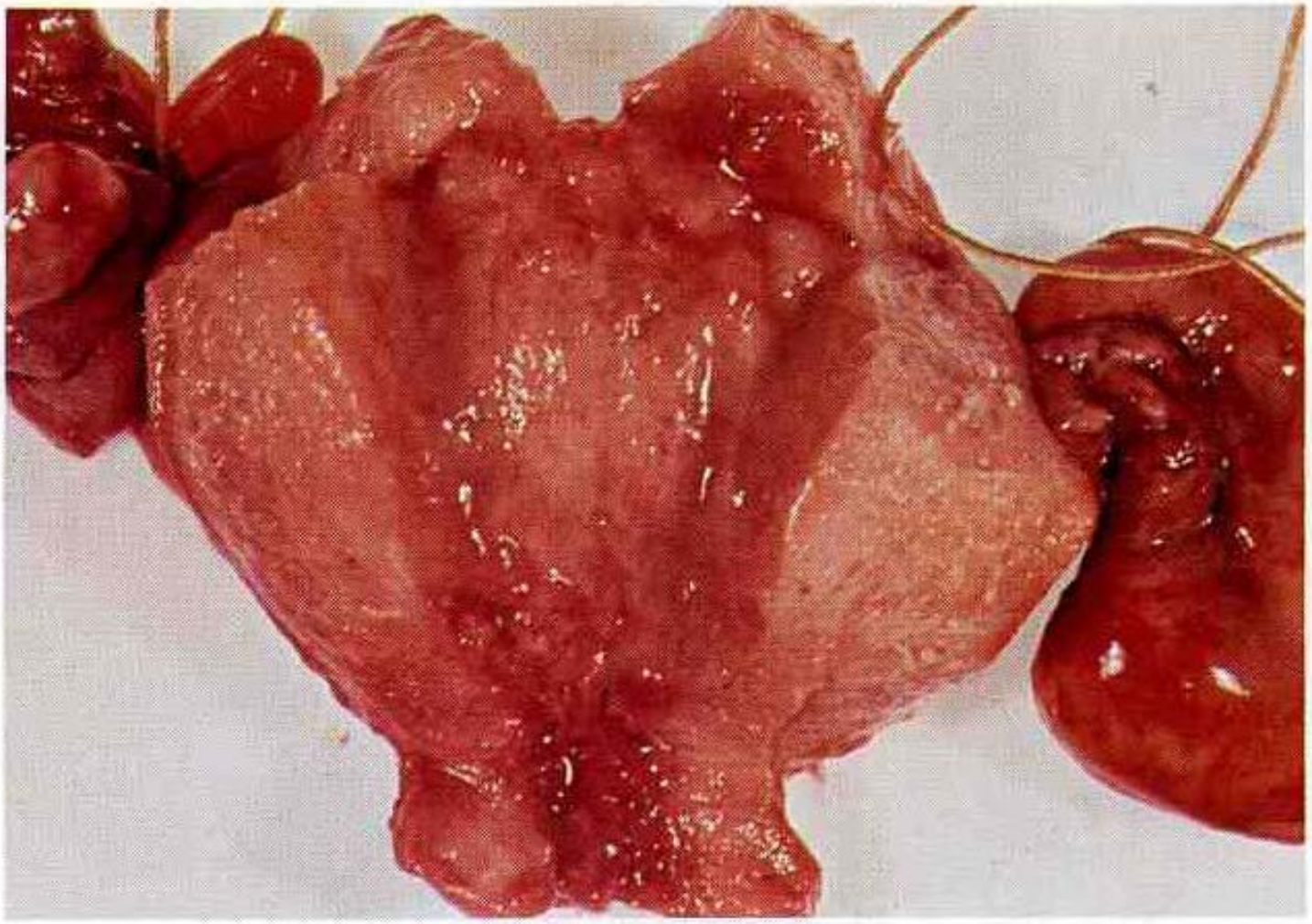


Serous type of endometrial carcinoma C, Showing formation of papillae & marked cytoplasmic atypia. **D,** Immunohistochemical stain for p53 reveals accumulation of mutant p53 in the serous carcinoma





Endometrium adenocarcinoma: 3 irregular fundal pale cancer nodules in the opened uterus.



12.42 Adenocarcinoma: endometrium

Tumors of the myometrium

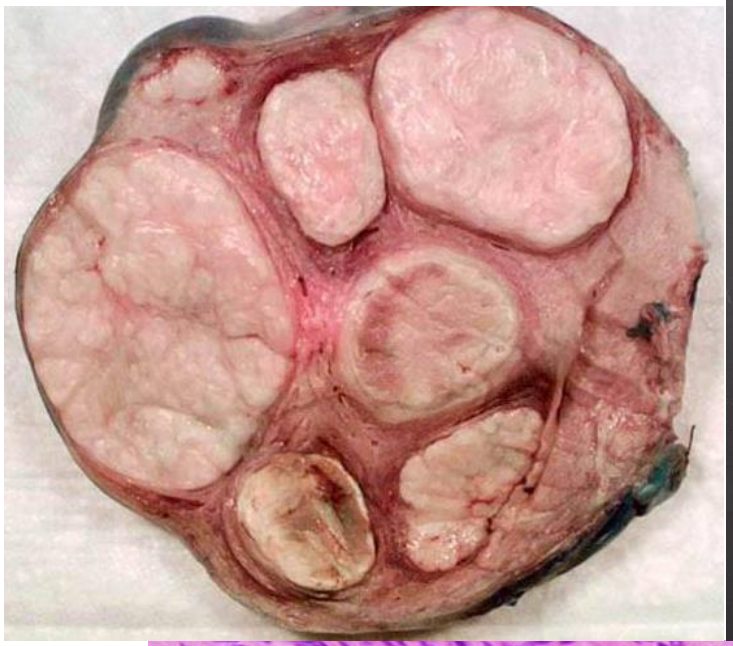
- **Lieomyoma= fibroids**
- Benign tumor of smooth muscle cells
- Most common benign tumor in females (30% -50% in reproductive life).
- Estrogen-dependent; shrink after menopause.

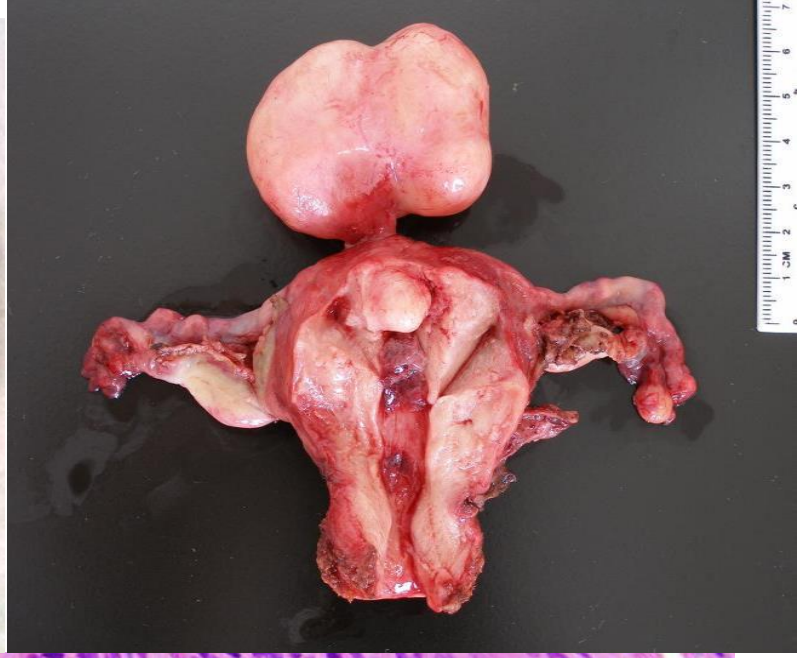
Grossly, are firm, white, **not encapsulated, sharply** circumscribed masses, with a characteristic
firm gray-white masses with whorled cut surface.
Tumor may be **single**, but **most** often they are **multiple.**
Size rang from **small (1 gram)** to **massive** T.

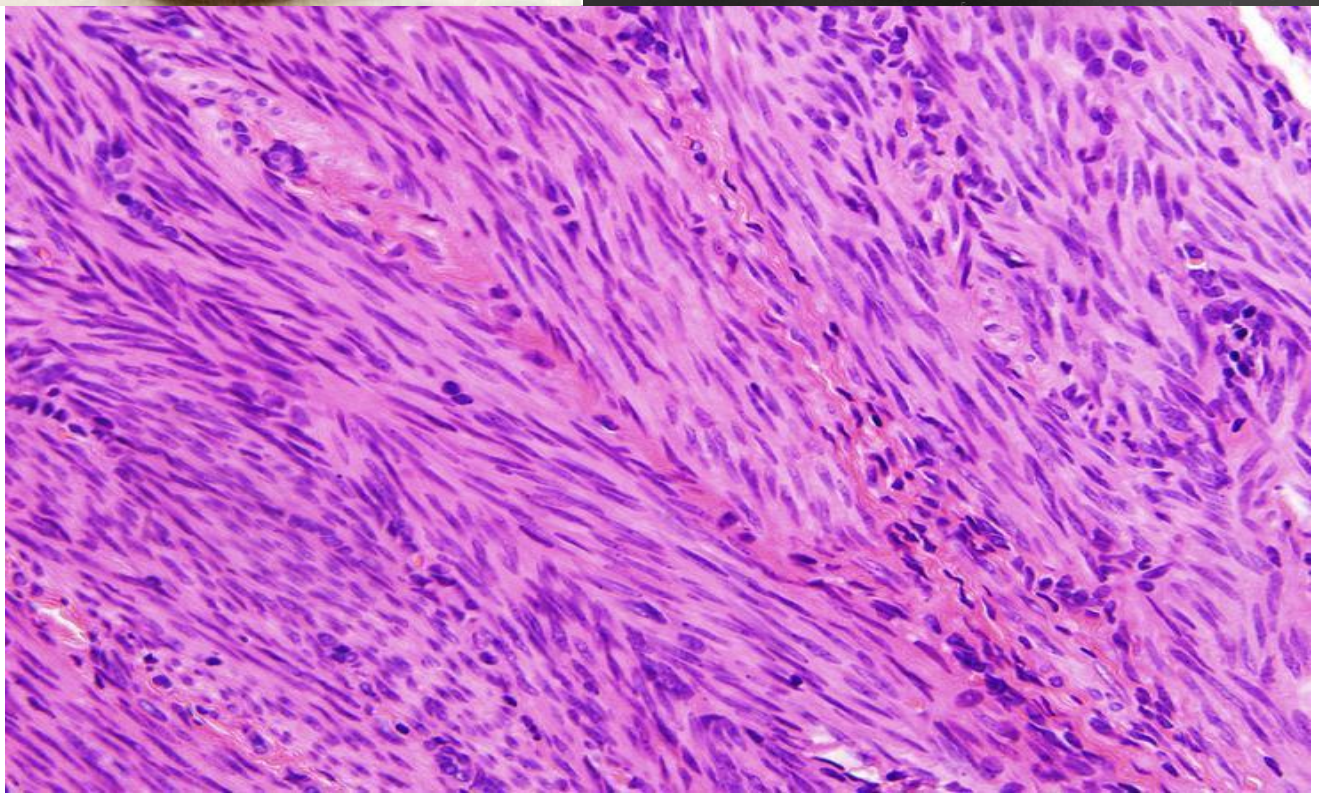
Lieomyomas

- Location: (intramural), (submucosal), or(subserosal).
- Changes include May develop hemorrhage, cystic changes or calcification.
- Larger **L** may develop ischemic necrosis (if extensive, called Red degeneration, causing **severe pain,** which requires it's removal), areas of hemorrhage& cystic softening,& after menopause, they may become densely collagenous& calcified.

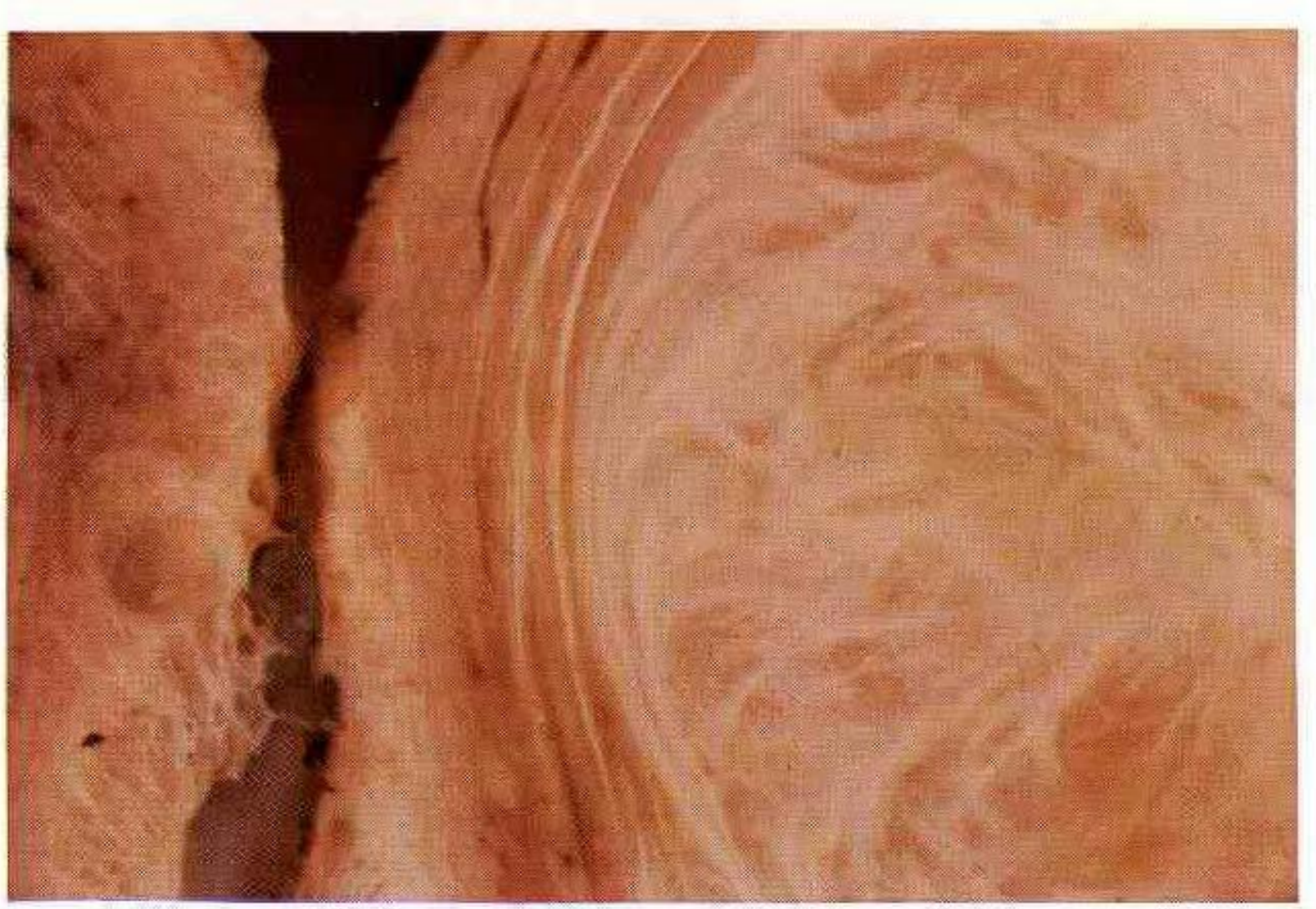
- **•Clinically**: asymptomatic or symptomatic; menorrhagia; a dragging sensation, anemia, etc...
- Leiomyomas almost **never** transform into sarcomas, and the presence of multiple lesions does not increase the risk of malignancy.





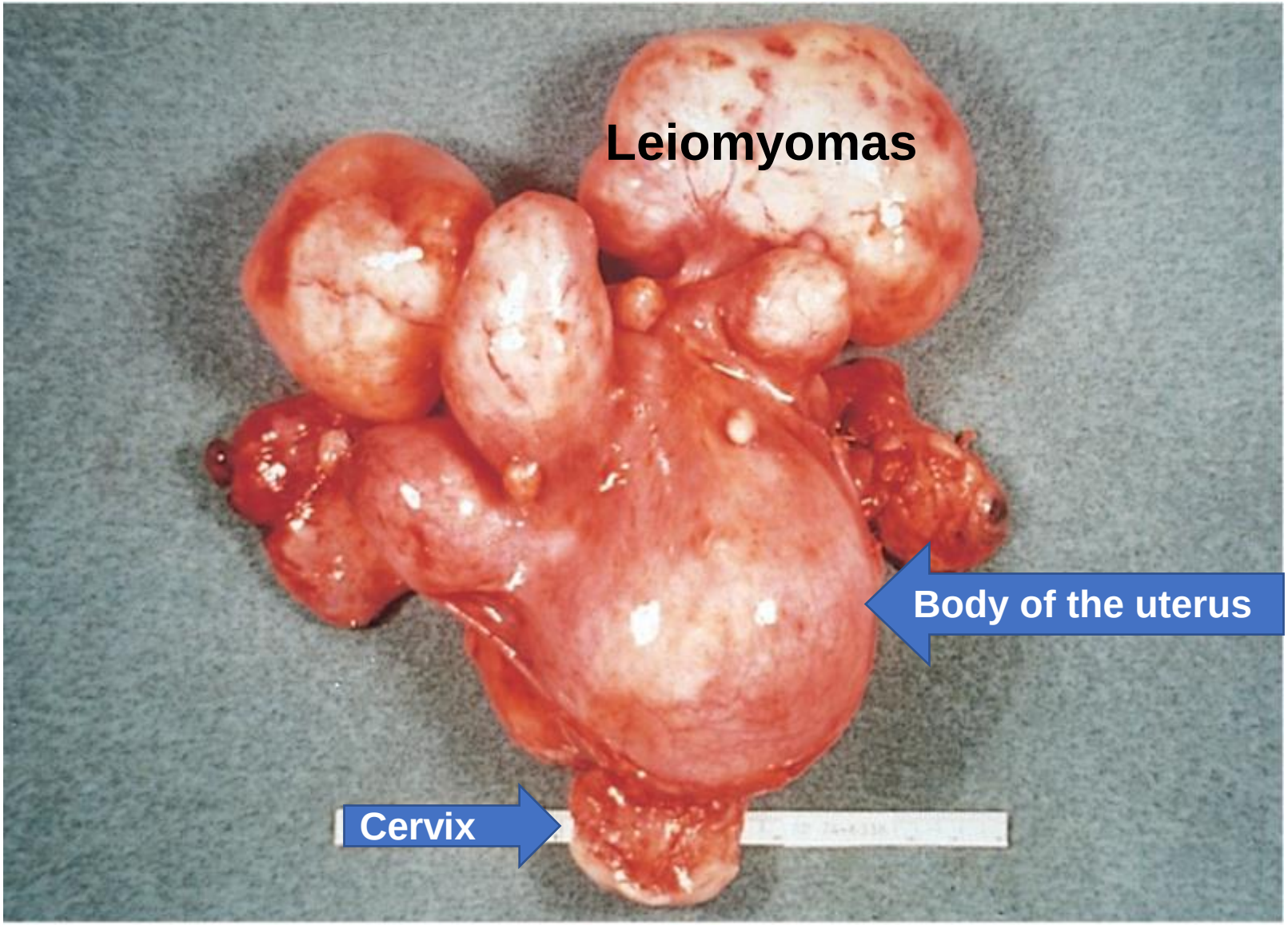


Leiomyoma: uterus. C/S of leiomyoma, showing the characteristic (1) shiny, pinkish-white whorled appearance of the tumor, & (2) the well-developed **false**capsule of compressed muscle & fibrous tissue around the it.

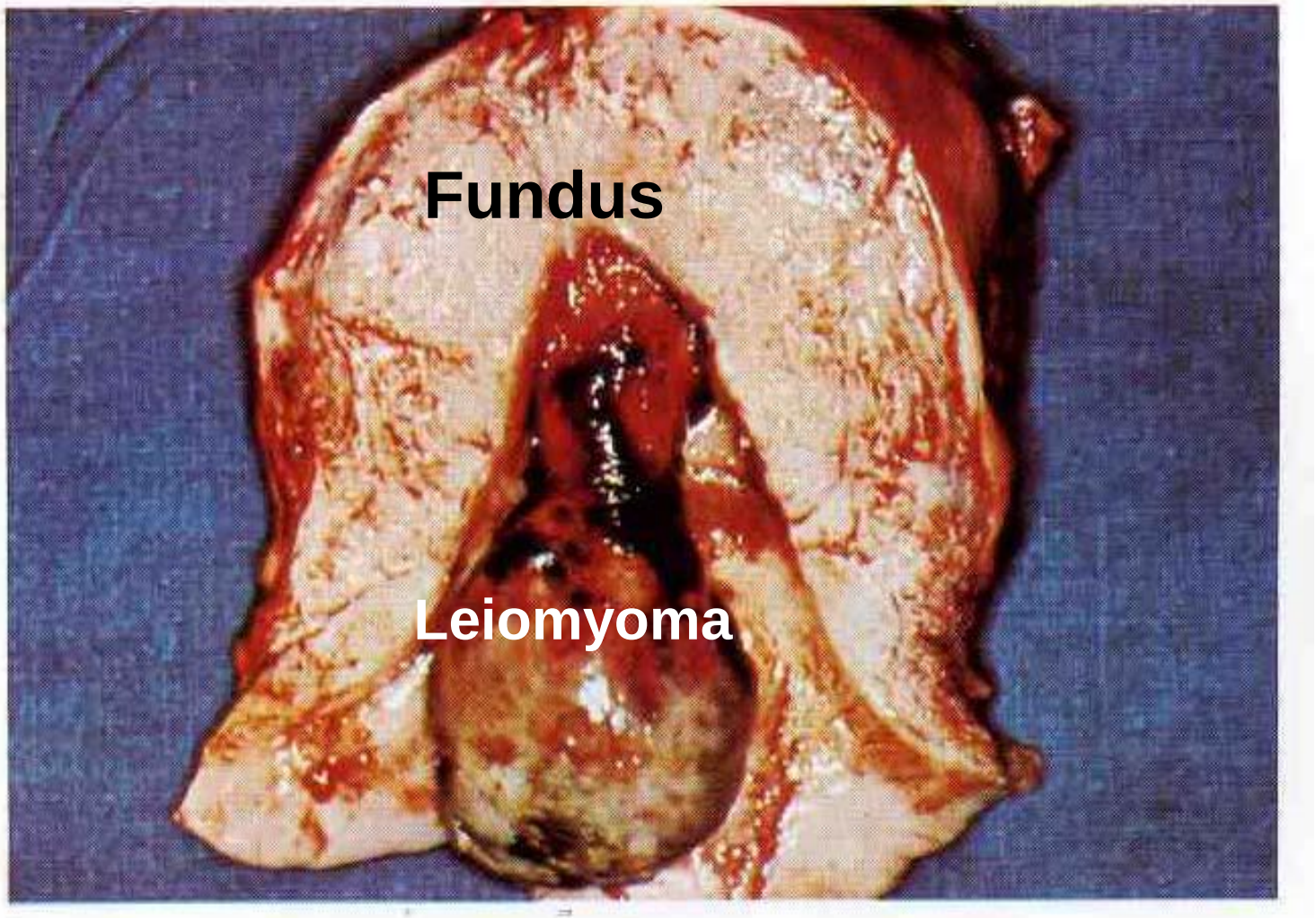


12.32 Leiomyoma: uterus

Uterus: Multiple large pedunculated subserosal **leiomyomas**, protruding from the dome of the fundus



Leiomyoma; uterus. Pedunculated submucosal leiomyoma, arising from the fundus & protruding through the cervical os. **Torsion** of the pedicle results in impairment of the tumor blood supply with its subsequent necrosis & gangrene.



12.35 Leiomyoma: uterus

Lieomyosarcoma

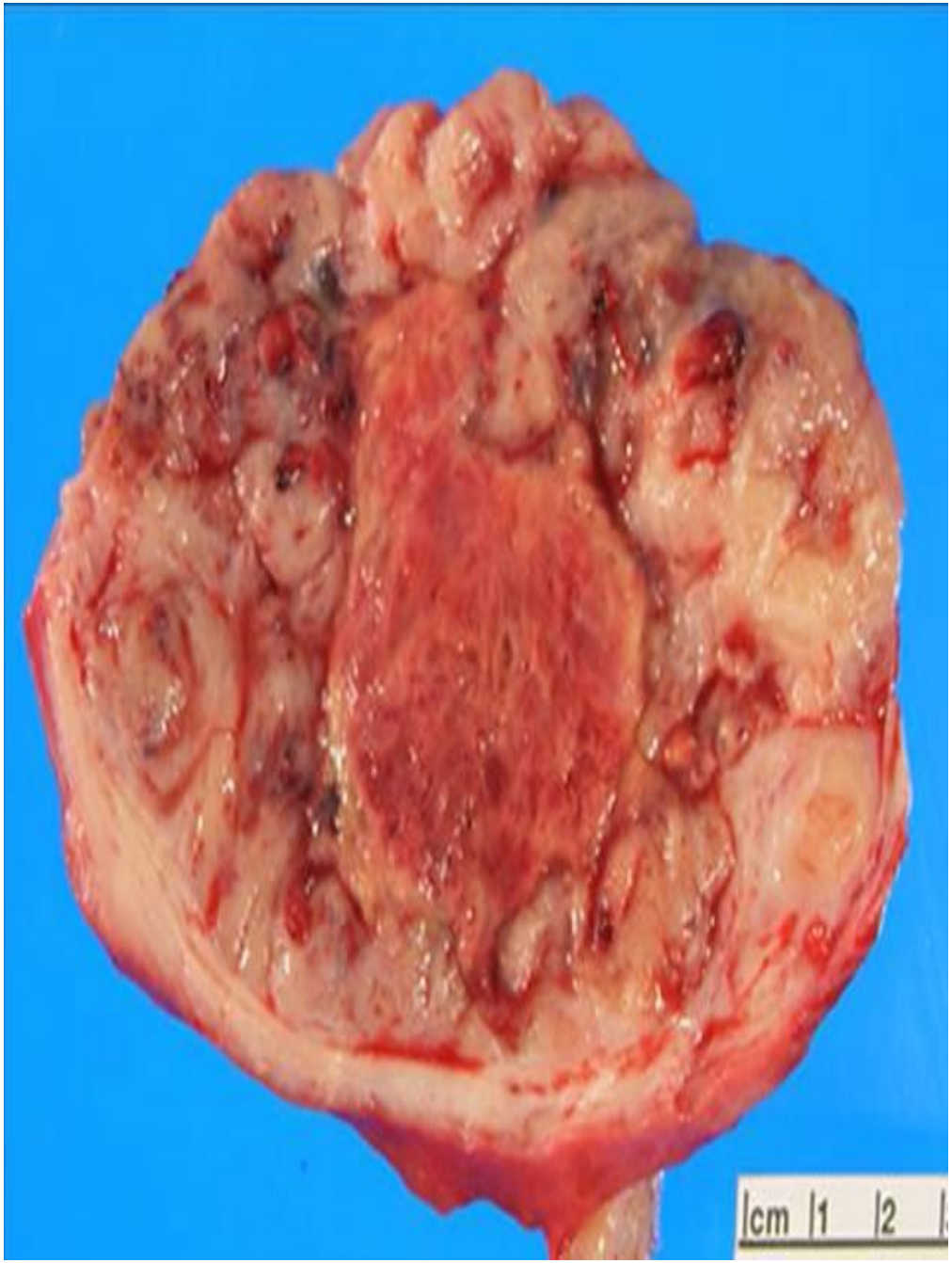
- Malignant counterpart of leiomyoma.
- Typically **arise de novo** from the mesenchymal cells of the myometrium, not from preexisting leiomyomas.
- Almost always solitary tumors, in contrast to the frequently multiple benign leiomyomas.

❑ **Grossly,**leiomyosarcomas may develop as:

(a) bulky masses **infiltrating** the uterine wall.

(b) **polypoid** lesions.

- They are frequently Soft ,Hemorrhagic, necrotic, infiltrative borders.
- Diagnosis: coagulative necrosis, cytological atypia, and mitotic activity.
- Recurrence common, and metastasize, 5-year survival rate 40%.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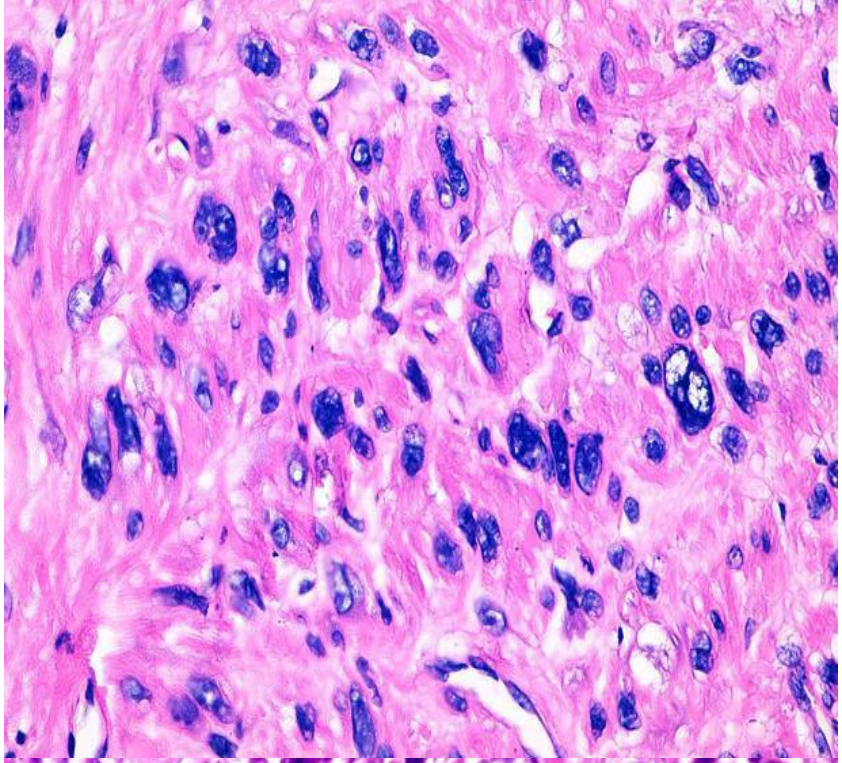
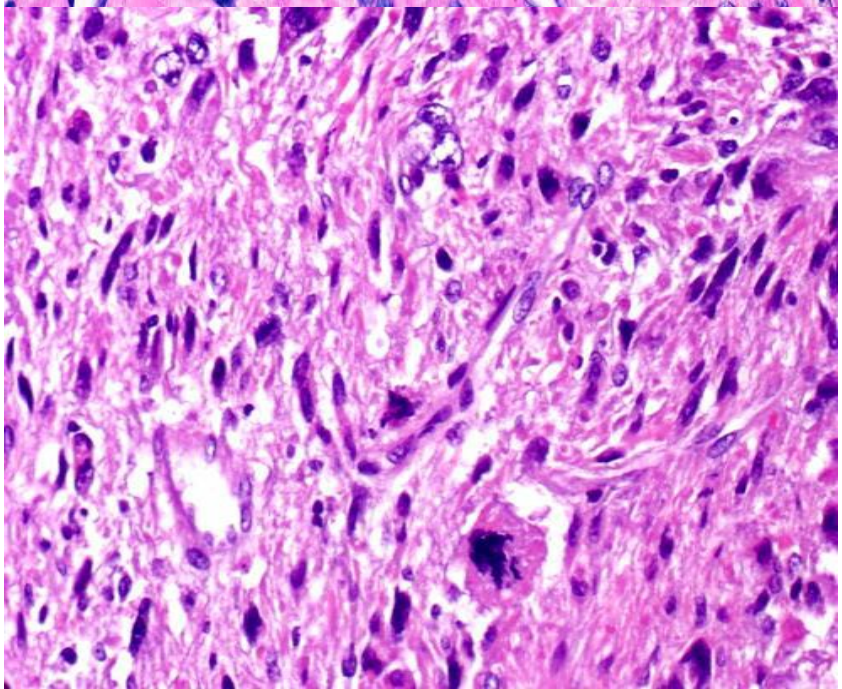




Ovary ,Ovarian Cysts

- There are various types of ovarian cysts, such as dermoid cysts and endometrioma cysts. However, **functional cysts are the most common type.** The two types of functional cysts include **folliclular and corpus luteum cysts.**

Follicle cyst (follicular)❑

- During a woman's menstrual cycle, an egg grows in a sac called a follicle. This sac is located inside the ovaries. In most cases, this follicle or sac breaks open and releases an egg. But if the follicle doesn't break open, the fluid inside the follicle can form a cyst on the ovary.

Corpus luteum cysts❑

- Follicle sacs typically dissolve after releasing an egg. But if the sac doesn't dissolve and the opening of the follicle seals, additional fluid can develop inside the sac, and this accumulation of fluid causes a corpus luteum cyst.

Symptoms of an ovarian cyst

- Often times, ovarian cysts do not cause any symptoms. However, symptoms can appear as the cyst grows. Symptoms may include:

- abdominal bloating or swelling
- painful bowel movements
- pelvic pain before or during the menstrual cycle
- painful intercourse
- pain in the lower back or thighs
- breast tenderness
- nausea and vomiting

Complication

- Most ovarian cysts are benign and naturally go away on their own without treatment. These cysts cause little, if any, symptoms. But in a rare case, your doctor may detect a cancerous cystic ovarian mass during a routine examination.
- Ovarian torsion is another rare complication of ovarian cysts. This is when a large cyst causes an ovary to twist or move from its original position. Blood supply to the ovary is cut off, and if not treated, it can cause damage or death to the ovarian tissue. Although uncommon, ovarian torsion accounts for nearly 3 percent of emergency gynecologic surgeries.
- Ruptured cysts, which are also rare, can cause intense pain and internal bleeding. This complication increases your risk of an infection and can be life-threatening if left untreated.

Ovarian Neoplastic Tumor

- 5th most common cancer in women.
- 5^{th} leading cause of cancer death in women.
- 3 Origins of primary ovarian tumors:

I-The multipotential **surface (coelomic) epithelium,**Tumor of which account for the great majority (75%) of primary ovarian T, & their malignant forms account for **90% of ovarian cancers.**

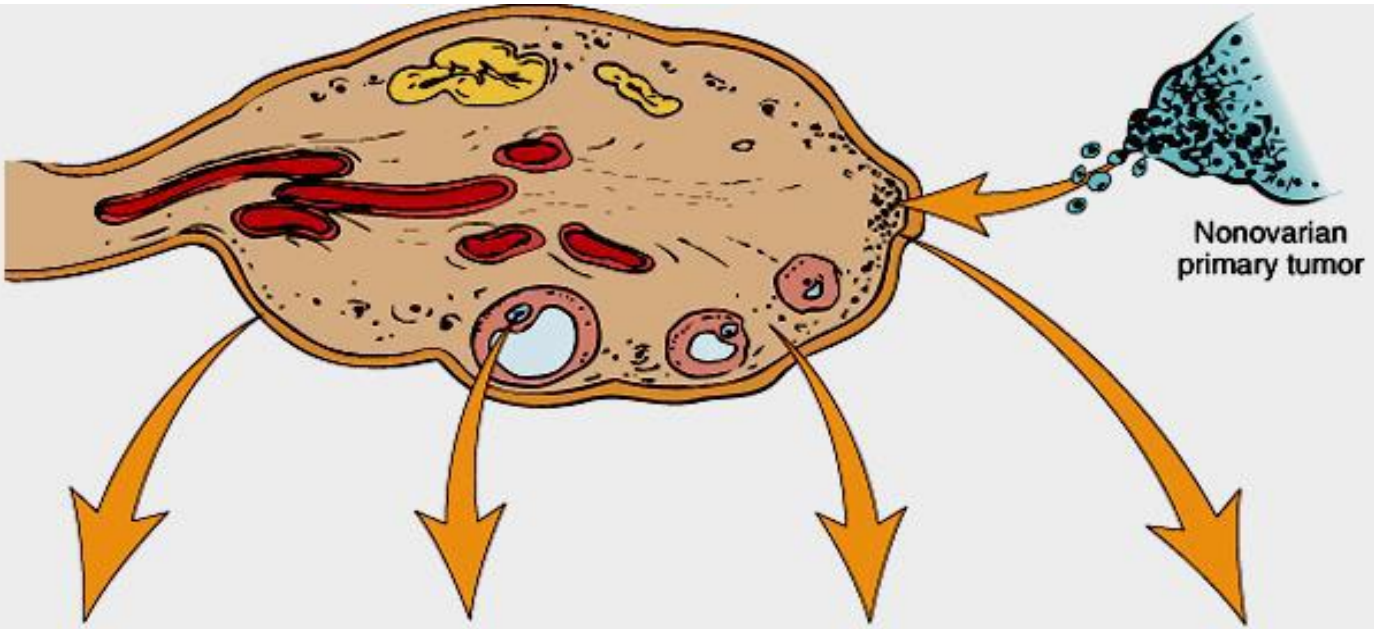
II- The totipotential **germ cells**

III- The multipotential **sex cord/stromal** cells **.**

- Each of these cell types gives rise to a variety of tumors

Both II & III T collectively are less frequent &, although they constitute 25% of all ovarian T, they account for **10% of ovarian cancers**.

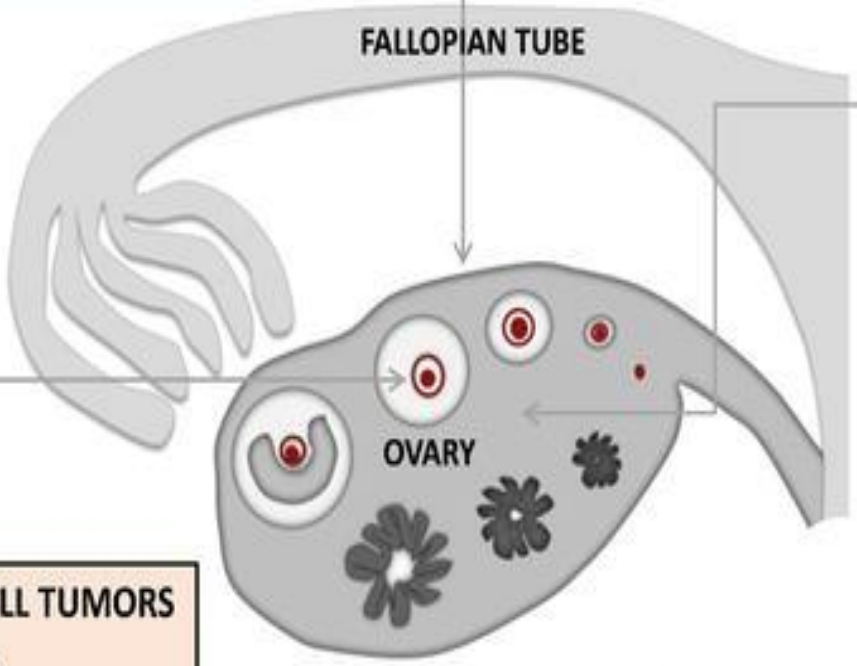
Derivation of various ovarian tumors & some data on their frequency & age distribution



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65%–70%	15%–20%	5%–10%	5%
Proportion of malignant ovarian tumors	90%	3%–5%	2%–3%	5%
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor • Cystadenofibroma	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa-theca cell tumor • Sertoli-Leydig cell tumor	

OVARIAN EPITHELIAL CANCER

- High-Grade Serous Carcinomas
- Low-Grade Serous Carcinomas
- Clear cell carcinoma
- Endometrioid
- Mucinous



OVARIAN SEX CHORD-STROMAL TUMORS

Stromal tumors

1. Fibroma
2. Thecoma
3. Fibrosarcoma
4. Leydig cell tumor
5. Steroid cell tumor
6. Sclerosing stromal tumor

Sex chord tumors

1. Adult granulosa cell tumor
2. Juvenile granulosa tumor
3. Sertoli cell tumor
4. Sex chord tumor with annular tubules

Mixed sex chord-stromal tumors

1. Sertoli-Leydig cell tumor

OVARIAN GERM CELL TUMORS

1. Dysgerminoma
2. Immature teratoma
3. Yolk sac tumors
4. Mixed germ cell tumors

SMALL CELL CARCINOMA OF THE OVARY

1. SCCO - hypercalcemic type
2. SCCO - pulmonary type

TUMOR CLASSIFICATION

EPITHELIAL SURFACE AND STROMA TUMORS

- Serosous
- Mucinous
- Endometrioid
- Clear cell
- Trancitional cell
- Epithelial stromal

SEXUAL CORD

- Granulosa
- Fibromas
- Tecomas
- Fibrotecomas
- Sertoli-leydig

GERM CELL

- Teratoma
- DYsgerminoma
- Yolk sac tumor
- Mixed tumor

EXTRAOVARIAN METASTATIC

Pathogenesis –familial cases

- Risk factors: **nulliparity** and **family history**.
  - use of OCPs may **reduce** risk.
  - Only 5%-10% are familial
- molecular pathogenesis: mutations in **BRCA1**and **BRCA**2 **genes.**
- There is **5% to 10%** only of ovarian ca **are familial (like Breast Ca)**. The majority of **hereditary** ovarian & breast cancers seem to be caused by **mutations in the** BRCA1**&** BRCA2 **genes. Indeed**, with mutations in these genes, there is increase **risk for both ovarian & breast cancers.**

Pathogenesis-Sporadic cases

- BRCA mutations: 10% of sporadic cases
- other important molecular pathways:
- **p53** is mutated in **50%** of all ovarian cancers.
- **HER2/NEU** over-expression (35%)
- **K-RAS** protein over-expression (30%) mostly mucinous cystadenocarcinomas.

Surface epithelial Tumor -Types

1-Serous
2-Mucinous
3-Endometrioid
4-Clear cell
5-Brenner

❑ **All types include benign, borderline, and malignant tumors**
(I) Benign lesions usually cystic (cystadenoma), or with an **accompanying stromal component (cystadenofibroma);**
(II) Malignant tumors may be cystic (cystadenocarcinoma), solid (carcinoma), or combine.
(III) Intermediate = **borderline**= tumors of low malignant potential=low-grade cancers with limited invasive potential, which have a better prognosis than the fully malignant ovarian carcinomas.

Serous tumor

- **the most frequent ovarian tumors.**
- Include: 60% benign, 15% borderline, and 25% malignant.
- **the most common malignant ovarian tumors (60%).**
- **Genetics:**
- **BRAF** and **K-RAS** mutations → borderline & low grade cancers
- **p53** and **BRCA1** mutations → High-grade serous carcinomas
- Grossly ;most serous T are large(10-40 cm inØ)spherical or ovoid cysts.
- 25% of the benign forms are bilateral .
- The serosal covering of benign is smooth& glistening, while that of the carcinoma is irregularly nodular from tumor penetration of serosa.
- O/S,smaller cystic T are unilocular, {with single cavity}; but larger ones are usually divided by multiple septa into a multiloculated cyst.
- The cystic spaces are usually filled with a clear serous fluid, but mucus may also be present.
- Papillary projections into the cystic cavities are usually seen, more marked in malignant T

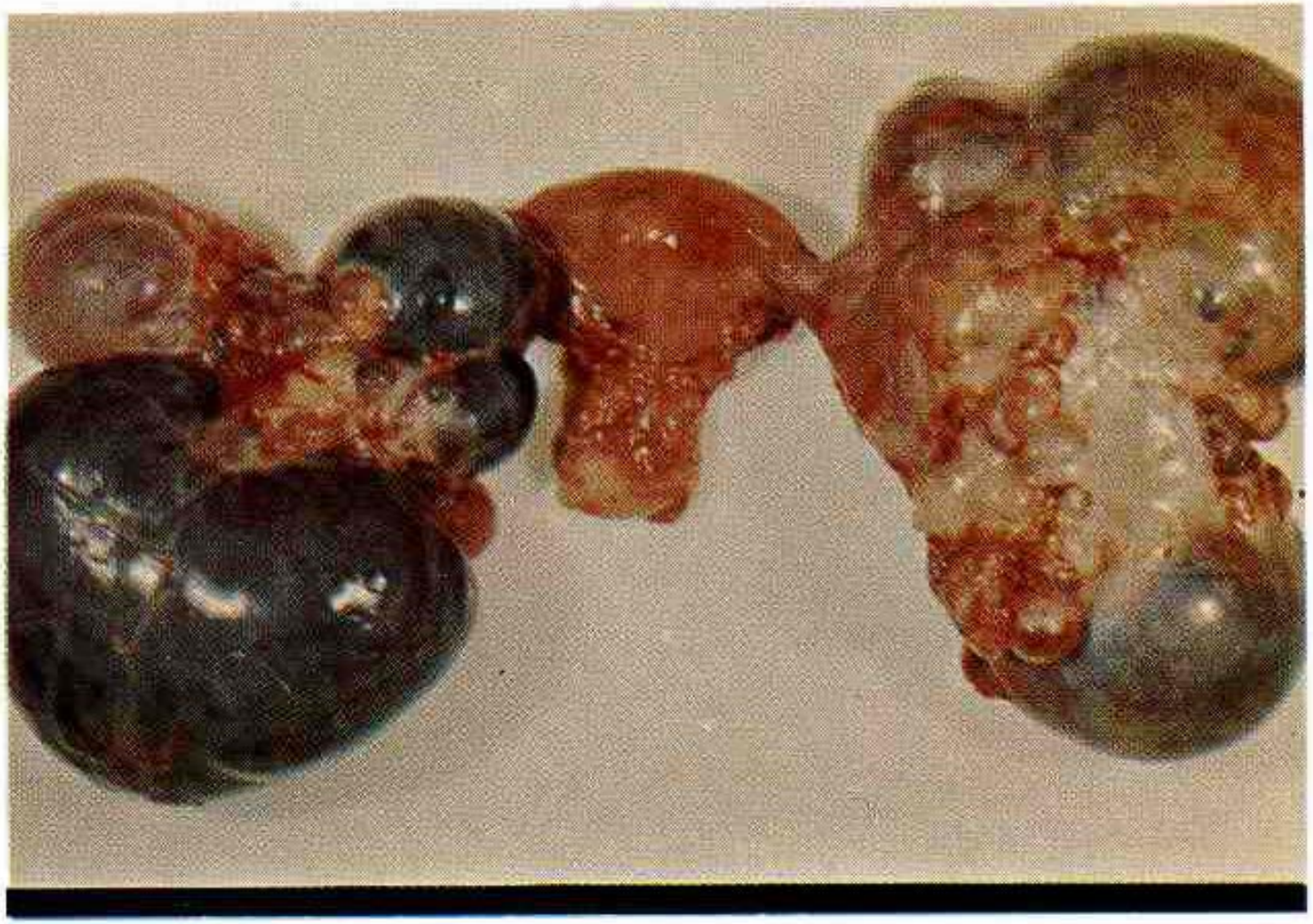
Morphology :

- The benign tumor are: (a) lined by a single layer of tall, ciliated or dome-shaped secretory columnar epithelium cells.
- (b) Psammoma bodies(concentrically laminated calcified concretions) are commonly seen in the tips of papillae.
- When frank carcinoma develops: (a) anaplasiao f the lining cells appears, as does (b) invasion of the stroma, & capsule.
- Papillary formations are complex & multilayered, with invasion of the axial fibrous tissue by nests or totally undifferentiated sheets of malignant cells.

- Between these benign & malignant serous tumors are tumors of low malignant potential,with milder cytologic atypia & typically, little or no stromal invasion.

- Malignant serous T spread through (a) metastatic seeding of the peritoneal cavity, & (b) through lymphatics to regional LN, including periaortic LNs, but distant lymphatic & hematogenous metastases are rare

Bilateral benign serous cystadenomas of the ovary. An irregular, lobulated masses replacing both ovaries. The bluish discoloration is due to hemorrhage into the cyst.



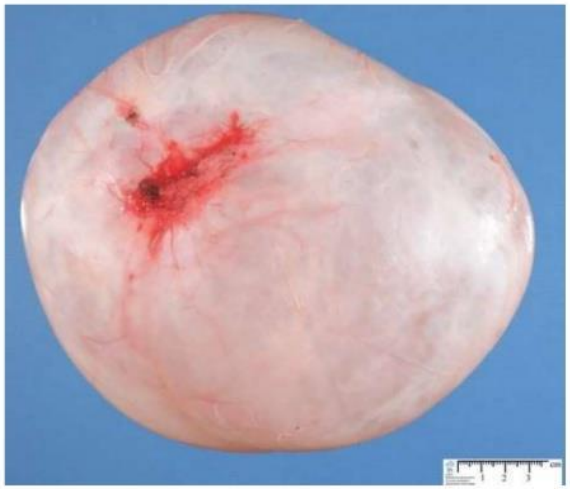
12.60 Serous cystadenomas: ovaries

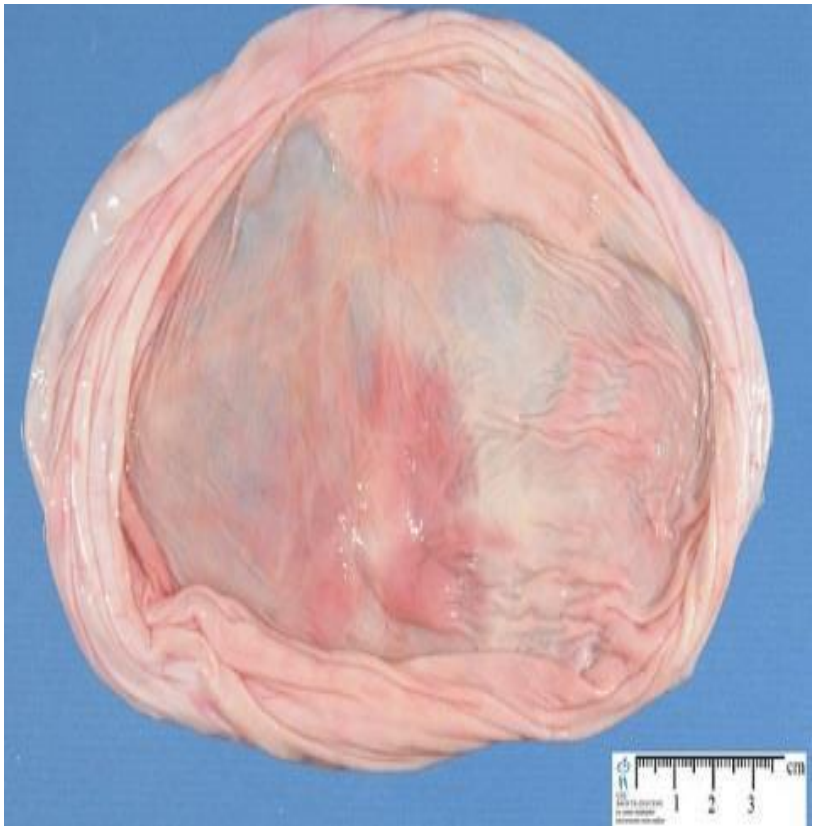
Morphology

Benign serous tumors:

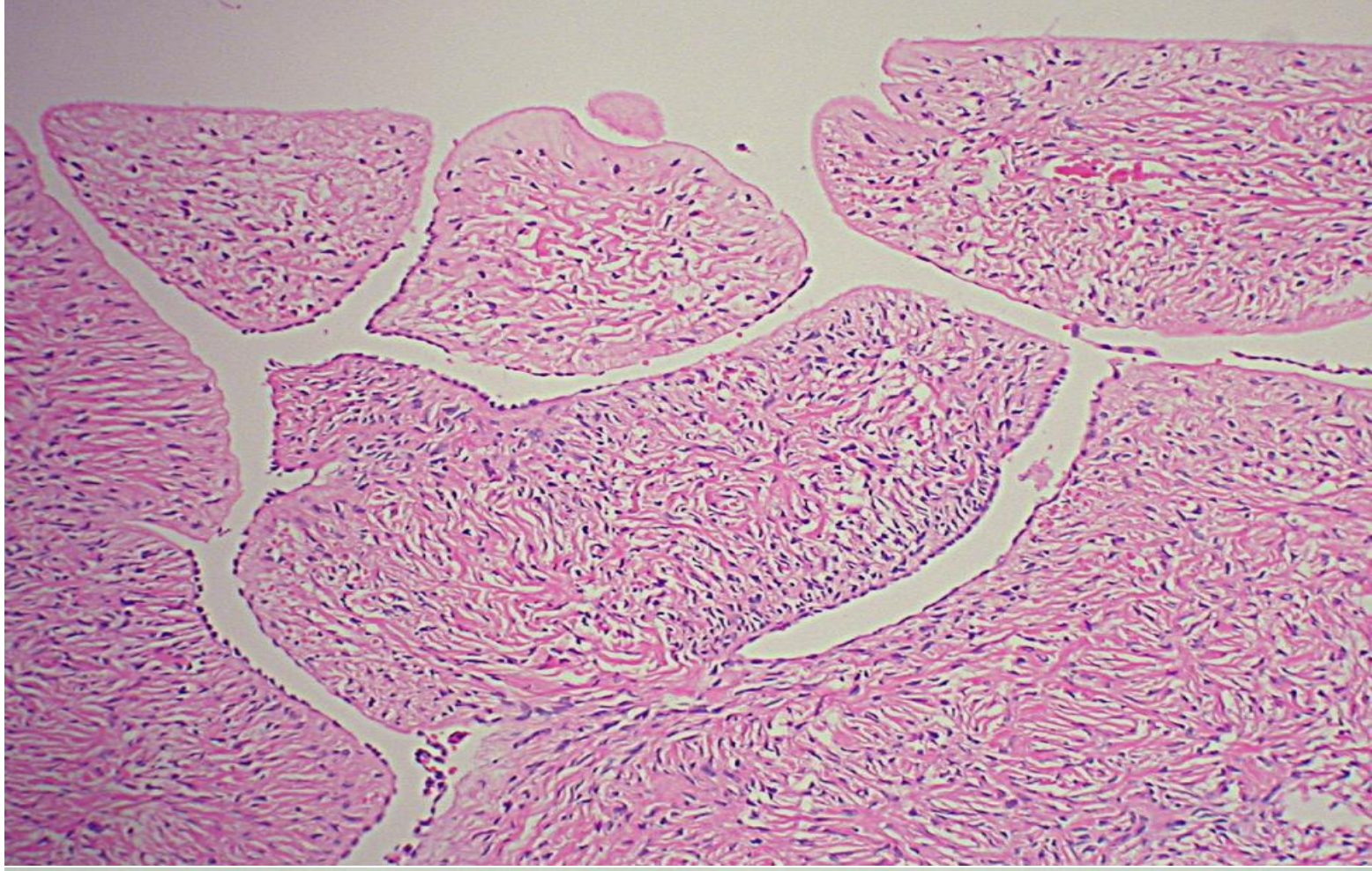
- large cystic, (30 cm).
- May be bilateral.
- filled with a clear serous fluid
- **single layer** of columnar epithelium. Some cells are ciliated.
- **Psammoma bodies**(laminated calcified concretions) are common in tips of papillae of **all** serous tumors

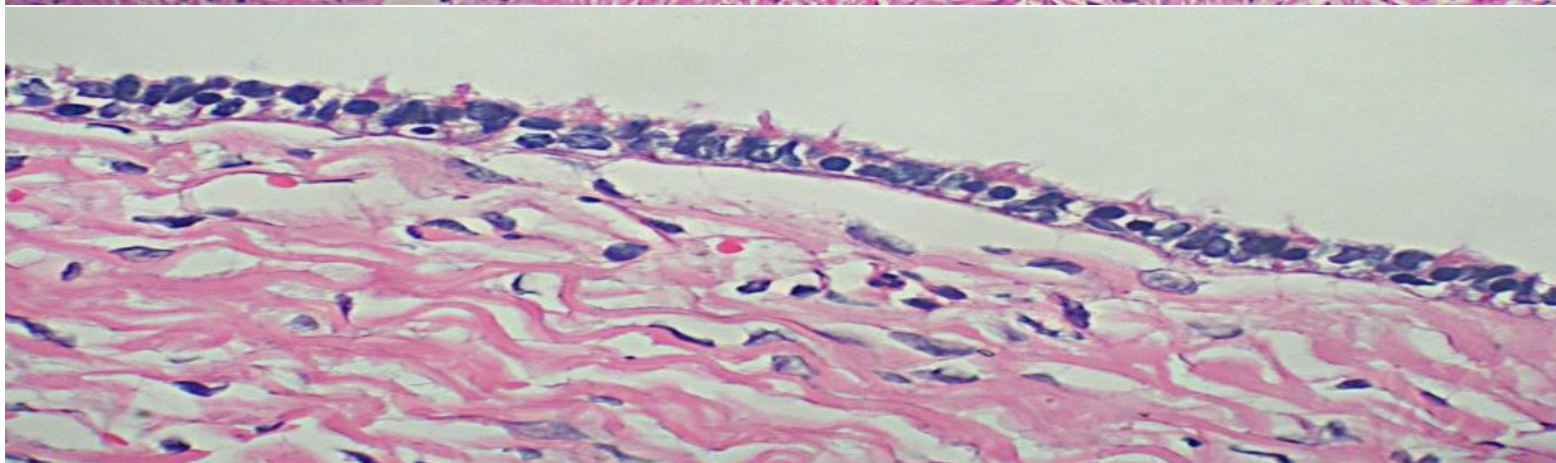
SEROUS CYSTADENOMA





Benign Serous Tumor



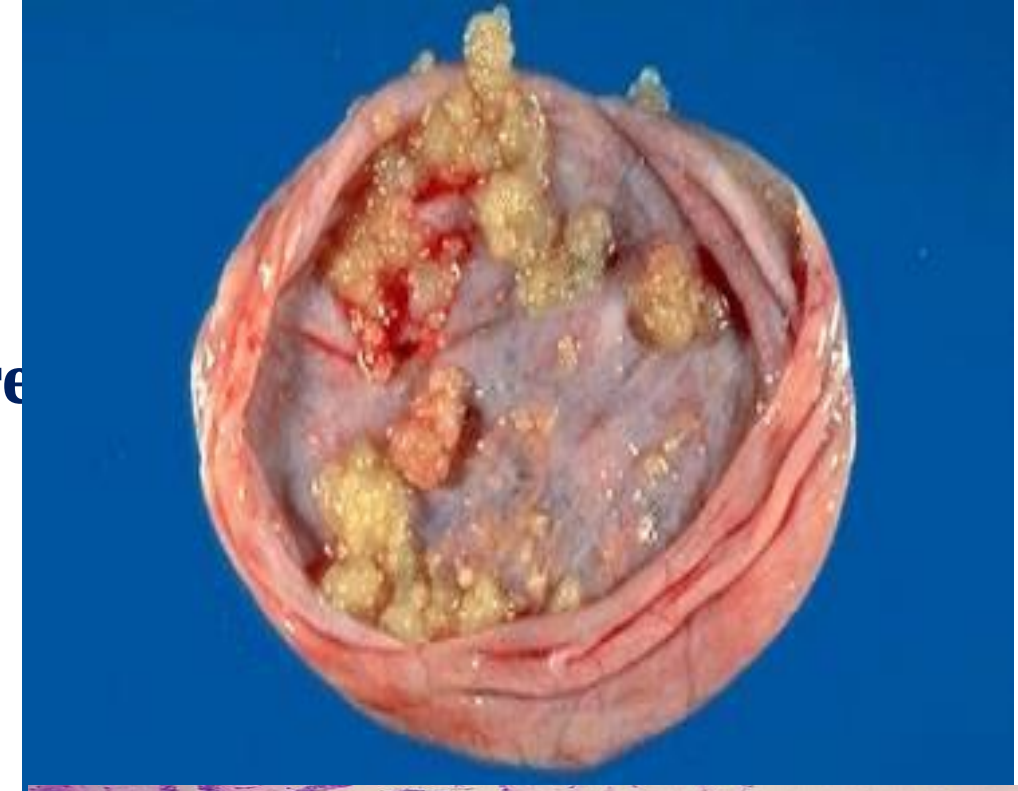


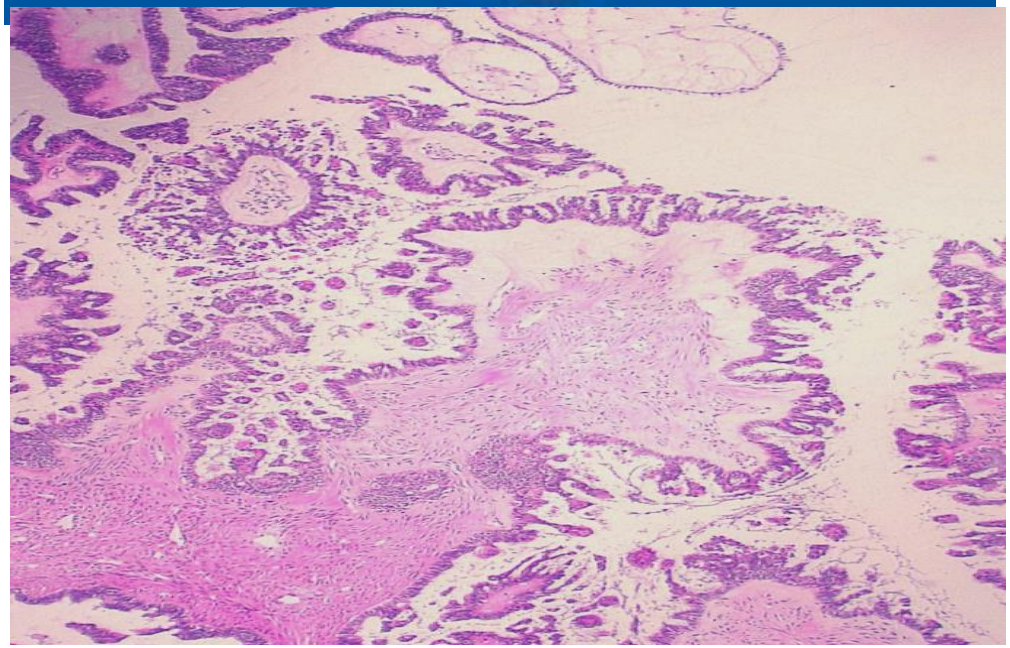
Borderline Serous tumor

More complex architecture

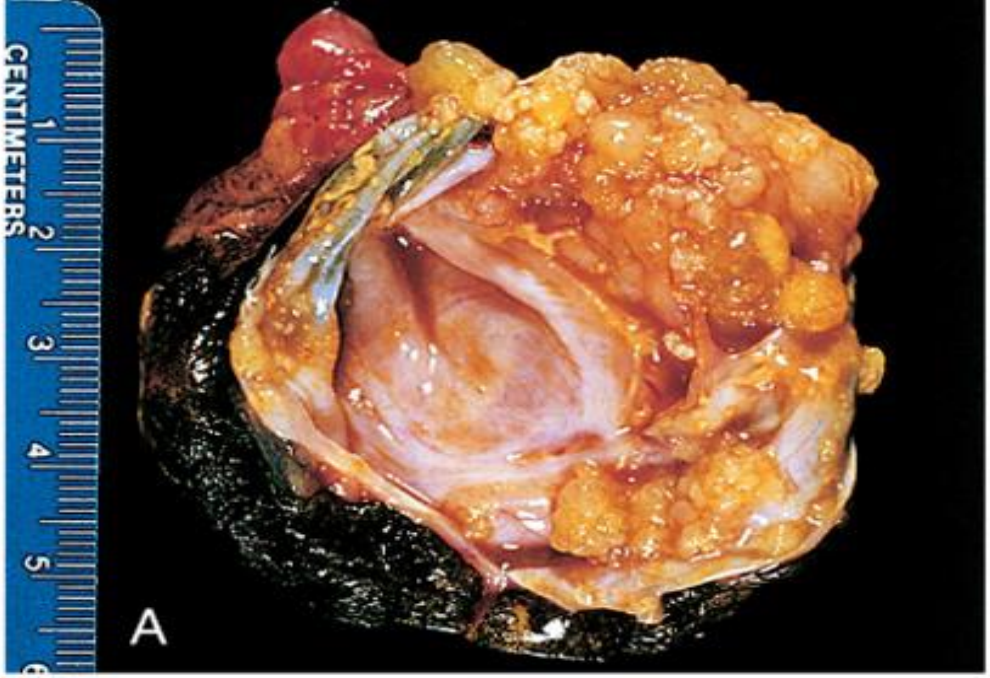
- **mild cytological atypia**
- **but no stromal invasion.**
- **might be associated with peritoneal implants**

- **Prognosis intermediate between benign and malignant types (survival with peritoneal metastases 75%)**

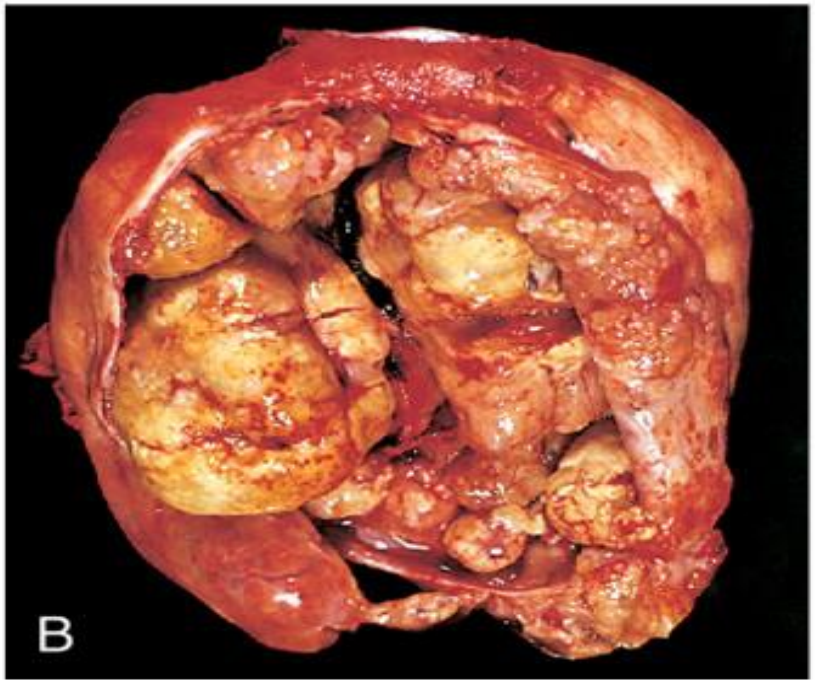




A, Borderline serous cystadenoma.
Opened cyst cavity lined by delicate papillary tumor growths

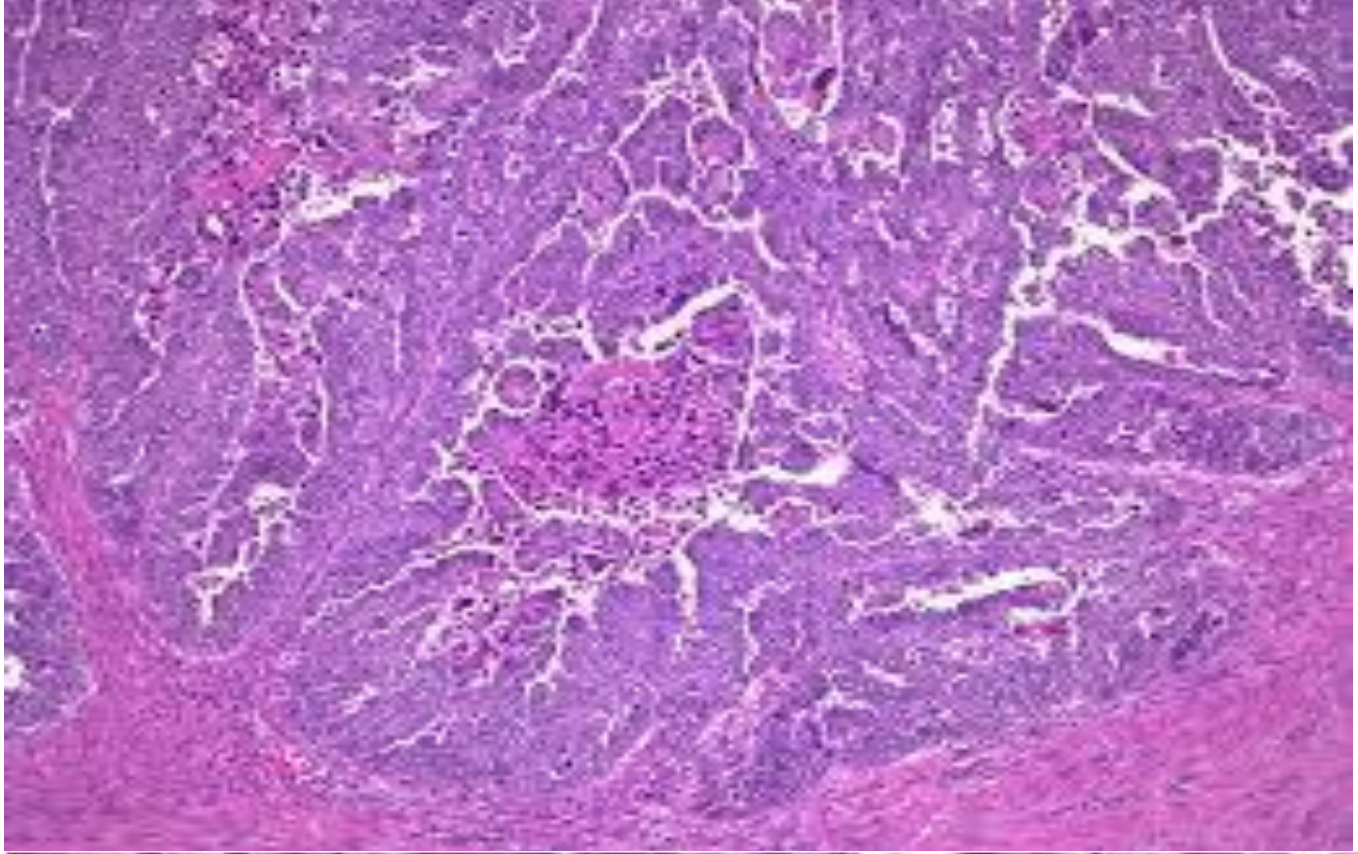


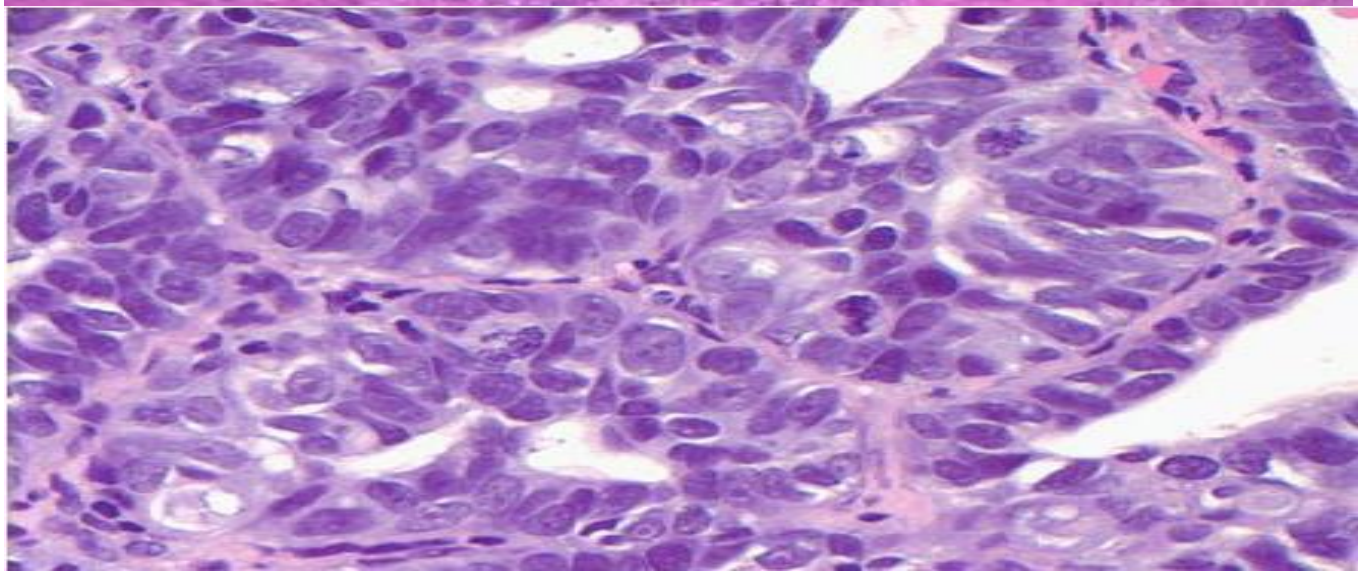
B,Cystadenocarcinoma:
Opened cyst reveal a large, bulky tumor mass



Malignant Serous Carcinoma

- Anaplasia of cells and invasion of the stroma.
- Prognosis poor, depends on stage at the time of diagnosis.





Mucinous Ovarian Tumor

- **Mucin-secreting** cells. their mucin-secreting epithelium cell lining, similar to that of the endocervical mucosa,
- are less likely to be malignant than the serous T (80% are benign mucinous cystadenomas),
- Depending on the architectural complexity:

❖ 80% benign; 10% borderline; **10% malignant** (cystadenocarcinoma)

- **Usually large** and **multilocular**.
- Psammoma bodies **not** found.
- Stage is major determinant of prognosis

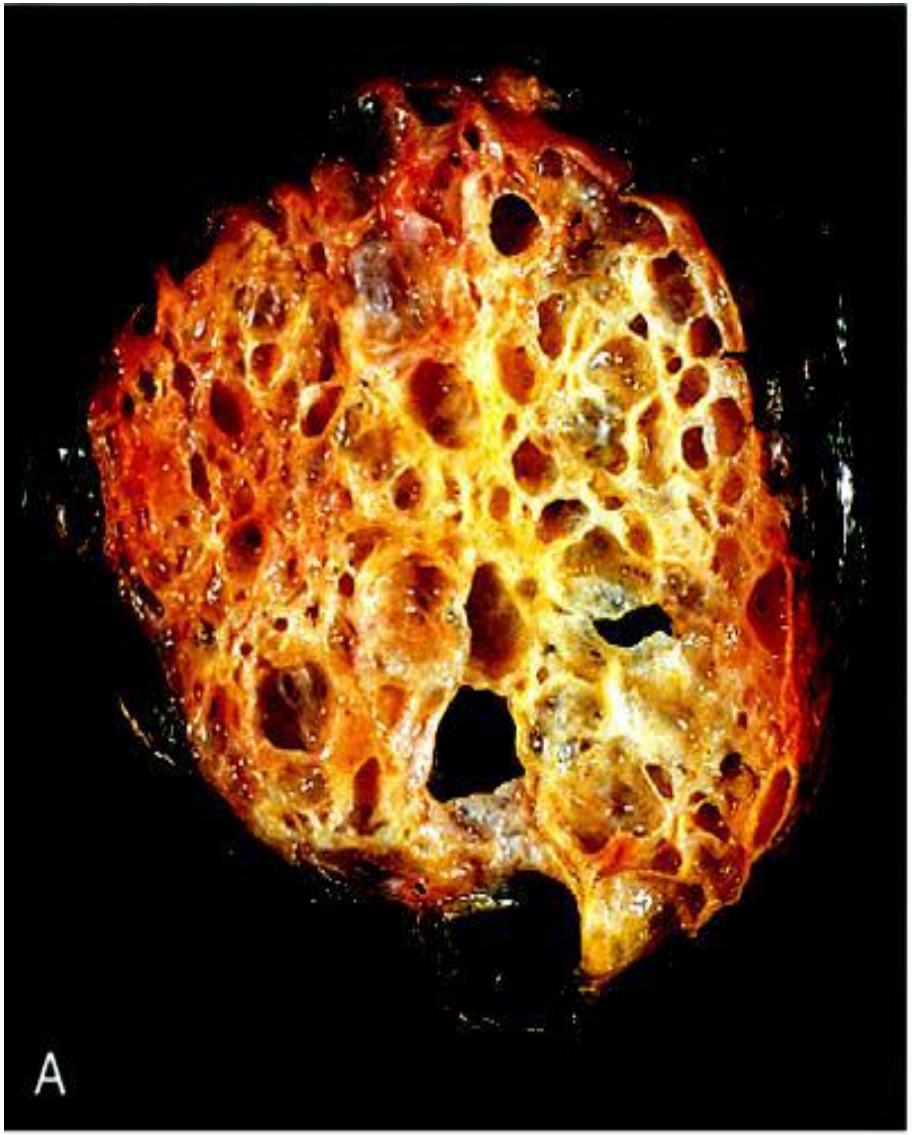
- Much **less likely to be bilateral,** with only 5% of benign & 20% of malignant mucinous tumors been **bilateral.**

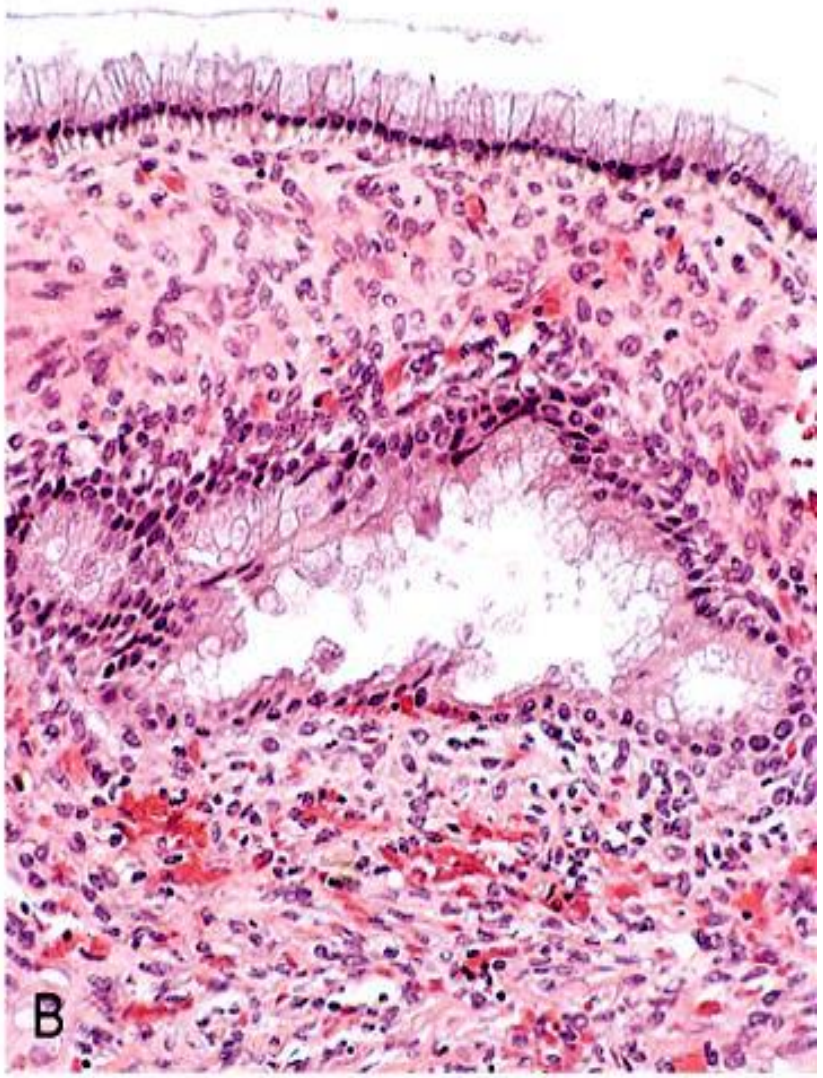
- **bilateral mucinous ca** of the ovary must be differentiated from metastatic adenocarcinoma in the ovaries (Krukenberg tumor), which may present as ovarian masses.
- **Grossly** , mucinous T are similar to serous T, except that filled by mucin.The presence of prominent papillation, serosal penetration, & solid areas, point to malignancy.

- Implantation of mucinous T cells in the peritoneum with production of copious amounts of mucin is called **pseudomyxoma peritonei;** the vast majority of these cases are caused by metastasis from the GIT tumors, primarily the appendix.

- Metastasis of mucinous ca of the GIT to the ovaries (**Krukenberg tumor**) may also mimic an ovarian primary,

Mucinous ovarian tumors





Endometrioid Tumors

Grossly:

- these T may be solid or cystic, but some develop as a mass projecting from the wall of an endometriotic ovarian cyst filled with chocolate-colored fluid.
- they are distinguished by the formation of tubular glands, similar to those of the endometrium, within the linings of cystic spaces.
- Are usually malignant, although benign & borderline forms exist,and bilateral in 30% of cases.
- 15% to 30% of women with these ovarian T have a concomitant endometrial carcinoma of the endometrium.
- Similar to endometrial endometrioid cancer, ovarian endometrioid carcinomas have mutations in the PTEN suppressor gene.

Germ cell tumor

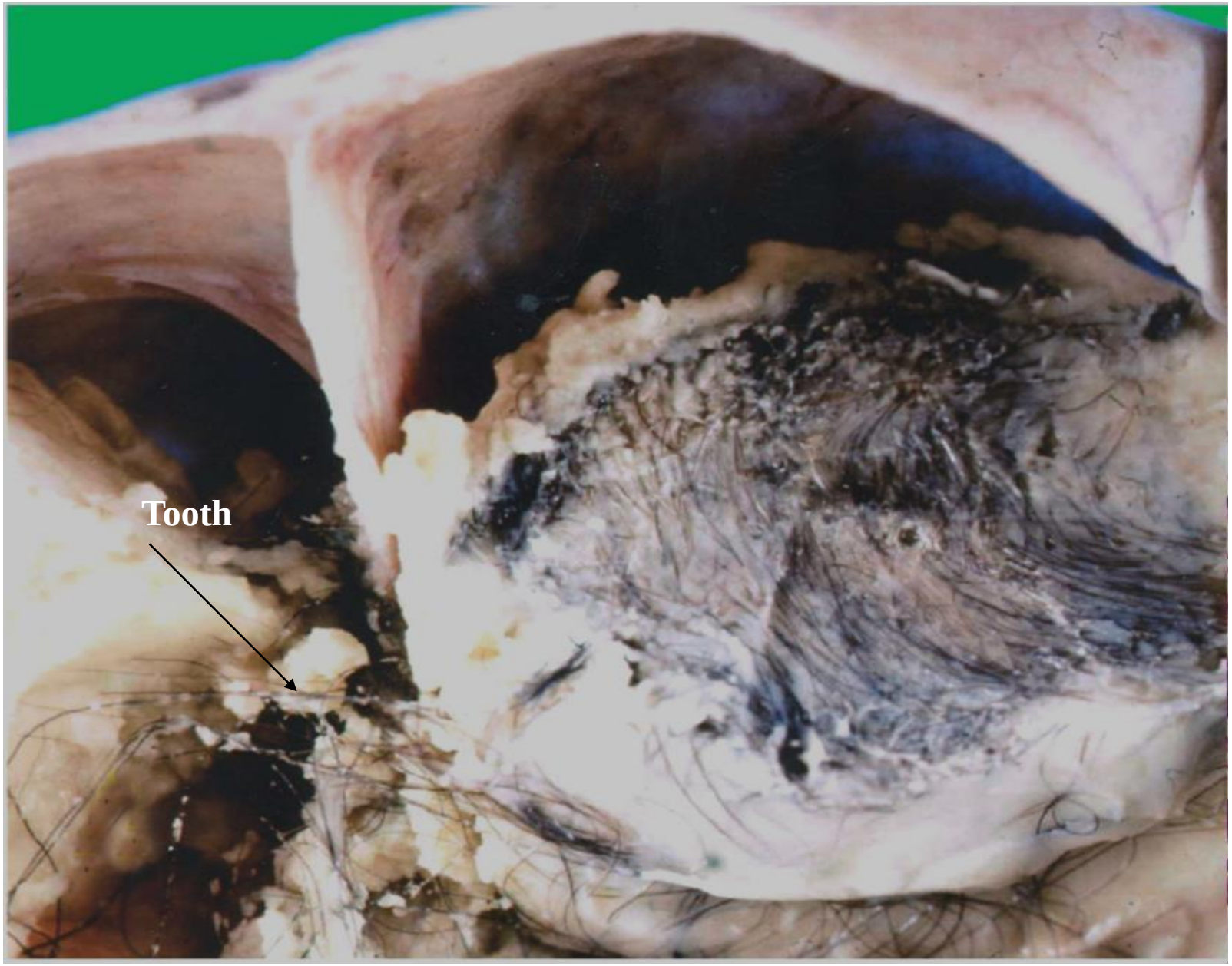
- **testicular epithelial tumors are very rare.**
- **benign cystic teratomas are never seen in the testis, while testicular malignant germ-cell tumors are the most common**
- **Teratomas constitute 20% of ovarian T.**
- **Majority of teratomas are Benign in ovaries.**
- **The immature malignant variant is rare (5-10%).**

Benign (Mature) Cystic Teratomas :

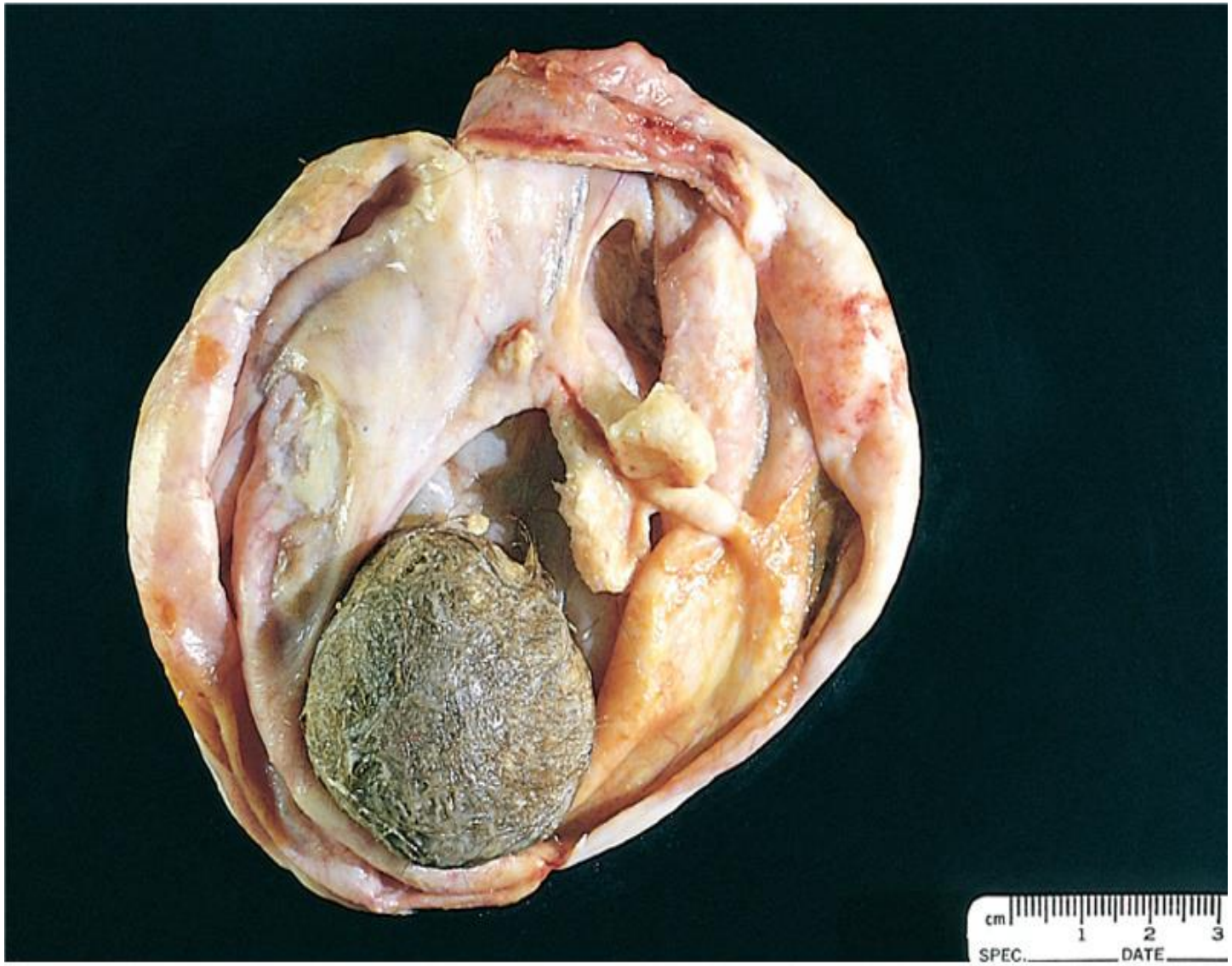
- All are marked by full **differentiation** from totipotential germ cells into mature tissues, representing all three germ cell layers: ectoderm, endoderm, & mesoderm.

- Most are discovered in young women (**1-20 years)** as an ovarian **masses** or incidentally found by X-ray
- Grossly: cyst filled with sebaceous secretion and hair; bone and cartilage; epithelium, or teeth.
- 1% →malignant transformation.
- torsion (10% to 15% of cases).
- Most discovered incidentally.
- 90% unilateral.
- **Struma ovarii** composed entirely of **mature thyroid tissue** appearing as small or large solid, unilateral brown ovarian masses. Interestingly may hyper function & produce thyrotoxicosis**.**

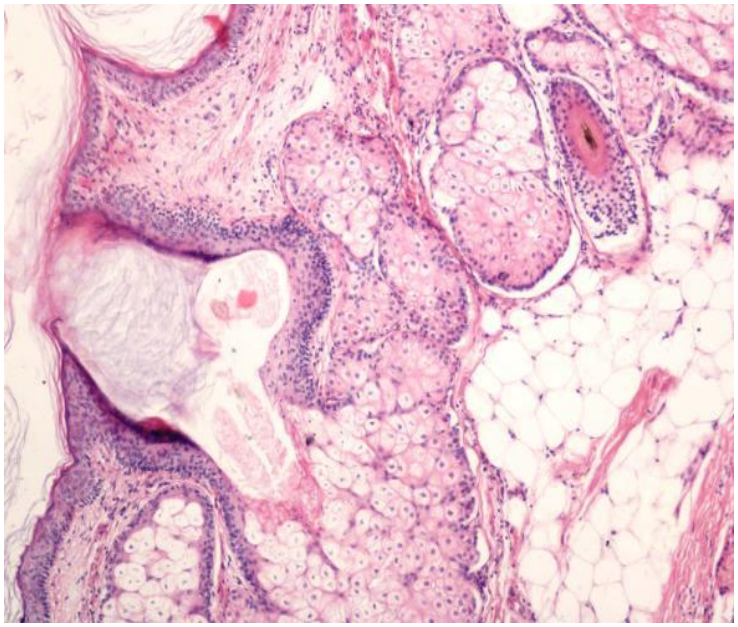
Benign (Mature) Cystic Teratomas

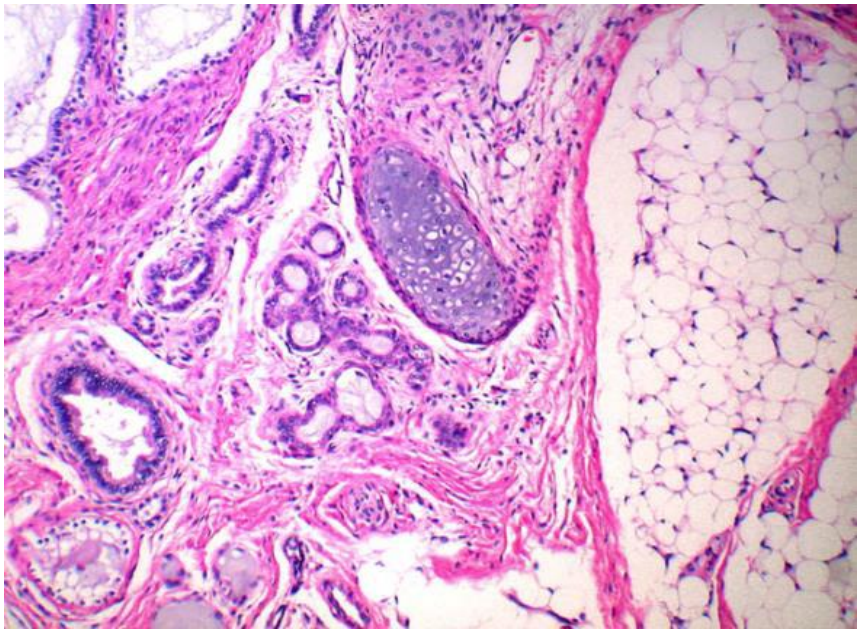


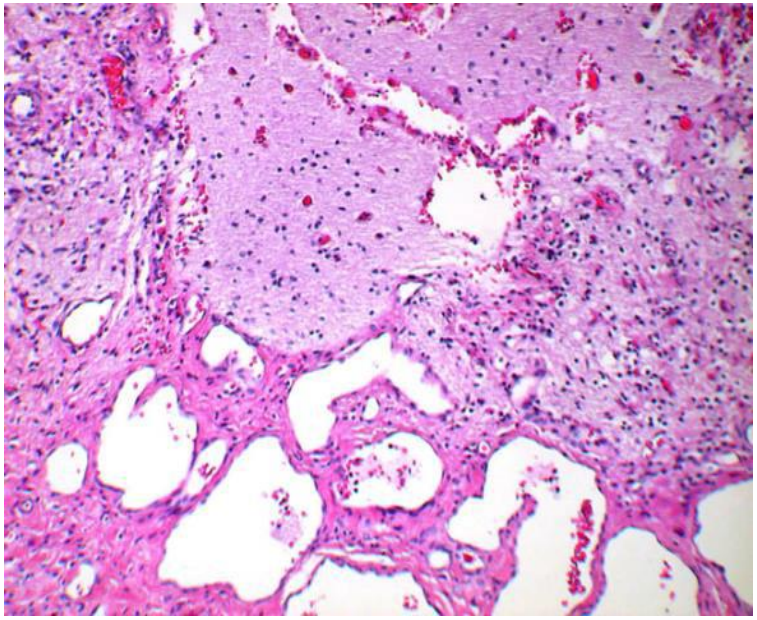
Opened mature cystic teratoma (dermoid cyst) of the ovary with a ball of hair.

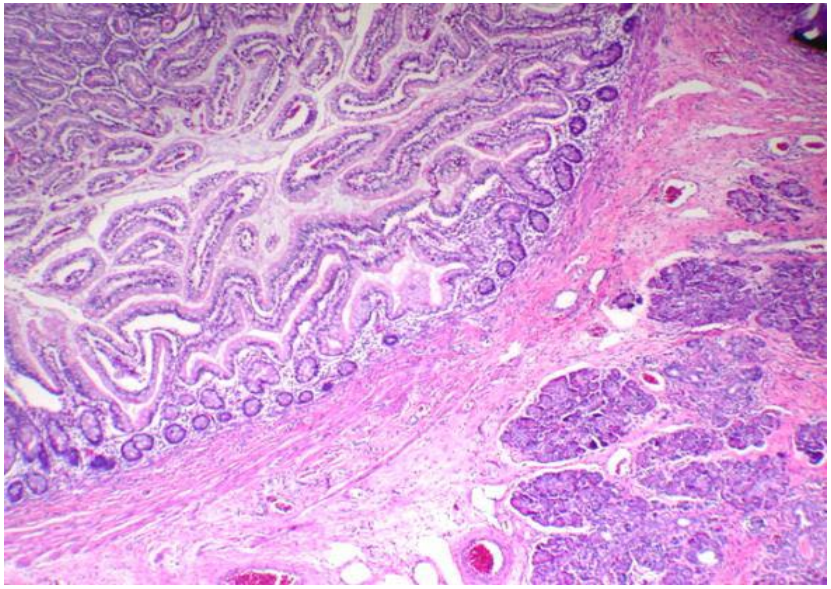


Benign (Mature) Cystic Teratomas

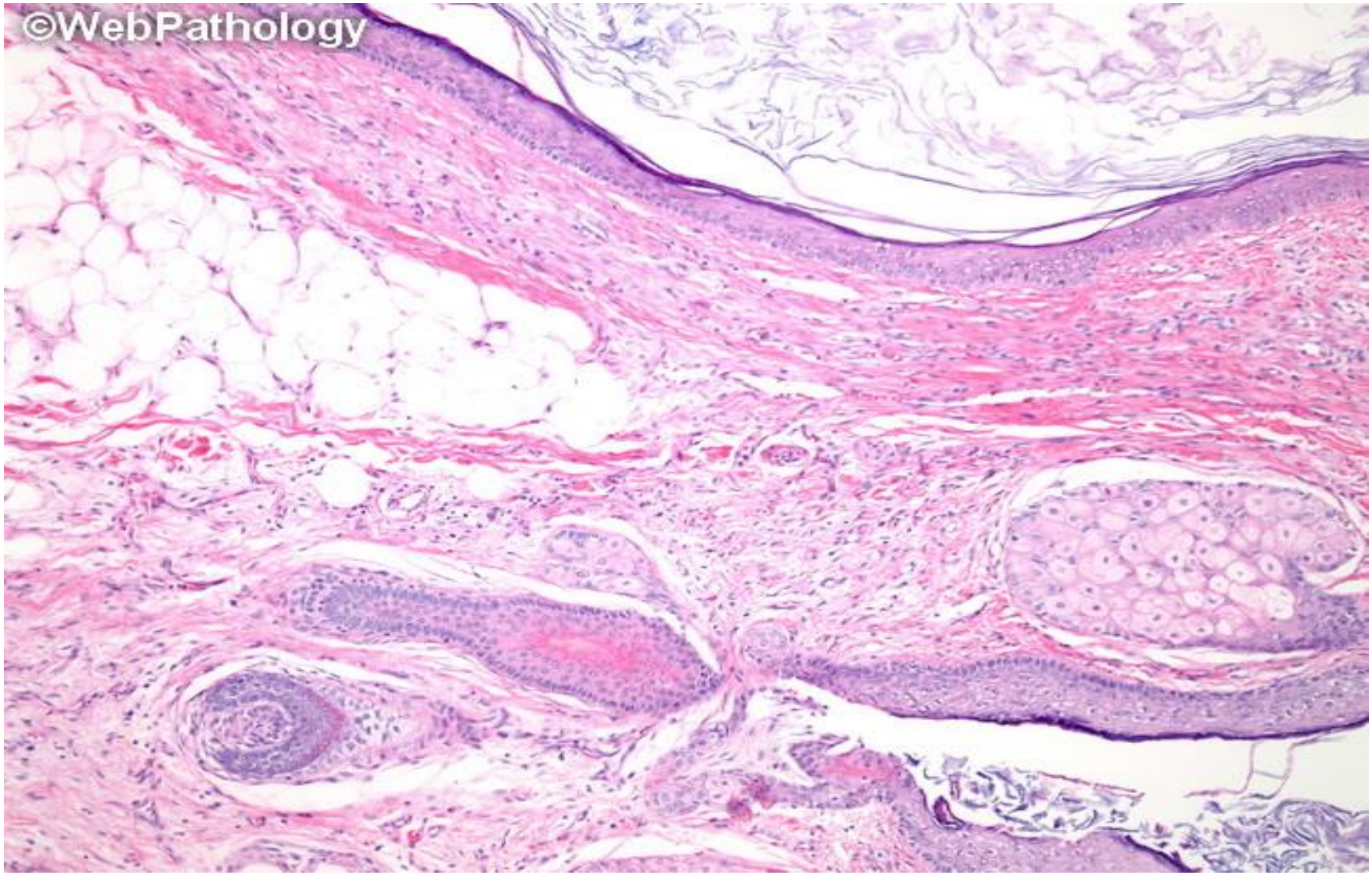








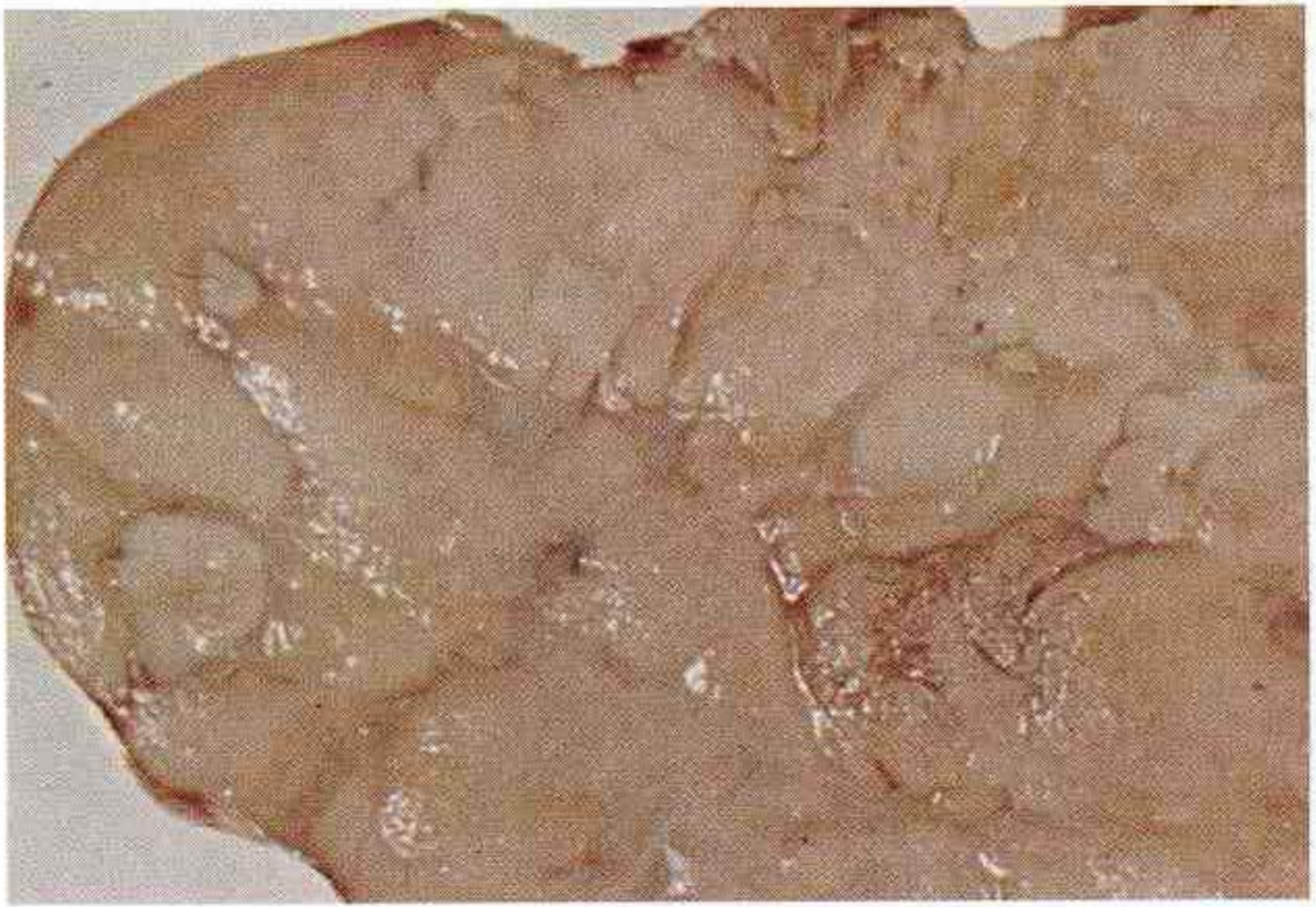
Mature Cystic Teratoma (Ovary) showing cystic spaces lined by **stratified squamous epithelium containing sebaceous glands and hair follicles**. Mature adipose tissue is also seen. Same case as the previous two images.



Dysgerminoma

- Counterpart of testicular seminoma
- 2nd to 3rd decades.
- occur with gonadal dysgenesis.
- All are malignant, but only one-third aggressive & spread;
- All radiosensitive with 80% cure.
- Mostly unilateral, solid, small to large potato-like gray masses

Dysgerminoma: ovary =counterpart of testicular **seminoma**. The C/S is **potato**-like, solid, lobulated, pinkish-grey with foci of whitish necrosis.



12.63 Dysgerminoma: ovary

Sex Cord Tumors;

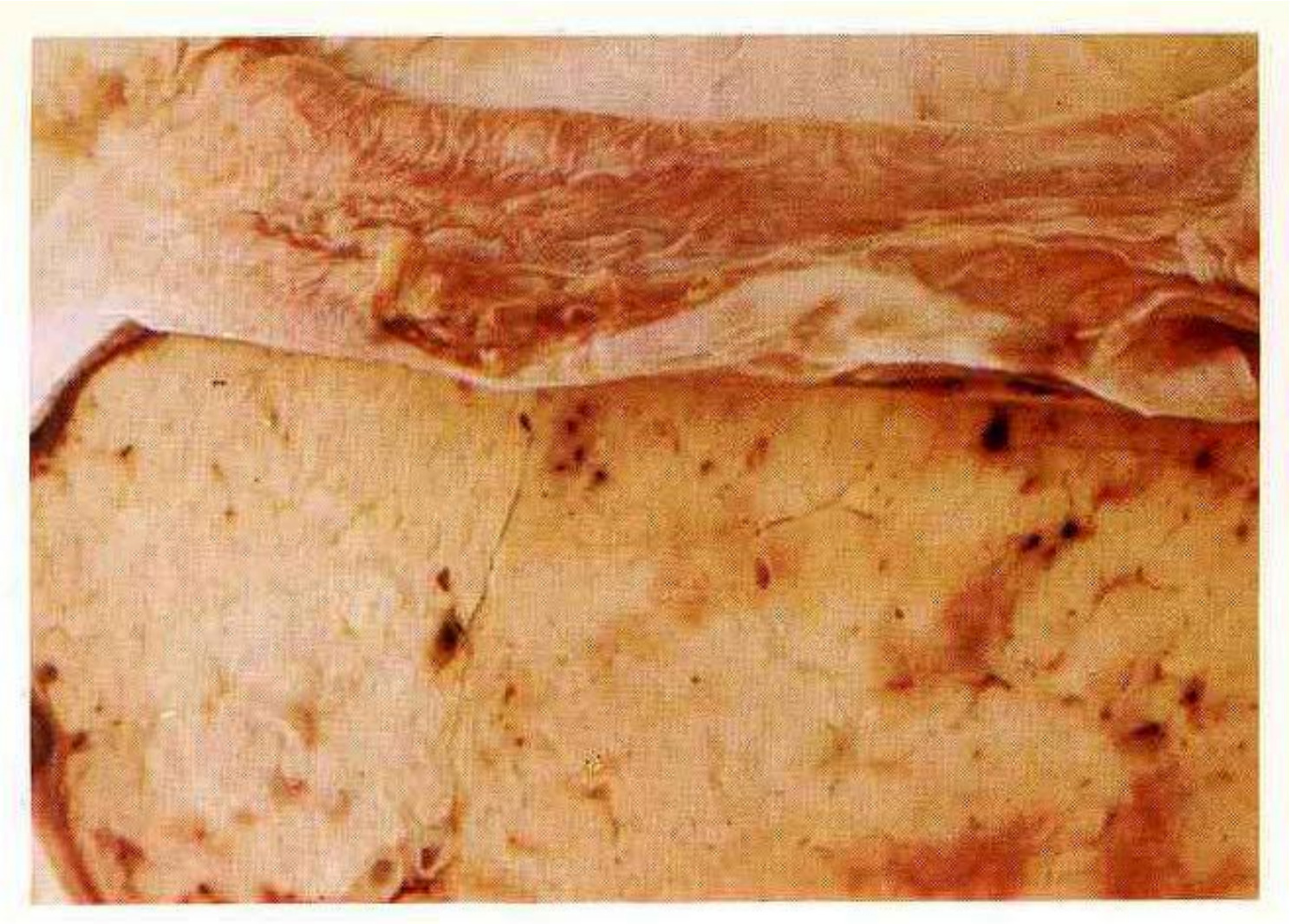
(I) Granulosa-thecal cell:

- (5-10% of all ovarian T).
- Mostly postmenopausal, but may occur at any age.
- Unilateral, small to large, gray to yellow with cystic spaces.
- Morphology :composed of mixture of: (1) cuboidal granulosa cells (may recapitulate ovarian follicle as Call-Exner bodies, arrange in cords, sheets, or strands, Mostly benign, but malignant granulosa cell T are seen in 5% to 25% of cases, & (2) spindled/plump lipid-laden thecal cells which elaborate large amounts of estrogen promoting endometrial or breast ca.

(II) Thecoma-fibroma:

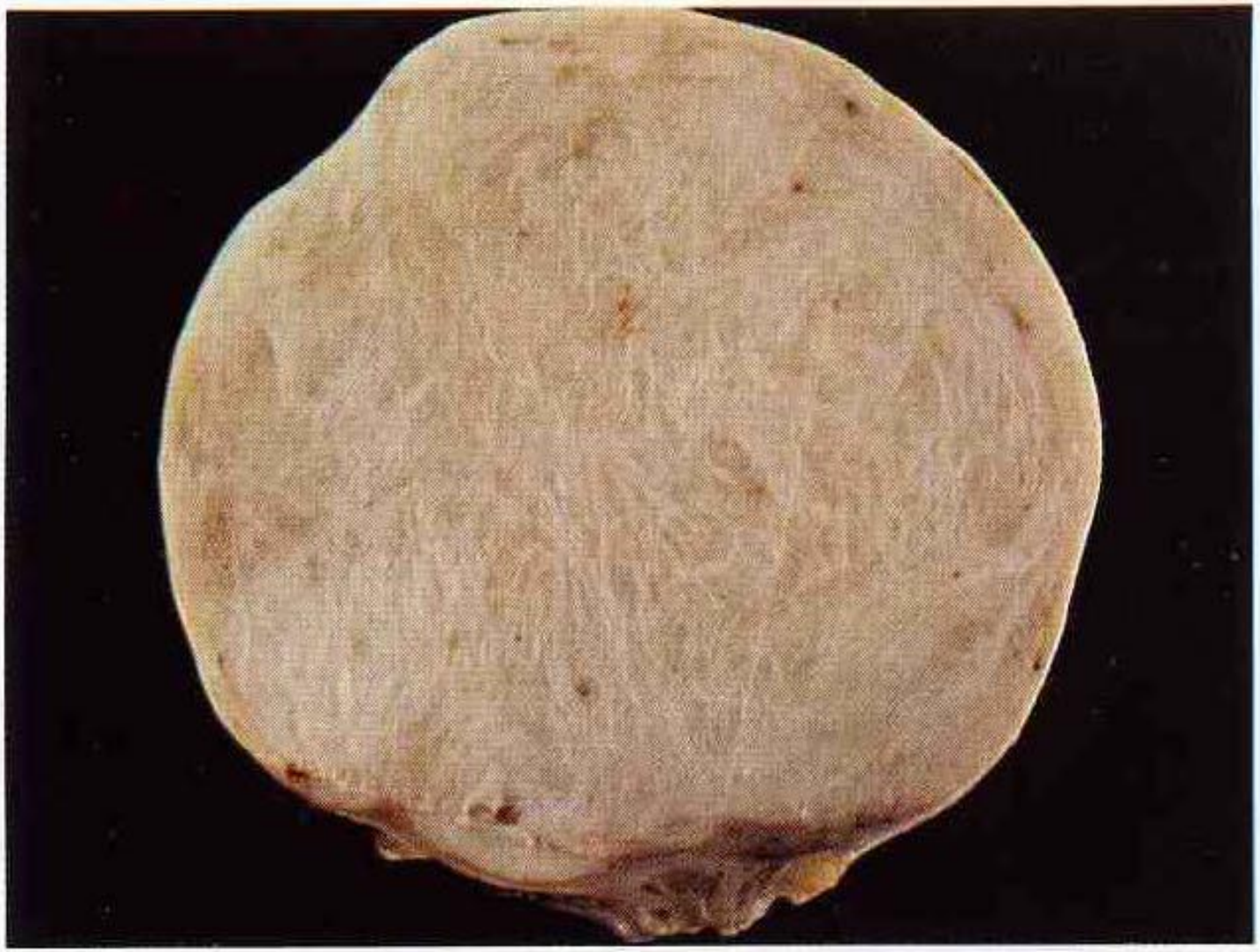
- Any age, Benign, unilateral, Solid, & gray
- Morphology: fibrocytes, to yellow (lipid-laden) plump thecal cells.
- Most are hormonally inactive; few elaborate estrogens.
- **For obscure reasons, about 40% produce ascites + hydrothorax = (Meig's syndrome).**

Granulosa cell tumor: ovary. Unilateral, solid encapsulated, C/S is yellow with foci of hemorrhage.



12.67 Granulosa cell tumour: ovary

Fibroma: ovary. Spherical, firm & smooth-surfaced, O/S whorled with fibrous trabeculae.



12.66 Fibroma: ovary

(III) Sertoli-Leydig cell: All ages, Unilateral,
★Usually small, gray to yellow-brown, & solid. ★Recaps (simulate) testis development, with tubules or cords & plump pink Sertoli cells;
★Many masculinizing or defeminizing.
★ Rarely malignant.

➔**Metastases to Ovary = Krukenberg tumors**

- ★Older ages, Mostly **bilateral**
- ★Solid gray-white masses up to 20 cm in ø(1 Kg)
- Anaplastic T cells in cords, glands, dispersed through fibrous background.
- Cells may be "signet-ring" mucin-secreting.
  ★Primaries are GIT, breast, & lung.

Clinical Correlation of all Ovarian Tumors

- clinical presentation of all is similar:
  - pain, gastrointestinal complaints, urinary frequency; rarely torsion producing severe abdominal pain mimicking an "acute abdomen."
  - Ascites (in Fibromas and malignant serous tumors).
  - Functioning ovarian tumors often come to attention because of hormonal production (Estrogens or androgens).
- **Most** ovarian T are asymptomatic until they are well advanced.
- **30%** of all ovarian T are discovered incidentally on routine gynecologic examination!

Pathology of Fallopian Tube

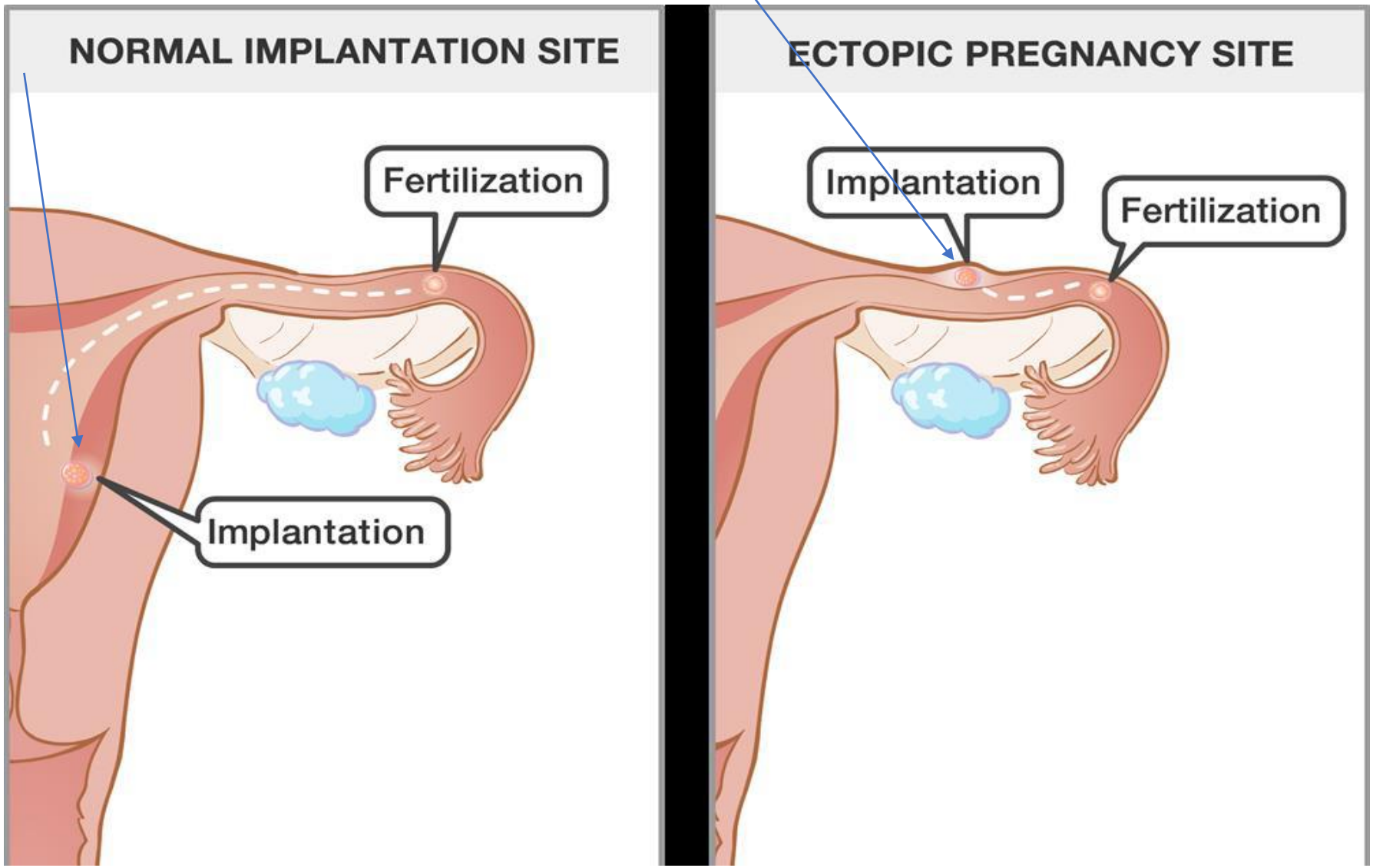
الحمل خارج الرحمEctopic pregnancy

- implantation of the fertilized ovum outside uterus
- Incidence: 1%
- 90% of cases →in fallopian tubes
- other sites: ovaries, abdominal cavity
- Predisposing factors: tubal obstruction (50%)

PID; tumors; endometriosis; **IUCD**..

- In 50% : no anatomic cause can be demonstrated.

Normal Versus ectopic pregnancy.



Ectopic Pregnancy

- Early: Grossly, EP in all sites is characterized by fairly normal early development of the embryo, with the formation of placental tissue, decidual changes & the amniotic sac.
- Later: the placenta burrows (hole) through tubal wall causing intratubal **hematoma (hematosalpinx) and intraperitoneal hemorrhage.**
- Rupture of an ectopic pregnancy: intense abdominal pain **(acute abdomen)**, often followed by shock.(EMERGENCY)
- **Prompt surgical intervention is necessary.**
- **Histological diagnosis & confirmation** depends on the visualization of the ® **placental villi or, rarely, of the embryo.**

- **Until rupture occurs**, **EP** may be indistinguishable from a normal pregnancy, with amenorrhea & elevation of serum & urinary hCG (Positive pregnancy test).

- Under the influence of hCG, the **endometrium** undergoes characteristic hypersecretory & decidual changes called ® **Arias Stella Reaction** (in 50% of cases), But, as expected, there are **NO chorionic villi in the uterus**.
- However, the **absence** of elevated hCG levels & positive pregnancy test **does not exclude** the diagnosis of EP because poor attachment with necrosis of the placenta is common.

- **Rupture of an EP may be catastrophic, with** sudden onset of intense abdominal pain & signs of an **acute abdomen**, often followed by sever hemorrhage & hypovolemic shock. Prompt surgical intervention is **life-saving**

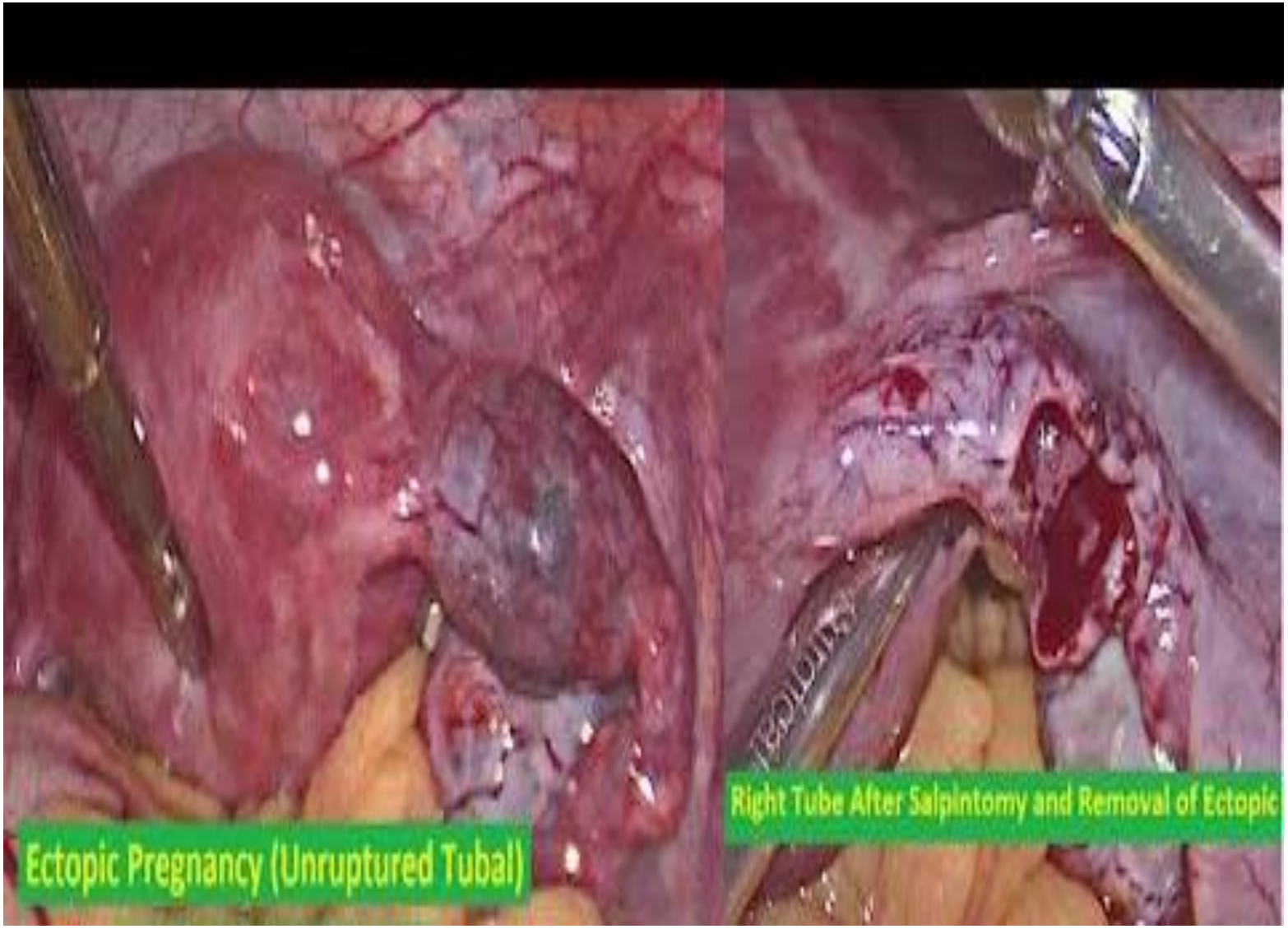
Tubal malignancy

- considered rare.

- **most common histo. type is serous carcinoma.**

- increased in women with **BRCA mutations (**In studies of prophylactic oophorectomies:10% →occult foci of malignancy in fimbria).

- Because **of access to peritoneal cavity**, fallopian tube carcinomas frequently spread to omentum and peritoneal cavity at time of presentation (advanced).


Ectopic Pregnancy (Unruptured Tubal)
Right Tube After Salpintomy and Removal of Ectopic

GESTATIONAL TROPHOBLASTIC DISEASE

- Gestational trophoblastic T are divided into 3 categories, ranging in their aggressiveness from the:
- (I) Benign, Complete & Partial Hydatidiform moles (HM),
- (II) Invasive mole.
- (III) highly malignant Choriocarcinomas (Chorio ca).

- All trophoblastic T elaborate human chorionic gonadotropin (hCG), which can be detected in the circulating blood & urine (used for the diagnosis of pregnancy) at titers considerably higher than those found during normal pregnancy ;the titers progressively rising from HM, to invasive mole, to Choriocarcinoma.

- The fall or the rise in the hCG level in the blood or urine can be used also to monitor the effectiveness of treatment.
- Clinicians therefore prefer the term gestational trophoblastic disease, because the response to therapy as judged by the HCG titers is significantly more important than the anatomic segregation of one lesion from another.

Hydatidiform Mole (HM): Complete & Partial

- Typical HM appears grossly as grape like structure, is a voluminous mass of swollen, cystically dilated chorionic villi.
- The swollen villi are covered by varying amounts of normal to highly atypical chorionic epithelium.
- HM is due to an abnormal contribution of paternal chromosomes in gestation.

- Two distinctives subtypes of HM, complete& partial have been characterized & the 2 patterns result from abnormal fertilization, in which a:

- **Complete HM,** an empty egg is fertilized by 2 spermatozoa(or a diploid sperm),yielding a diploid karyotype (46, XX or, uncommonly, 46, XY) composed entirely paternal genes.

- The complete HM does not permit embryogenesis & therefore never contains fetal parts. All of the chorionic villi are abnormal, & the chorionic epithelial cells are diploid & all chromosomes are paternal.

- **While Partial HM,a** normal egg is fertilized by 2 spermatozoa (or a diploid sperm),resulting in a triploid karyotype (69, XXY) with a preponderance of paternal genes.

- The partial HM is compatible with early embryo formation & therefore contains fetal parts, has some normal chorionic villi, & is always triploid & having 2 sets of paternal chromosomes.

Table showing Features of Complete	&	Partial HM:
Karyotype: 46, XX (46, XY)		Triploid (69, XXY)
Villous edema: All villi		All villi
Trophoblast Proliferation: Diffuse & circumferential		Focal & slight
Atypia: Often present		Absent
Serum hCG: Elevated		Less elevated
hCG in tissue: ++++		+
Progress to choriocarcinoma: 2%		Rare

- Complete HM incidence is about 1/1000 pregnancies in the US & other Western countries. For unknown reasons there is a much higher incidence in Asian countries.

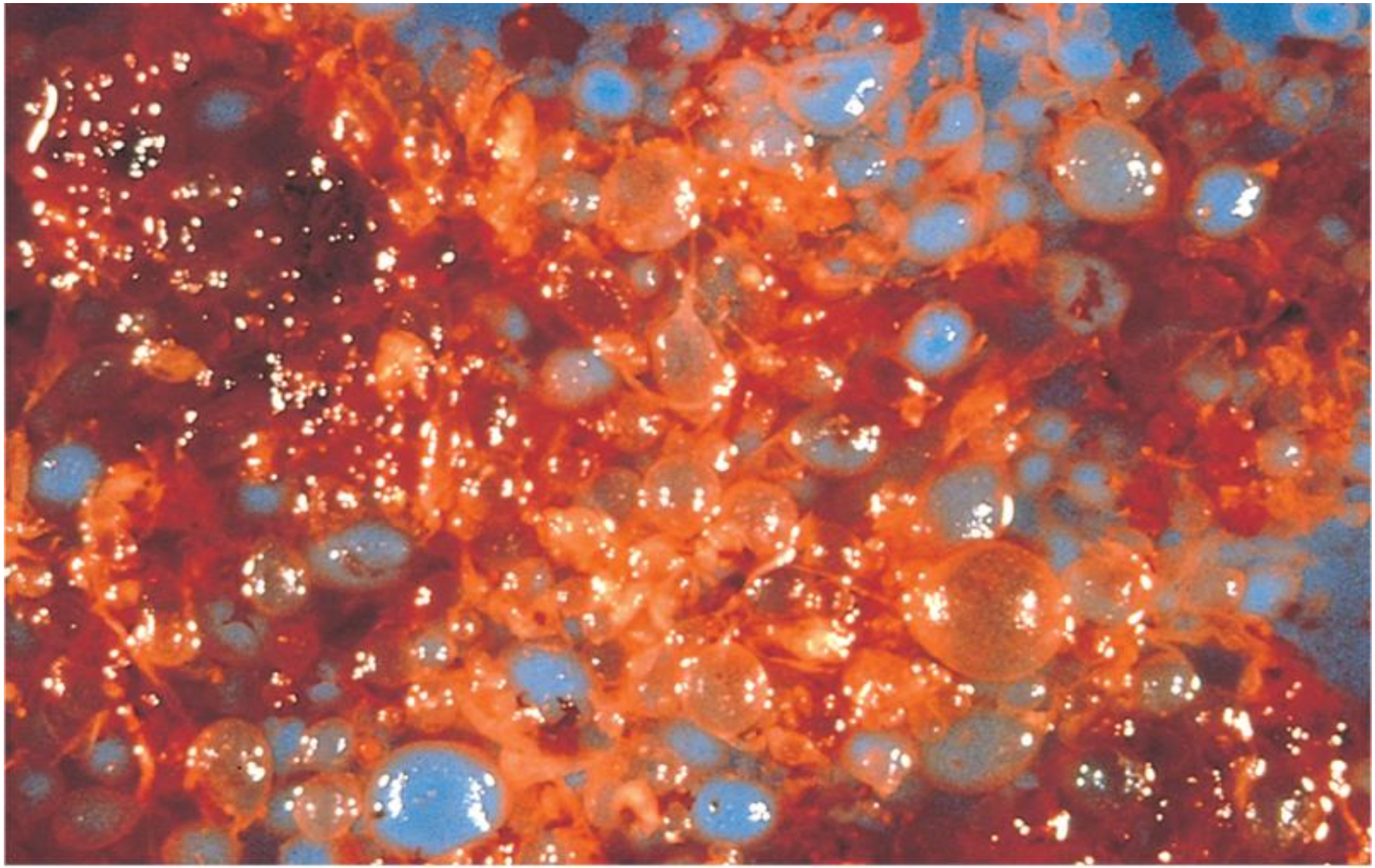
- HM are most common before age 20 years & after age 40 years, & a history of HM increase the risk in subsequent pregnancies.

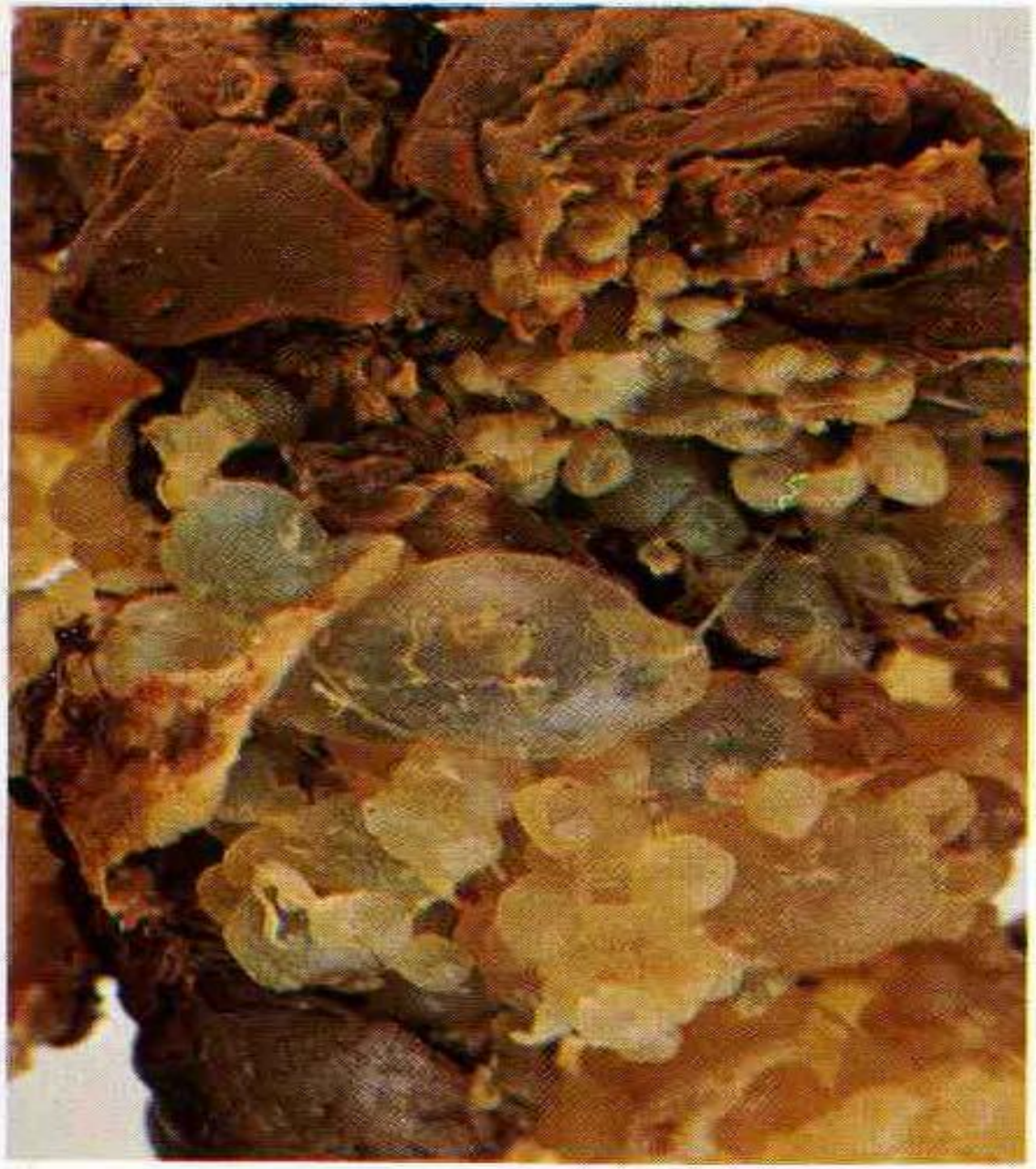
- HM is traditionally discovered at 12 to 14 weeks of pregnancy because of a gestation that was "too large for dates," however;…

- An **early diagnosis** of HM can be done by
  - (1) early monitoring of pregnancies by ultrasound **(U/S)** which reveal **typical absence of fetal parts, or fetal heart sounds,**
  - **(2) by detecting elevations of hCG** in the maternal blood .

- **Grossly**, in early HM, the uterus may be normal in size; but in fully developed HM the uterine cavity is **larger** than the expected date, **filled** with a delicate, friable mass of thin-walled, translucent cystic structures **.**Fetal parts are not seen in complete HM but are common in partial HM.
- H, the **complete mole** shows:
- (I) **Hydropic swelling** of chorionic villi, with loose, edematous & myxomatous stroma.
- (II) Virtual **absence of vascularization** of villi.
- (III) **Proliferation** of both cytotrophoblast & syncytiotrophoblast of the chorionic epithelium which may be mild, or striking circumferential hyperplasia.

Complete hydatidiform mole suspended in saline showing numerous swollen (hydropic) villi.



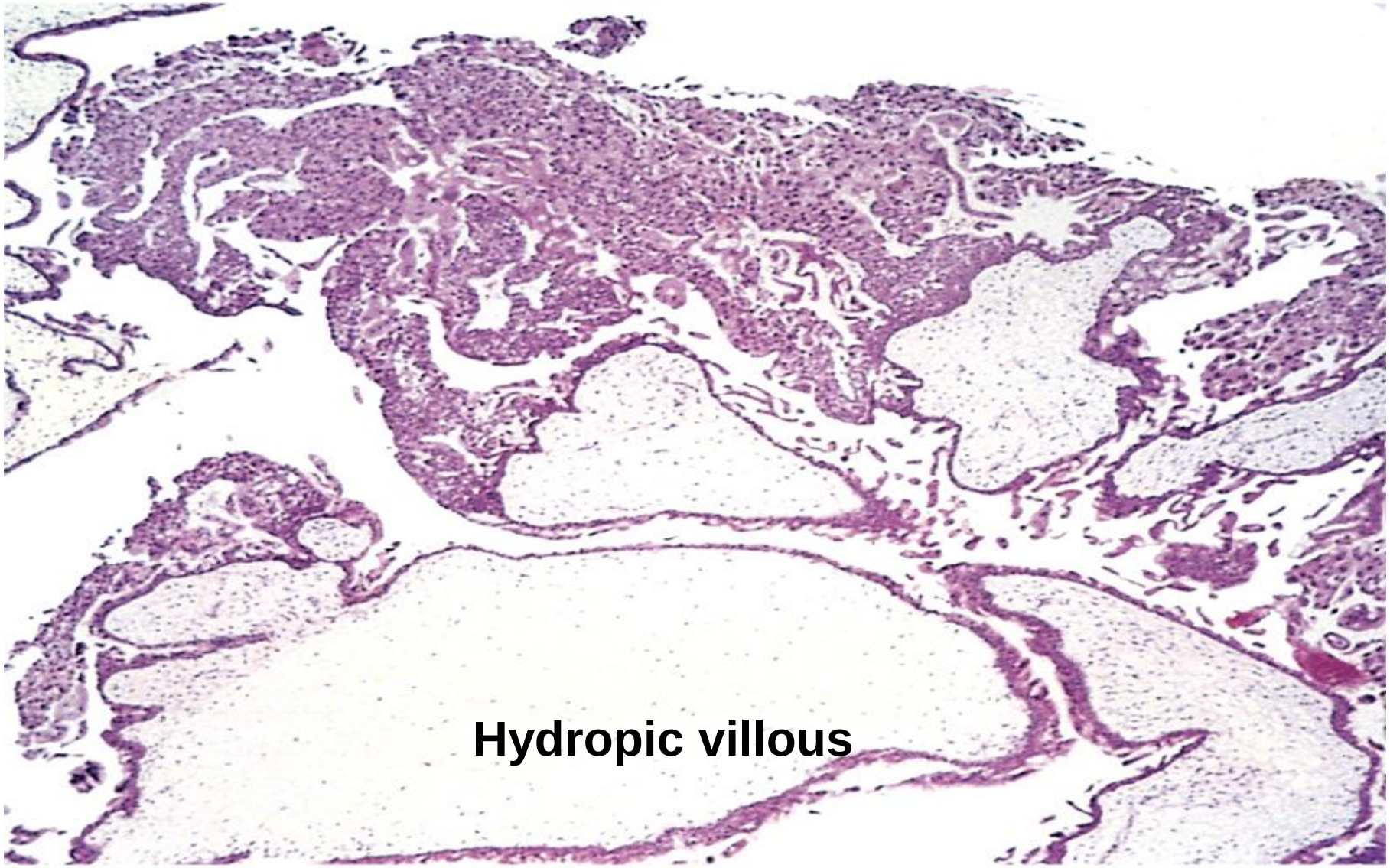


12.49 Hydatidiform mole

Hydatidiform mole.

Mass of grape-like, discrete, rounded translucent vesicles which consist of hydropic & cystic chorionic villi.

Complete HM showing (1) distended hydropic villi, (2)absence of BV & (2) proliferation of the chorionic epithelium (above).



- **Microscopically** : in **partial moles** the
- (1) villous edema involves only **some** of the villi &
- (2) the trophoblastic proliferation is **focal & slight**.
- (3) the villi have a characteristic irregular **scalloped** margin,
- (4) in most cases of partial HM there is evidence of an **embryo** or fetus, which may be in the form of fetal RBCs in placental villi or, in some cases, a fully formed fetus that, despite a triploid karyotype, is morphologically nearly normal in appearance.
- **Prognosis**: Overall, 80% to 90% of HM do not recur after thorough curettage; **10%**of complete HMs are invasive, & **2% to 3% give rise to chorio ca**.
- Partial HM rarely give rise to choriocarcinomas.
- With complete HM, monitoring the post-curettage blood & urinary β-subunit of hCG concentrations, permits detection of incomplete removal or a more ominous complication which can be treated by **chemotherapy, which is almost always curative.**

Invasive Mole

- **Invasive moles are complete HM that are more invasive locally but do not metastasize.**
- An invasive mole retains hydropic villi (which are absent in choriocarcinoma),
- Microscopically : the villi epithelium shows
- (1) **atypical** hyperplastic cytotrophoblast & syncytiotrophoblasts proliferation &
- (2) **penetration of the uterine wall deeply, possibly causing rupture**& sometimes serous **hemorrhage**.
- Local spread to the broad ligament & vagina may also occur.
- **Although they are invasive, metastases do not occur.**

- Hydropic villi may embolize to distant organs, such as lungs or brain, but these emboli do not constitute true metastases & may actually regress spontaneously. Invasive mole is **difficult to remove completely by curettage**, because of the greater depth of myometrium invasion.

- So, serum hCG may remain elevated & required further treatment by **chemotherapy** which is fortunately **curative** in most cases.

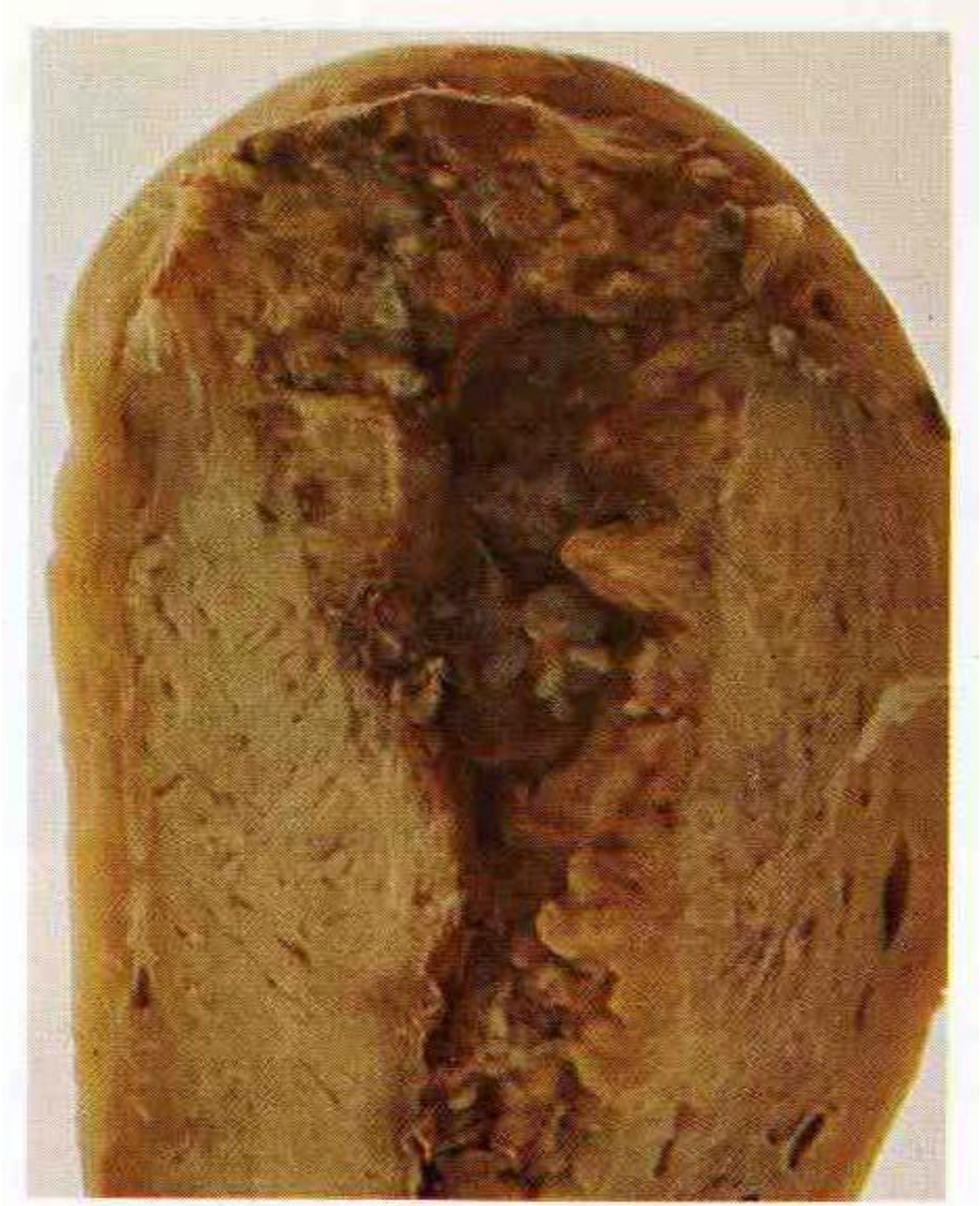
Choriocarcinoma (Chorio ca)

- Very aggressive malignant T, **arises either from gestational chorionic epithelium** or, less frequently, from **totipotential cells within the gonads (testis or ovary) or elsewhere.**

- Chorio ca are **rare** in the West, & in the US but are much more common (X15 fold) in Asian & African countries.
- The risk is more before age 20 & is significantly elevated after age 40.
- **50%**of chorio ca arise in complete HM;
- **25%**arise after an abortion,
- **25%** occurs during what had been a normal pregnancy.

Most chorio ca are discovered by the appearance of

- (1) **bloody uterine discharge** accompanied by
- (2) a **rising titer of β-hCG** in blood & urine (much higher than those associated with a HM),
- (3) the **absence of marked uterine enlargement**, such as would be anticipated with a HM.



12.50 Hydatidiform mole: uterus

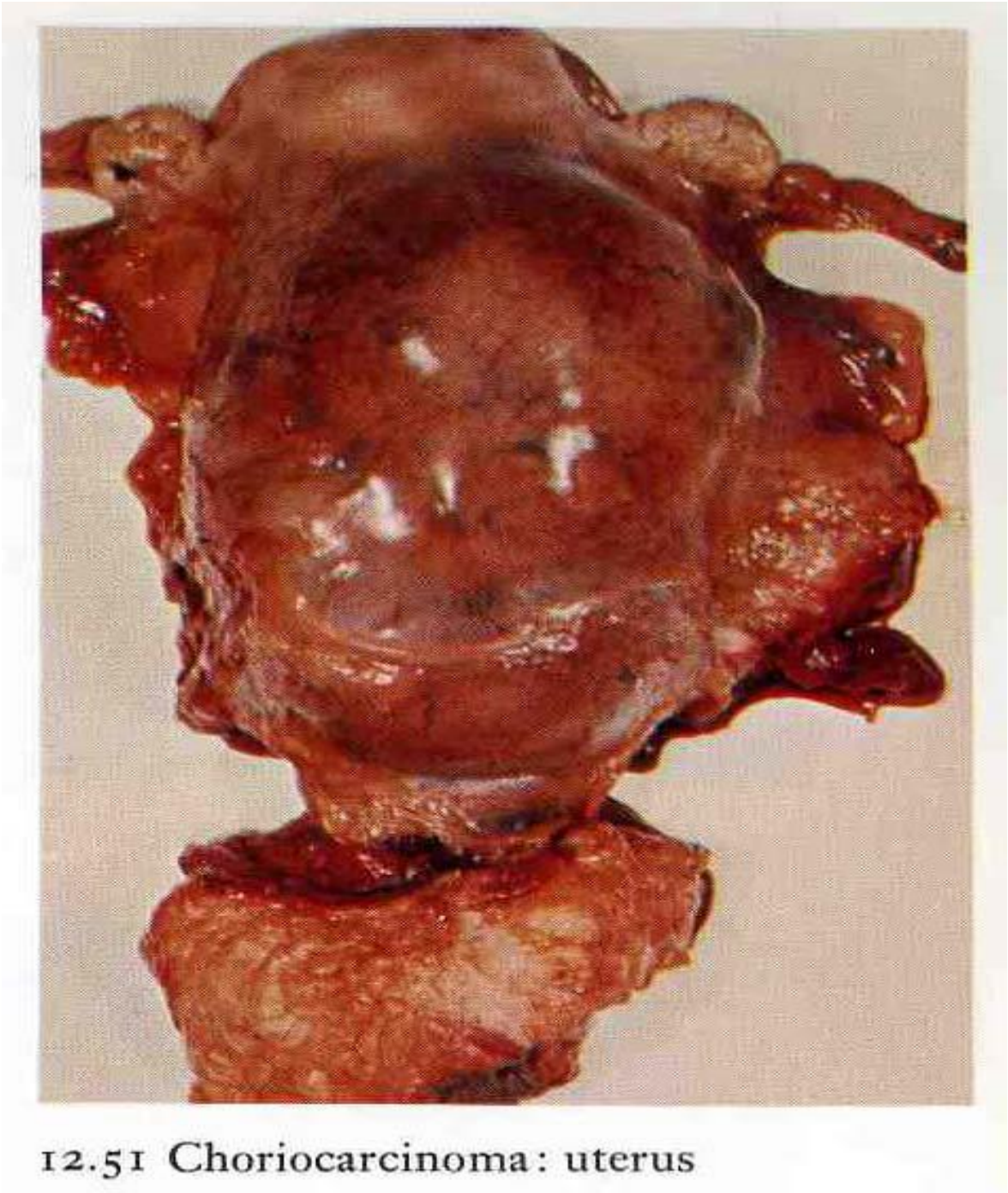
Invasive hydatidifrom mole.

★Uterus sagittal section, showing grape-like vesicles in the cavity, extensively invading the myometrial muscular wall locally (as a result of proliferating trophoblastic activity). The lesion sometimes may **cause (1) hemorrhage, (2) uterine wall perforation**.

❖Grossly:

- ❖**C**horio ca is very hemorrhagic, necrotic T mass within the uterus, so much so that, sometimes, the histologic diagnosis is difficult. Indeed, the primary lesion may self-destruct, & only the metastases “mets” tell the story.
- ❖Very early, the T invades into the myometrium & into BV.

- ❖Microscopically:, in contrast to HM & invasive moles, the chorionic villi are not formed & are never seen; instead, the T is purely epithelial, composed of anaplastic cytotrophoblast & syncytiotrophoblast .
- ❖When discovered, most chorioca are widely disseminated via the blood, most often to the lungs (50%), vagina (30% to 40%), brain, liver, & kidneys.
- ❖ Lymphatic invasion is uncommon

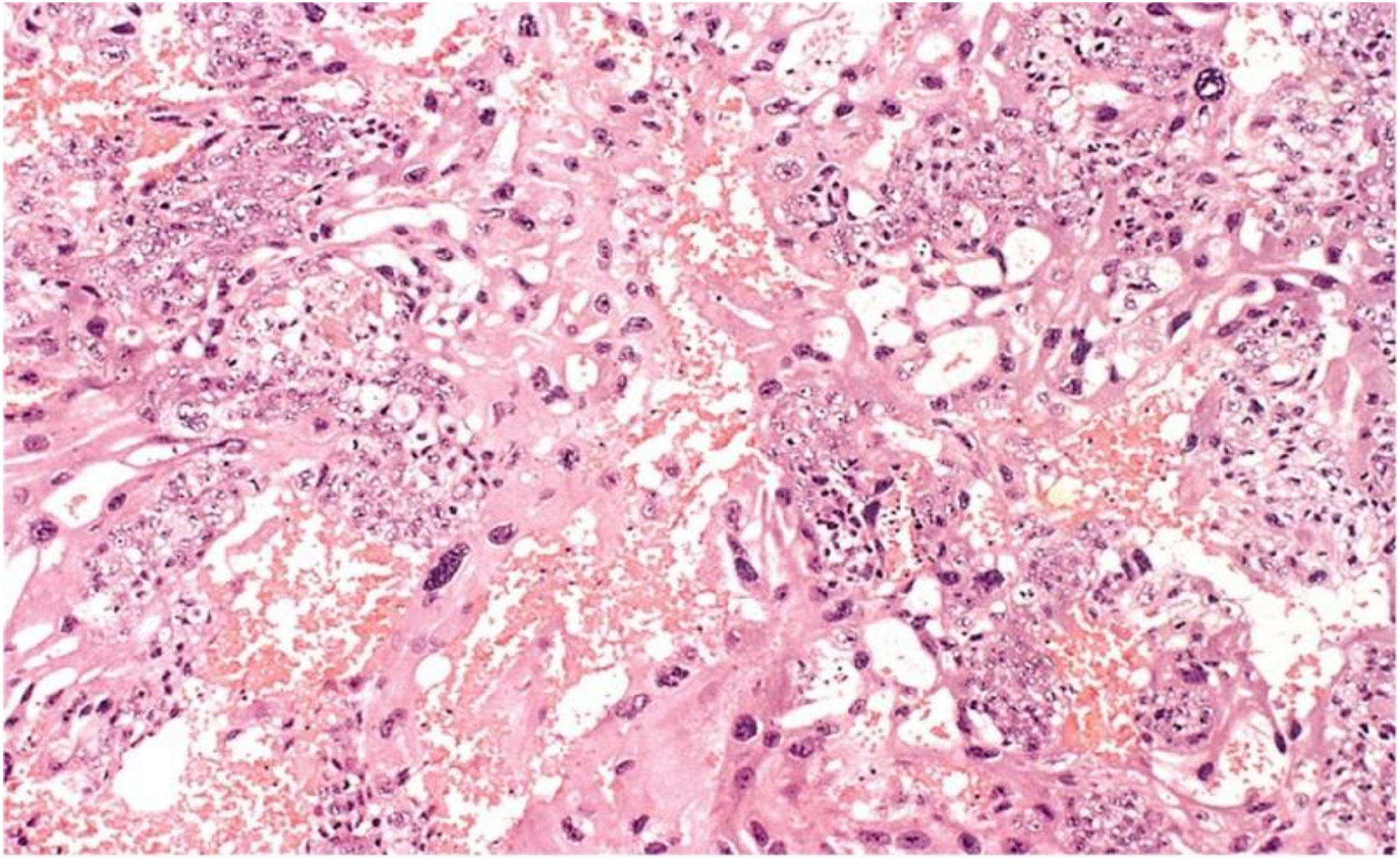


12.51 Choriocarcinoma: uterus

Choriocarcinoma: uterus.

The tumor forms a large mass which has expanded the lower part of the body of the uterus & invaded the cervix & the upper vagina

Choriocarcinoma showing: both (1) Neoplastic cytotrophoblasts & syncytiotrophoblasts; & (2) Complete **absence** of chorionic villi.



- Despite the extreme aggressiveness of chorio ca, which made them uniformly fatal in the past, **chemotherapy** has achieved remarkable results with nearly 100% cure, even with T that have spread beyond the pelvis & vagina & into the lungs.
- Equally remarkable are reports of healthy infants born later to these survivors!
- By contrast, there is poor response to chemotherapy in chorio ca that arise in the gonads (ovary or testis).
- This striking difference in prognosis may be related to the presence of paternal antigens on placental chorio ca but not on gonadal lesions. Conceivably (Possibly), a maternal immune response against the foreign (paternal) antigens helps by acting as an adjunct to chemotherapy.

Breast Disease

Clinical presentation of breast disease

- **Pain**:

-cyclic: diffuse, premenstrual edema and swelling.

-noncyclic: Localized, ruptured cyst or physical trauma, or infection

-Almost all painful masses are **benign** except for 10% of cases that relates to cancers

- **Inflammation**:

-causes edematous and erythematous breast.

-most often caused by infections (during lactation and breastfeeding).

-An important mimic of inflammatory breast cancer

- **Nipple discharge:**
- **Normal:** when small in quantity and bilateral.
- **Milky discharges (galactorrhea):**

- are associated with elevated prolactin levels (pituitary adenoma), hypothyroidism, or endocrine anovulatory syndromes, patients taking OCPs, tricyclic antidepressants, methyldopa, or phenothiazines.

- **Bloody or serous discharges**:

- commonly due to large duct papillomas and cysts.
- During pregnancy, result from the rapid growth and remodeling of the breast.
- **BUT spontaneous, unilateral, and bloody discharge increases concern for malignancy**.

❑ Palpable masses:

-95% are benign

-all palpable masses require evaluation.

-**The most common palpable lesions are cysts, fibroadenomas, and invasive carcinomas**

-generally detected when they are 2 to 3 cm in size.

❑Gynecomastia:

-The only common breast symptom in **males**.

-resulting from an imbalance between estrogens, which stimulate breast tissue, and androgens, which counteract these effects.

❑ General Consideration in Breast disease

- The underlying cause is **benign** in >90% of cases.
- The likelihood of malignancy increases with **age**:

▪ the risk of nipple discharge being due to cancer increases from 7% in women <60 years vs. 30% in women >60.

▪ only 10% of palpable masses in women <40 years are carcinomas vs. 60% in women >50.

- Of women with cancer:

❑ about 45% have symptoms

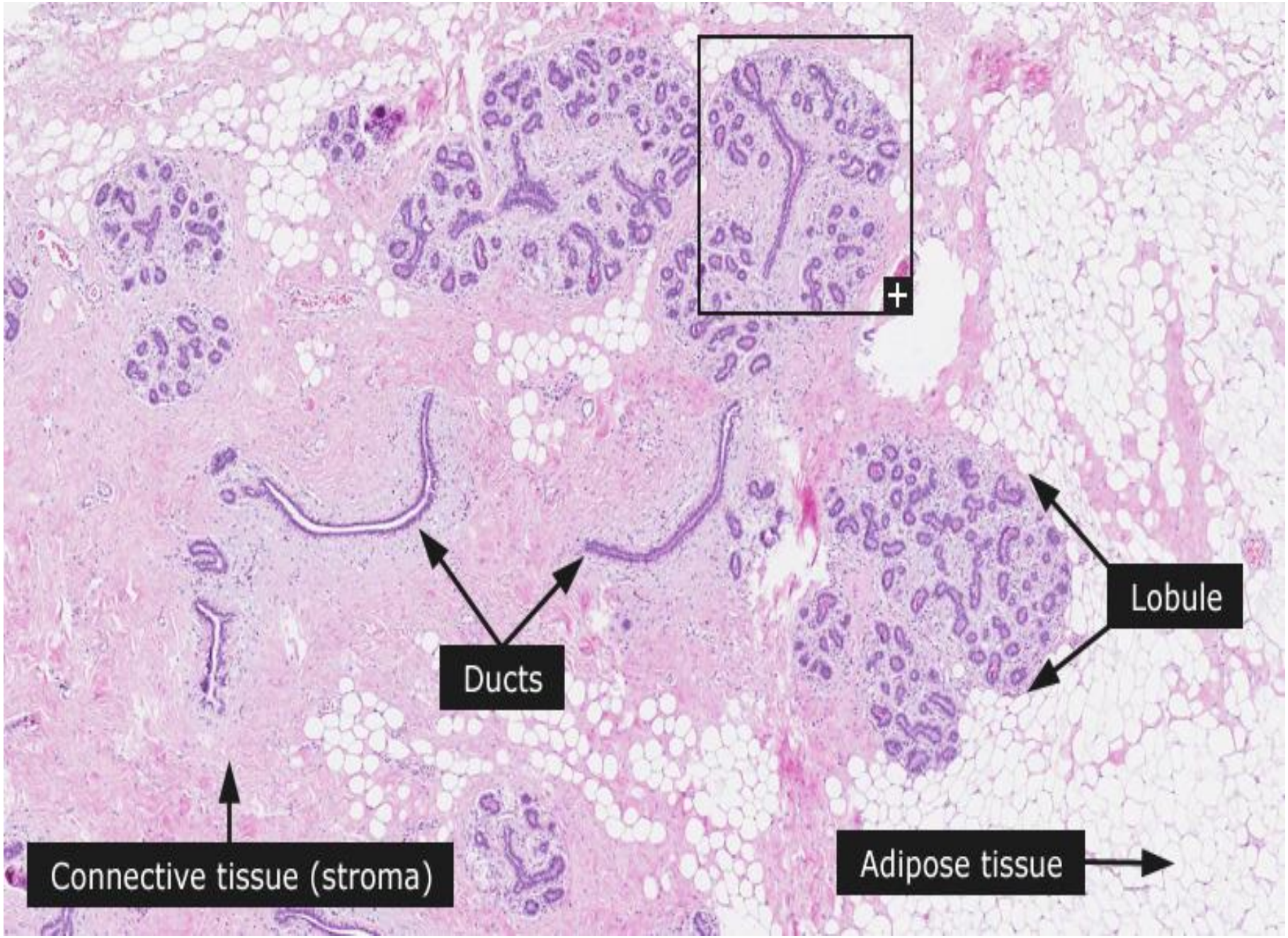
❑ Palpable mass>>>> pain> nipple discharge > inflammatory changes

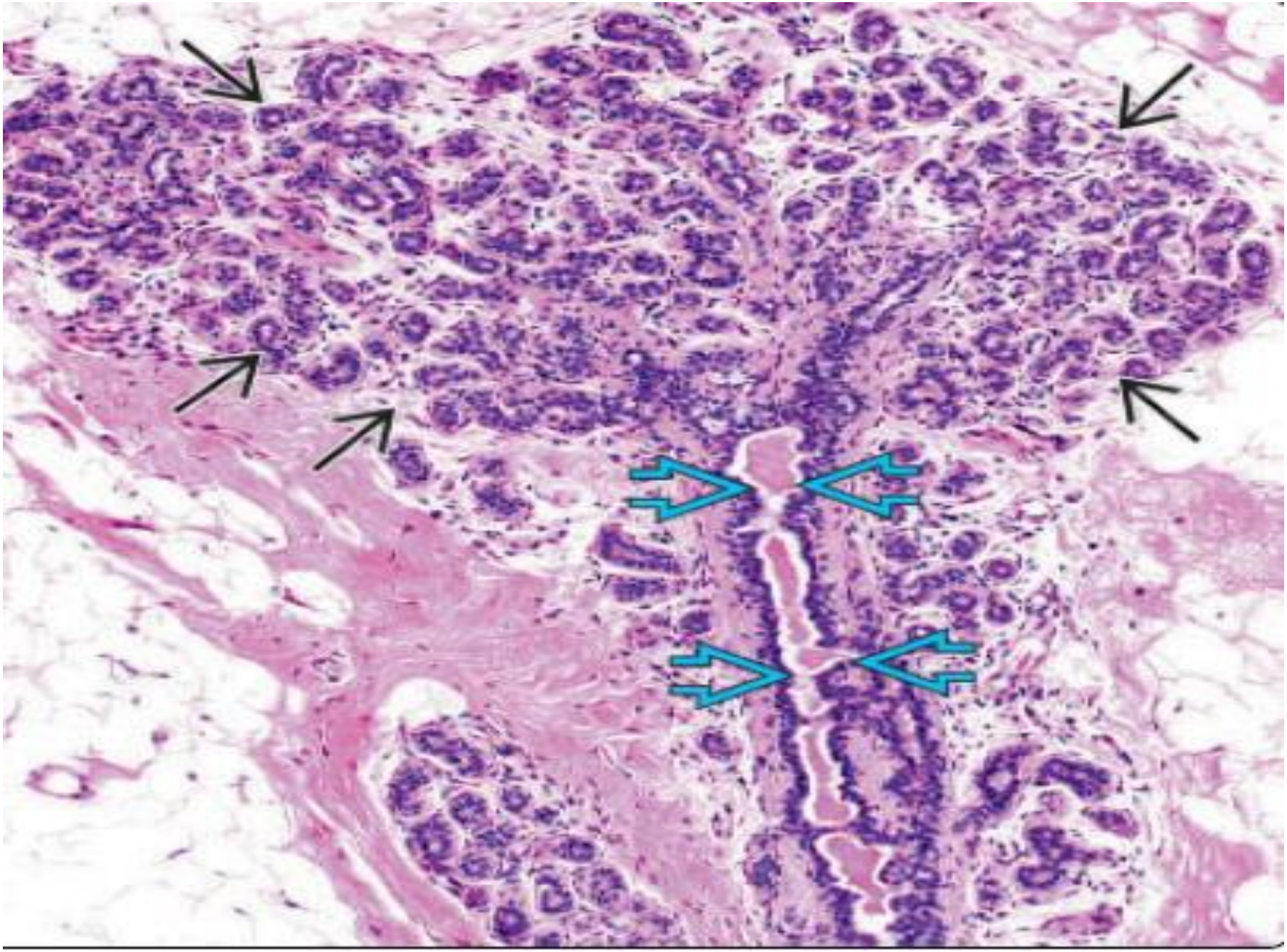
❑ the remainder come to attention through screening tests

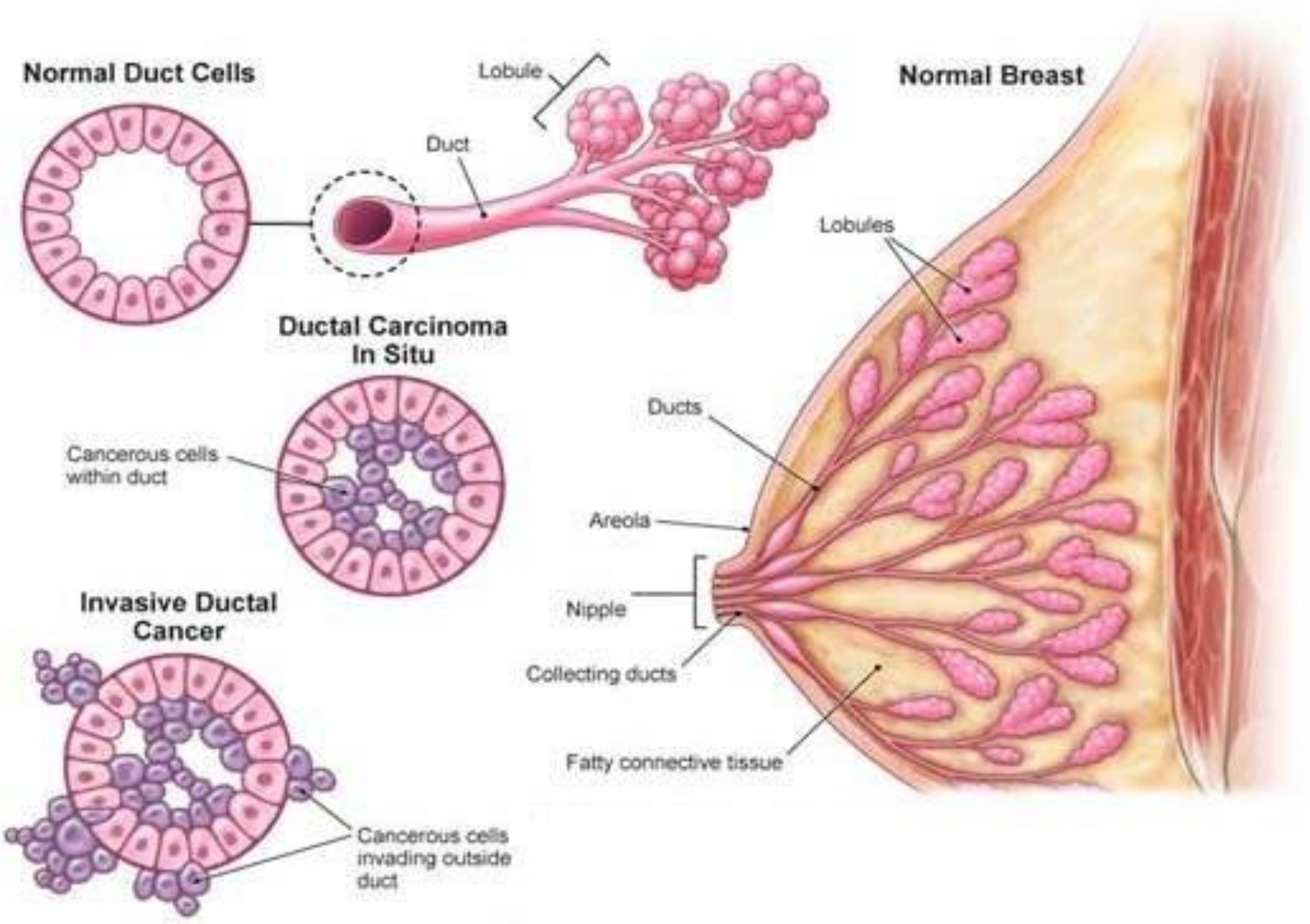
Mammographic Screening

- detects early, non palpable asymptomatic breast carcinomas before metastasis.
- the average size of invasive carcinomas detected by mammography is about 1 cm, at this stage only 15% will have metastasized to regional lymph nodes.

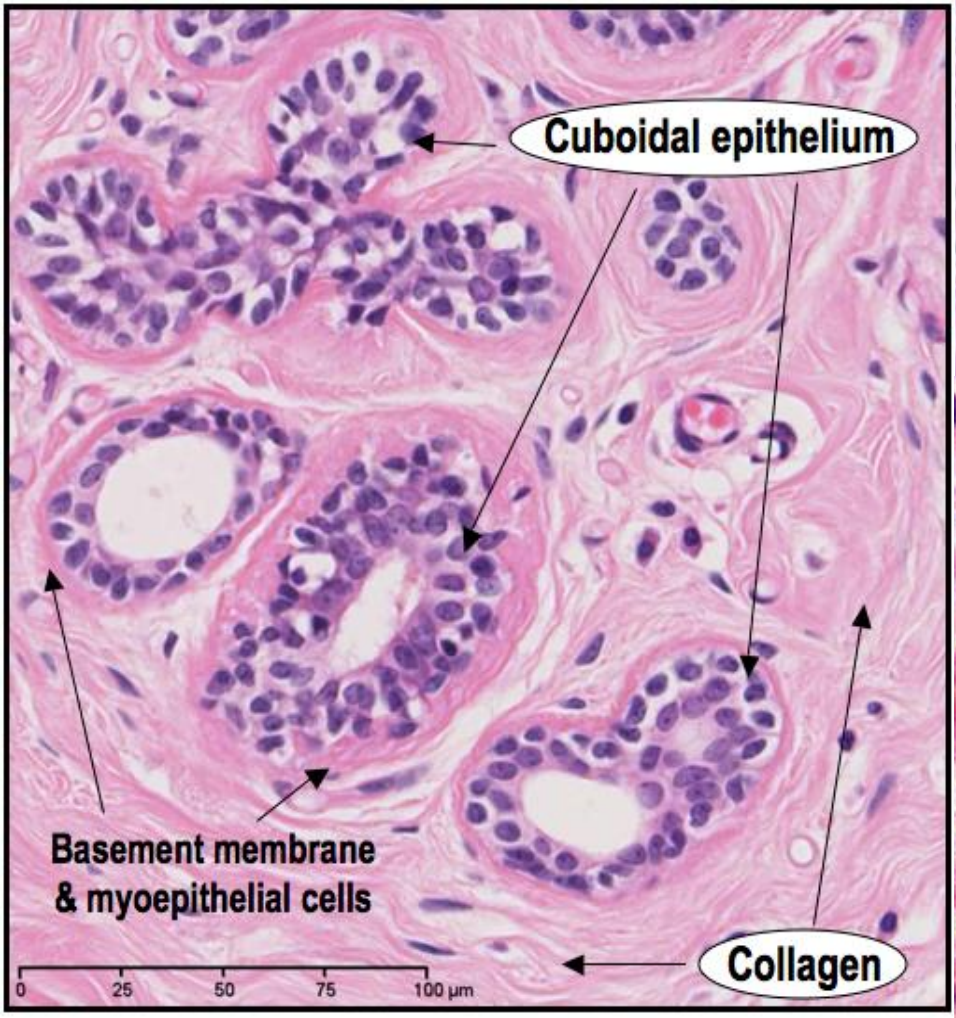
- The sensitivity and specificity of mammography increase with age→due to replacement of the fibrous, radiodense tissue of young women with the fatty, radiolucent tissue of older women

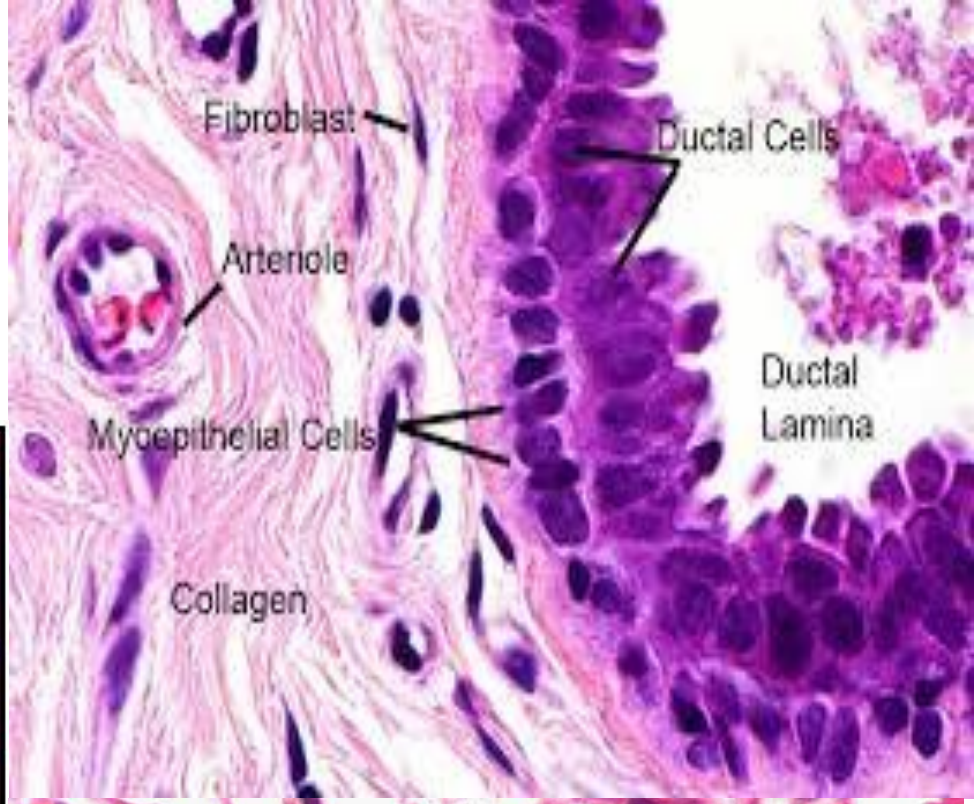

Ducts
Lobule
Connective tissue (stroma)
Adipose tissue

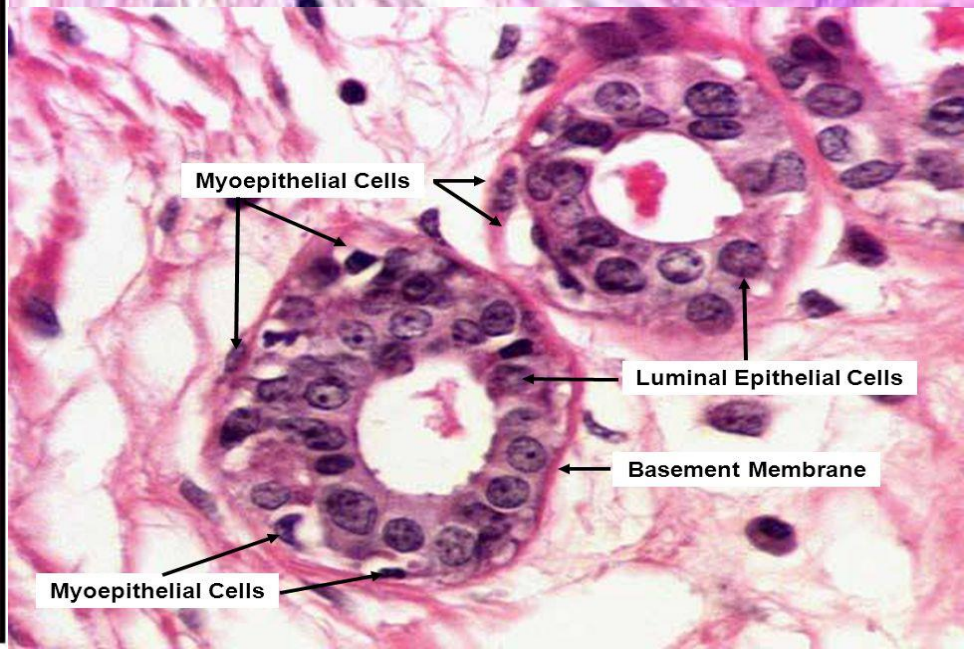



Normal Duct Cells
Lobule
Duct
Normal Breast
Lobules
Ductal Carcinoma In Situ
Cancerous cells within duct
Ducts
Areola
Nipple
Collecting ducts
Fatty connective tissue
Invasive Ductal Cancer
Cancerous cells invading outside duct

Normal breast Histology







BREAST

Congenital anomalies

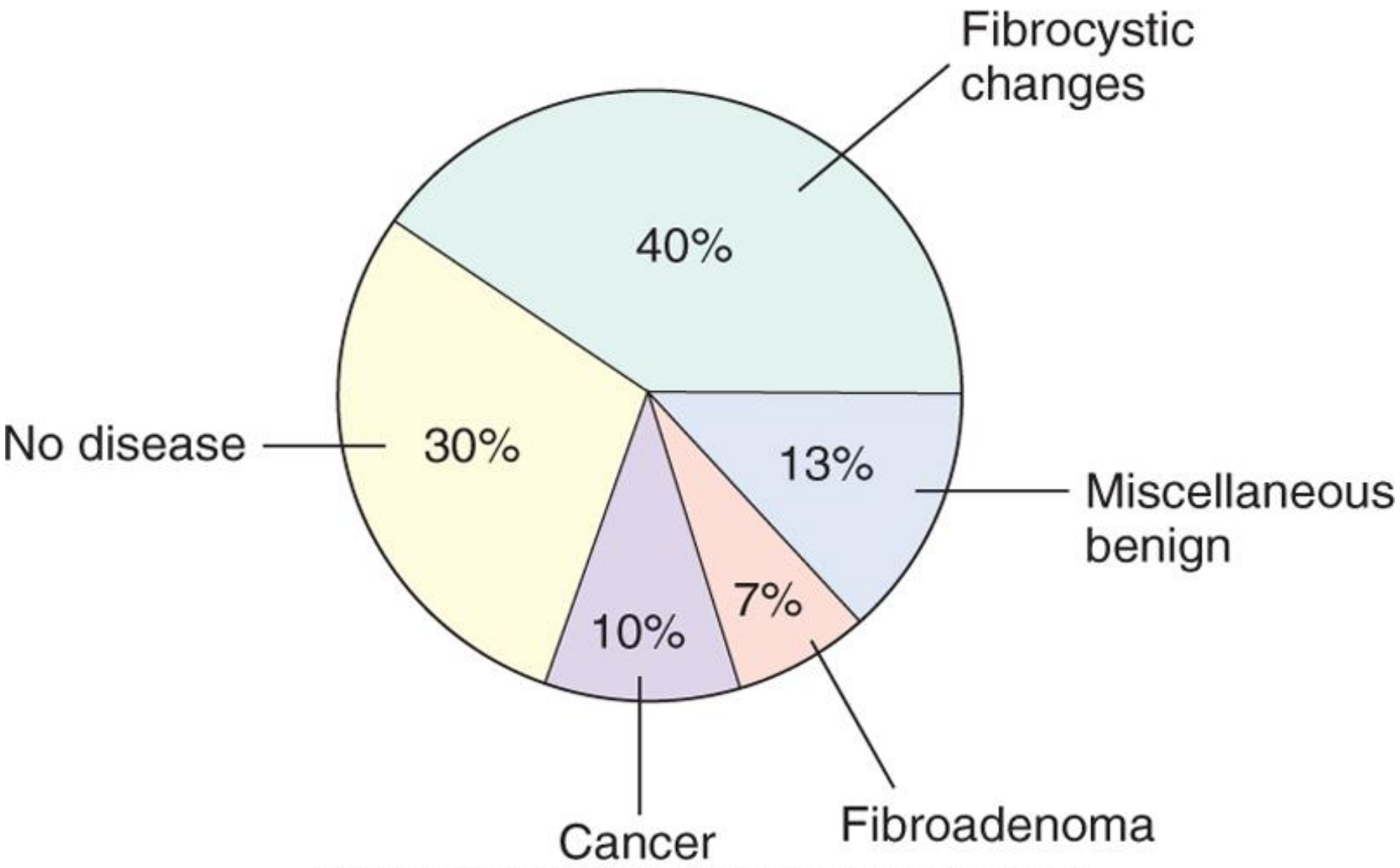
- Some women have sufficient irregularity of the normal breast tissue to cause them to seek clinical attention.

- Supernumerary nipples or breasts may be found along the embryonic ridge (milk line, especially the **axilla**) & are subject to the same diseases that affect the definitive breasts.

- Congenital inversion of the nipple is significant because similar changes may be produced by breast **ca**.

- Galactocele is painful cystic dilation of an obstructed ductthat arises during lactation, which may rupture, inciting a local inflammatory reaction & fibrosis that may arouse suspicion of breast **ca.**

The finding in **a** series of women seeking evaluation of apparent breast “lump”.



Inflammatory lesions of the breast

- rare
- caused by infections, autoimmune disease, or foreign body–type reactions.

- Clinically: erythema, edema, pain and focal tenderness.
- Mostly infectious agent is ***Staphylococcus aureus***

- Enters via fissures in nipple skin during the first weeks of breast feeding→lactational abscesses.
- If untreated, tissue necrosis →fistula tracks opening onto the skin.

- **Treatment**: antibiotics and continued expression of milk. Rarely, surgical incision and drainage is required.

- Note: Because inflammatory diseases are rare, the possibility that the symptoms are caused by inflammatory carcinoma **should always be considered.**

INFLAMMATIONS OF THE BREAST

Includes: (1) acute mastitis, (2) mammary duct ectasia,& (3) traumatic fat necrosis, **none** of which are associated with ↑risk of ca.

- All three are uncommon & during the acute stages usually cause **pain & tenderness** in the involved areas

Acute mastitis

- Develops when bacteria gain access to the breast tissue through the ducts; when there is inspissation of secretions; through fissures in the nipples, which usually develop during the early weeks of nursing (lactation)or from various forms of dermatitis involving the nipple.

- **Grossly, staphylococcal infections induce single or multiple abscesses** accompanied by its typical clinical features. They are usually small, when large they may heal with residual foci of **scarring** that are palpable as localized areas of induration (that mimic ca).

- **Streptococcal infections** generally spread throughout the entire breast, causing pain, marked swelling, & breast tenderness, usually heal by resolution

Mammary duct ectasia (Peri-ductal or Plasma Cell Mastitis)

- Is a **non-bacterial** chronic inflammation of the breast associated with
- (1) **inspissation of breast secretions in the main excretory ducts**
- **(2) ductal dilation & rupture** leading to reactive inflammatory changes in the surrounding tissue.
- It is an **uncommon condition**, usually encountered in women in their 40s & 50s who have borne children.

- **Grossly,** usually the inflammatory changes are confined to an area drained by one or several major excretory ducts of the nipple with ↑firmness of the tissue. **O/S dilated rope like ducts** are seen from which thick, cheesy secretions can be extruded.
- Histopath, the **(1)dilated ducts are filled by granular debris**, WBCs, mainly **lipid-laden macrophages,**
- **(2)**the duct epithelium lining is generally destroyed, &

- **(3)**the most distinguishing features is the **prominence of a lymphocytic & plasma cell infiltration around the duct**
- Mammary duct ectasia is of principal importance because it leads to induration of the breast substance &, more significantly, to retraction of the skin or nipple, mimicking the changes caused by ca.

Traumatic fat necrosis

- Is an uncommon lesion, significant only because it produces a mass, mimicking ca.
- Most (but not all) women with this condition report some antecedent trauma to the breast.
- Grossly, the early lesion is sharply localized, small, often tender, less than 2 cm in Ø.
- Histopath: a central focus of necrotic fat cells surrounded by neutrophils & lipid-filled macrophages, later enclosed by fibrous tissue& mononuclear leukocytes.
- Eventually, the focus is replaced by scar tissue, or the debris becomes cystic, surrounded by a scar.
- Calcifications

FIBROCYSTIC CHANGES (disease)

- **Very common condition**, in which changes in the female B range from innocuous, to patterns associated with an ↑ risk of ca.
- These changes have been called **fibrocystic disease**.
- **Most** of these changes have little clinical significance except that **some**(stromal fibrosis & microcysts or macrocysts) **produce palpable "lumps“,** which must be distinguished from cancer by examination of fine needle aspiration (FNA) material or, **more definitively by biopsy & histologic evaluation.**
- A **small minority** represents forms of epithelial hyperplasia that are clinically important.
- This range of changes is the **consequence of an** exaggeration & distortion of the cyclic breast changes that occur normally in the menstrual cycle.
- Estrogenic therapy & oral contraceptives do not seem to ↑the incidence of these alterations; indeed, oral contraceptives may decrease the risk.

Benign Epithelial lesions

- The majority are incidental findings detected by mammography.
- Benign changes are divided into three groups:
- **Non proliferative changes**: is not associated with an increased risk of breast cancer.
- **Proliferative disease without atypia**: polyclonal hyperplasias& associated with 1.5-2 folds increase risk of breast cancer.
- **Proliferative disease with atypia**: monoclonal "**precancers**" & associated with 4-5 folds increase risk of breast cancer in **both** breast

Non Proliferative breast changes (fibrocystic changes).

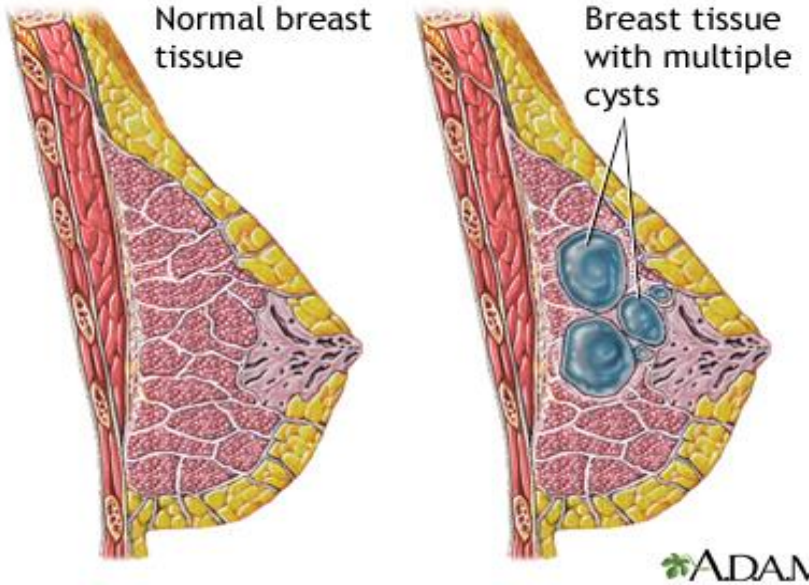
- Common
- There are three principal morphologic changes:

(1) cystic change, often with apocrine metaplasia (most common)

- Although it may present as a single large cyst within one breast, the disorder is usually multifocal& often bilateral,

(2) Fibrosis.

(3) Adenosis

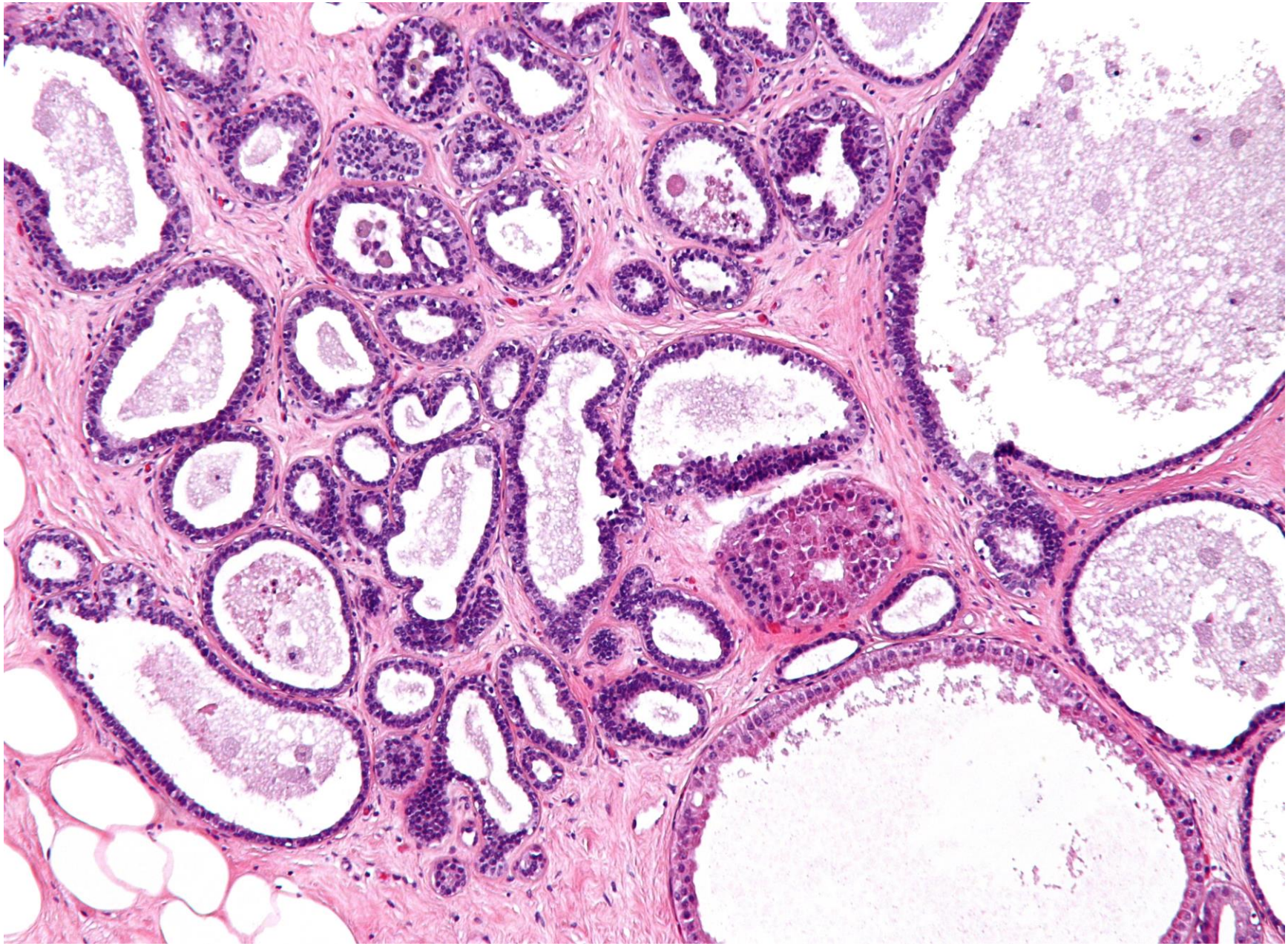


- H/P:The smaller cysts epithelium is cuboidal to columnar & is sometimes multilayered in focal areas.

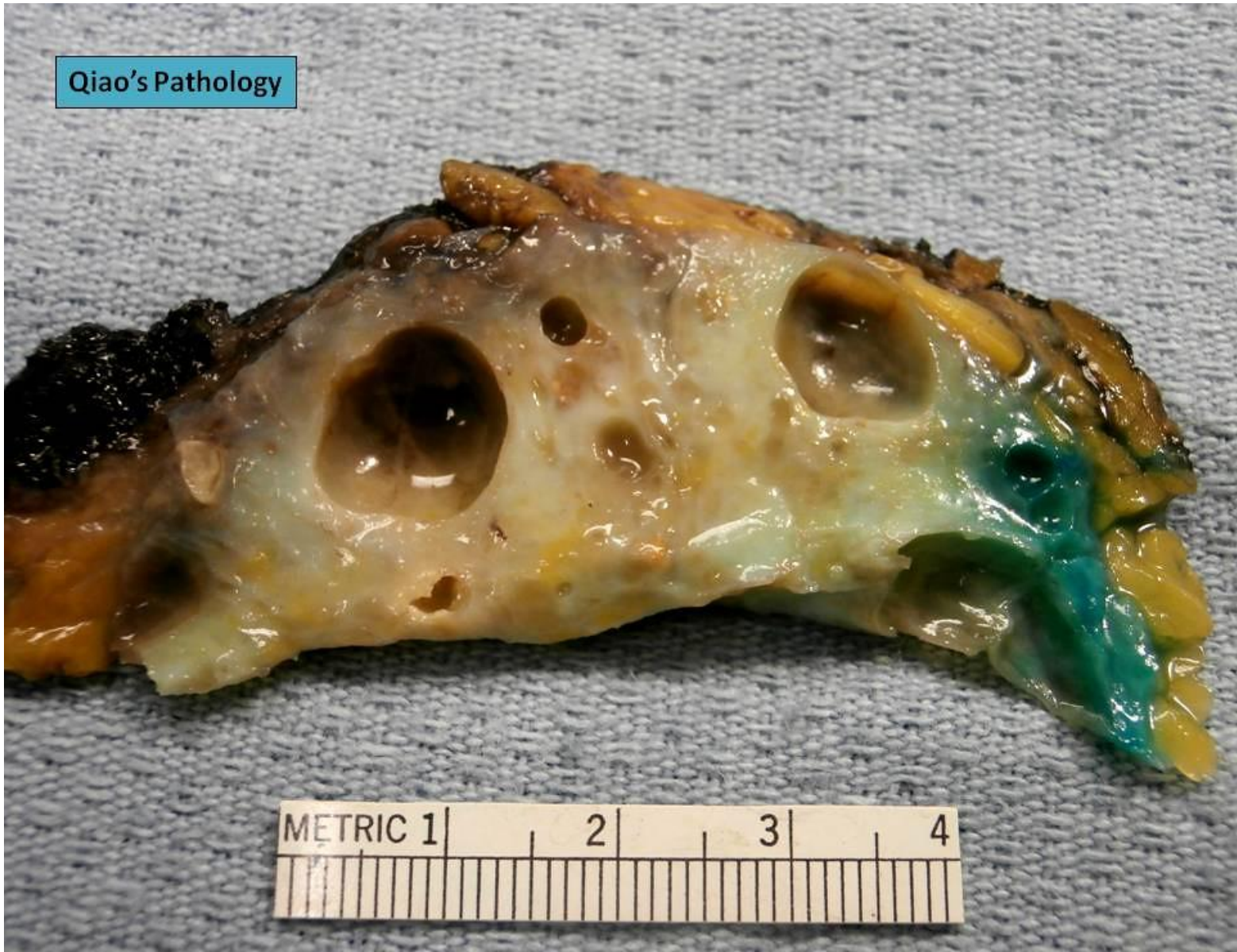
- In larger cysts it may be flattened or even totally atrophic .

- Frequently, cysts are lined by large polygonal cells, with abundant granular eosinophilic cytoplasm & small, round, deeply chromatic nuclei, called **apocrine metaplasia ;**this is **virtually always benign**.
- The stroma surrounding the cysts consist of compressed fibrous tissue.
- A stromal **lymphocytic infiltrate is common** in all variants of fibrocystic change (proliferative & non proliferative)

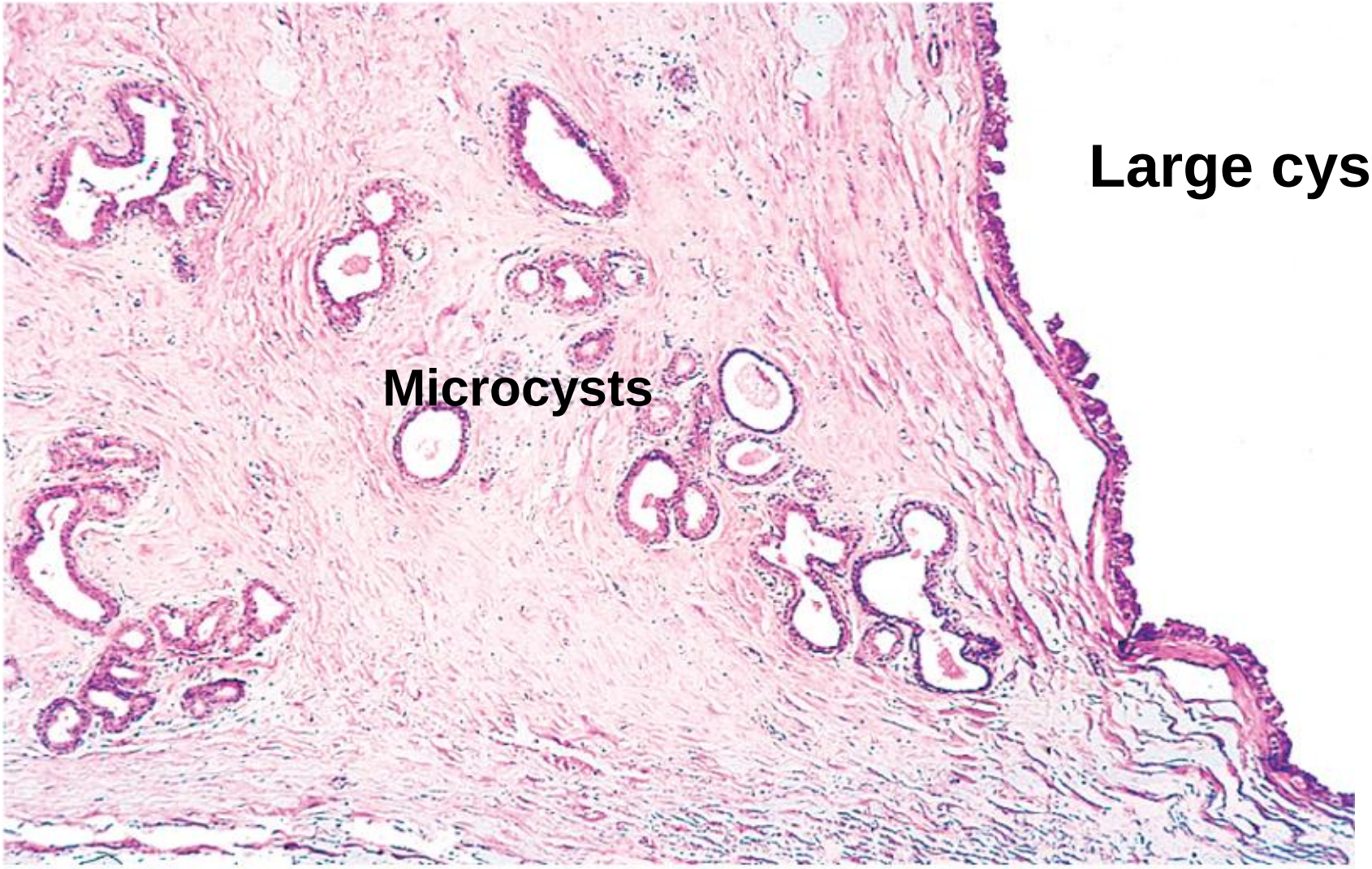
Fibrocystic disease of the breast



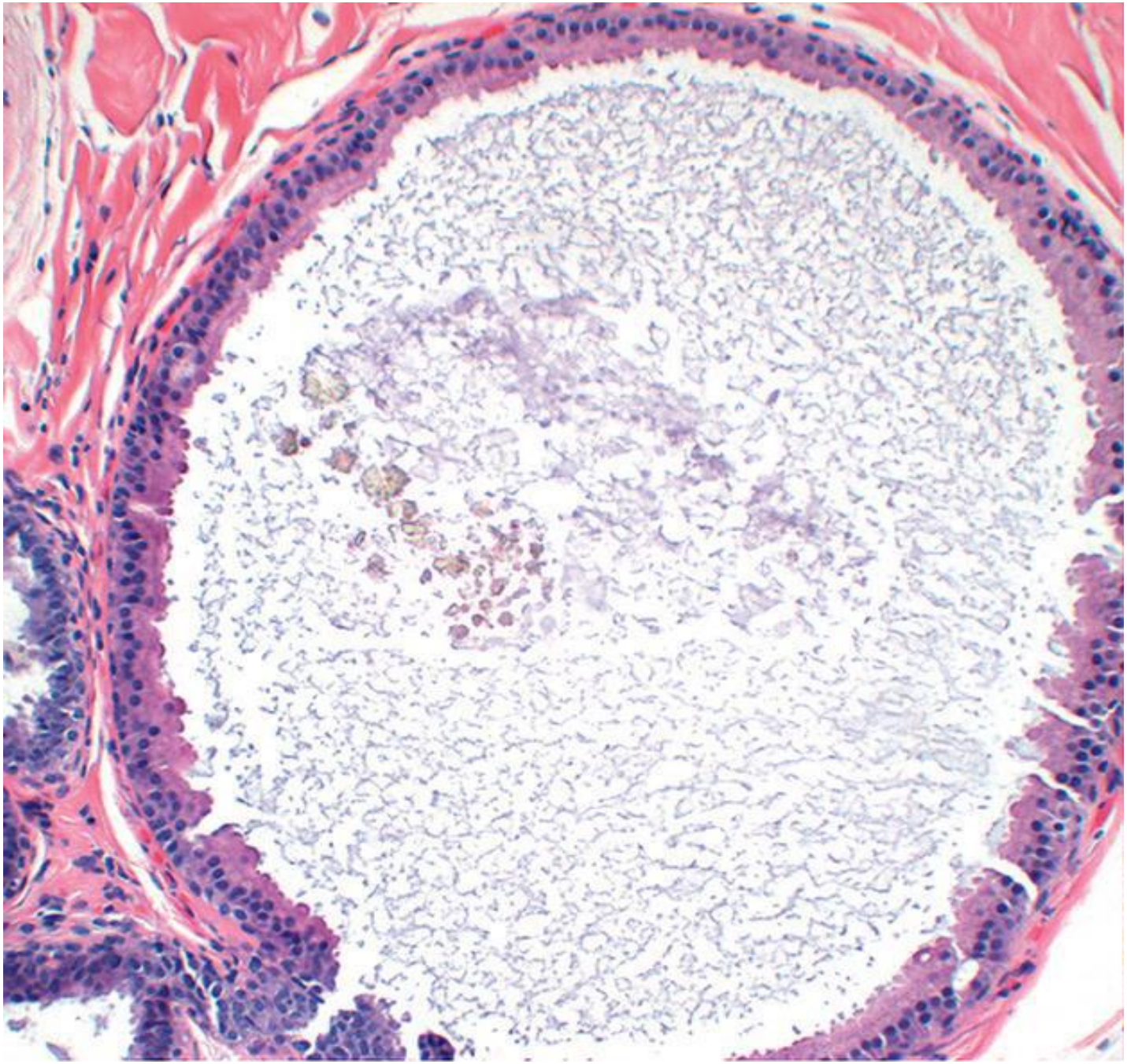
Fibrocystic disease: breast. Replacement of the normal breast tissue by greyish-white **fibrous** tissue, within which are multiple small & large **cysts**.



Histology of fibrocystic change of the breast revealing dilatation of the ducts producing **microcysts**&, at right, the wall of a **large cyst** with visible lining epithelial cells



Non-Proliferative Disease .Apocrine Cyst



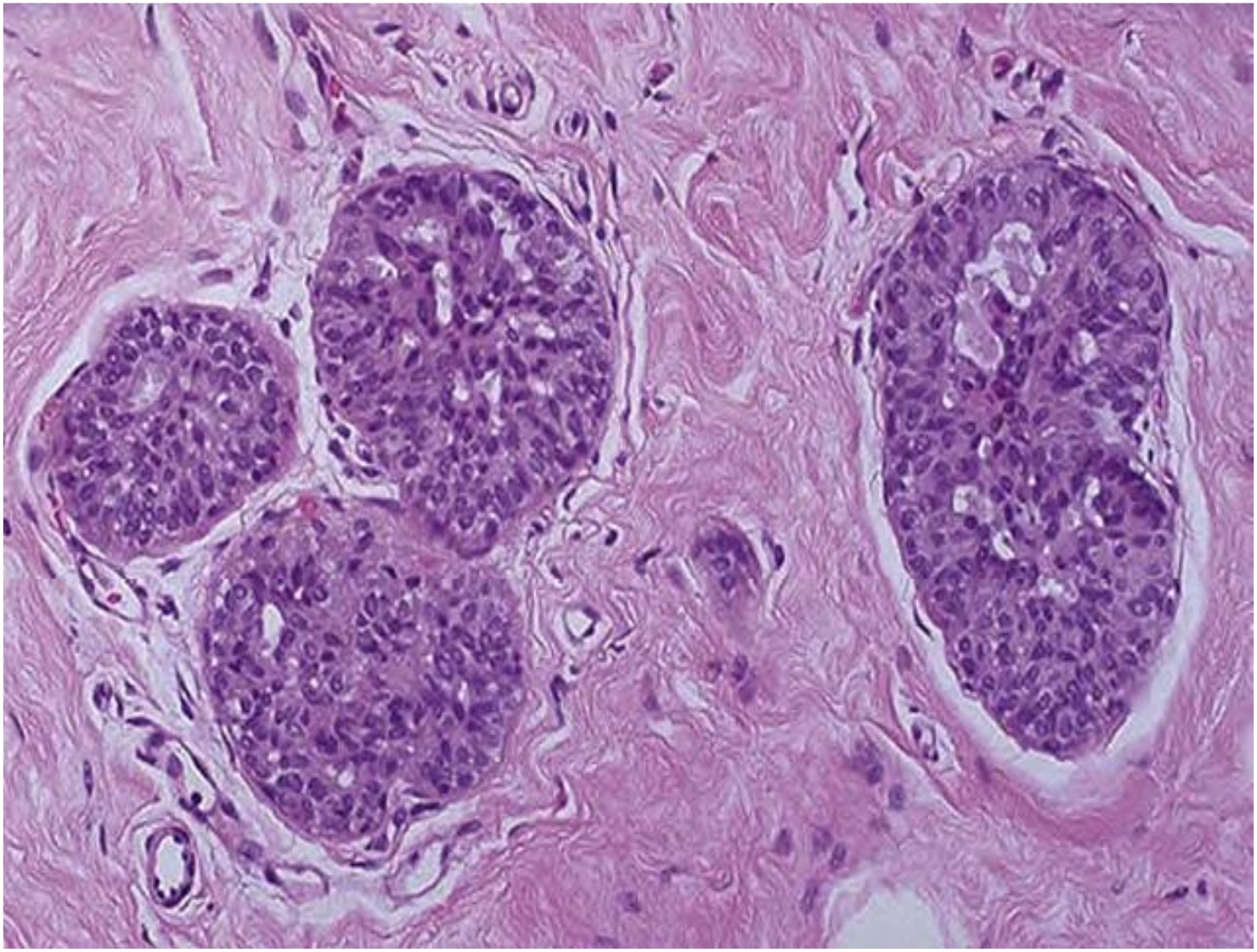
Proliferative disease without Atypia

Includes:

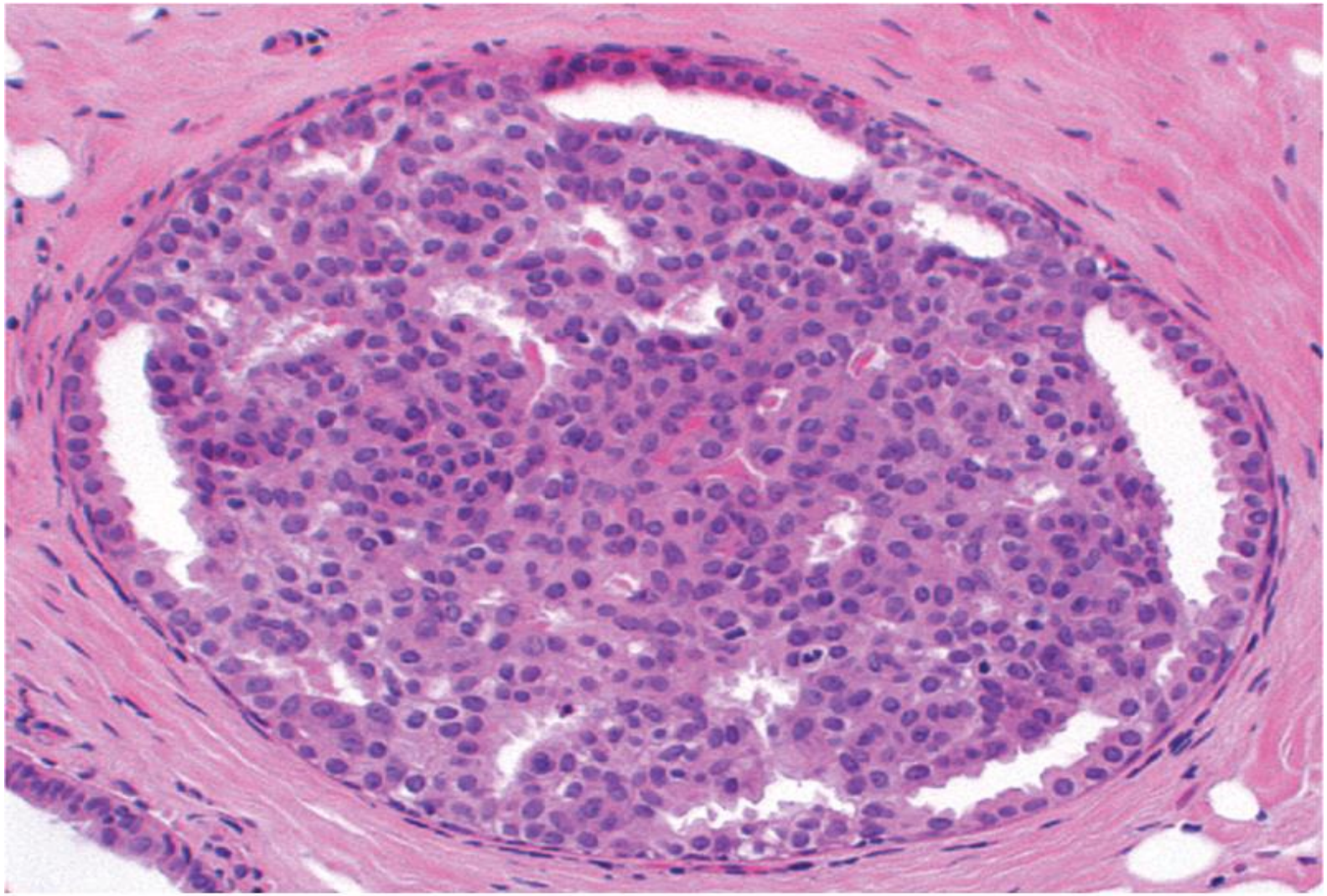
- epithelial hyperplasia
- sclerosing adenosis
- complex sclerosing lesion
- papilloma

- associated with varying degrees of epithelial cell proliferation.
- **associated with a small increase in the risk of subsequent carcinoma in either breast.**
- not clonal and are not commonly found to have genetic changes.
- are predictors of risk but unlikely to be true precursors of carcinoma.

Epithelial hyperplasia ,,the epithelial cells are multilayered filling the duct and the acini, **myoepithelial cells are increased** , no epithelial atypia



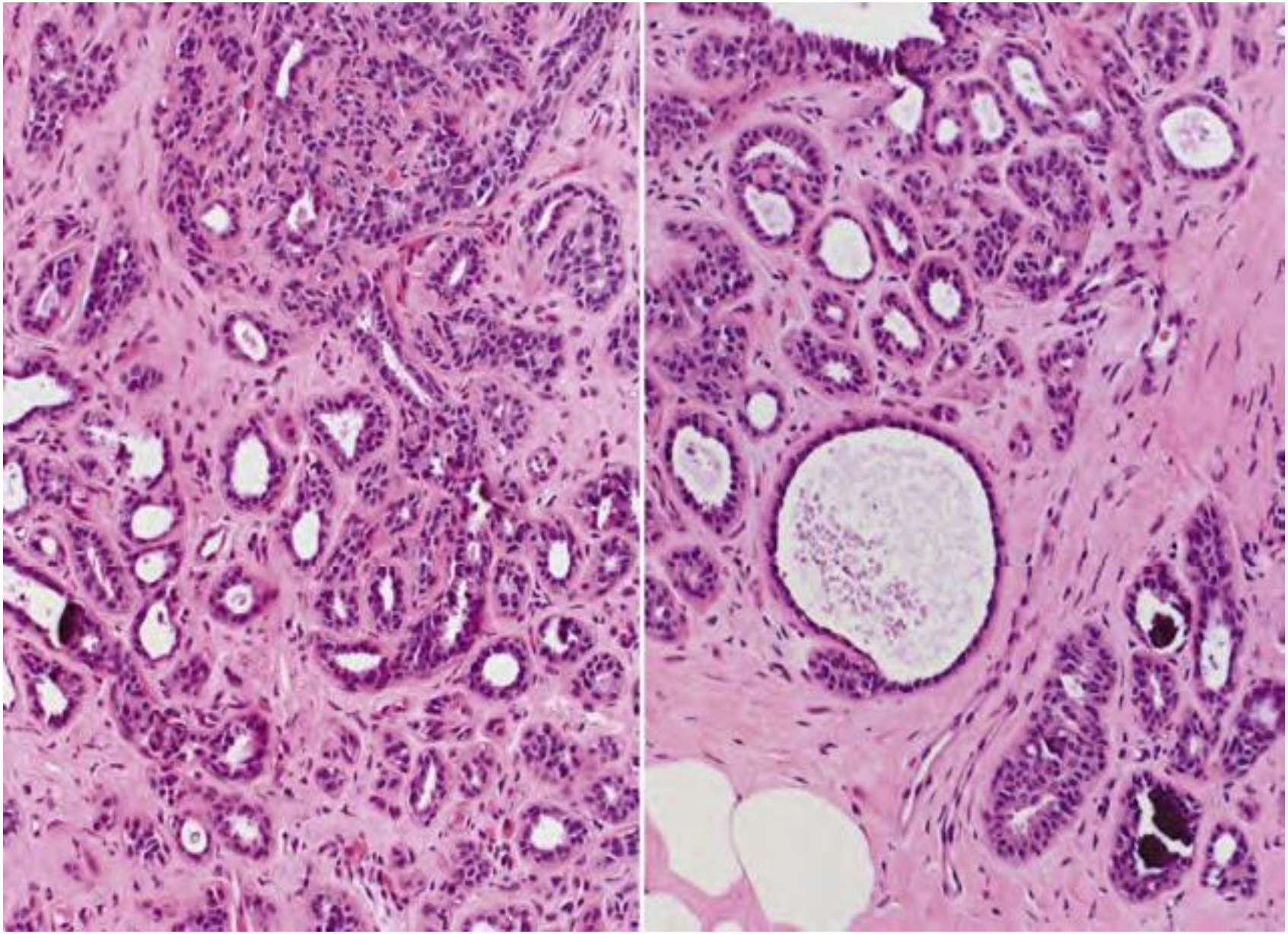
Epithelial hyperplasia . The duct lumen is filled with a **heterogeneous** population of cells of different morphologies. **Irregular slit-like fenestrations** are **prominent at the periphery.**



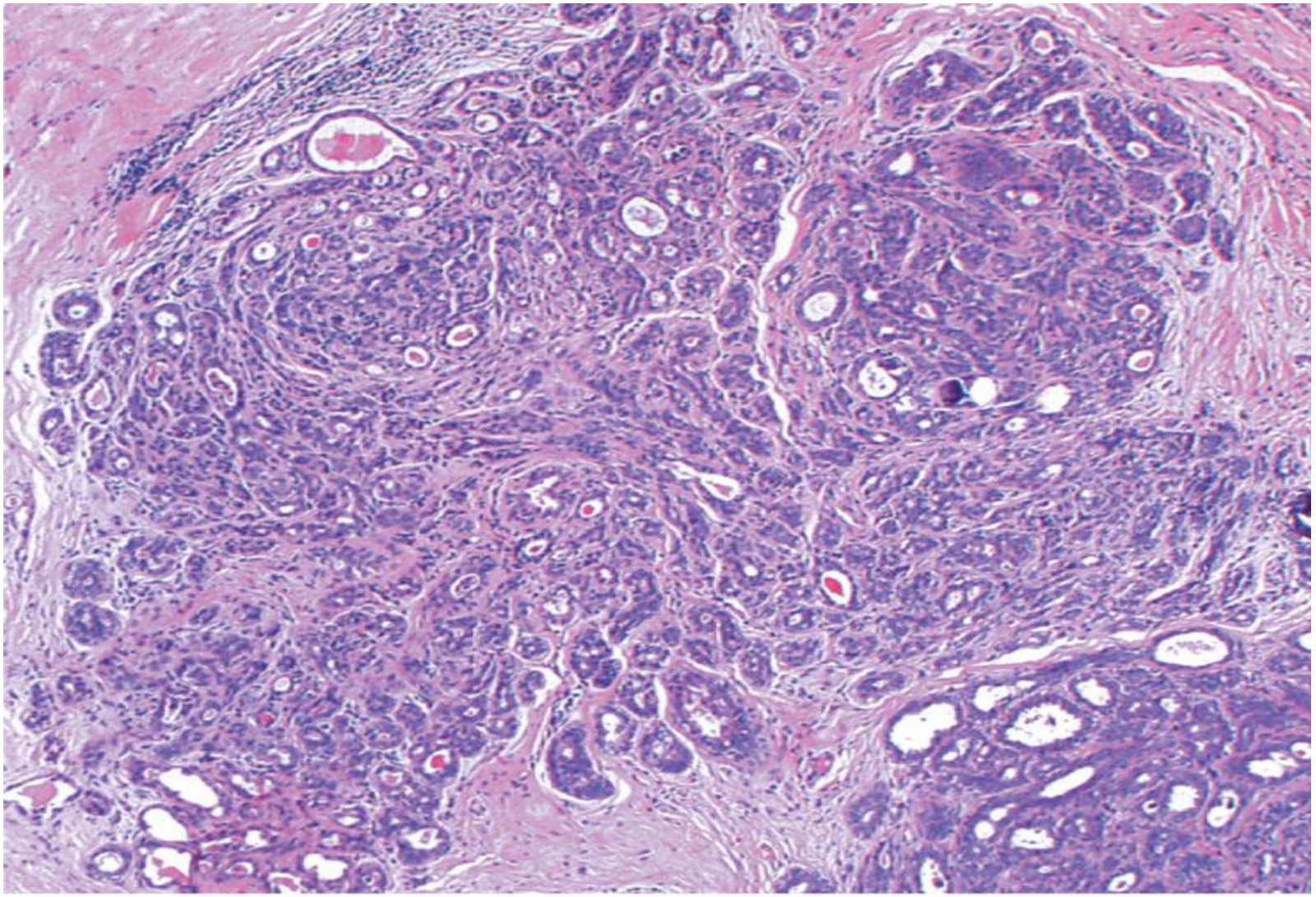
Sclerosing adenosis

- Aggregated glands or proliferating ductules may be virtually back to back, with single or multiple layers of cells in contact with one another **(adenosis).**
- Marked stromal **(sclerosing fibrosis)**compress & distort the proliferating epithelium, is always associated with the adenosis; hence, the designation **sclerosing adenosis.**
- **This overgrowth of fibrous tissue may completely compress the lumina of the acini & ducts, so that they appear as solid cords of cells**, a pattern may be difficult to distinguish histologically from an invasive scirrhous **ca**.
- The presence of double layers of epithelium & the identification of **myoepithelial elements** are helpful in suggesting a **benign diagnosis**.
- Although sclerosing adenosis is sometimes difficult to differentiate clinically & histologically from ca, it is associated with only a minimally ↑risk of progression to ca.

Sclerosing Adenosis



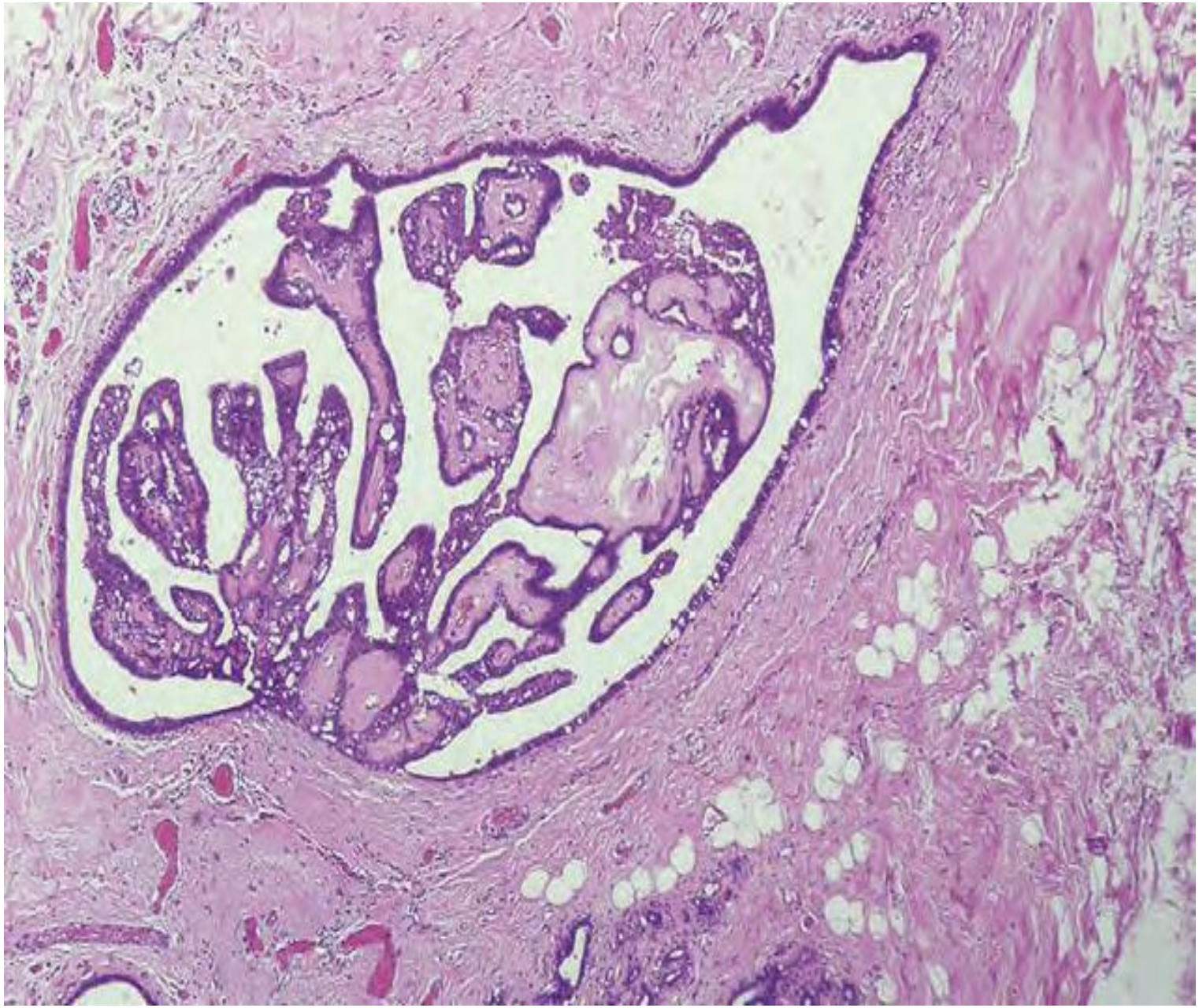
Sclerosing adenosis . Enlarged terminal duct lobular unit. The acini are compressed & distorted by the surrounding dense stroma. **Unlike carcinomas**: •the acini are arranged in a swirling pattern, & •the outer border is usually well circumscribed.



Ductal papillomatosis

- with proliferating epithelium projecting in multiple small **papillary projections** into the ductal lumen.
- The degree of hyperplasia, manifested in part by the number of layers of intraductal epithelial proliferation, can be mild, moderate, or severe;

Intraductal Papilloma of the breast



Proliferative Lesions with atypia

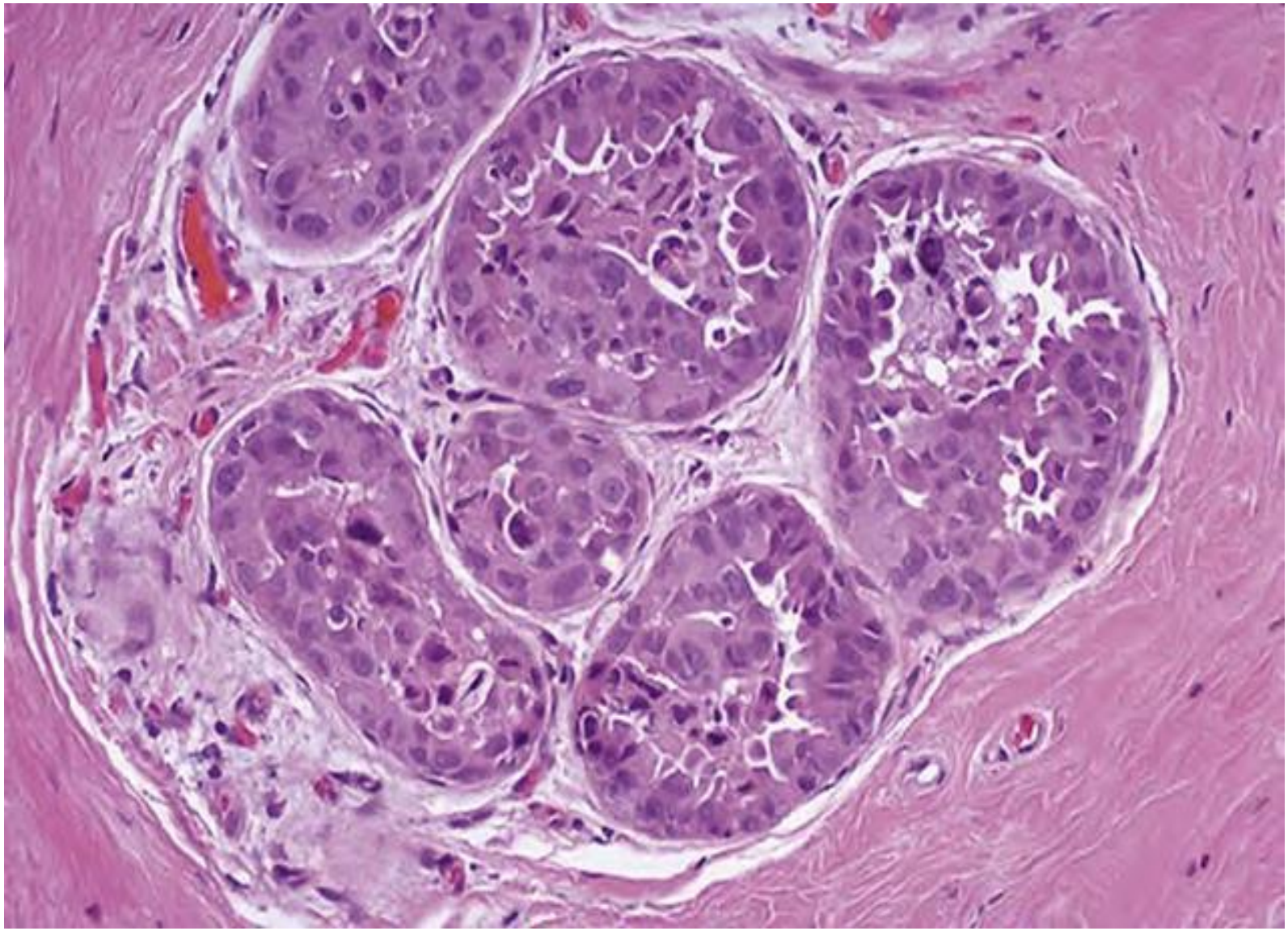
- **atypical lobular hyperplasia (ALH):** resembles lobular carcinoma in situ (LCIS).
- **atypical ductal hyperplasia (ADH):** resembles ductal carcinoma in situ (DCIS)

- are clonal proliferations having some, but not all, histologic features that are required for the diagnosis of carcinoma in situ.

- Associated with a moderately increased risk of carcinoma

- Atypical Hyperplasia in which the hyperplastic cells become monomorphic with complex architectural patterns, having changes approaching those of ductal ca in situ (**DCIS**) such hyperplasia is called **atypical.**
- The line separating the epithelial hyperplasias without atypia from atypical hyperplasia is important but difficult to define, just as it is difficult to clearly distinguish between atypical hyperplasia & ca in situ.
- Immunohistochemical (IHC) stains provide information and aid in the differential diagnosis of challenging epithelial lesions of the breast.

Atypical Ductal Hyperplasia



Non-Invasive In-situ Carcinoma

- **include:**

1. Ductal carcinoma in situ, DCIS
2. Lobular carcinoma in situ, LCIS

- both types arise from cells in the terminal duct that give rise to lobules.
- LCIS usually expands involved lobules, whereas DCIS distorts lobules into duct like spaces
- **By definition both confined by a basement membrane and do not invade into stroma or lymphovascularchannels**

Lobular carcinoma in Situ

- Lobular Carcinoma in Situ (LCIS) is a malignancy of the secretory lobules of the breast that is contained within the basement membrane . They are much rarer than DCIS
- Malignant clonal proliferation of cells within lobules.
- Cells grow in a discohesive fashion→an **acquired loss of the tumor suppressive adhesion protein E-cadherin**.
- The term “lobular” was used to describe this lesion because the cells expand but do not distort involved spaces and, thus, the underlying lobular architecture is preserved.
- LCIS is usually asymptomatic, much like DCIS, however LCIS is not associated with microcalcifications but instead usually diagnosed as an incidental finding during biopsy of the breast.

Ductal Carcinoma in Situ

- **Ductal carcinoma in situ** (DCIS) is the **most common type** of non-invasive breast malignancy and currently comprises around 20% of all breast cancers diagnosed.
- It is a **malignancy of the ductal tissue of the breast** that is contained within the basement membrane , yet **20-30% of cases** (who do not receive treatment) **will develop invasive disease**.
- malignant clonal proliferation of epithelial cells within ducts .
- DCIS has a wide variety of histologic appearances including:
- solid, comedo, cribriform, papillary, and micropapillary
- Ranges from low to high nuclear grade (pleomorphic).

comedo subtype:

- extensive central necrosis. (The name derives from the toothpaste-like necrotic tissue).
- **Frequently associated with Calcifications**→detected by mammography

Management DCIS

- The prognosis : excellent (97% long-term survival **after** simple mastectomy).

- Any detected localised DCIS should be **treated with complete wide excision**, ensuring the surrounding tissue of all margins have no residual disease.
- Cases of **widespread or multifocal DCIS** normally requires **complete mastectomy**.
- Significance: adjacent invasive CA; become invasive if untreated (1/3 of cases)

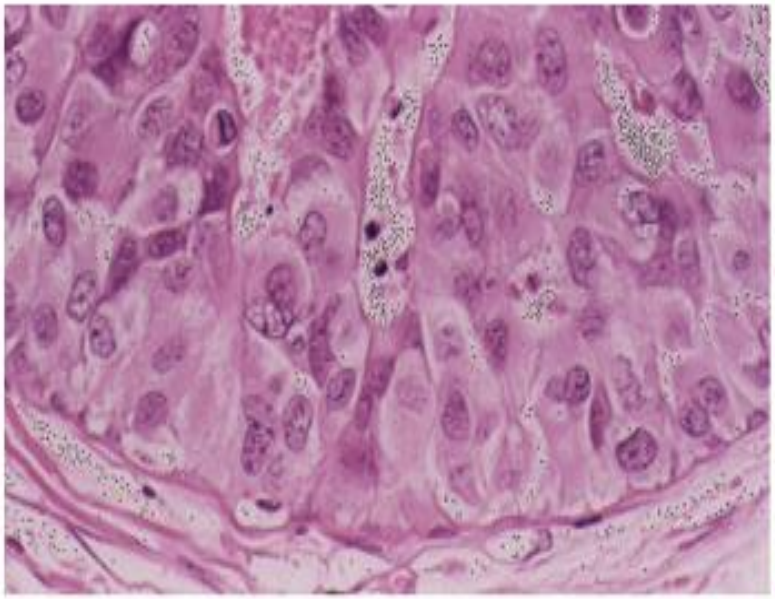
Management of LCIS

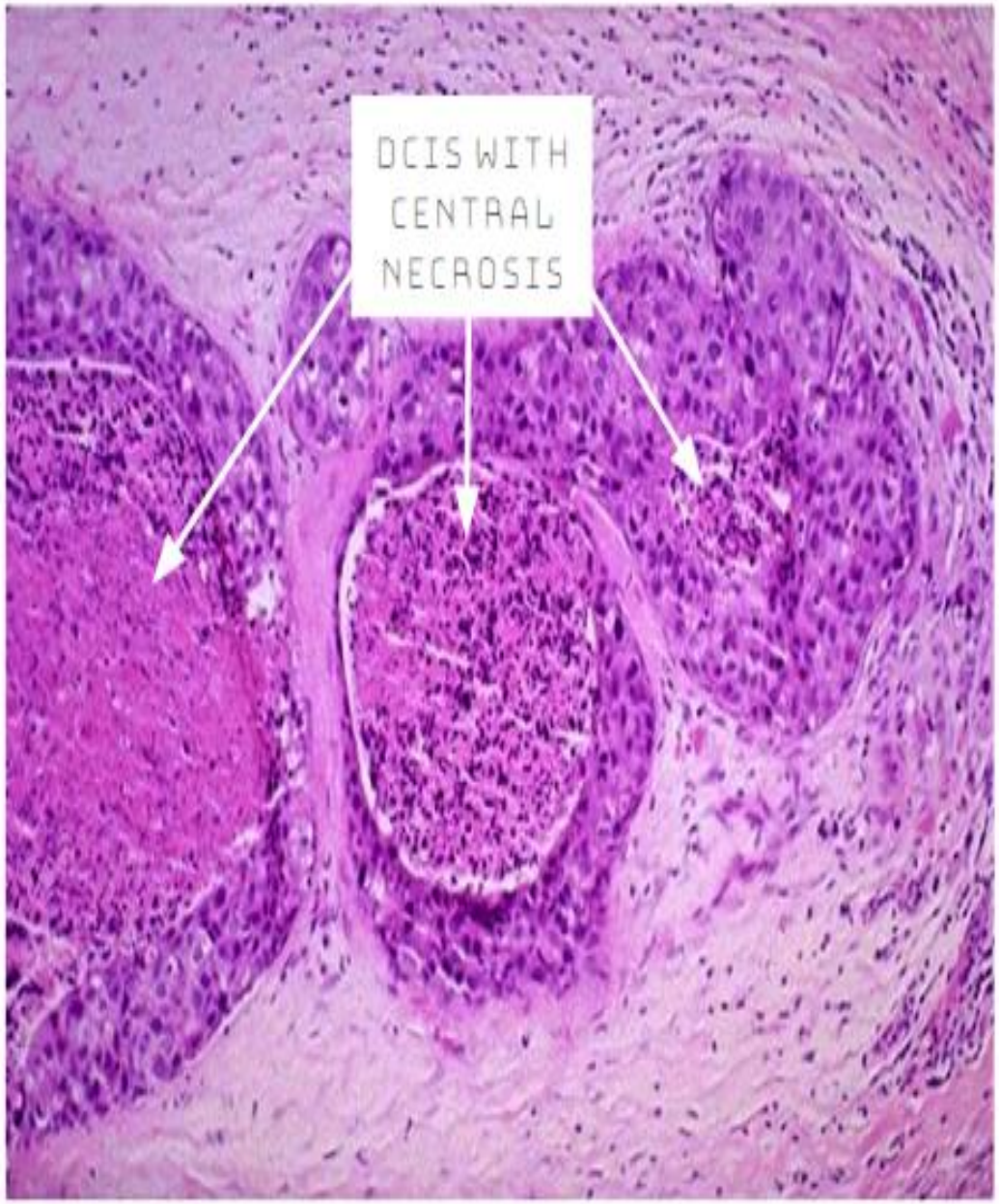
- Management of LCIS is dependent on extent of disease. Low grade LCIS is usually treated by monitoring rather than excision.

- When an invasive component is identified, it is less likely to be associated with axillary nodal metastasis than with DCIS. Bilateral prophylactic mastectomy can be potentially indicated if individuals possess the BRCA1 or BRCA2 genes.

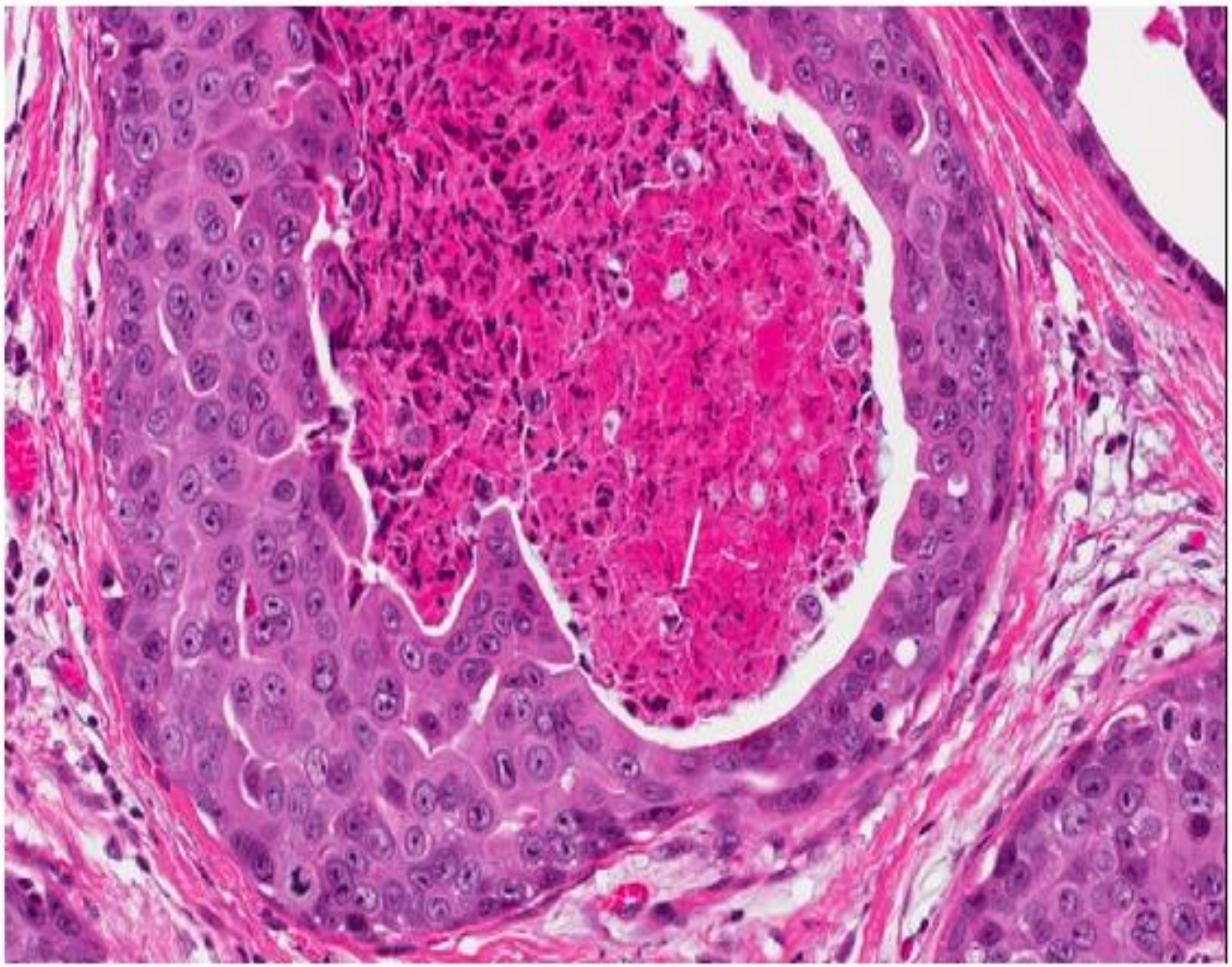
Microcalcifications, seen on mammograms, are often the result of necrotic intraductal material which has calcified. Let's make this quite simple...

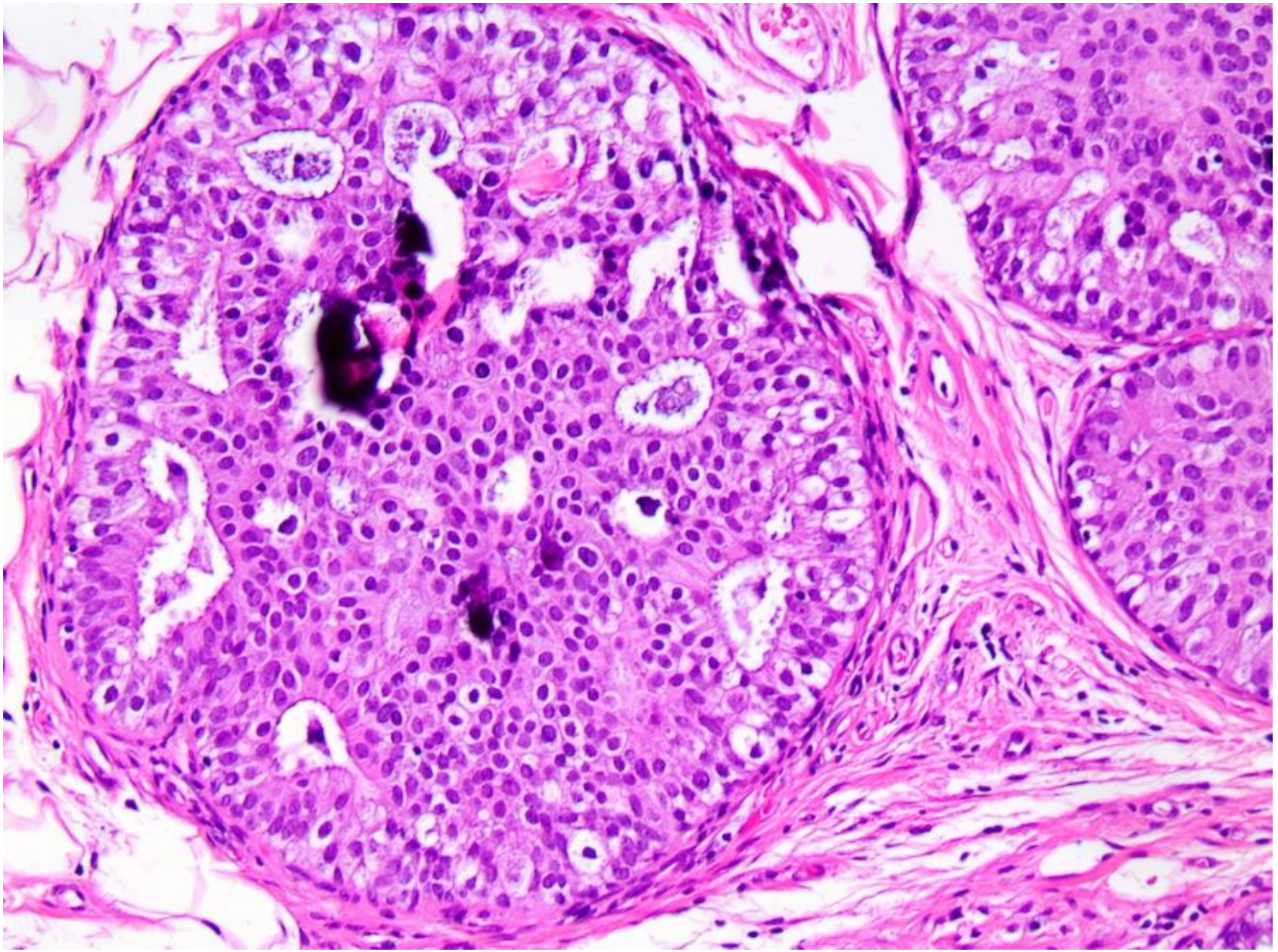
NECROSIS in a hyperplastic duct is usually DCIS!!

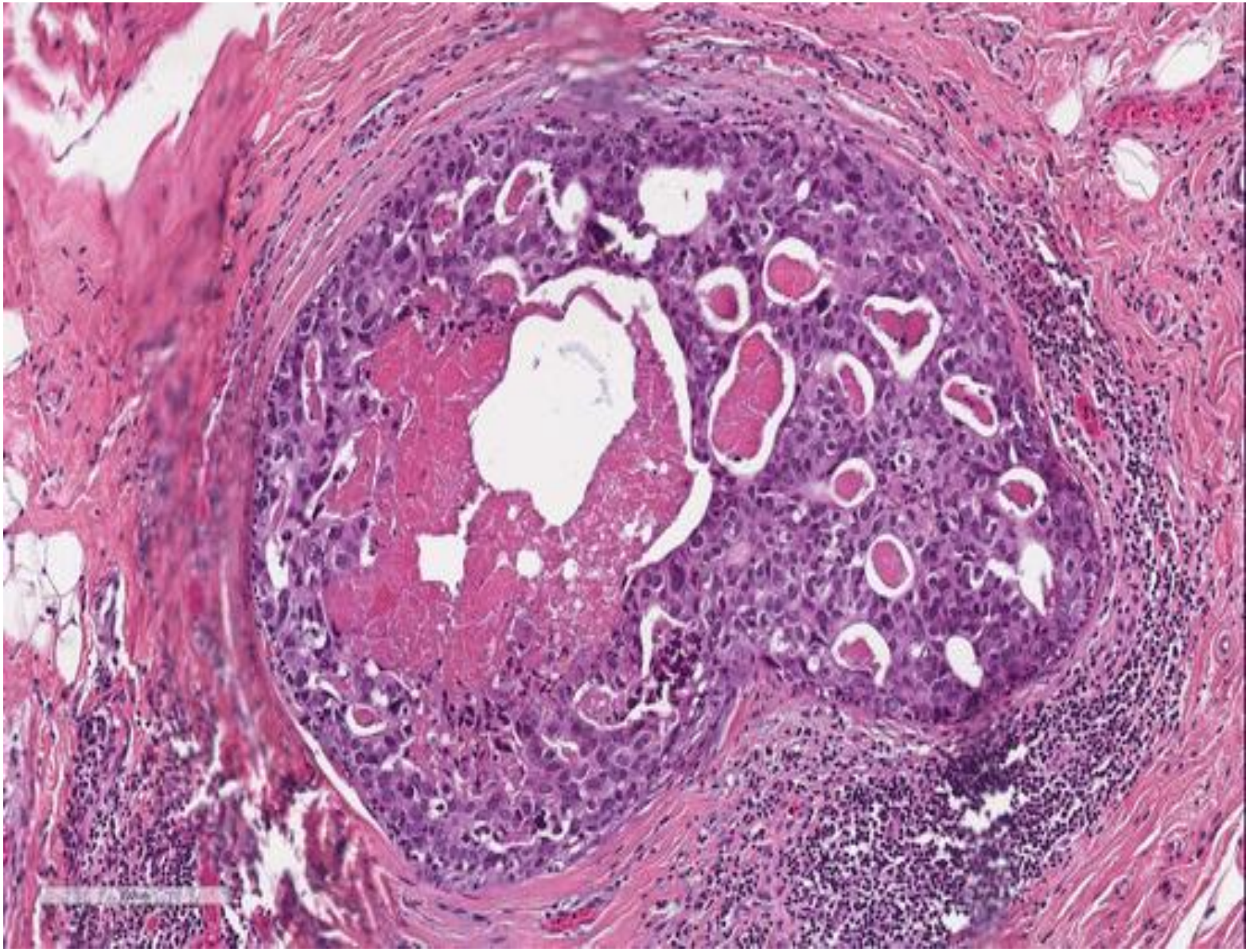




DCIS with central necrosis







The Relationship of Fibrocystic Changes to Breast Ca

The following statements represent opinion of the relationship:

- Minimal or no ↑ riskof breast ca:fibrosis, microscopic or macroscopic cysts, apocrine metaplasia, mild hyperplasia, fibroadenoma.
- Slightly ↑risk(X1.5-2 times):hyperplasia without atypia, ductal papillomatosis & sclerosing adenosis.

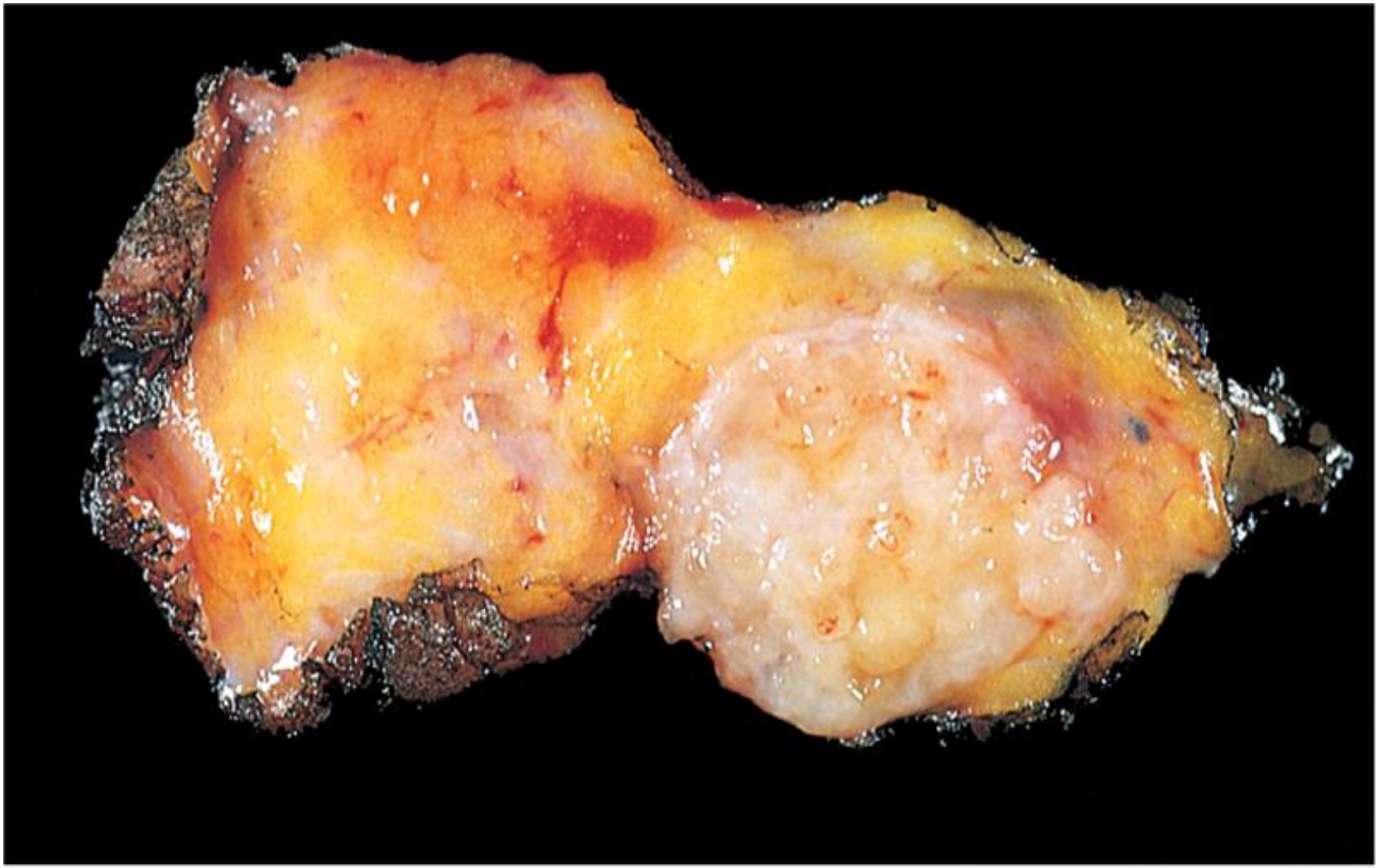
- Significantly ↑risk(X5 times): ductular or lobular **atypical hyperplasia**(seen in 15% of biopsies). Proliferative lesions may be multifocal, & the risk of subsequent ca extends to both breasts.
- A family history of breast ca may ↑the risk in all categories(e.g., to X10-fold with atypical hyperplasia).
- Fortunately ,most women who have lumps related to fibrocystic change can be reassured that there is little or no ↑predisposition to ca.

The most important lesions of the female breast are TUMORS

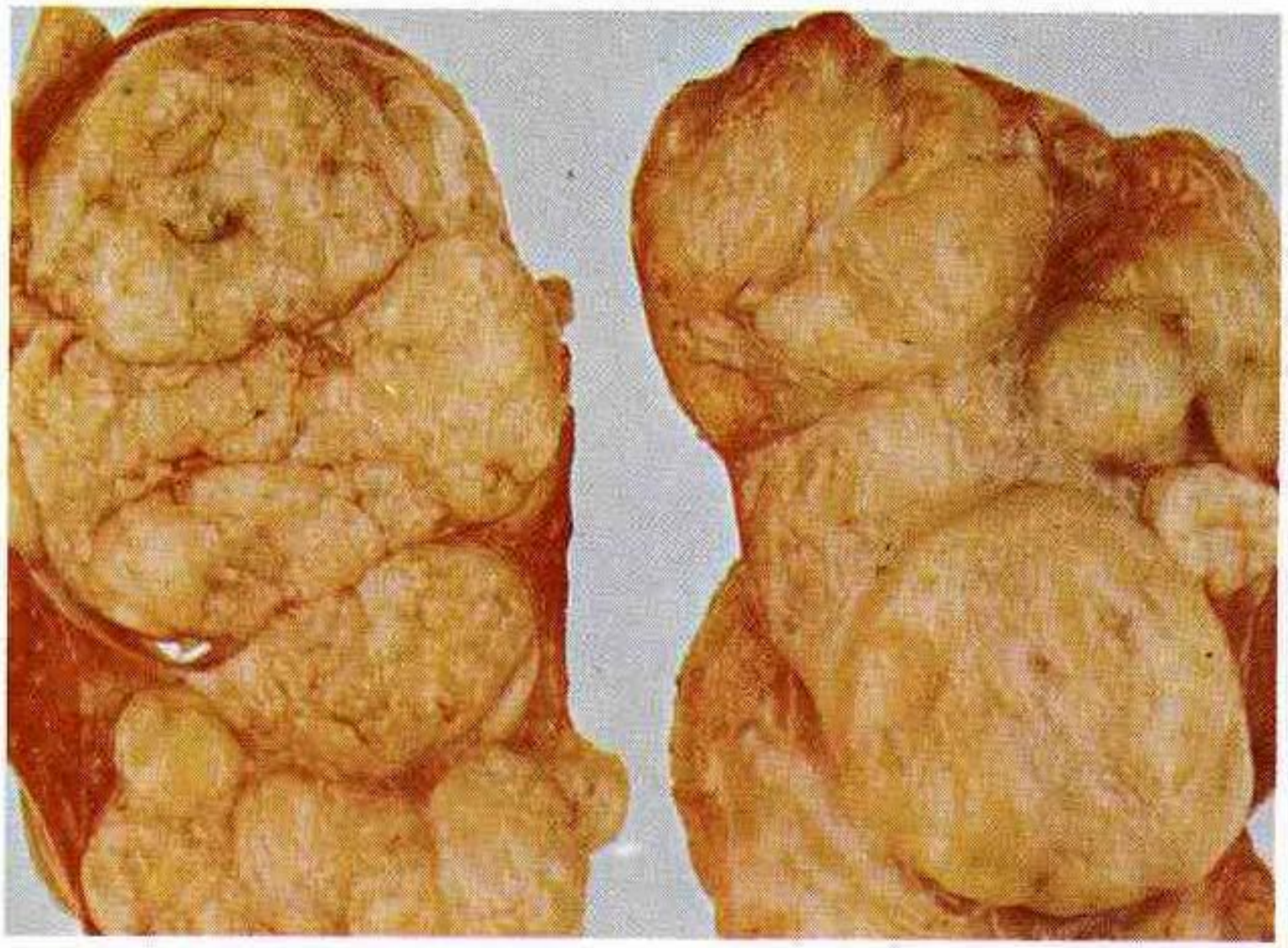
- **Fibroadenoma (FA)**

- Most common benign tumor of the female breast.
- An absolute or relative increase in estrogen activity is thought to contribute to its development. It may enlarge late in the menstrual cycle & during pregnancy; while it may regress & calcify after menopause.
- Usually appear in young women; the peak incidence is in the 3rd decade (21 to 30 years) of life.
- Clinically as solitary, discrete, freely movable nodule (so-called Breast mouse), 1-10 cm in Ø. Rarely, multiple fibroadenomas are encountered &, Rarely, they exceed 10 cm in Ø(giant fibroadenoma).
- Whatever their size, they are usually easily "shelled out."

Fibroadenoma. A rubbery white, well-circumscribed mass, clearly demarcated from the surrounding yellow fatty adipose breast tissue. **On mammogram ,** fibroadenoma appears **denser** than the surrounding tissue because it does not contain adipose tissue.



Fibroadenoma: breast. Two large (6 cm in long axis) fibroadenomas are shown in section. Each is well-encapsulated, yellowish, lobulated & nodular



12.3 Fibroadenoma: breast

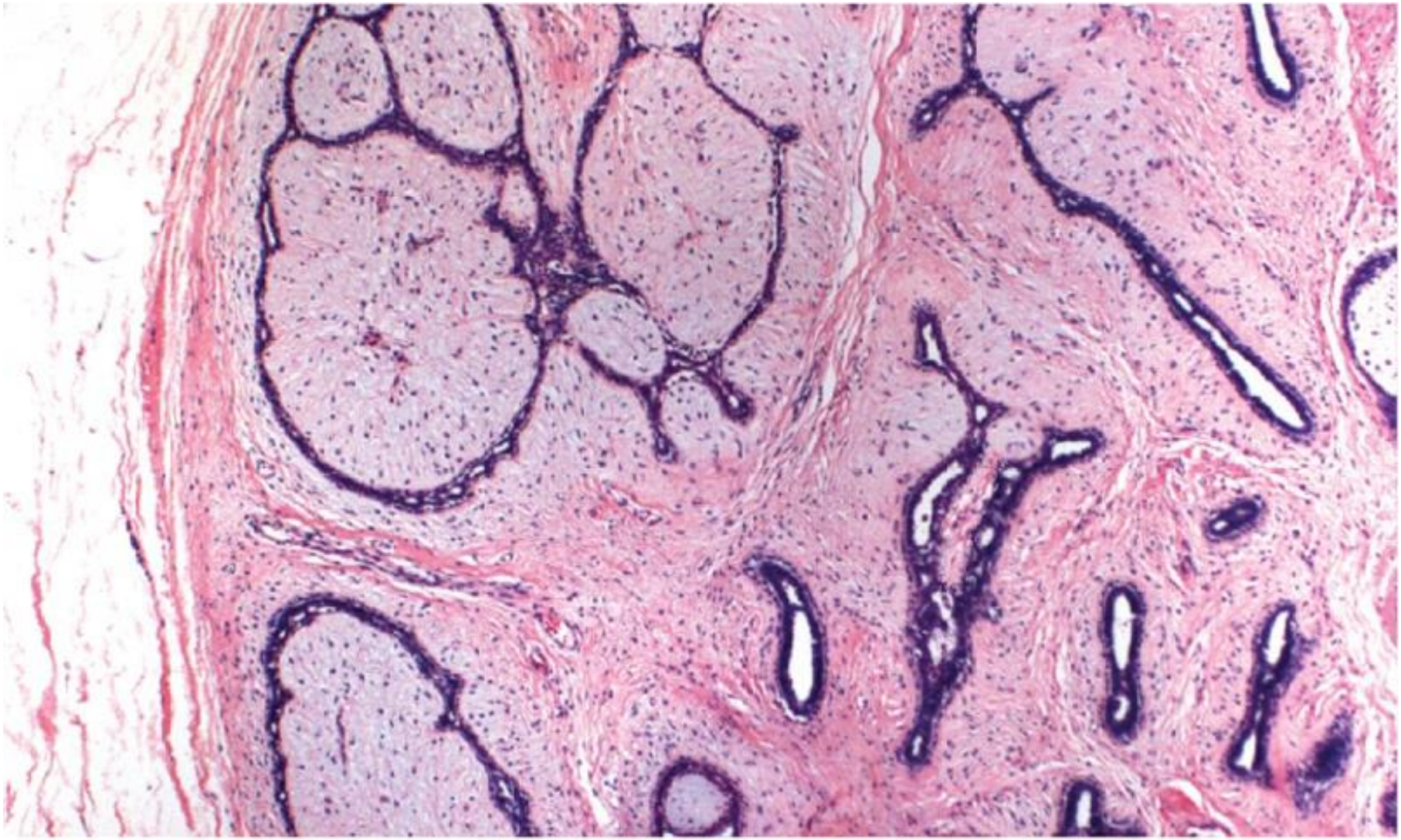
- Grossly, all FA are firm, with a uniform white cut section .
- H/P, there is (I) a loose fibroblastic stroma containing
- (II) duct-like, epithelium-lined spaces of various forms & sizes, lined with single or multiple layers of cells that are regular & have a well-defined, intact basement membrane.
- The ductal lumens or spaces are either:

•open, round to oval, & fairly regular, this type is called (pericanalicular FA) ,while in others…

•the lumens are compressed by extensive proliferation of the surrounding stroma, so they appear as slits or irregular star-shaped structures (intracanalicular FA),type .

- Fibroadenomas almost never become malignant.

Fibroadenoma, consisting of a proliferating intralobular stroma surrounding, pushing & distorting the associated epithelium. The border is sharply delimited, by a capsule from the surrounding tissue.



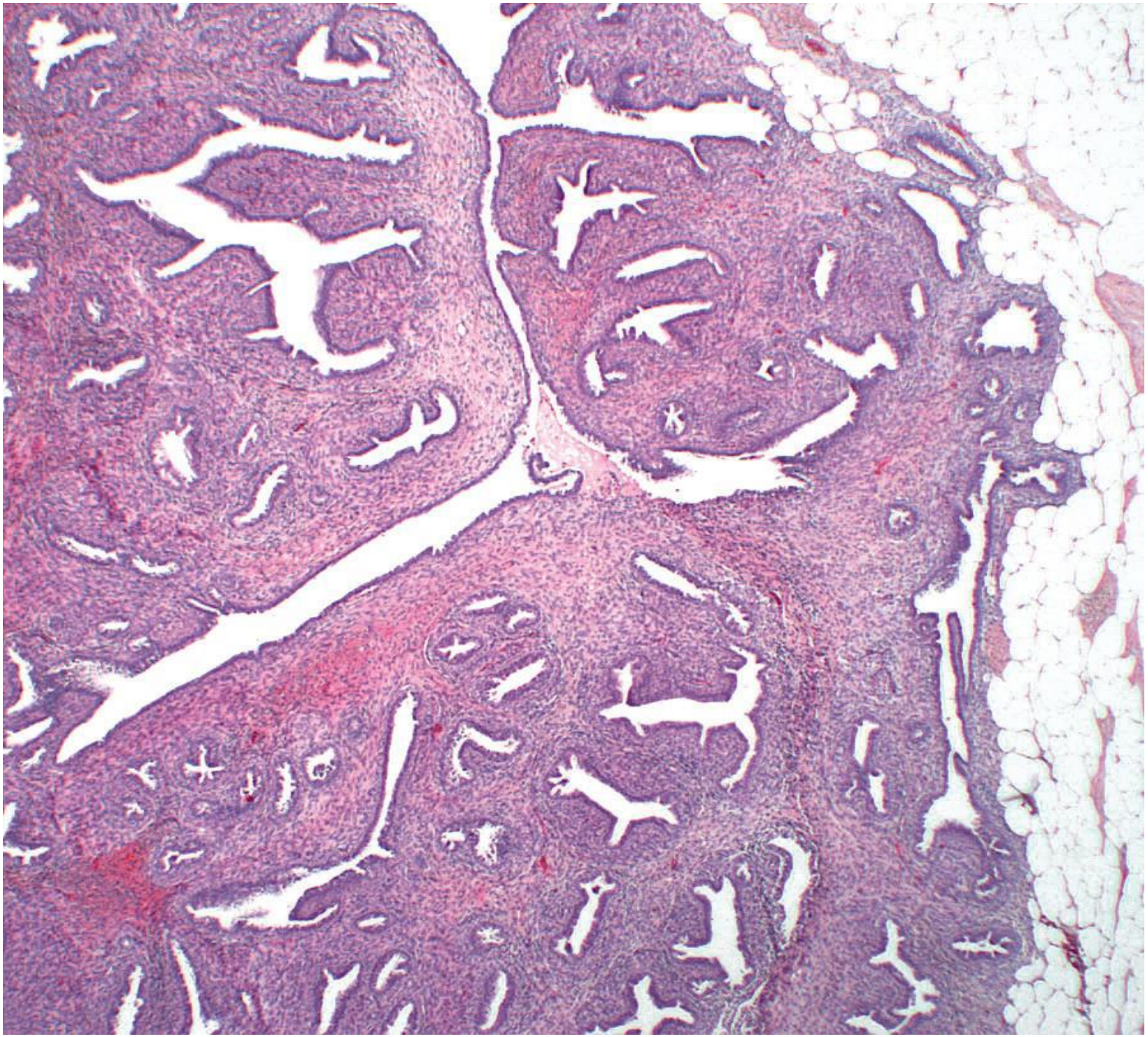
- **Phyllodes Tumor (T)**

- Phyllodes T are much less common than fibroadenomas & are thought to arise from the periductal stroma & not from preexisting fibroadenomas.
- Types: Most of these phyllodes **T** are benign, may be small (3-4 cm in ∅, **but most grow to large, possibly massive size,**distending the breast.
- **Some** become lobulated & cystic (because their section grossly exhibit leaflike clefts & slits, they have been designated phyllodes, from Greek, for "leaflike" T.

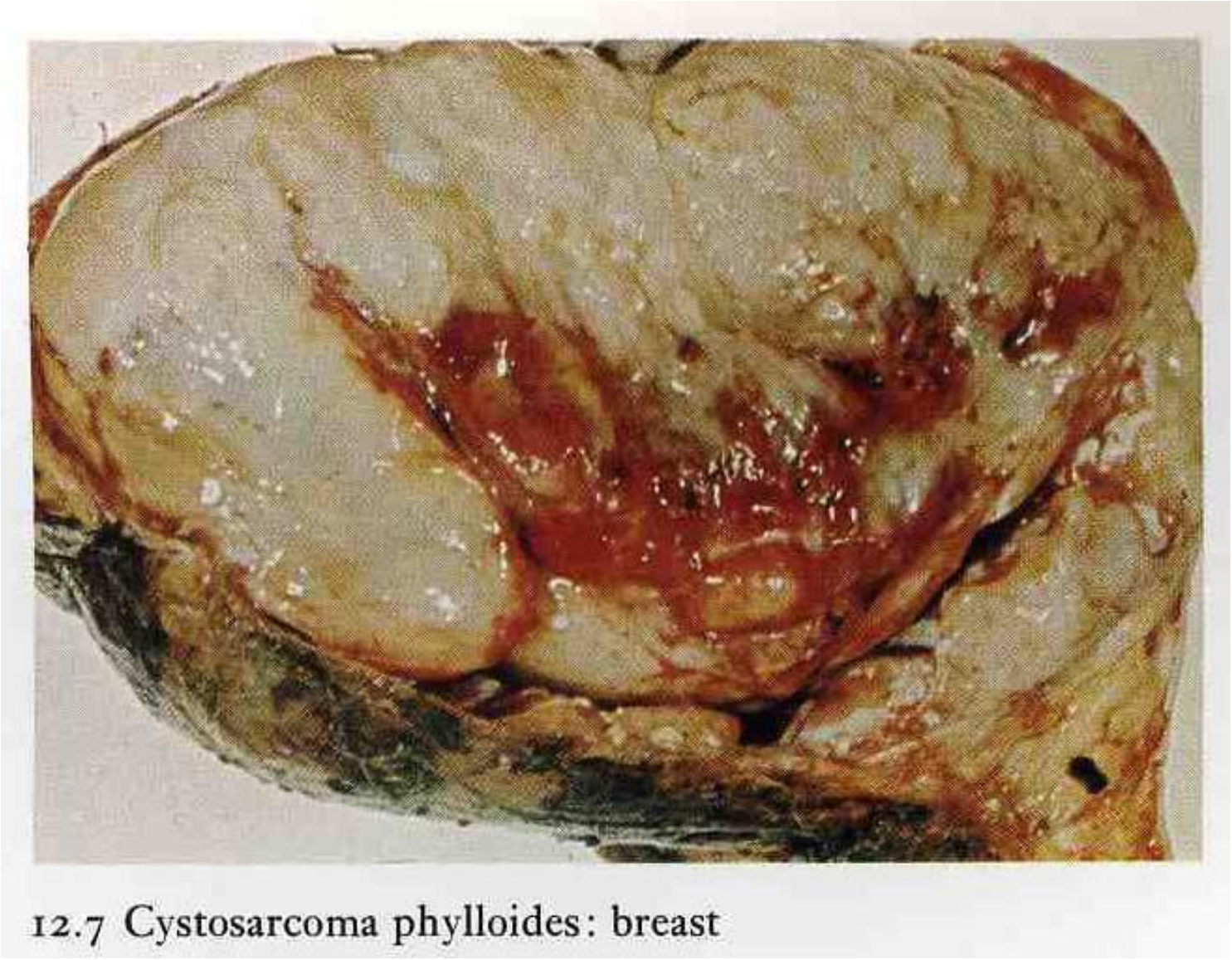
- Some of the phyllodes **T** show ↑stromal cellularity, anaplasia & high mitotic activity, accompanied by rapid ↑in size, usually with **invasion** of adjacent breast tissue.

- Most of these T remain localized & are cured by excision;
- Malignant phyllodes T (cystosarcoma phyllodes, may recur, but they tend to remain localized.
- Only the most malignant, (15% of cases), metastasize to distant sites

Phyllodes Tumor



Cystosarcoma phylloides breast. The Greek term is derived from the leaf like clefts & slits pattern of the tumor. C/S showing myxomatous tumor with extensive recent hemorrhage.



12.7 Cystosarcoma phylloides: breast

Intraductal Papilloma

- A benign papillary tumor growth within a duct.
- Most are solitary, found within the main lactiferous ducts or sinuses.
- They **present clinically** as a result of:

(1) the appearance of serous or bloody nipple discharge,

(2) the presence of a small **subareolar mass a few mm inØ,**

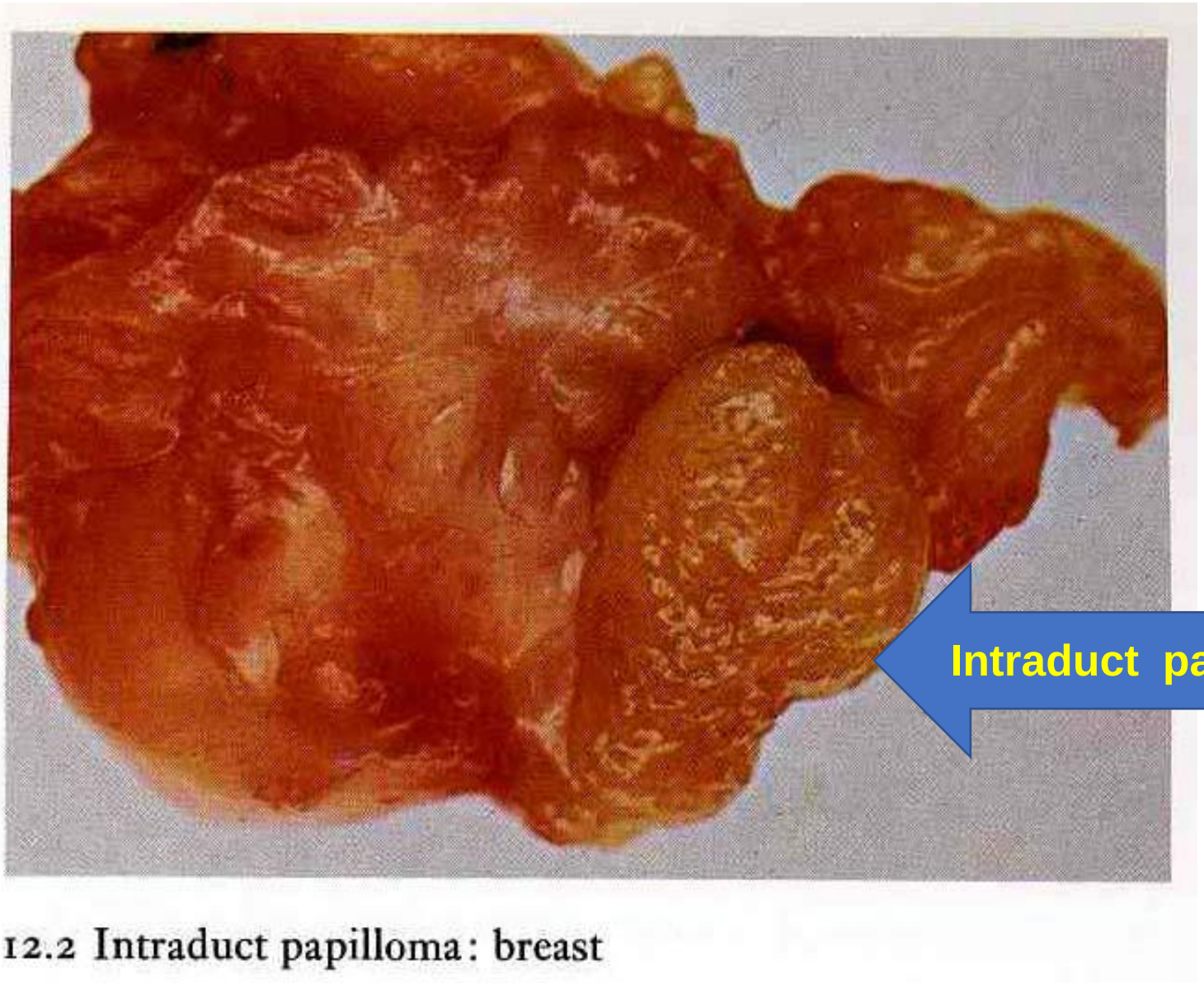
(3) **nipple retraction**.

- **Grossly, T** usually **solitary**, less than 1 cm in Ø, consisting of delicate, branching papillae within a dilated duct or cyst.

H/P:the multiple papillae have connective tissue stromal axis covered by cuboidal epithelial cells that are frequently **double layered** **(**epithelial layer overlying a myoepithelial layer).
☺**Solitary papilloma** almost always remains **benign**, but if ☹**multiple papillomas**, (intraductal papillomatosis), they sometimes become malignant.

- **Papillary carcinoma** must be excluded; it often lacks a myoepithelial component & shows either monotonous ductal epithelium or severe cytologic atypia.

Intraduct papilloma; breast. A firm, lobulated pale yellow papilloma (1.5 cm in ø) is present within a dilated duct. It has granular surface & forms a raspbeery-like nodule.



12.2 Intraduct papilloma: breast