Female Genital tract Pathology

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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.

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:

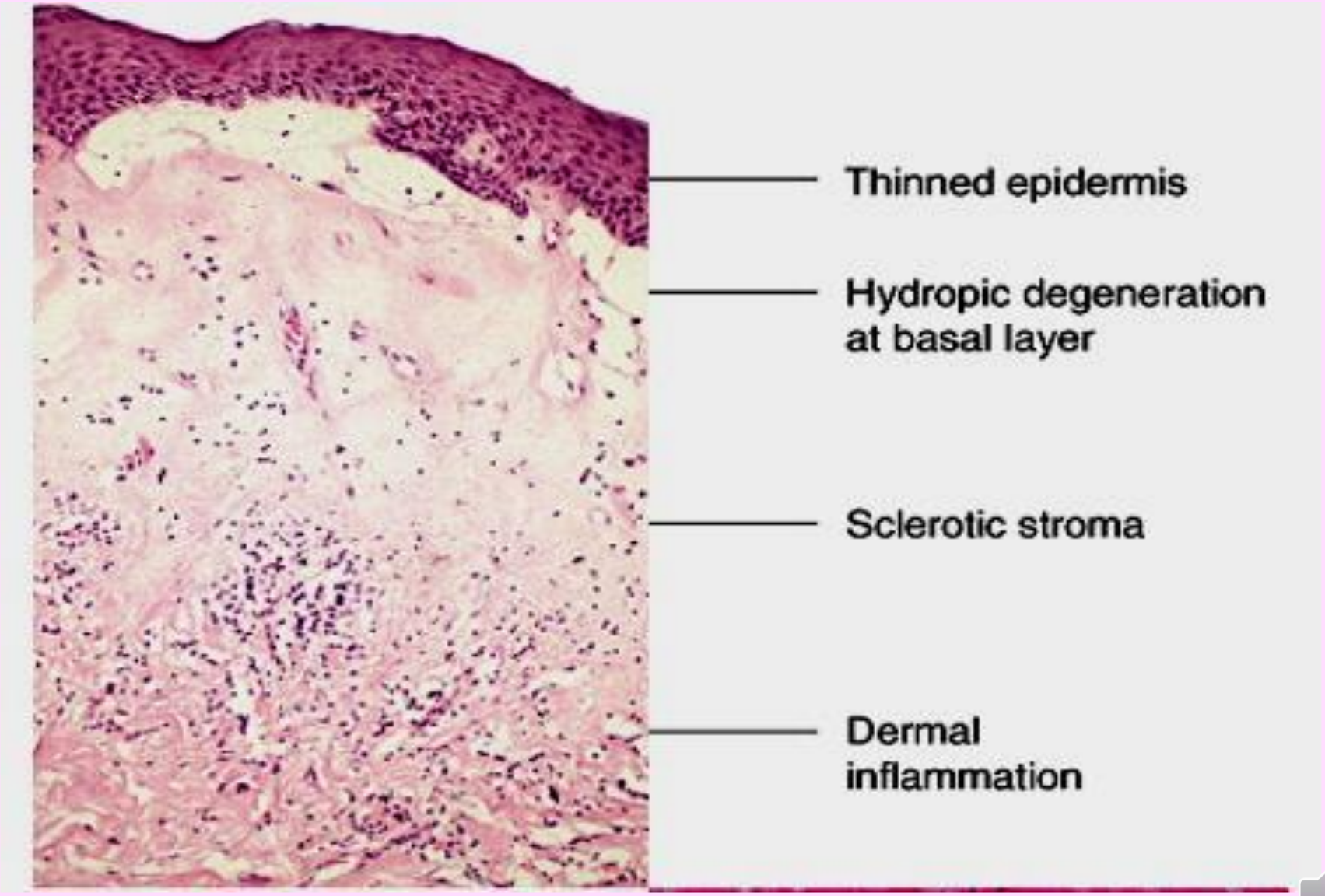
(1) **lichen sclerosis & (2) lichen simplex chronicus** , both are simply referred to as non-neoplastic epithelial disorders (to differentiate them from the premalignant lesions).

- 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

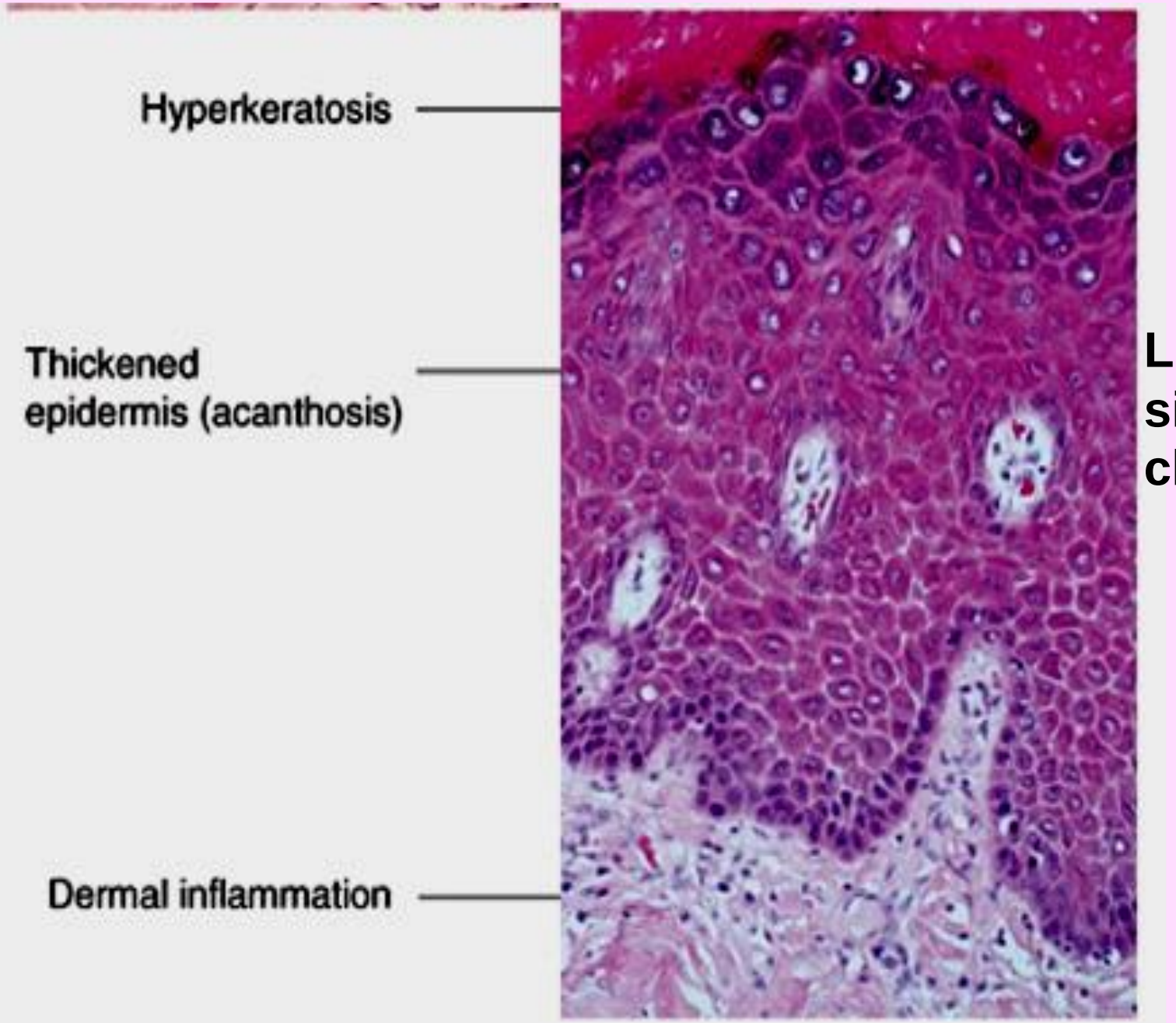


Lichen Simplex Chronicus

- 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,

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

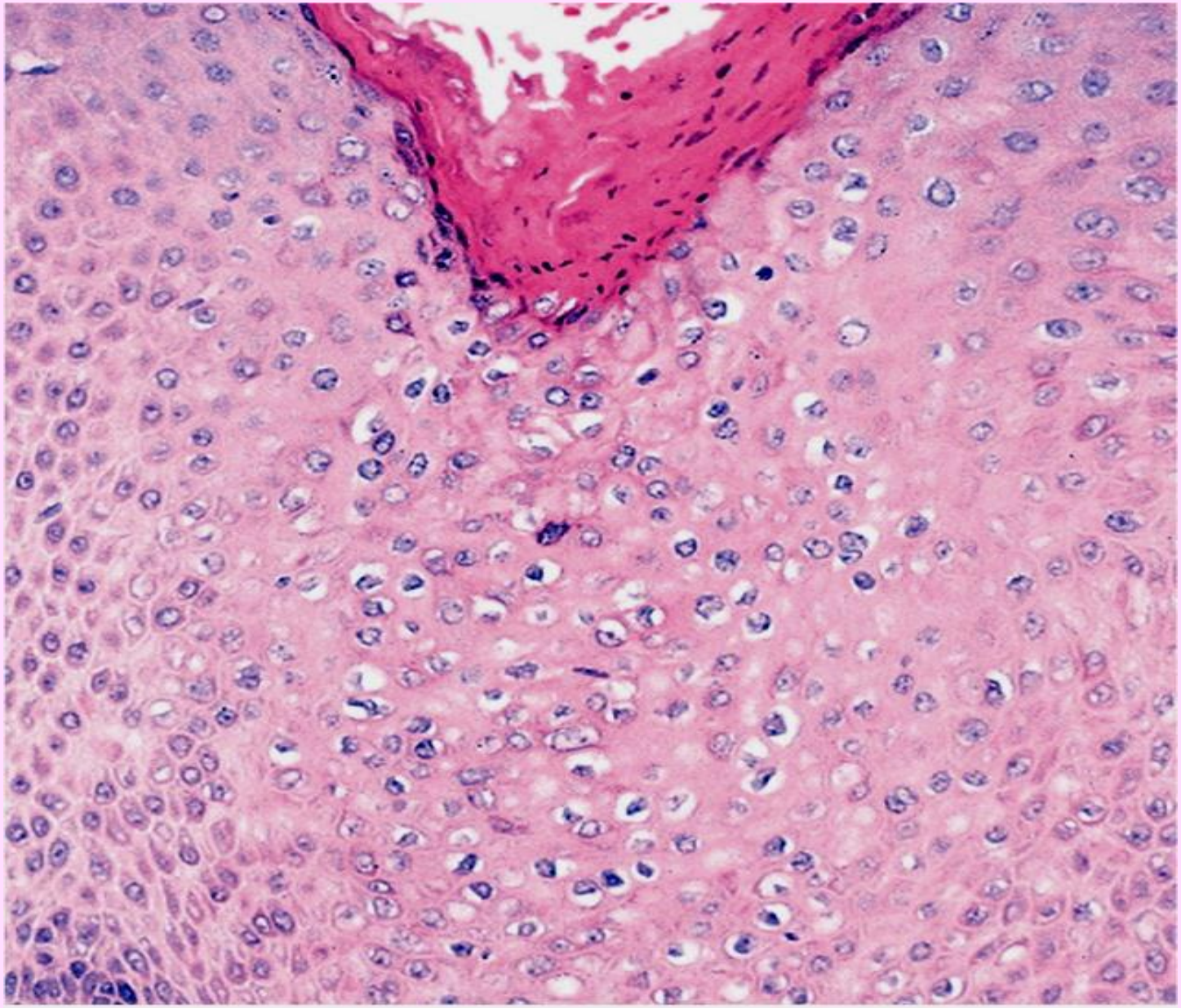
- They occur anywhere on the anogenital surface, usually **single**, but more often **multiple.**
- On the vulva, they range from a few mm to many cm in Ø& are red-pink to pink-brown

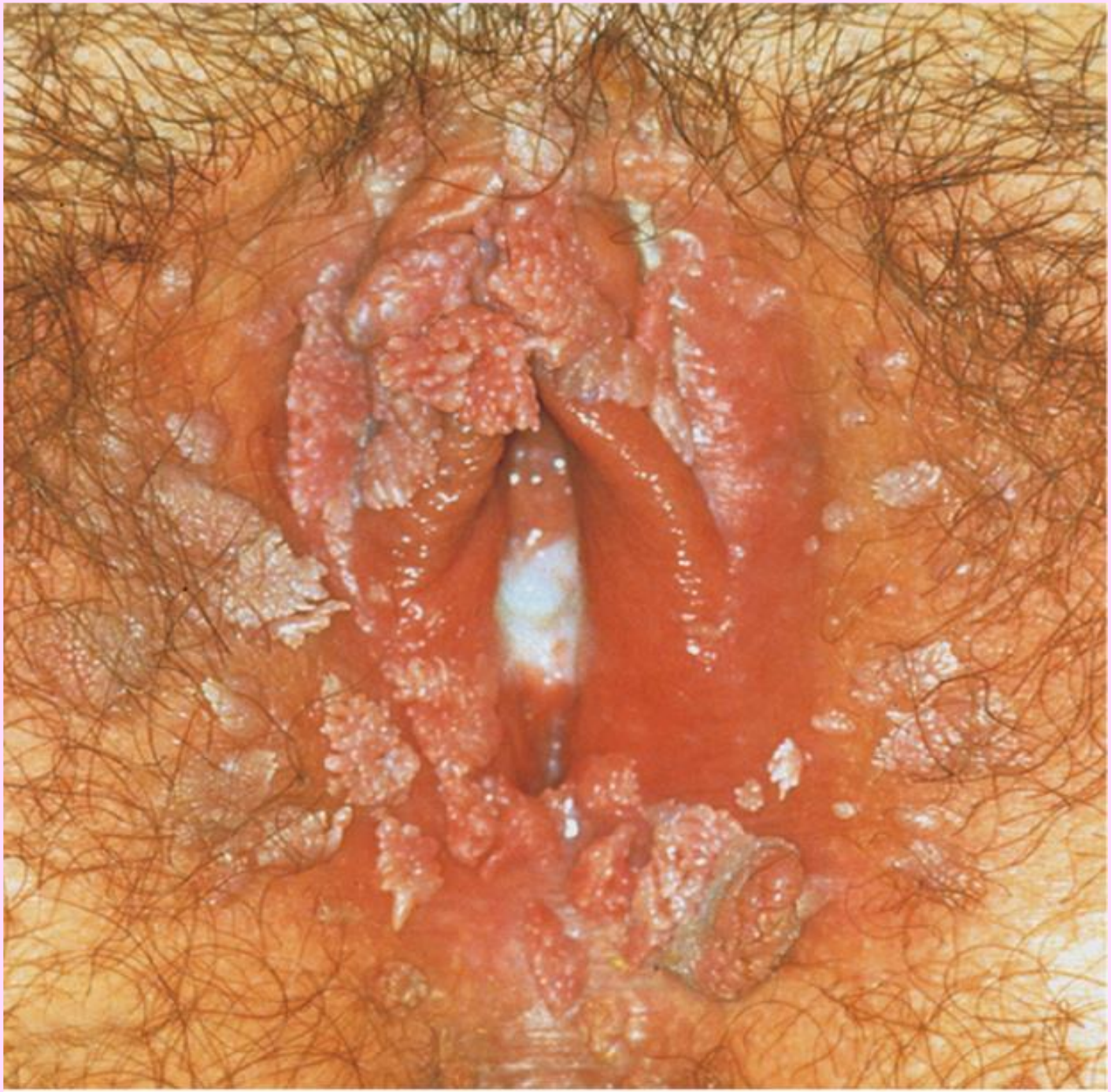
- **Anogenital warts (HPV type 6 and HPV type11)**
- They occur anywhere on the anogenital surface, usually **single**, but more often **multiple. On** the vulva, they range from a few mm to many cm in Ø& are red-pink to pink-brown.
- **Hallmark= koilocytosis(perinuclear cytoplasmic vacuolization + nuclear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

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

•Condyloma is not precancerous by itself.

Condyloma acuminatum





Numerous **condylomata acuminata** 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

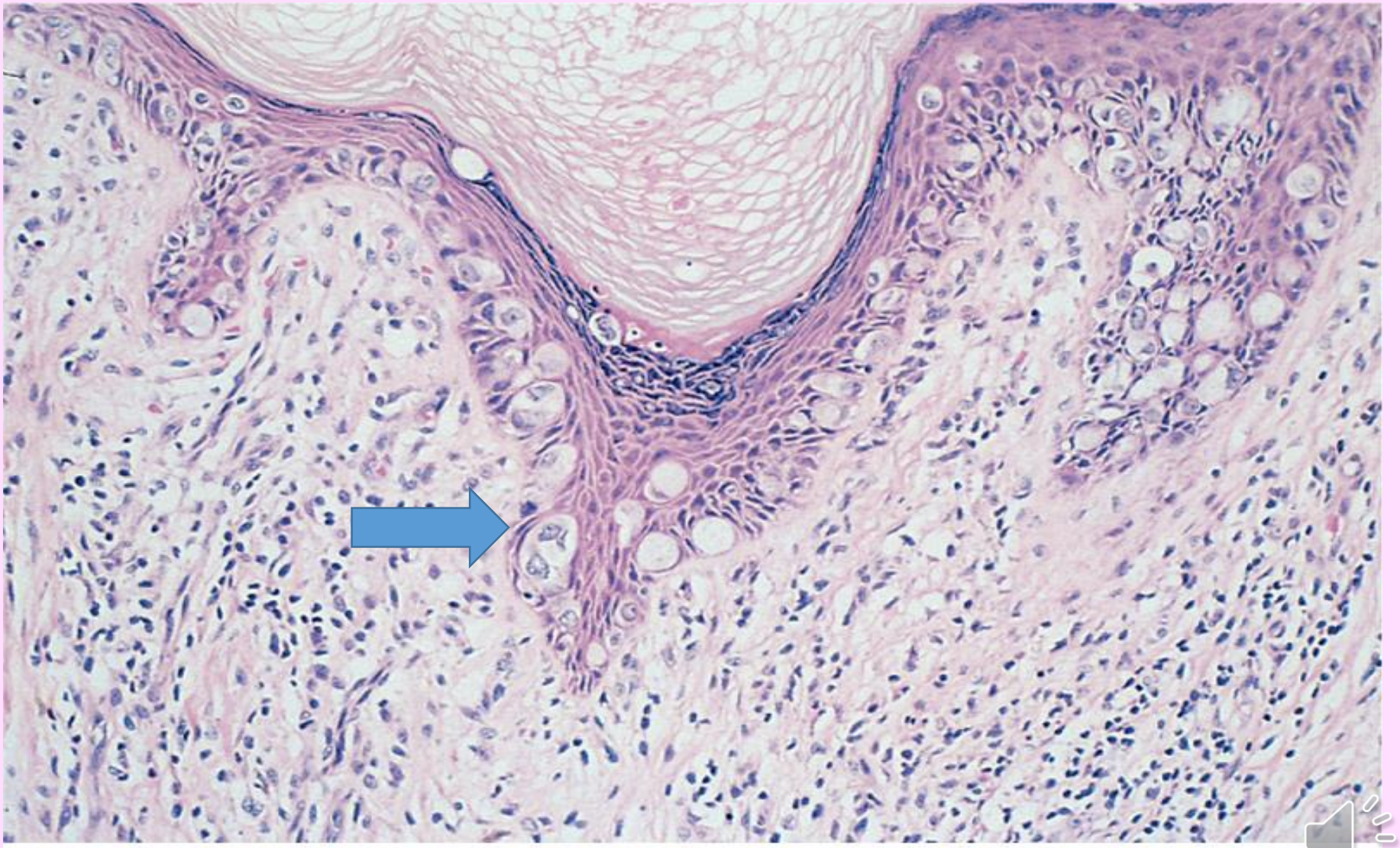
★Vulvar Paget disease like that of the breast, is essentially a form of **intraepithelial carcinoma**.

★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.

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**.

Sarcoma botryoides(embryonal rhabdomyosarcoma):

- Rare sarcoma of **skeletal** muscle type
- infants and **children**<5 years.
- soft polypoid masses (botryoides= grape-like).
- Primitive cells (**rhabdomyoblasts**)

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

- 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.

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 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.

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)

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 p53and 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**,

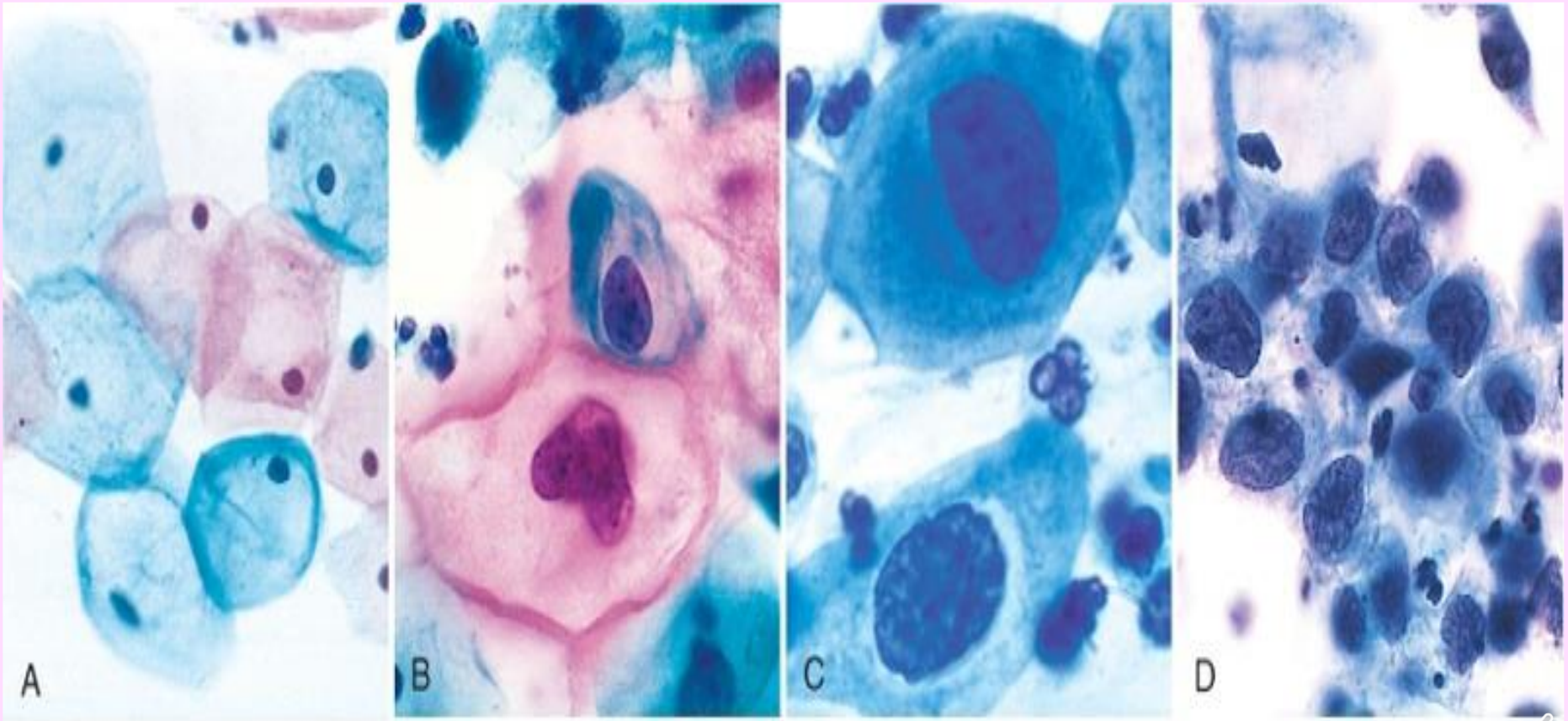
- with (1) maturation of keratinocytes delayed into the middle third of the epithelium, (2) cell & nuclear size pleomorphism, heterogeneity of nuclear chromatin & (3) **mitoses** above the basal layer, extending in to the middle third of the epithelium. The superficial layer of cells shows some differentiation.

(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 (F19-7& 19-8);** i.e., the differentiation of surface cells & koilocytotic changes have usually disappeared

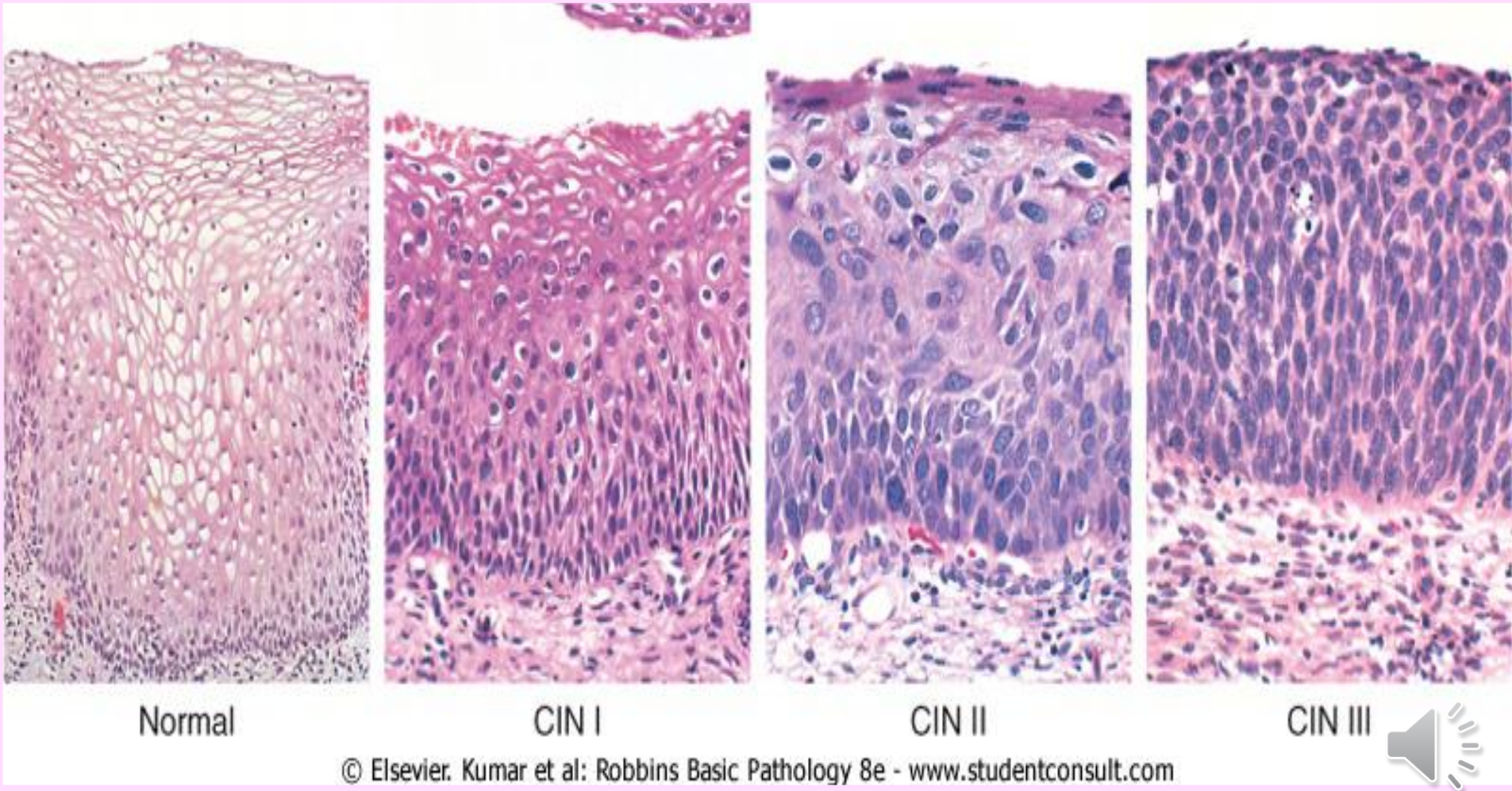
(IV) In time, dysplastic changes become more atypical & may extend into the end cervical glands, but **the alterations are confined to the epithelial layer & its glands. These** changes constitute **carcinoma in situ.**

➡ 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 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.

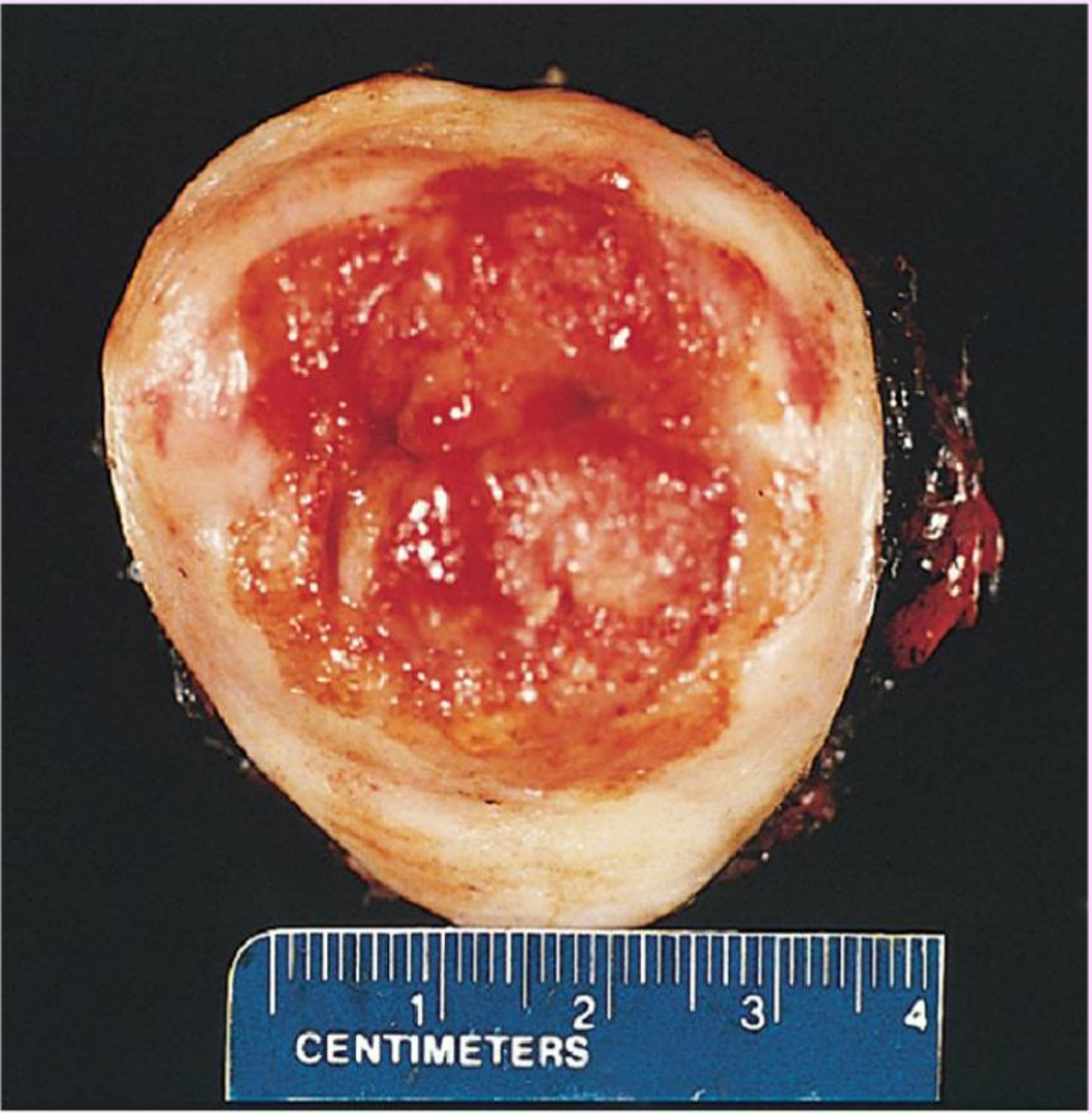
- Extension into the **parametrial** soft tissues can fix the uterus to the pelvic structures.

- 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.

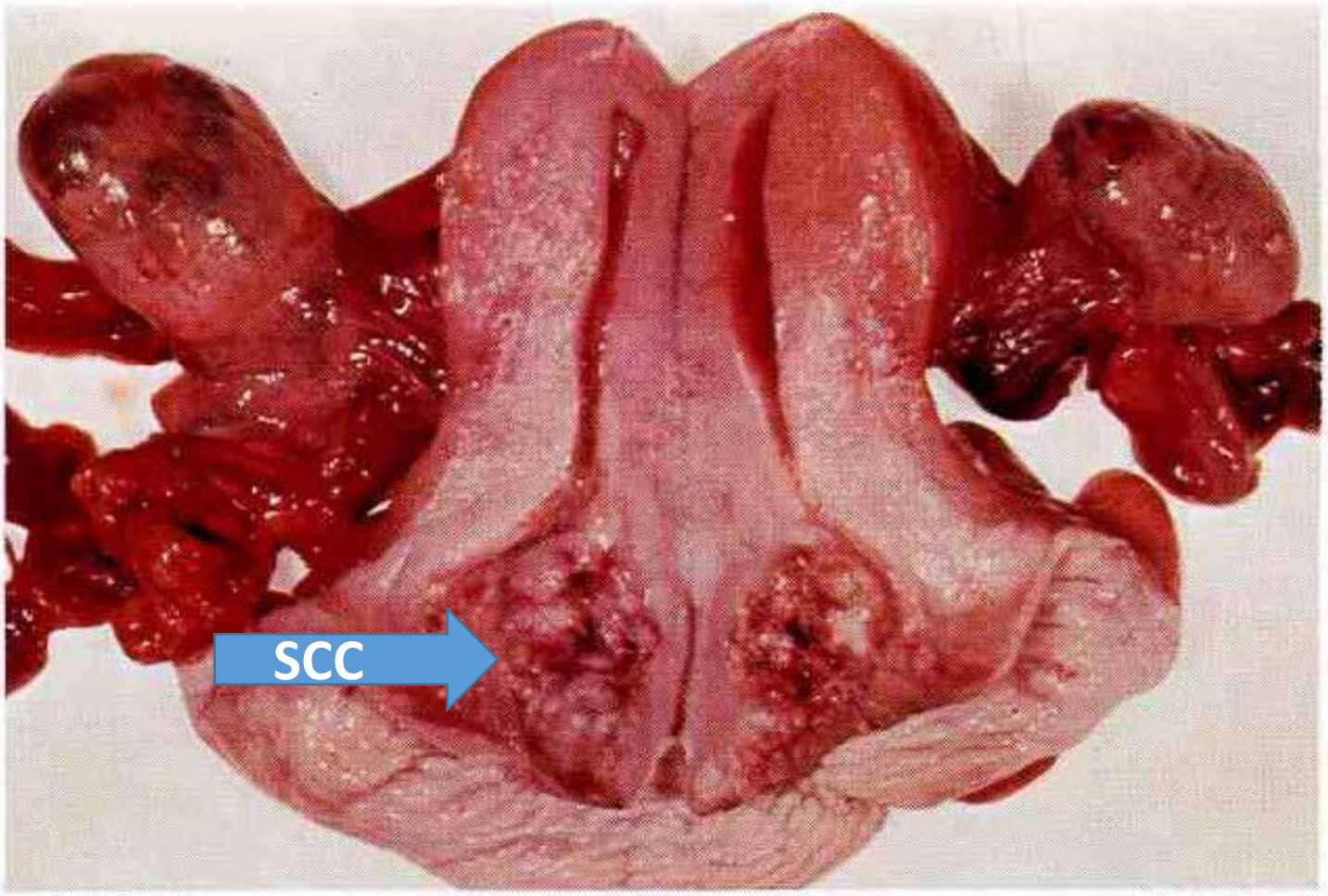
- With the exception of neuroendocrine T, which are uniformly aggressive in their behavior, the cervical ca are: ★graded from 1 to 3 based on cellular differentiation &

- staged from 1 to 4 depending on clinical spread.



Advanced Carcinoma of the cervix.

Squamous carcinoma: cervix. Irregular, ulcerating papillary tumor involving the ectocervix & extends over the posterior wall of the endocervix.



12.39 Squamous carcinoma: cervix

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.
- Such T may cause unexpected **vaginal bleeding, leukorrhea, painful coitus (dyspareunia), & dysuria**.

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

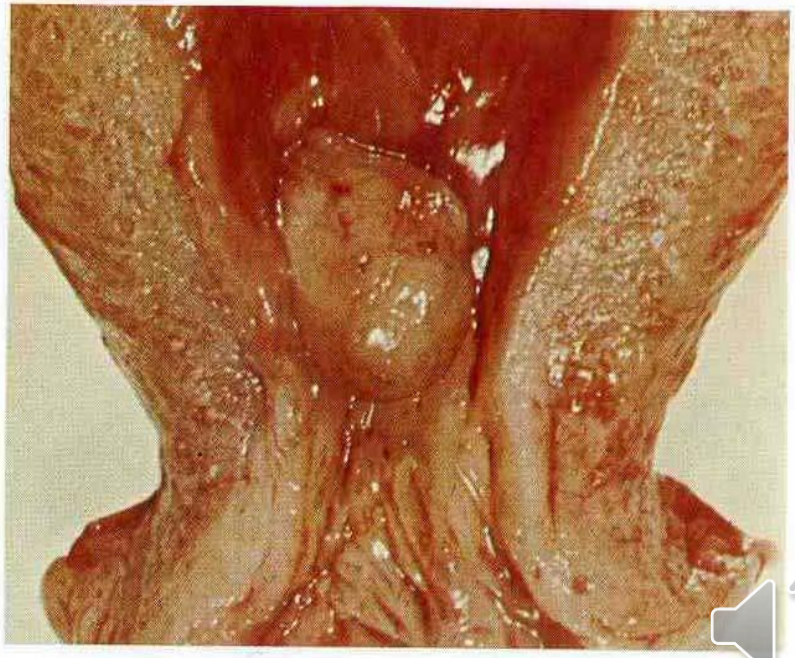
❑ **Prognosis**: the 5-year survival is as follows: Stage 0 (preinvasive), **100%**; stage 1, **90%**; stage 2, **82%**; stage 3, **35%**; & stage 4, **10%.**

❑ **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.

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

Uterine Pathology

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 lymphoplasmacytic 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.

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

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).

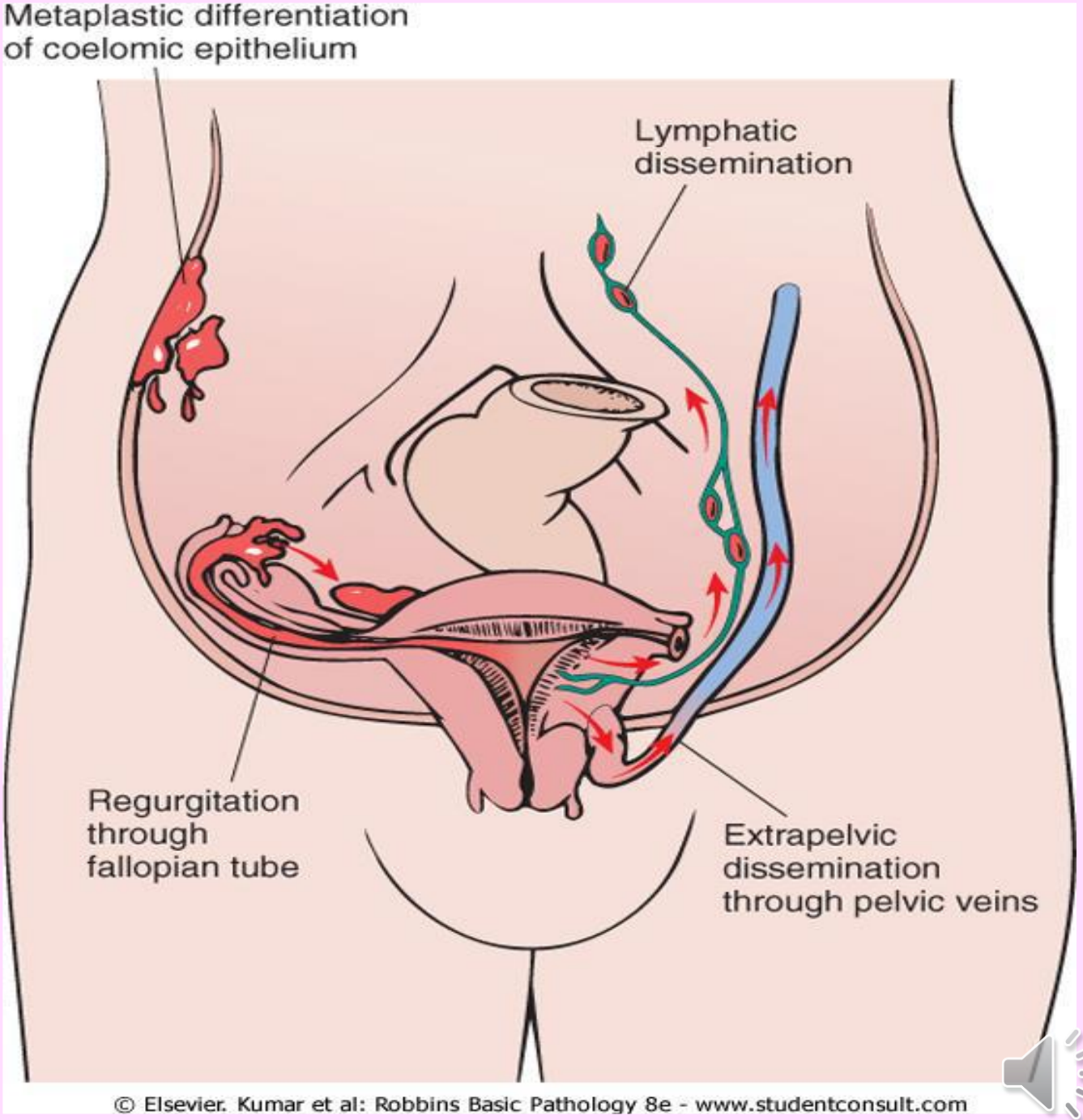
•Sometimes distant sites e.g. umbilicus, lymph nodes, lungs, etc

“Chocolate“ cyst in an ovary

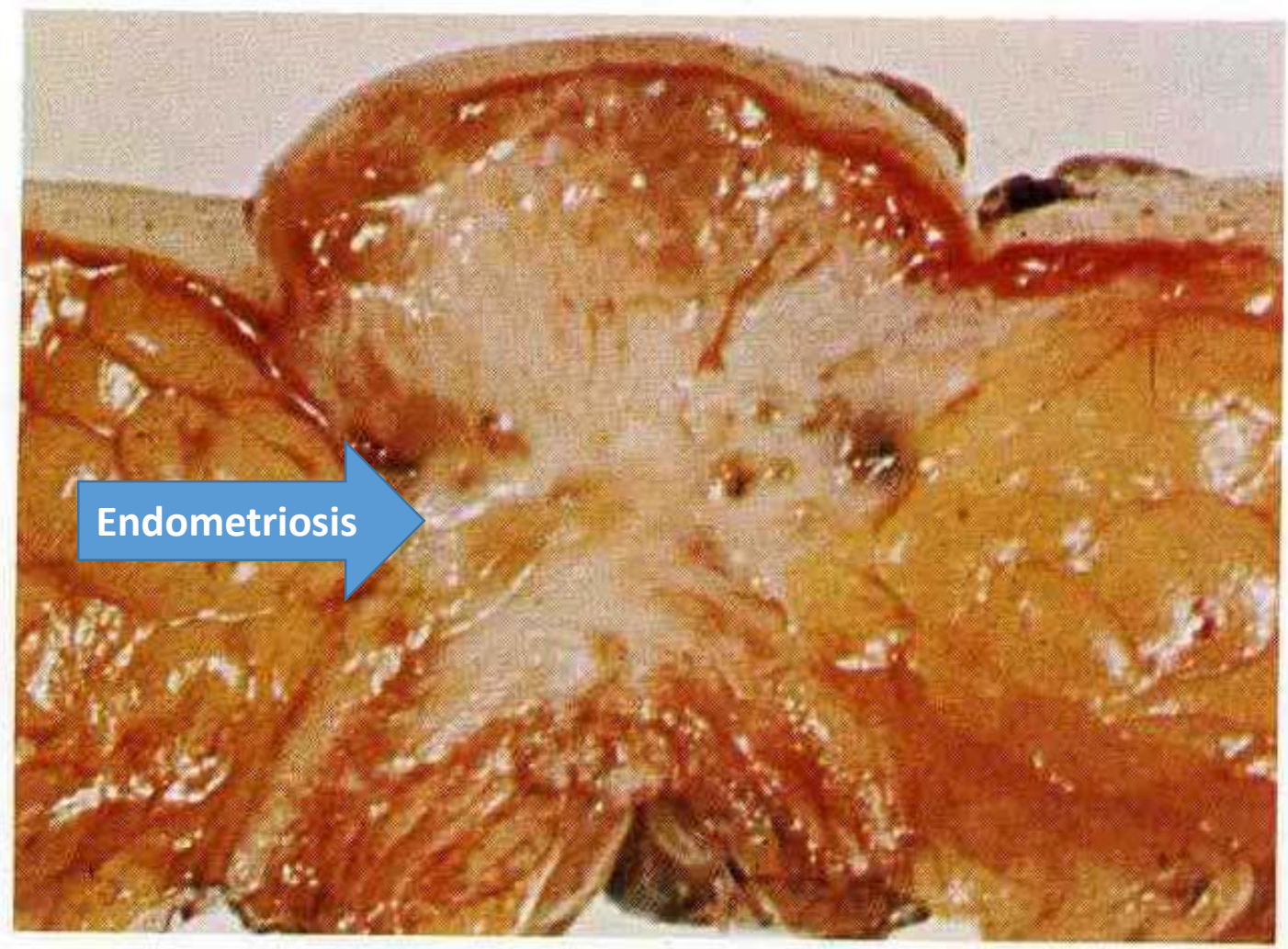
ENDOMETRIOSIS-Pathogenesis

- Three theories:
  - ***regurgitation theory.*** ***(***most accepted). Menstrual backflow through tubes and implantation..
  - ***metaplastic theory***. Endometrial differentiation of coelomic epithelium.
  - ***vascularorlymphatic 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 & organization of the blood leads to widespread fibrosis.
- Consequences: fibrosis, sealing of tubal fimbriated ends, and distortion of the ovaries.

- 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 & periuterine 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).**

DYSFUNCTIONAL UTERINE BLEEDING & ENDOMETRIAL HYPERPLASIA

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 or
(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.

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, nonsecretory 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

- prolonged or marked excess of **estrogen** relative to progestin →exaggerated proliferation →may progress to cancer
- severity is based on architectural crowding and cytological atypia, ranging from:

1-Simple hyperplasia
2-Complex hyperplasia
3-Atypical hyperplasia (20% risk of cancer).

- The 3 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 counterbalancing progestin;

Simple hyperplasia

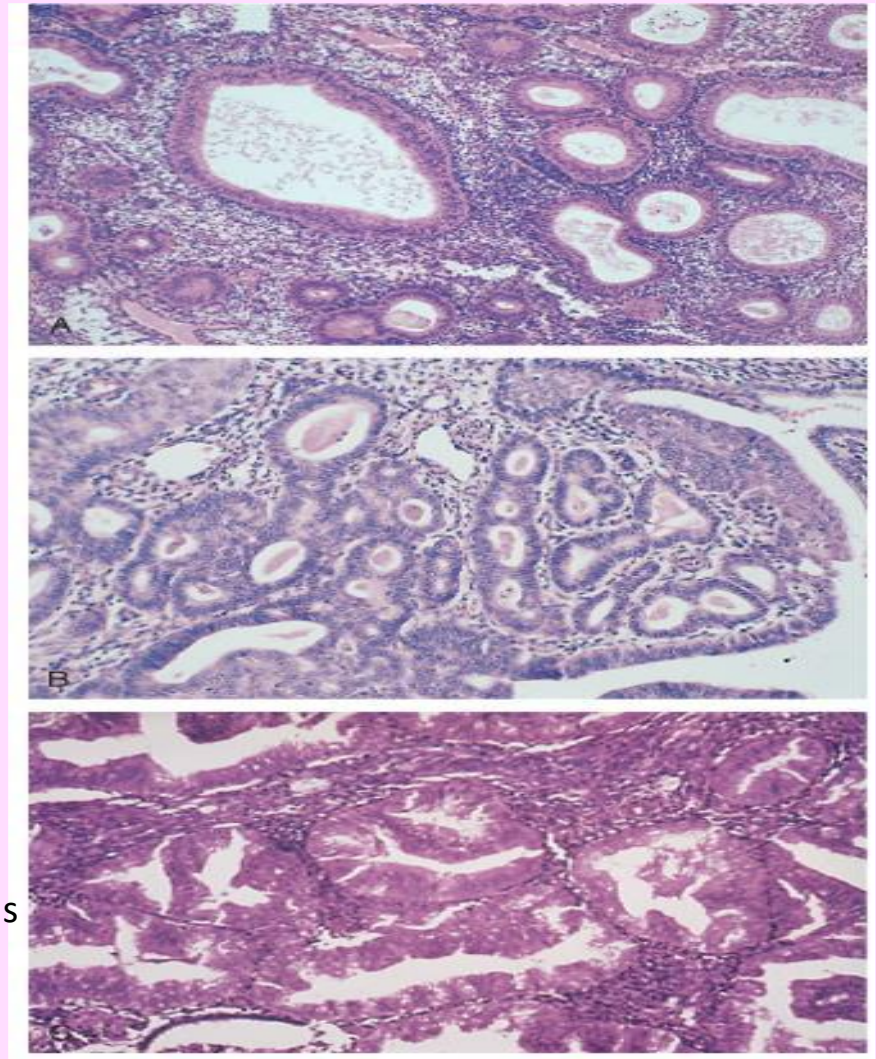
A, **An unovulatory** or "disordered" endometrium with dilatation of glands.

Complex Hyperplasia

displaying a nest of closely packed glands

Atypical Hyperplasia

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



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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.

Thanks ☺