Pathology of female genital tract -1

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- Diseases of the female genital tract
  - are extremely common
  - include
    - inflammatory conditions
    - other non-neoplastic conditions
    - Neoplasms
- Hormonally induced effects

Certain pathologic conditions are peculiar to specific segments of the female genital tract

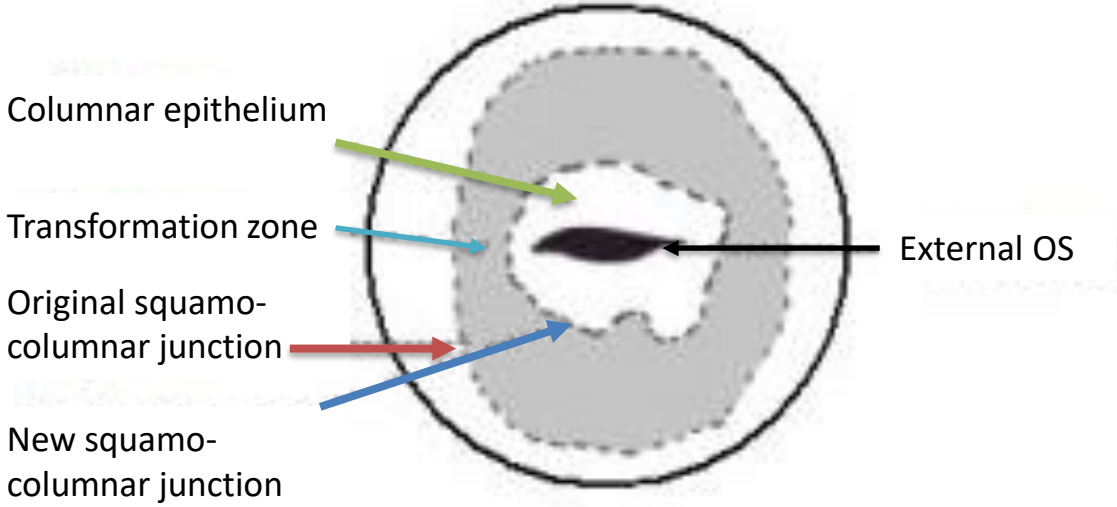
Objectives

At the end of this lecture you should be able to

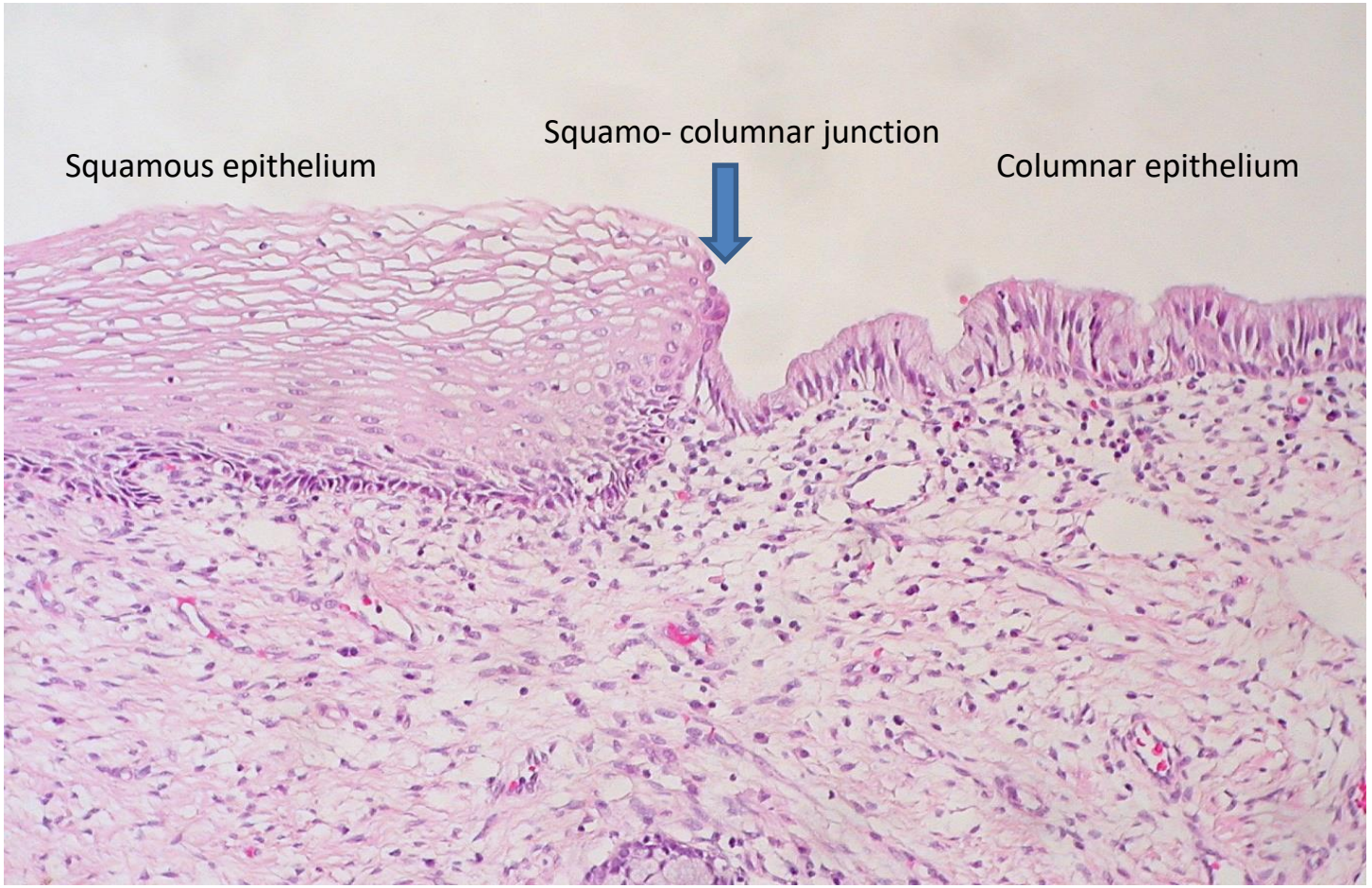
- Describe the pathogenesis of human papilloma virus (HPV) related lesions of the cervix
- Describe the morphological features of intraepithelial neoplasia and carcinoma of the cervix
- Briefly describe the non-neoplastic conditions of the cervix
- Briefly describe the premalignant and malignant conditions of the vulva and vagina

What is squamo-columnar transformation zone of the cervix?

- The area of the cervix where squamous metaplasia occurs

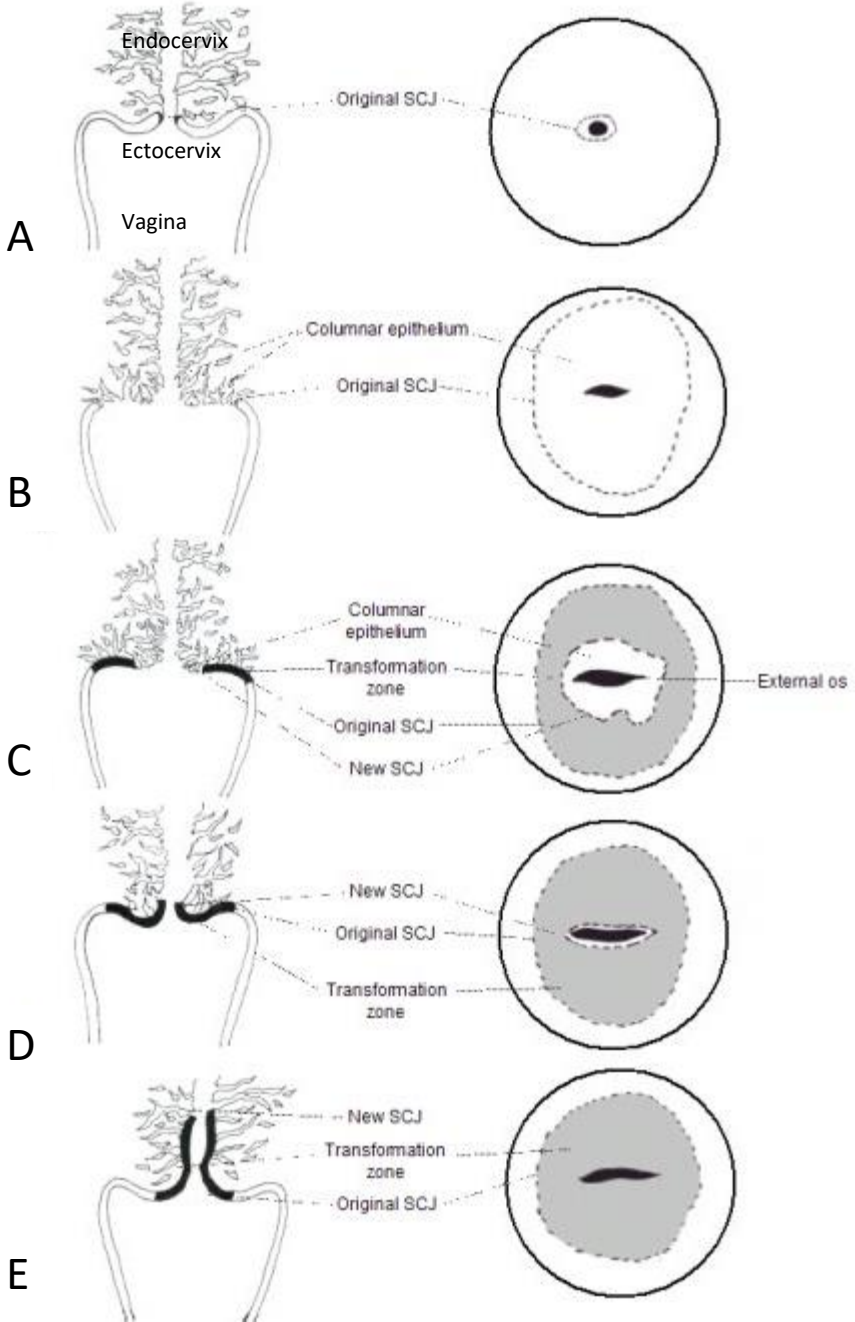


- Almost all manifestations of cervical carcinogenesis occur in this zone


Squamous epithelium
Squamo- columnar junction
Columnar epithelium

- Location of **squamo-columnar junction** in relation to the external os varies with
  - age
  - menstrual status
  - pregnancy
  - oral contraceptive use
- **Ectropion** - eversion of the columnar epithelium onto the ecto-cervix, occurs when the cervix grows rapidly and enlarges under the influence of oestrogen

Squamo-columnar junction of the cervix



A - Before menarche

B - After puberty and early menarche (ectropion)

C - Third decade

D - Premenopausal period

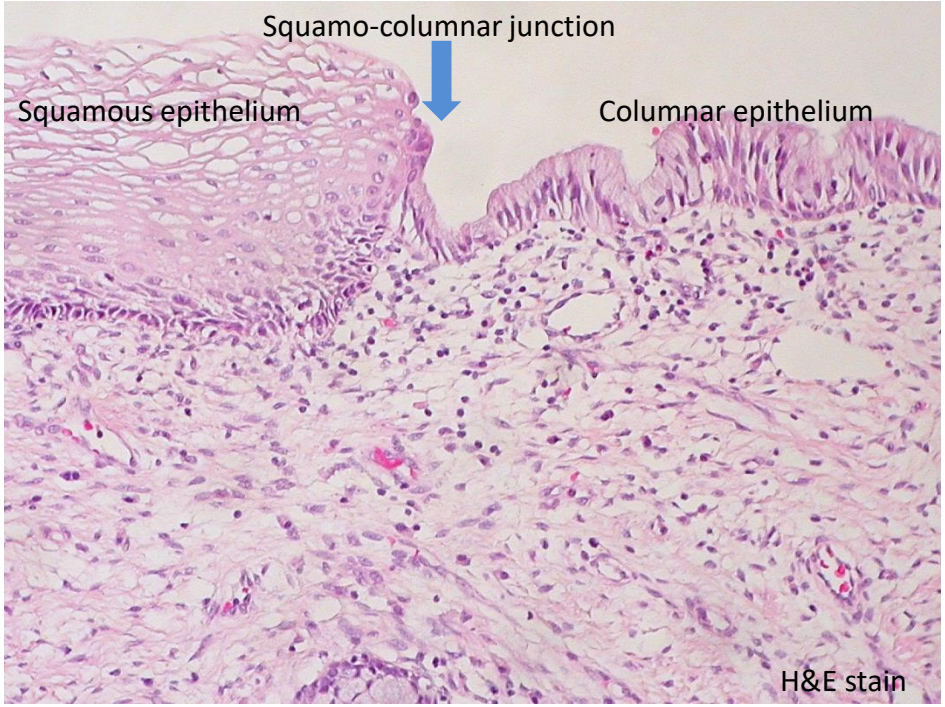
E - menopausal period

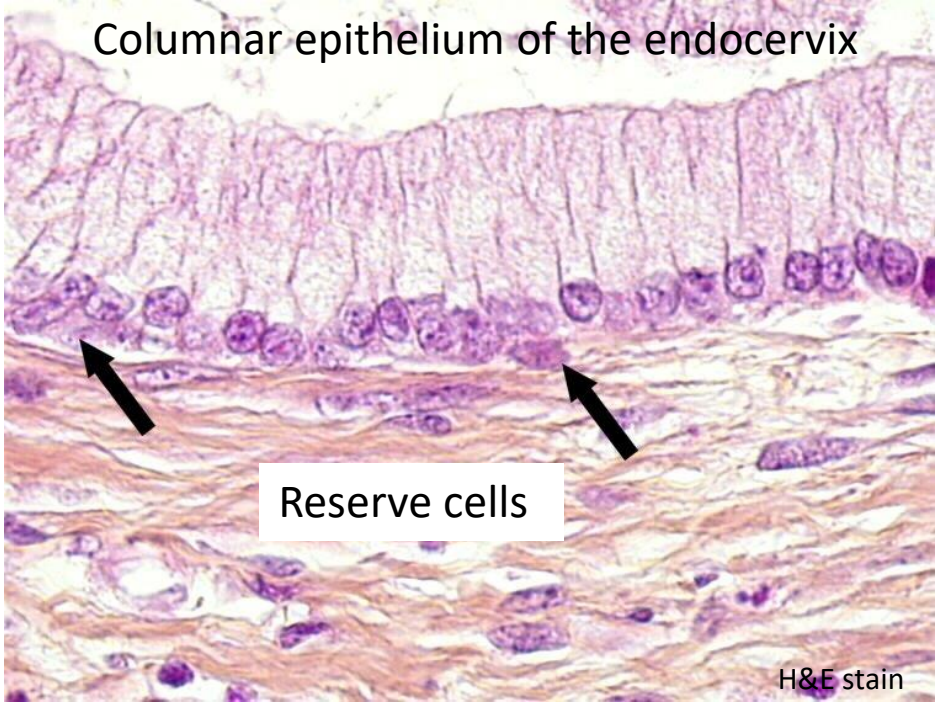
Squamous metaplasia of the cervix

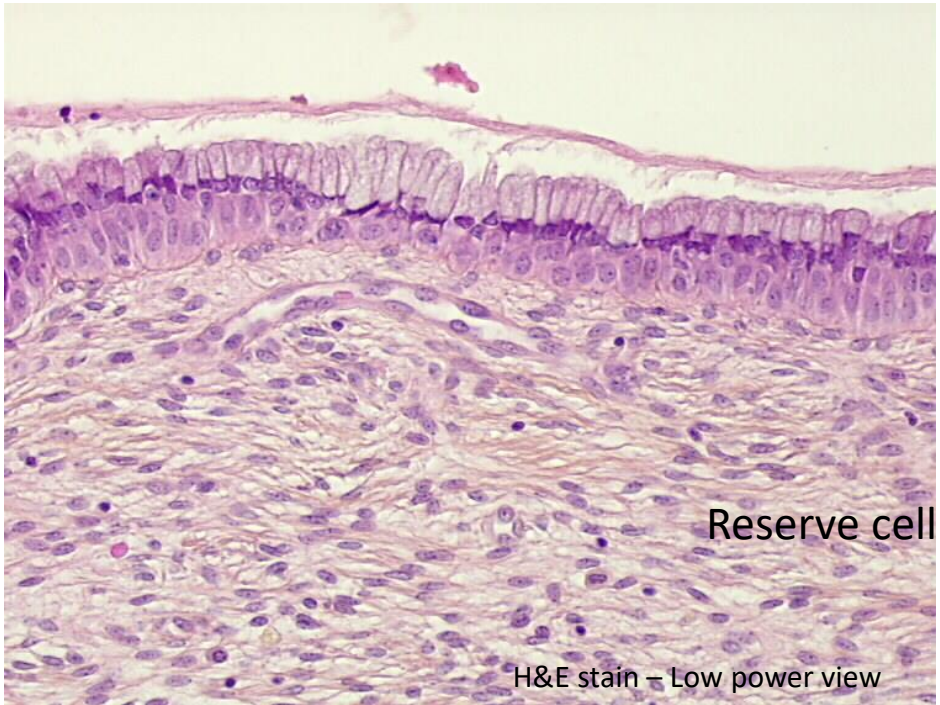
- Normally the columnar epithelium of the endocervix is protected by mucin
- When get exposed to the acidity of the vagina, these columnar cells get damaged
- Below the columnar epithelial cells of the cervix there are scattered cells called “reserve cells”

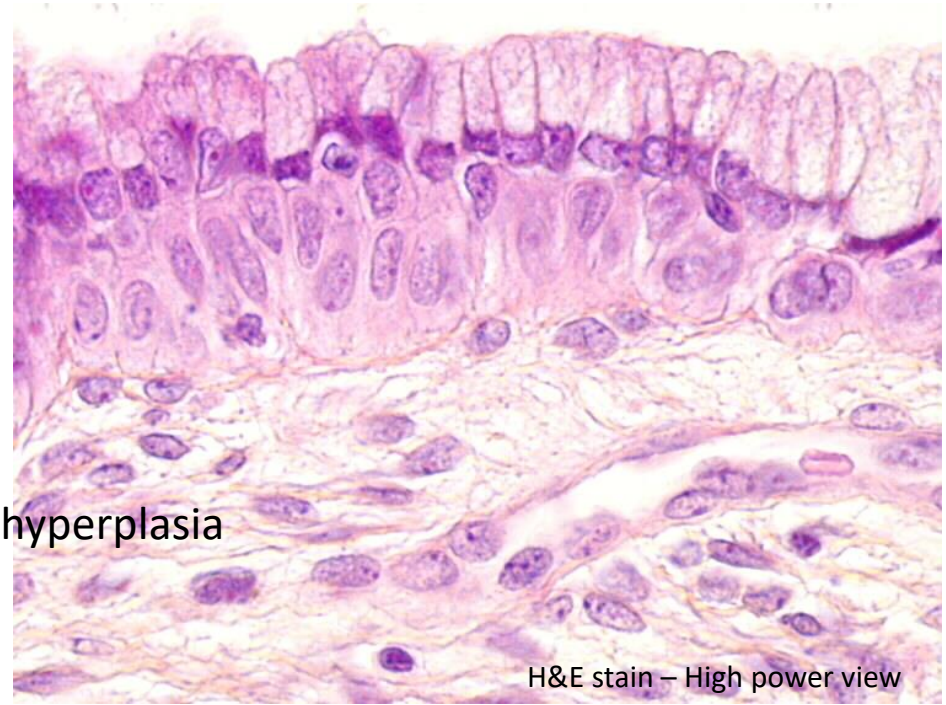
Squamous metaplasia of the cervix

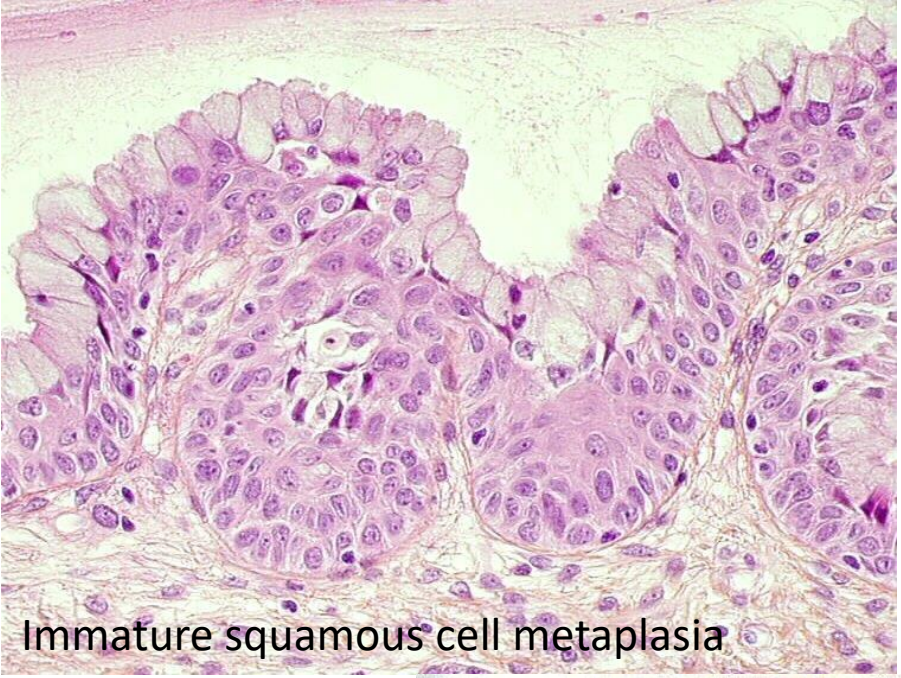
- When columnar epithelium is exposed and damaged due to vaginal acidity , there is
  - reserve cell hyperplasia and they
  - differentiate into squamous epithelium
- Resulting in squamous metaplasia

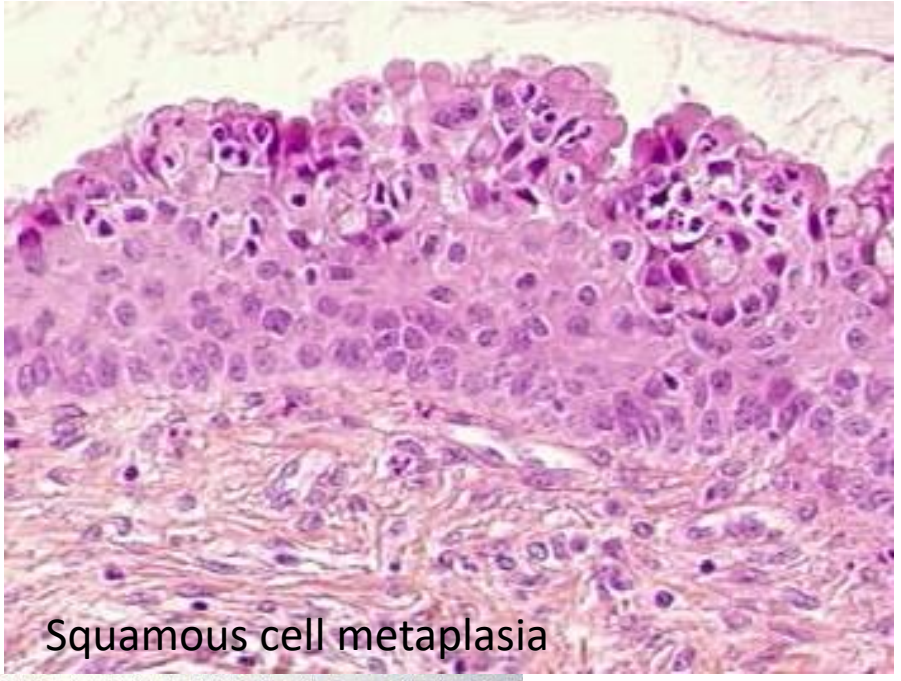

Squamo-columnar junction
Squamous epithelium
Columnar epithelium
H&E stain

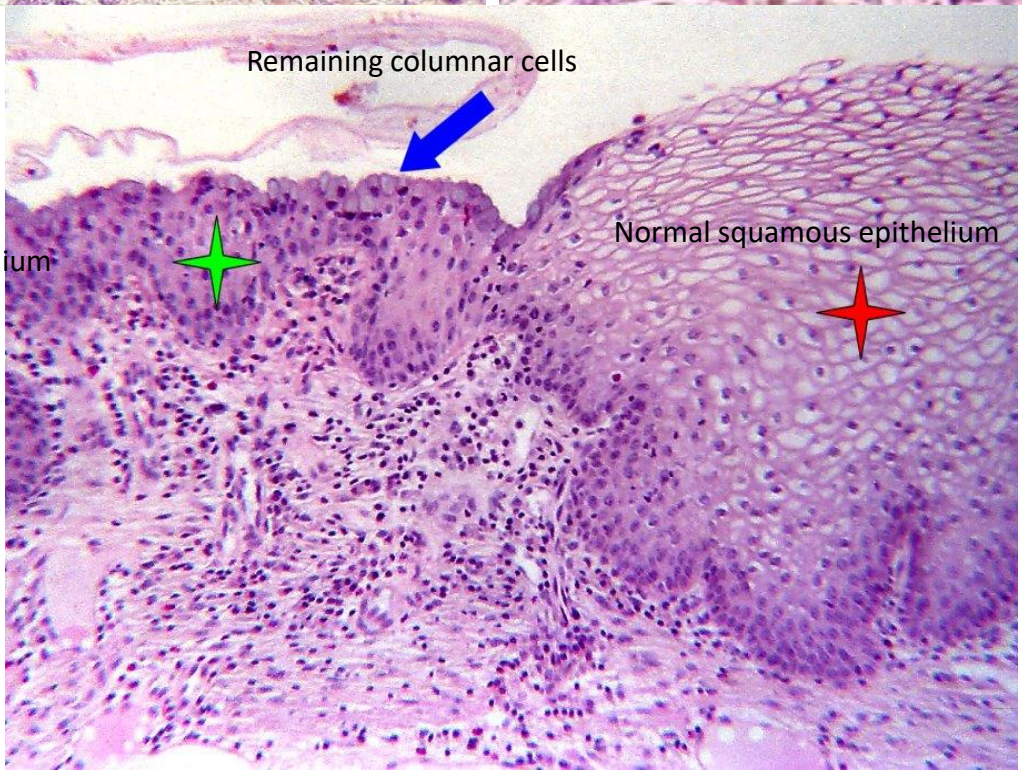

Columnar epithelium of the endocervix
Reserve cells
H&E stain

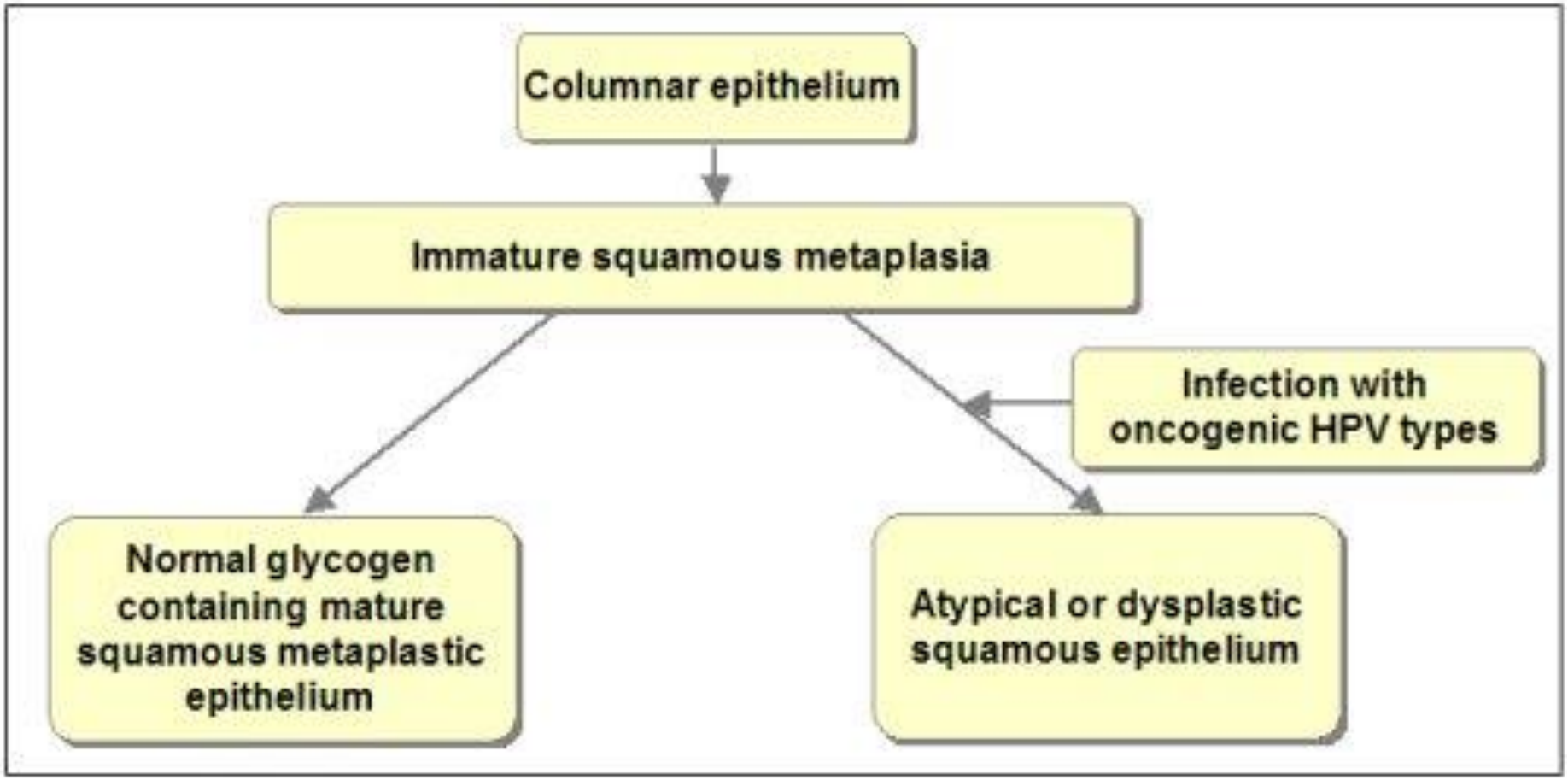

Reserve cell hyperplasia
H&E stain – Low power view


H&E stain – High power view


Immature squamous cell metaplasia


Squamous cell metaplasia


Remaining columnar cells
Normal squamous epithelium
Metaplastic squamous epithelium


Columnar epithelium
Immature squamous metaplasia
Infection with oncogenic HPV types
Normal glycogen containing mature squamous metaplastic epithelium
Atypical or dysplastic squamous epithelium

HPV infection of the lower female genital tract

- Extremely common
- Sexually transmitted agent
- Most are asymptomatic
- High peak of prevalence around 20 years of age
- With the development of host immunity , most are eliminated from the body
- Persisting infection is high with high risk oncogenic types

HPV infection of the lower female genital tract

- "High-risk"/carcinogenic types for cervical CA

  - type 16 (60% of CA) and type 18

  Other types: 31,33,35,39, 45,51,52,56,58, 59,68,73,82)

  Single most important factor in cervical carcinogenesis

- "Low-risk" types - type 6 and type11

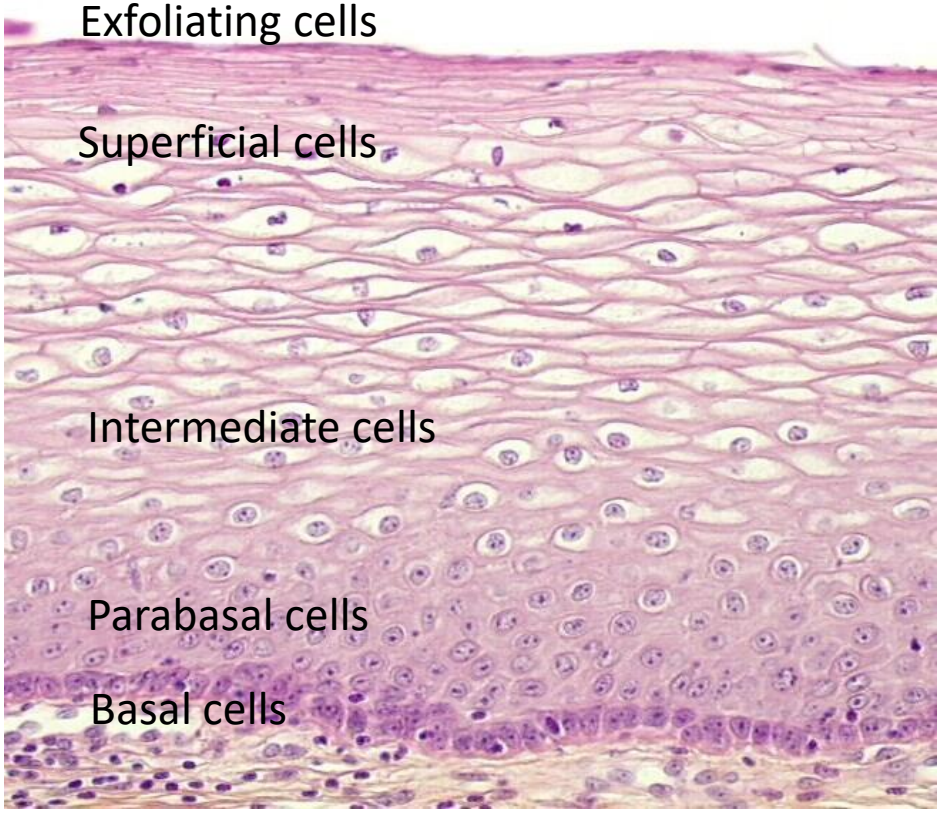
  (also 40,42,43,44,54,61,70, 72, 81,CP6108)

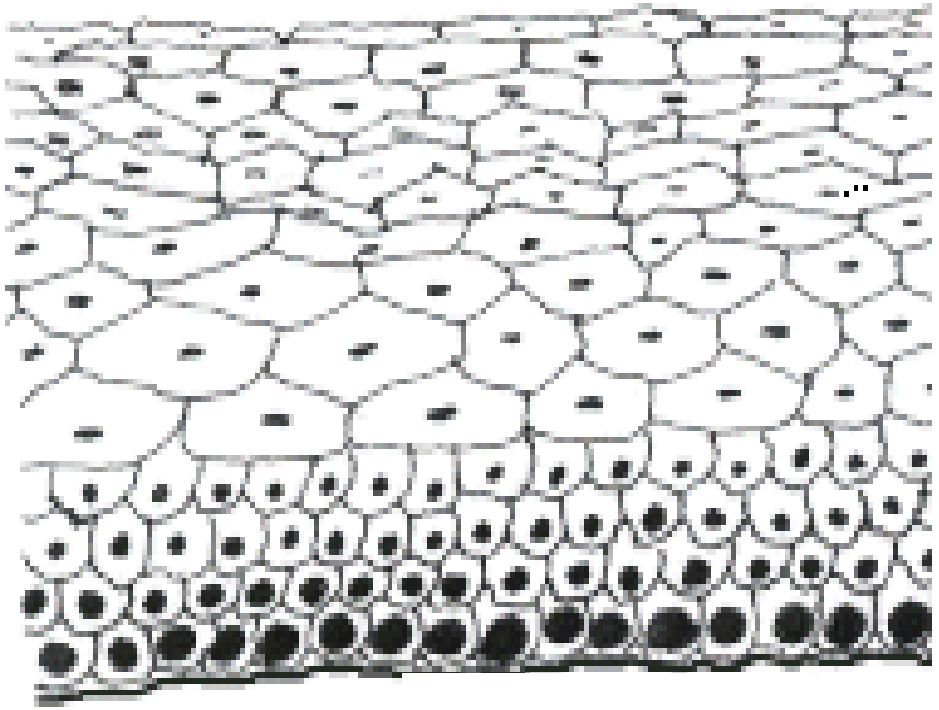
  Cause condyloma acuminatum

- Physical state of the virus
  - In cancer, viral DNA is integrated into host DNA
  - In condylomata and most precancerous lesions, present as free (episomal) viral DNA

- HPVs infect **immature metaplastic cells** in the transformation zone or immature basal cells of squamous epithelium in areas of epithelial damage

- Replicate in **mature squamous epithelium** resulting in cytopathic effects





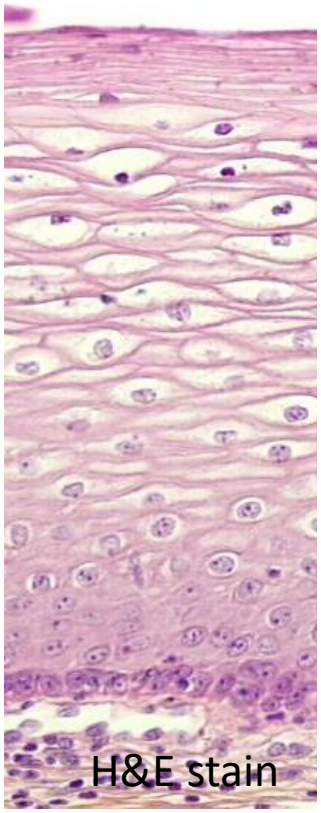
Normal ectocervix

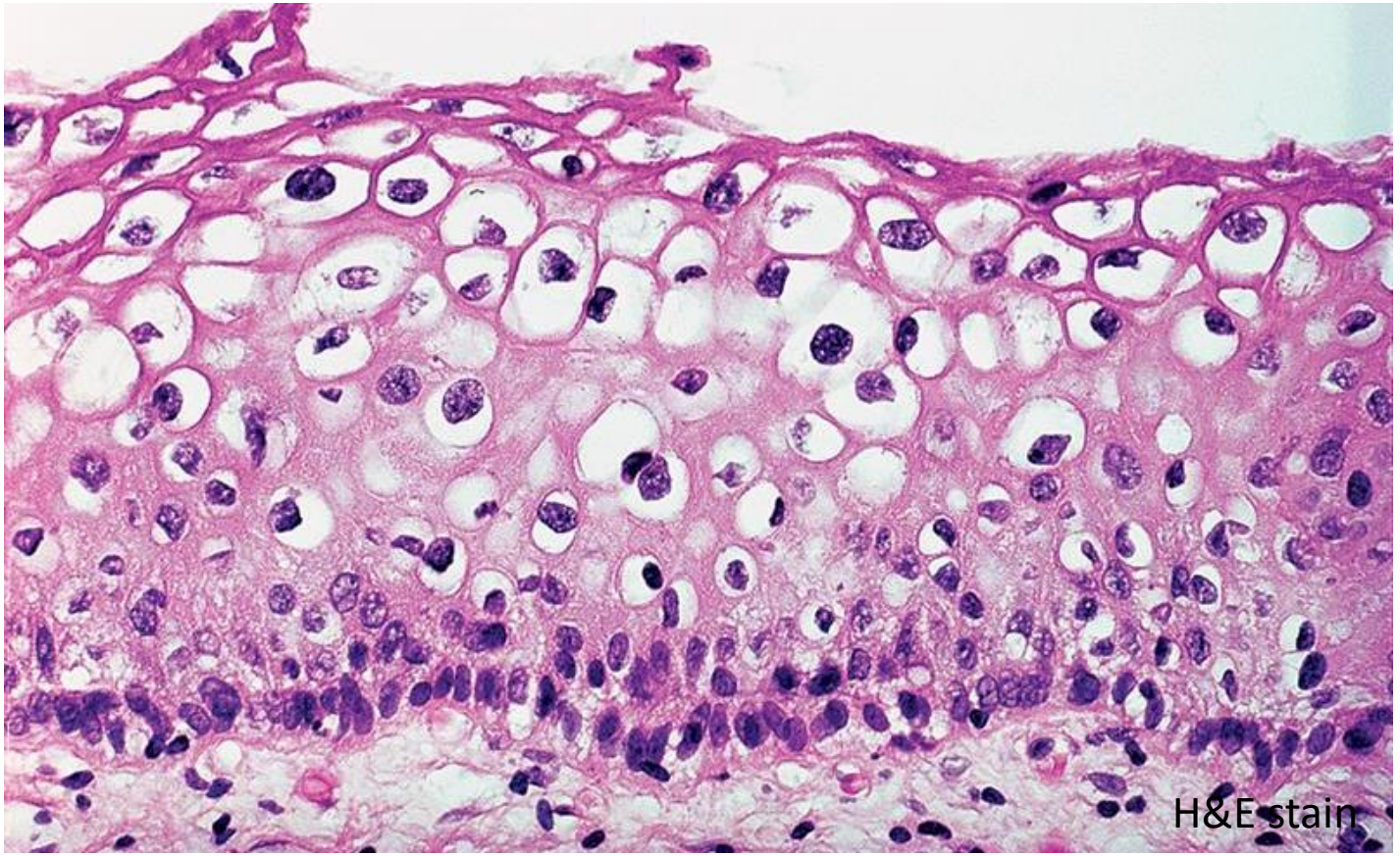
Lined by non-keratinized stratified squamous epithelium

HPV related cytopathic changes

Also known as **koilocytosis** / **koilocytic atypia**

- HPV disrupts the keratin matrix of the cell
  - Sharply outlined perinuclear vacuolation
  - Densely stained peripheral cytoplasm
  - Enlarged nuclei with undulating membrane
  - Binucleation and multinucleation





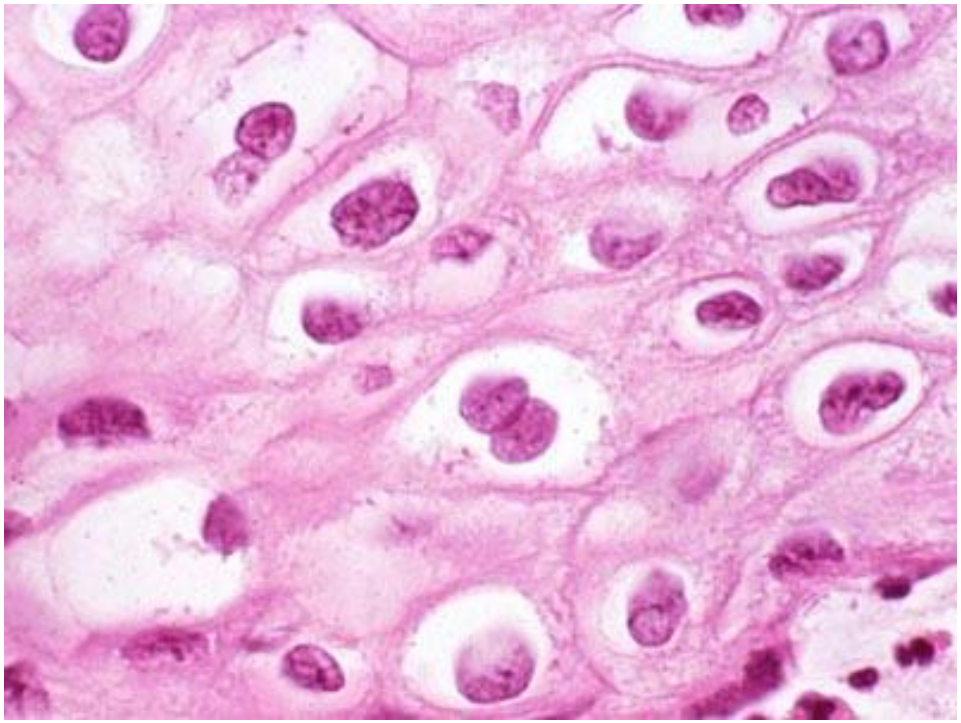
Note the HPV related changes of the

squamous epithelial cell **nuclei** - variation in size and shape

- enlargement

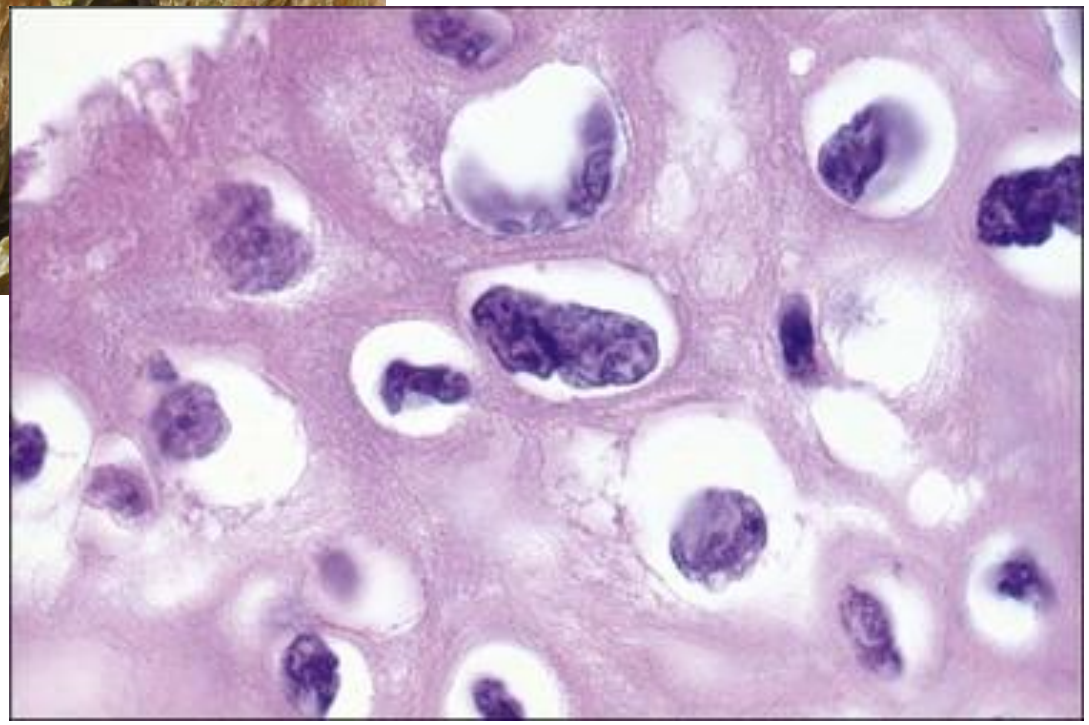
- hyperchromasia

and **cytoplasm** - perinuclear cytoplasmic halo



Binucleated cells

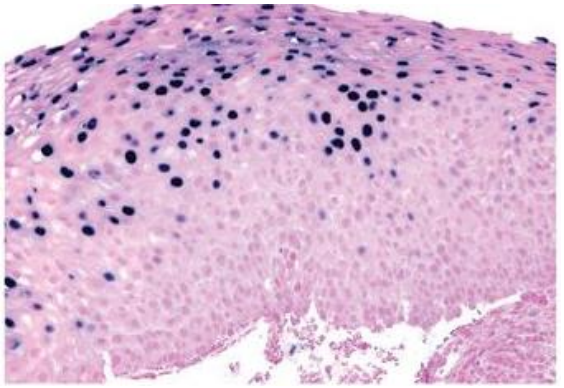
Raisins



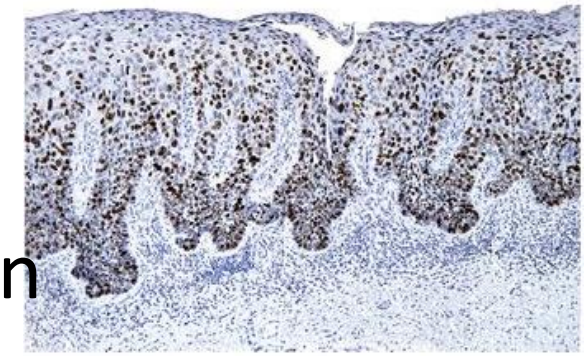
Raisinoid nuclei

Other investigations

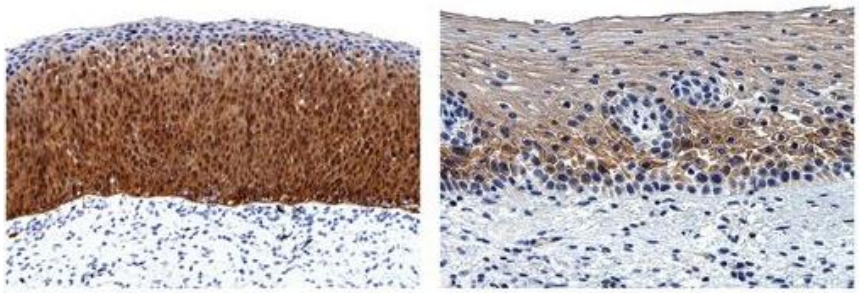
- Insitu hybridization test detects HPV DNA
  - Intense staining where there is a high viral load



- Immunostaining for Ki-67
  - Marker of cellular proliferation



- p16 - Cell cycle regulatory protein
  - Overexpression of p16 in HPV infection



HPV associated conditions of the cervix

- Benign conditions

  Condyloma acuminatum

- Premalignant lesions

  Cervical intraepithelial neoplasia (CIN)/ squamous intraepithelial lesion (SIL)

- Malignant neoplasms

  Squamous cell carcinoma

  Adenocarcinoma

  Neuroendocrine tumours

Dysplasia of the cervix - Classification

- Oldest

  Dysplasia (Mild, moderate, severe/ carcinoma in situ)

- Then simplified as

  CIN - CIN I, CIN II, CIN III

- Current classification (with regard to the treatment options)

  Low grade squamous intraepithelial lesion/ LSIL (CIN I)

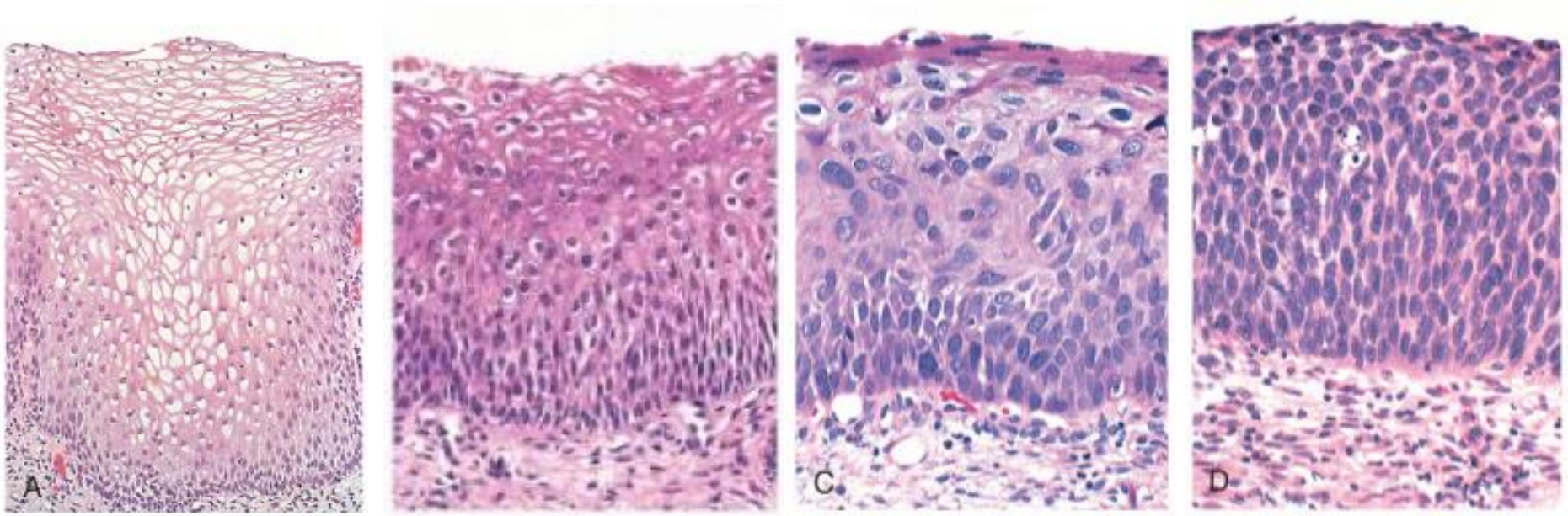
  High grade squamous intraepithelial lesion/ HSIL

  (CIN II, CIN III and intraepithelial carcinoma)

CIN and SIL

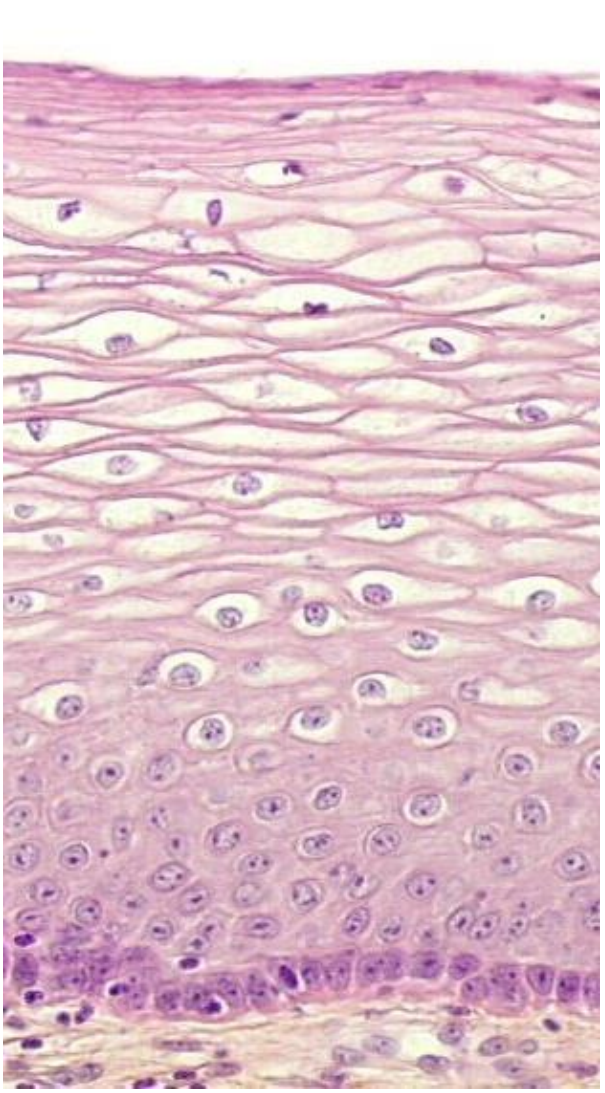
LSIL HSIL

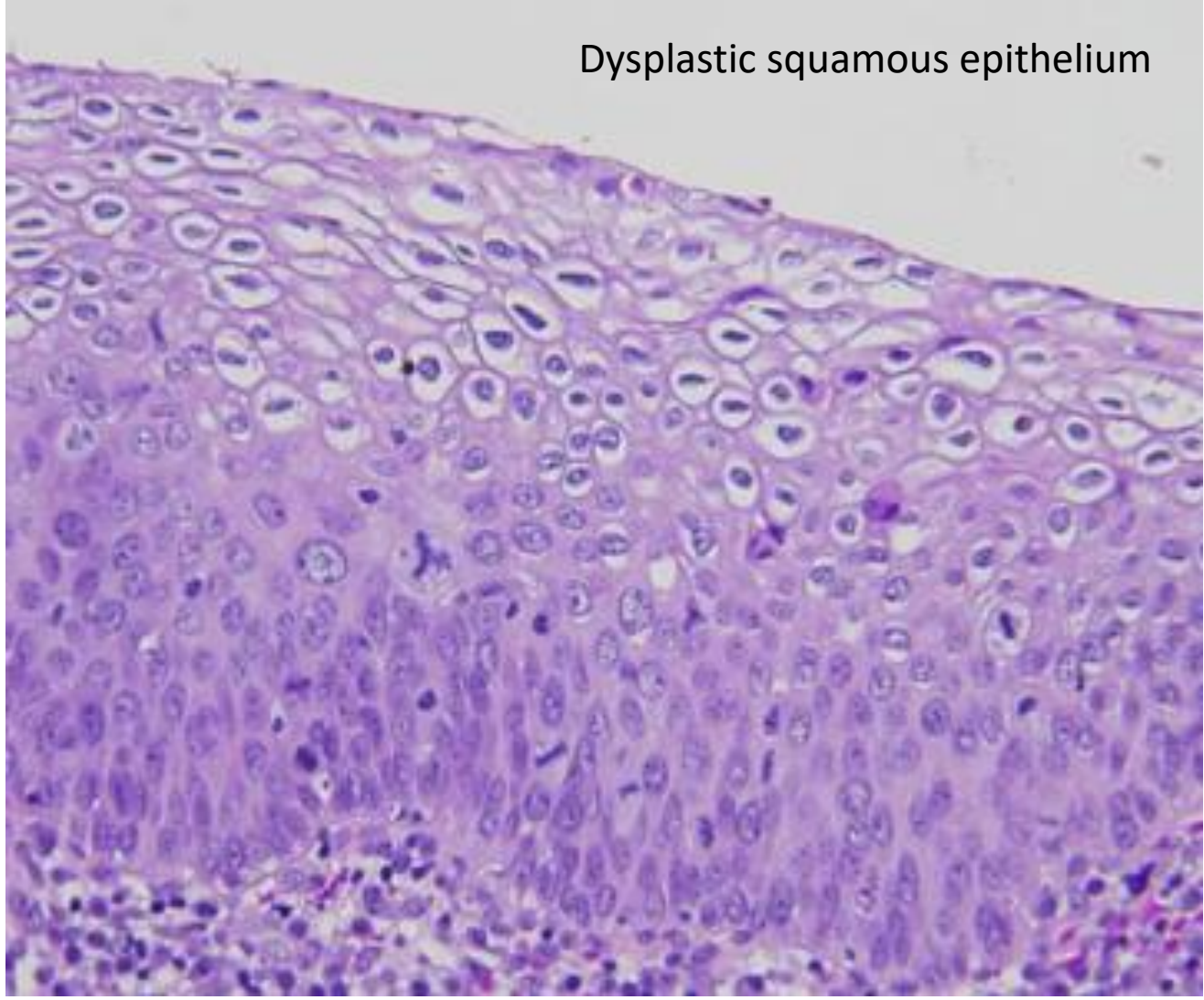
Normal CIN I CIN II CIN III



SIL

- Epithelial cell changes
  - Lack of maturation
  - Nuclear crowding and loss of polarity
  - Pleomorphism
  - Increased N/C ratio
  - Irregular nuclear outlines
  - Hyperchromatic nuclei (coarse nuclear chromatin)
  - Mitotic activity
    - Increased and present above the basal layer
    - +/- abnormal mitoses





- Lack of maturation
- Pleomorphism
  -Irregular nuclear outlines

- Nuclear crowding and loss of polarity
- Increased N/C ratio
- Hyperchromatic nuclei
- Mitotic activity Increased
  and present above the basal layer
  +/- abnormal mitoses

SIL

- The behaviour of the precursor lesions is complex
  Lowest grade - Most likely do not progress to carcinoma
  Greater degree of cellular atypia - Greater risk of developing carcinoma

- Not all lesions begin as low grade lesions

- May begin at any point depending on the viral and host factors

- Rate of progression - not uniform

Pap smear/ Pap test

- SIL may be asymptomatic for years
- Shed abnormal squamous cells

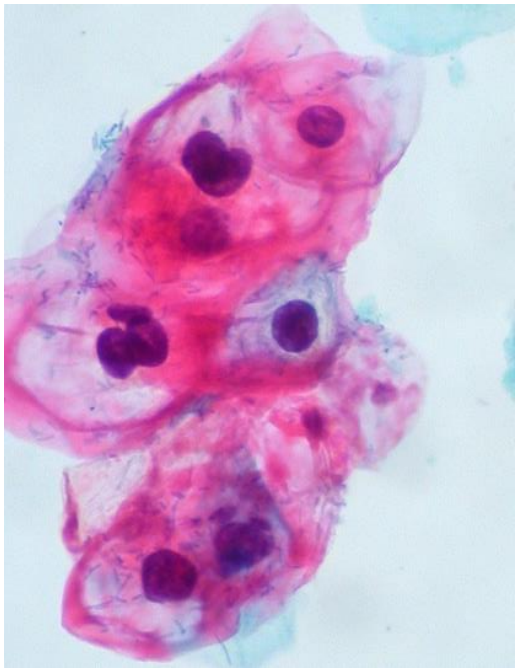
  - Basis for the screening test , Pap smear test
- Using spatula/ a brush, transformation zone of the cervix is circumferentially scraped
- Exfoliated cells are prepared for cytological examination

  Usual/conventional method - Pap smear

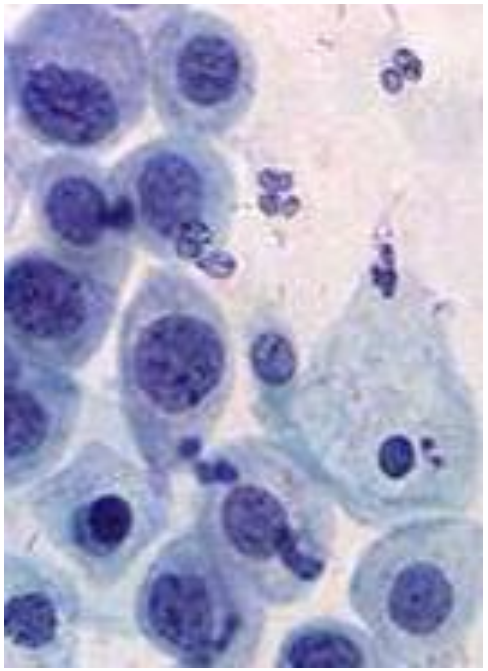
  Thinprep preparation is also available

Pap test/ Pap smear

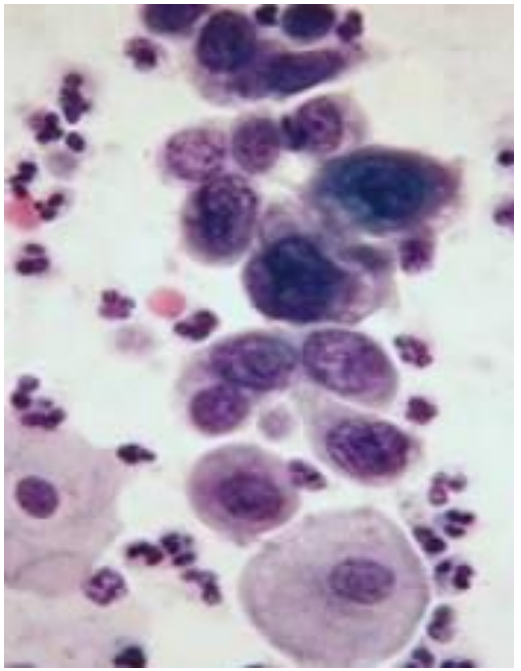
- Cells are smeared on a slide(conventional method
- Stained with Papanicolaou method



CIN I



CIN II

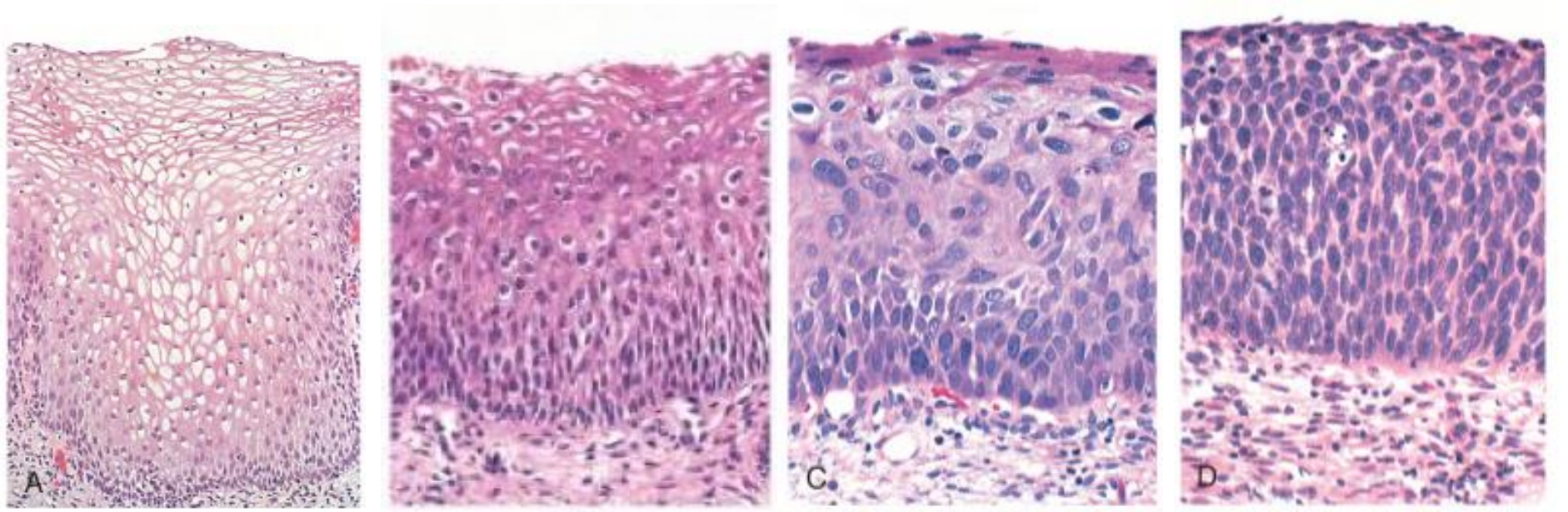


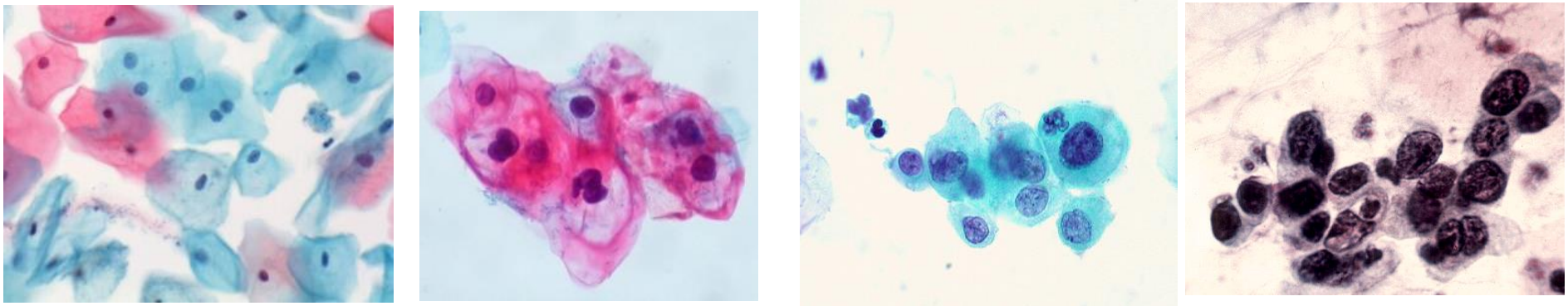
CIN III

CIN and SIL

LSIL HSIL

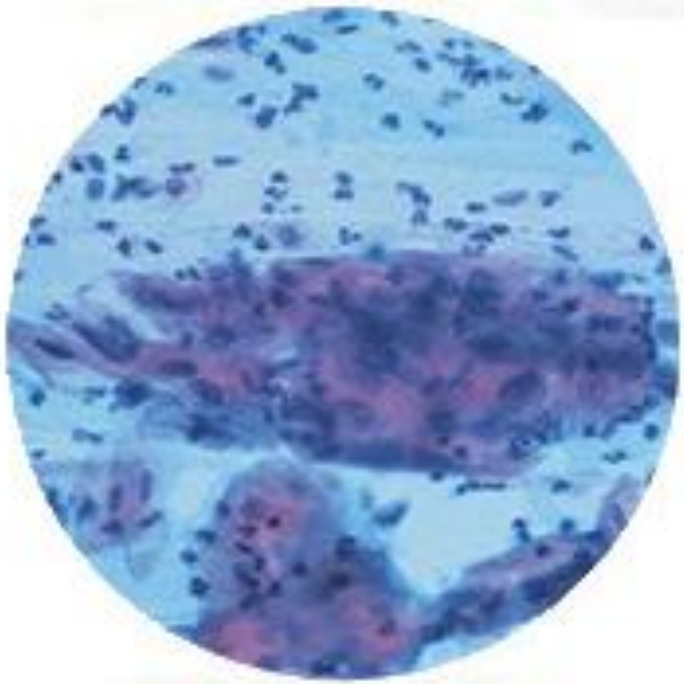
Normal CIN I CIN II CIN III





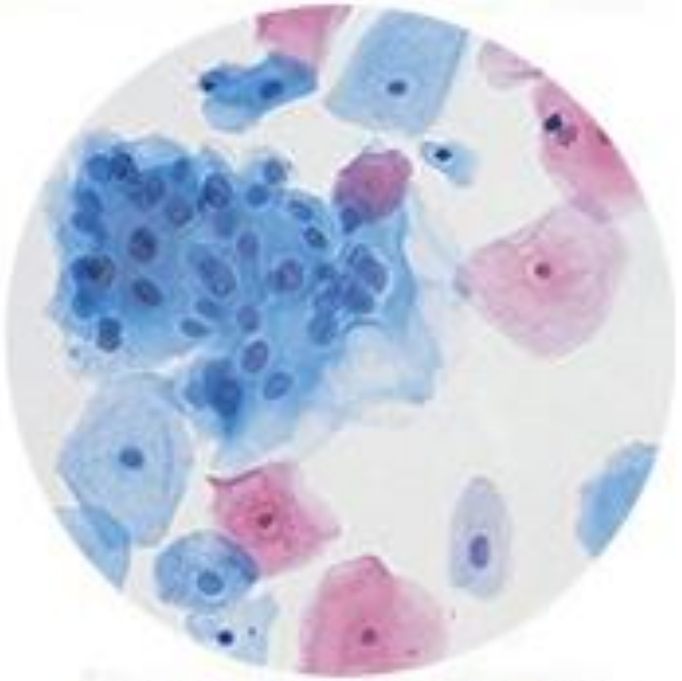
Pap smears

Pap smear - Cells are smeared on a slide



Difficult to visualise:
the conventional Pap test slide under a microscope

Thin prep - Cells are spun down onto a slide



Clear and more effective:
the ThinPrep® Pap test slide under a microscope

Cervical carcinoma

- **Squamous cell carcinoma (SCC)**

  Most common histological type

  HSIL - immediate precursor

- Adenocarcinoma

  Develop from adenocarcinoma insitu

- Others

  Adenosquamous carcinoma

  Neuroendocrine carcinoma

All are caused by high oncogenic risk HPVs

Risk factors for cervical cancer

- Related to both host and viral characteristics

Type of virus

Time of exposure

Presence of co-carcinogens

Multiple sexual partners

Male partner with multiple sexual partners

Young age at first intercourse

High parity

Persistent infection with high oncogenic risk HPVs

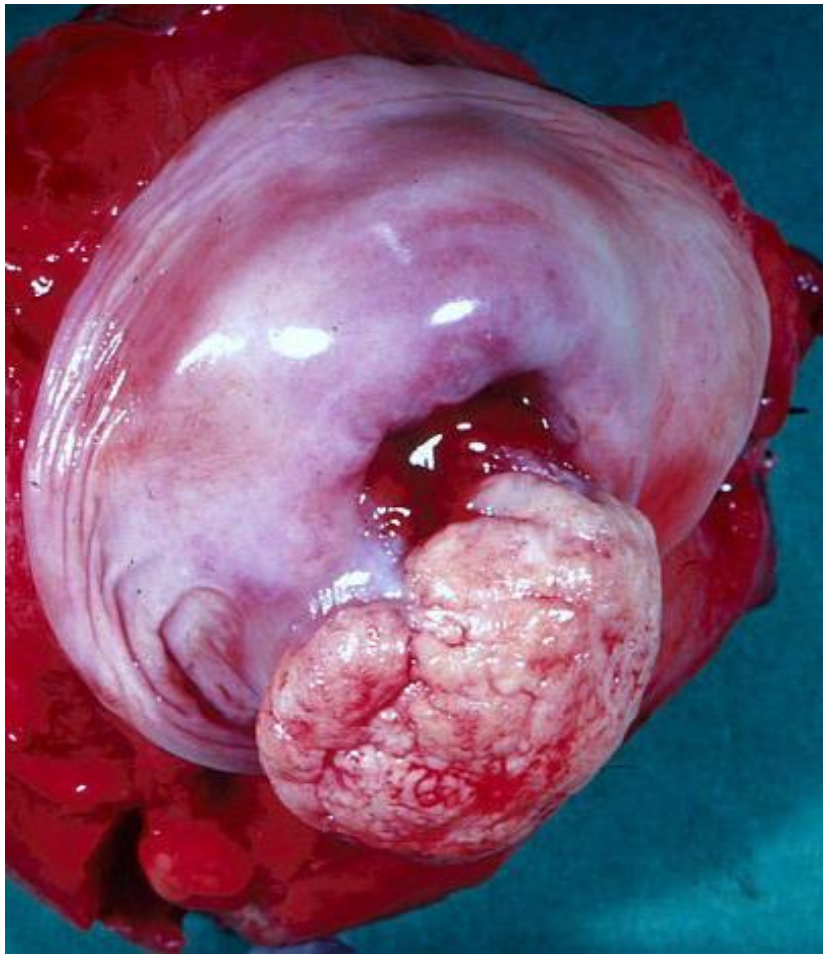
Immunosupppression

Certain HLA subtypes

Oral contraceptives – increase the risk

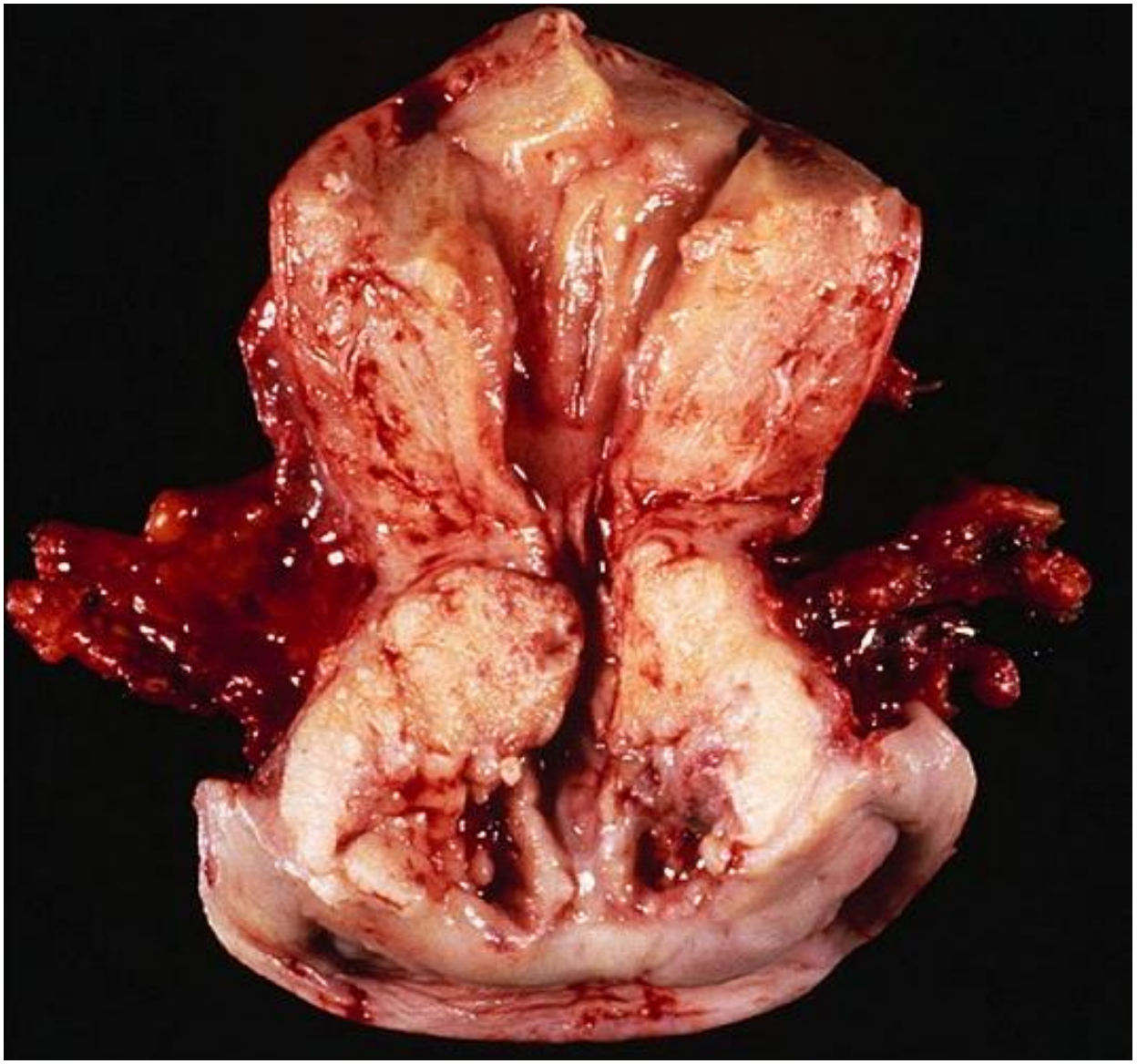
Use of nicotine – Important co-factor for HPV driven carcinogenesis

Cervical SCC - Macroscopy



Fungating/ exophytic growth

Ulcerative growth



Infiltrating type of cancer involving the cervix

Cervical SCC - Macroscopy

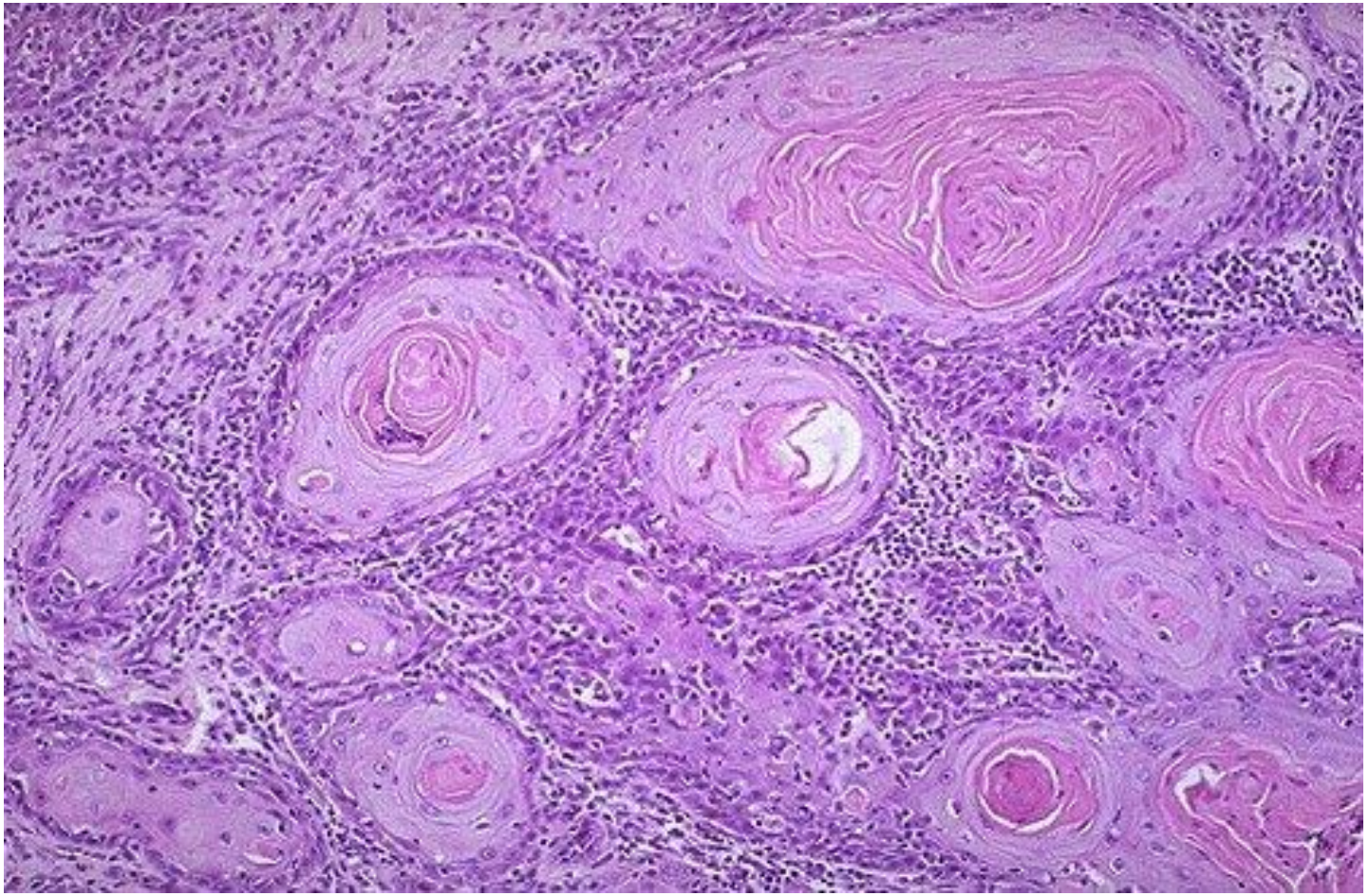
- Cut surface

  Solid, fleshy and friable tumour with

  Necrosis and

  Haemorrhage

Cervical SCC - Microscopy



Note: Infiltrating nests of squamous epithelim
keratin pearl formation

This is a well differentiated SCC

Cervix - SCC

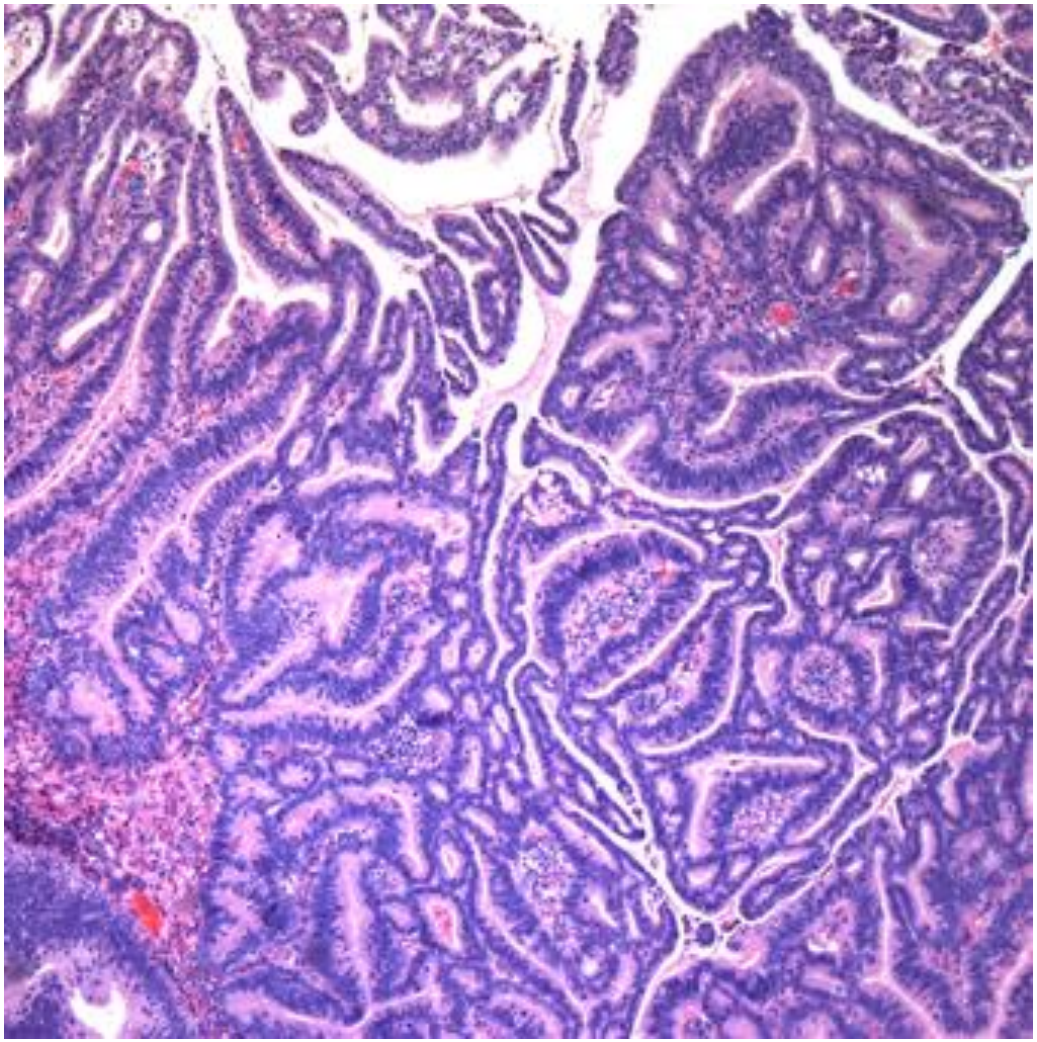
Direct spread

- Vagina
- Endometrium and myometrium
- Parametrium
- Adjoining structures - lower ureters, bladder , rectum

Lymphatic spread- Paracervical and external iliac nodes

Haematogenous spread – Liver, lung, bone marrow etc.

Adenocarcinoma - Microscopy



Note: Atypical closely packed glandular structures

WHO histological classification of tumours of the uterine cervix

Epithelial tumours
- Squamous tumours and precursors
  - Squamous cell carcinoma, not otherwise specified
    - Keratinizing
    - Non-keratinizing
    - Basaloid
    - Verrucous
    - Warty
    - Papillary
    - Lymphoepithelioma-like
    - Squamotransitional
  - Early invasive (microinvasive) squamous cell carcinoma
  - Squamous intraepithelial neoplasia
    - Cervical intraepithelial neoplasia (CIN) 3 / squamous cell carcinoma in situ
  - Benign squamous cell lesions
    - Condyloma acuminatum
    - Squamous papilloma
    - Fibroepithelial polyp
- Glandular tumours and precursors
  - Adenocarcinoma
    - Mucinous adenocarcinoma
      - Endocervical
      - Intestinal
      - Signet-ring cell
      - Minimal deviation
      - Villoglandular
    - Endometrioid adenocarcinoma
    - Clear cell adenocarcinoma
    - Serous adenocarcinoma
    - Mesonephric adenocarcinoma
  - Early invasive adenocarcinoma
  - Adenocarcinoma in situ
  - Glandular dysplasia
  - Benign glandular lesions
    - Müllerian papilloma
    - Endocervical polyp
- Other epithelial tumours
  - Adenosquamous carcinoma
    - Glassy cell carcinoma variant
  - Adenoid cystic carcinoma
  - Adenoid basal carcinoma
  - Neuroendocrine tumours
    - Carcinoid
    - Atypical carcinoid
    - Small cell carcinoma
    - Large cell neuroendocrine carcinoma
  - Undifferentiated carcinoma

Mesenchymal tumours and tumour-like conditions
- Leiomyosarcoma
- Endometrioid stromal sarcoma, low grade
- Undifferentiated endocervical sarcoma
- Sarcoma botryoides
- Alveolar soft part sarcoma
- Angiosarcoma
- Malignant peripheral nerve sheath tumour
- Leiomyoma
- Genital rhabdomyoma
- Postoperative spindle cell nodule

Mixed epithelial and mesenchymal tumours
- Carcinosarcoma (malignant müllerian mixed tumour; metaplastic carcinoma)
- Adenosarcoma
- Wilms tumour
- Adenofibroma
- Adenomyoma

Melanocytic tumours
- Malignant melanoma
- Blue naevus

Miscellaneous tumours
- Tumours of germ cell type
  - Yolk sac tumour
  - Dermoid cyst
  - Mature cystic teratoma

Lymphoid and haematopoetic tumours
- Malignant lymphoma (specify type)
- Leukaemia (specify type)

Secondary tumours

Cervix - inflammations

- Lactobacilli dominate the normal vaginal and cervical flora
- Produce lactic acid and suppress the growth of other pathogenic organisms
- At low pH lactobacilli produce bacteriotoxic H_2O_2

- What are the causes for higher, alkaline pH in vagina?

  eg. bleeding, sexual intercourse, antibiotic treatment

Cervix - inflammations

Acute and chronic cervicitis

- Mononuclear cell infiltrate (lymphocytes, plasma cells) or acute and chronic inflammatory cell infiltrate

- Chronic cervicitis may be associated with
  - erosion and ulceration of the epithelium
  - granulation tissue formation and
  - **regenerative changes of the epithelium**

  may result in non-specific abnormal Pap test

Cervix - inflammations

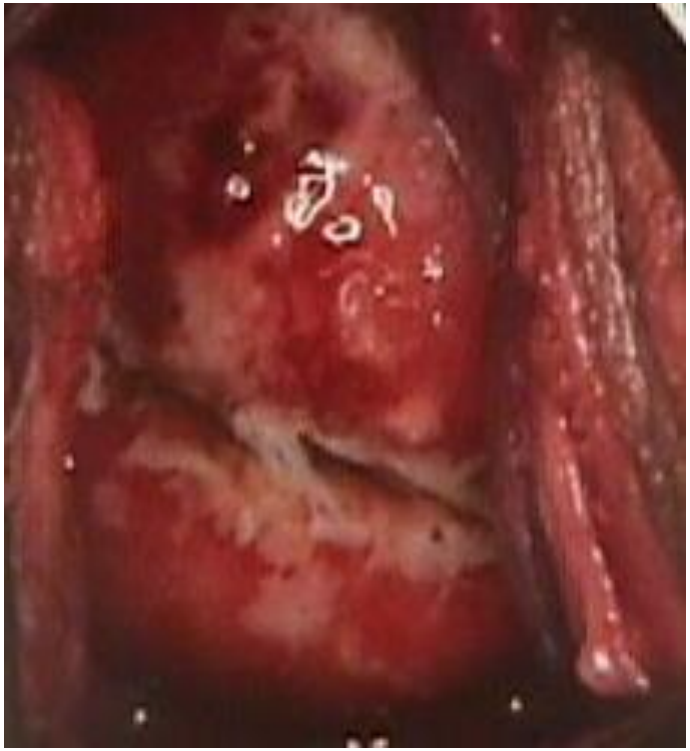
- Important to recognize
  - the presence of organisms
  - recognize the tissue reaction patterns associated with specific infections

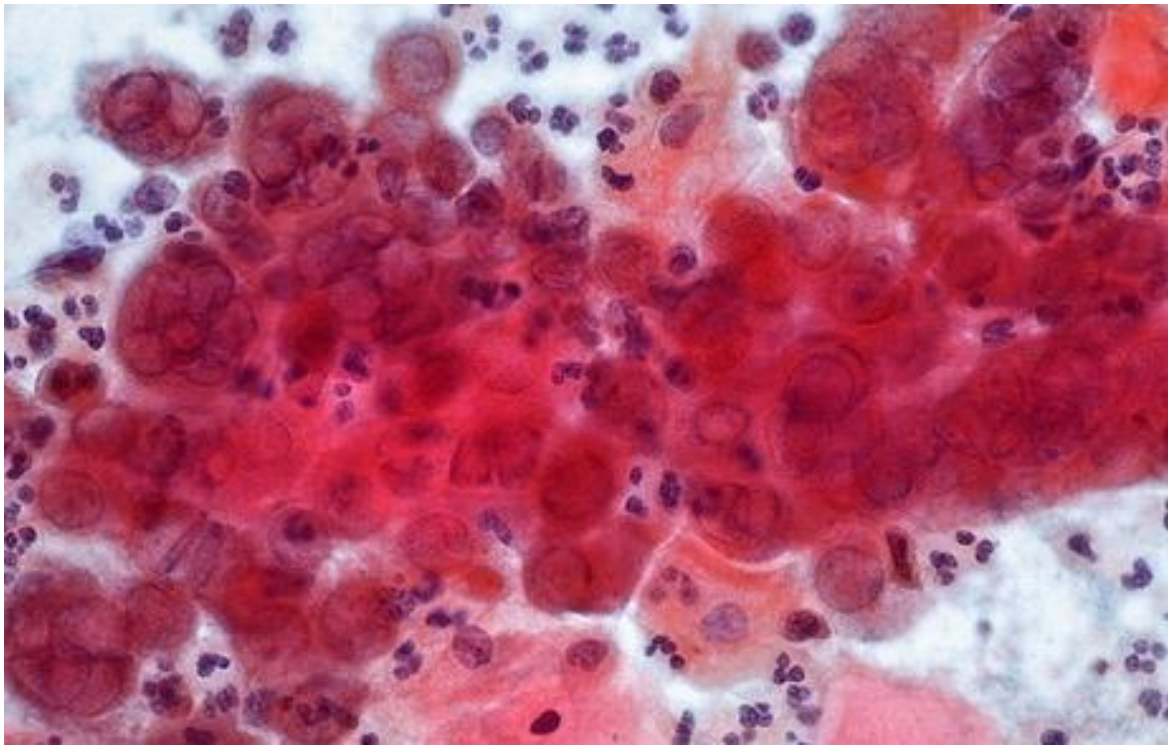
Herpes simplex infection

Macroscopy - ulceration

Microscopy - intranuclear inclusions in the epithelial cells

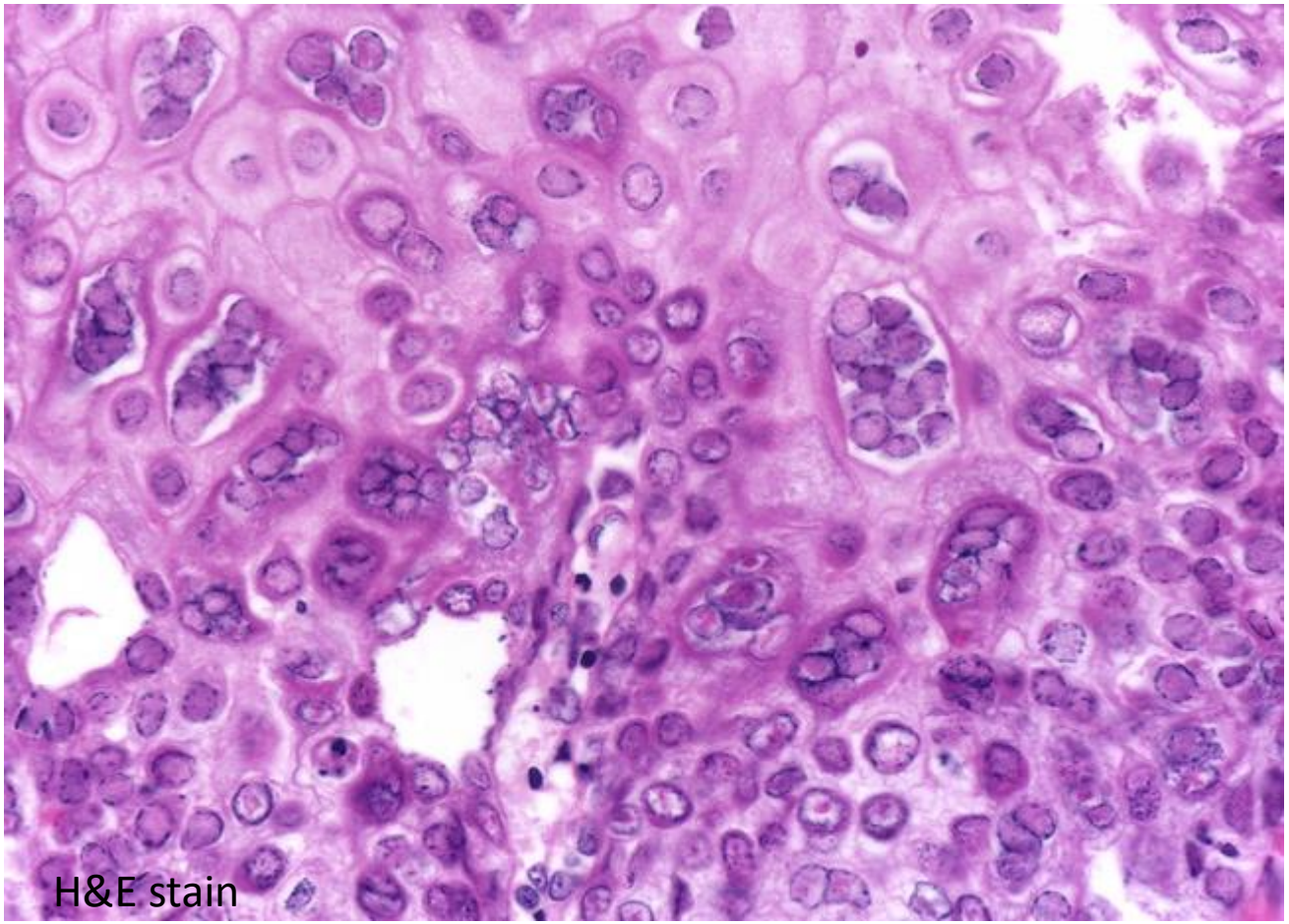
lymphocytic infiltrate

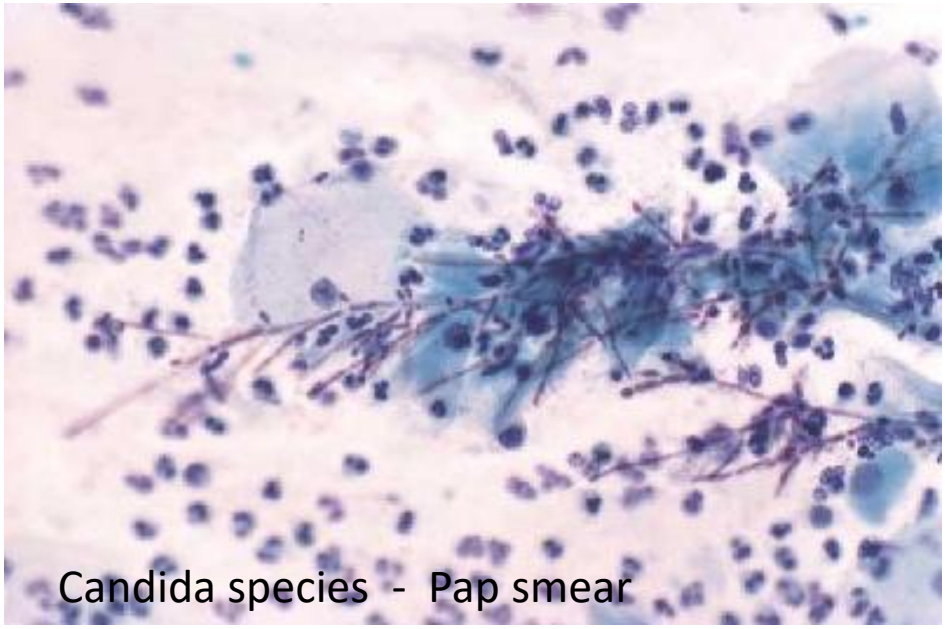




Herpes intranuclear inclusions– Pap smear

Herpes simplex cytopathic effect

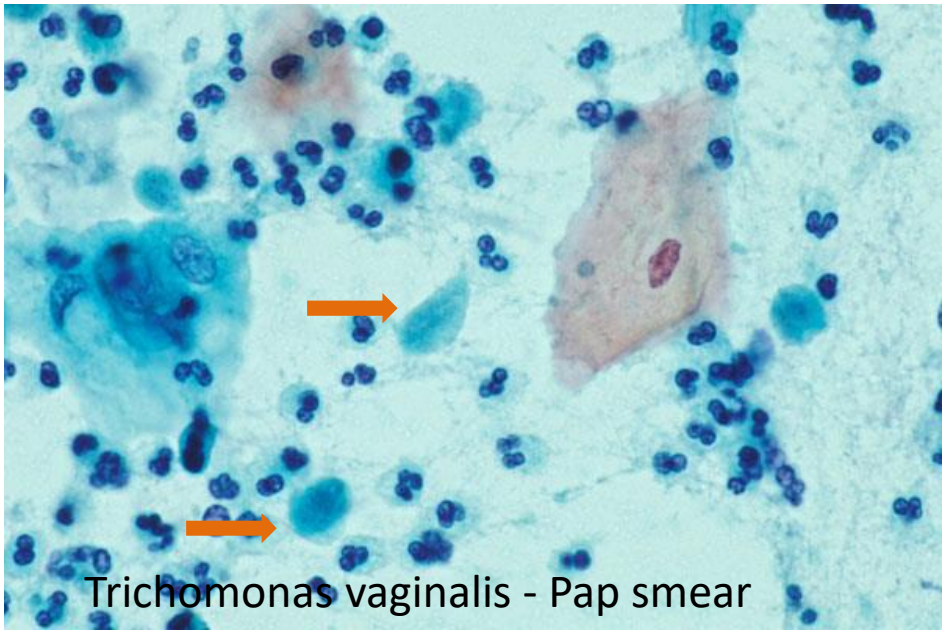




Candida species - Pap smear

Candida

Note: Candida hyphae



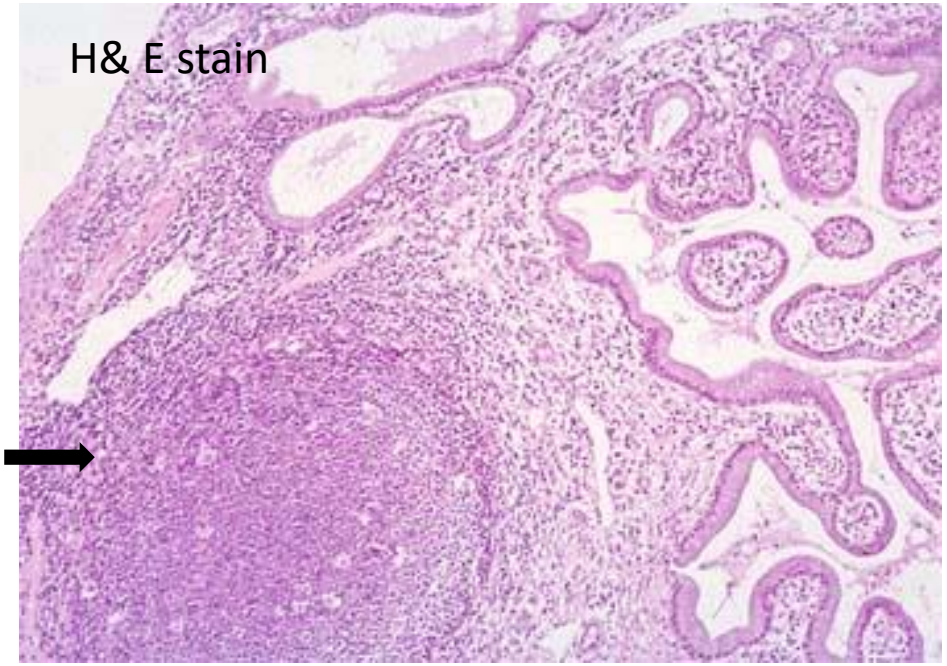
Trichomonas vaginalis - Pap smear

Trichomonas vaginalis

- Chlamydia trachomatis infection

  - lymphoid follicles with germinal centres and

  - prominent plasmacytic infiltrate



Cervix - Benign conditions

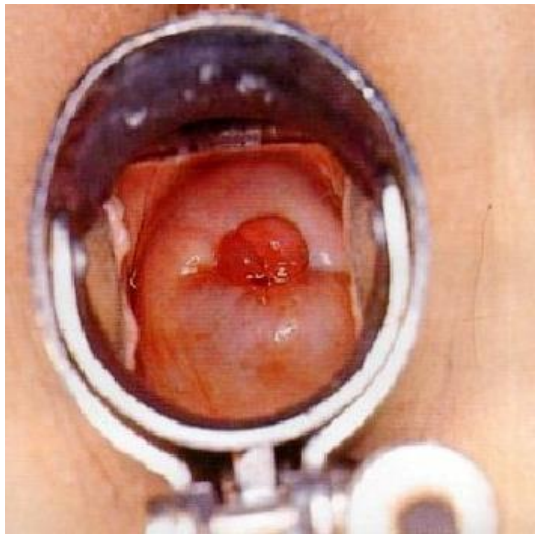
- Benign endocervical polyps

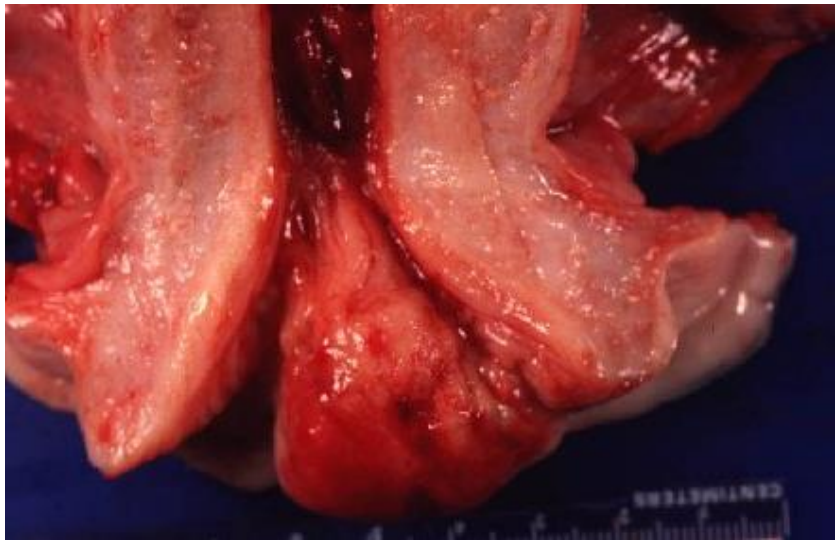
  Macroscopy

  Polypoidal lesion, pink brown/ grey colour

  Outer surface - Smooth/ eroded/ ulcerated

  Cut surface - Oedematous /myxoid

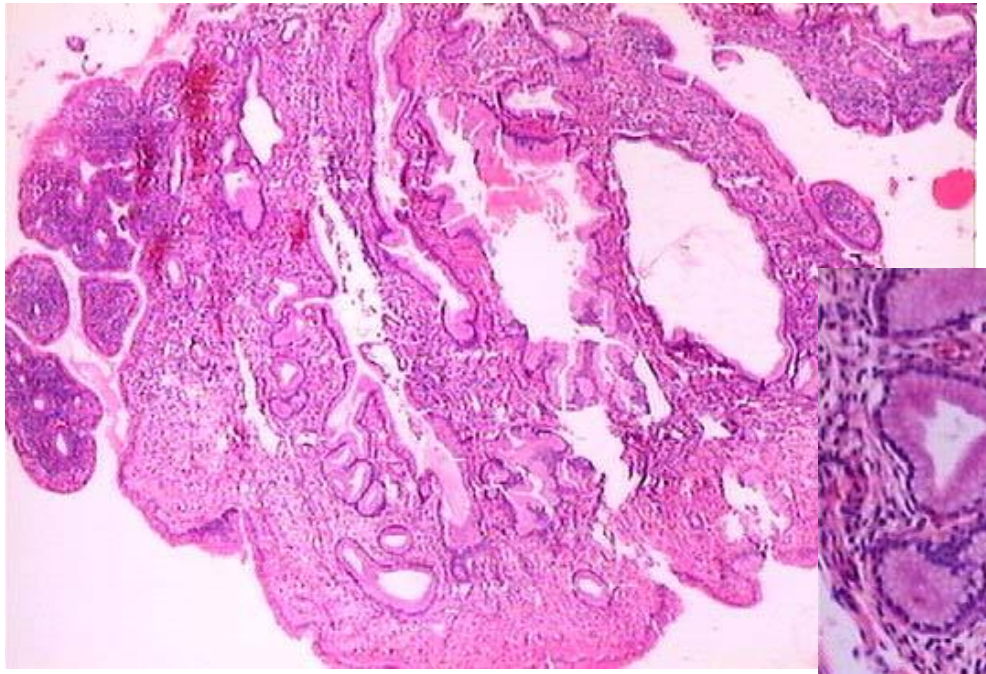


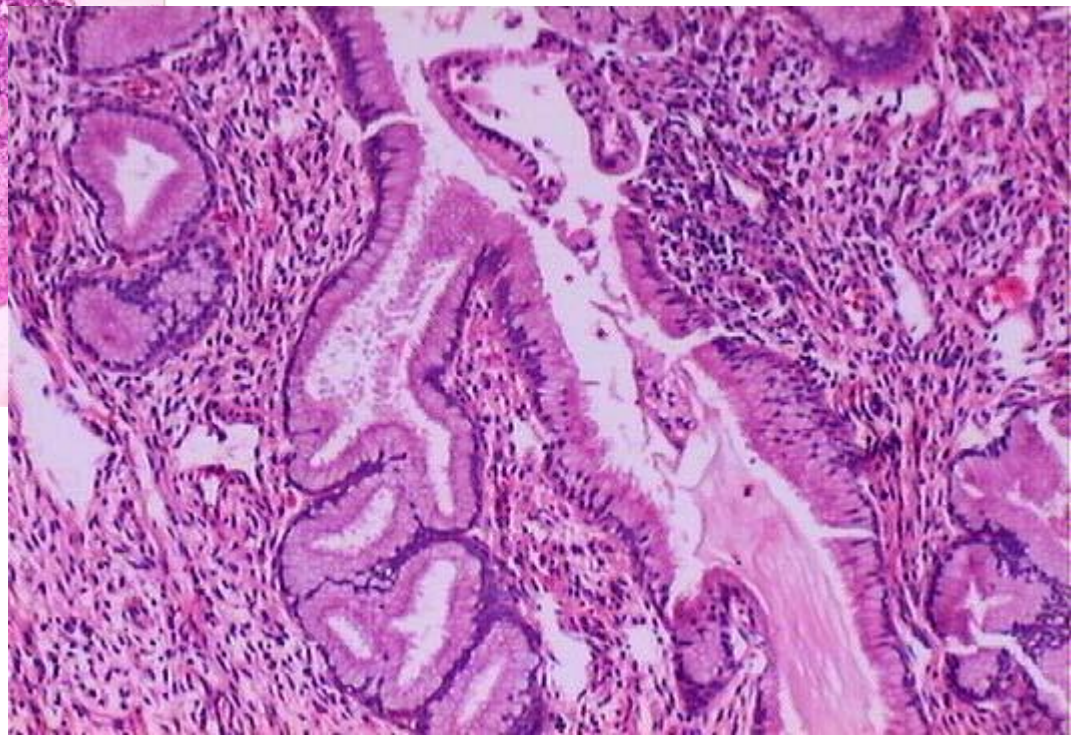


- Microscopy

  - dilated, mucus-secreting endocervical glands

  - inflammation and squamous metaplasia





Vulva

- Premalignant lesions

  Vulvar Intraepithelial Neoplasia (VIN)

- Malignant neoplasms (Uncommon)

  Squamous cell carcinoma (commonest)

    Some are associated with high risk HPV types

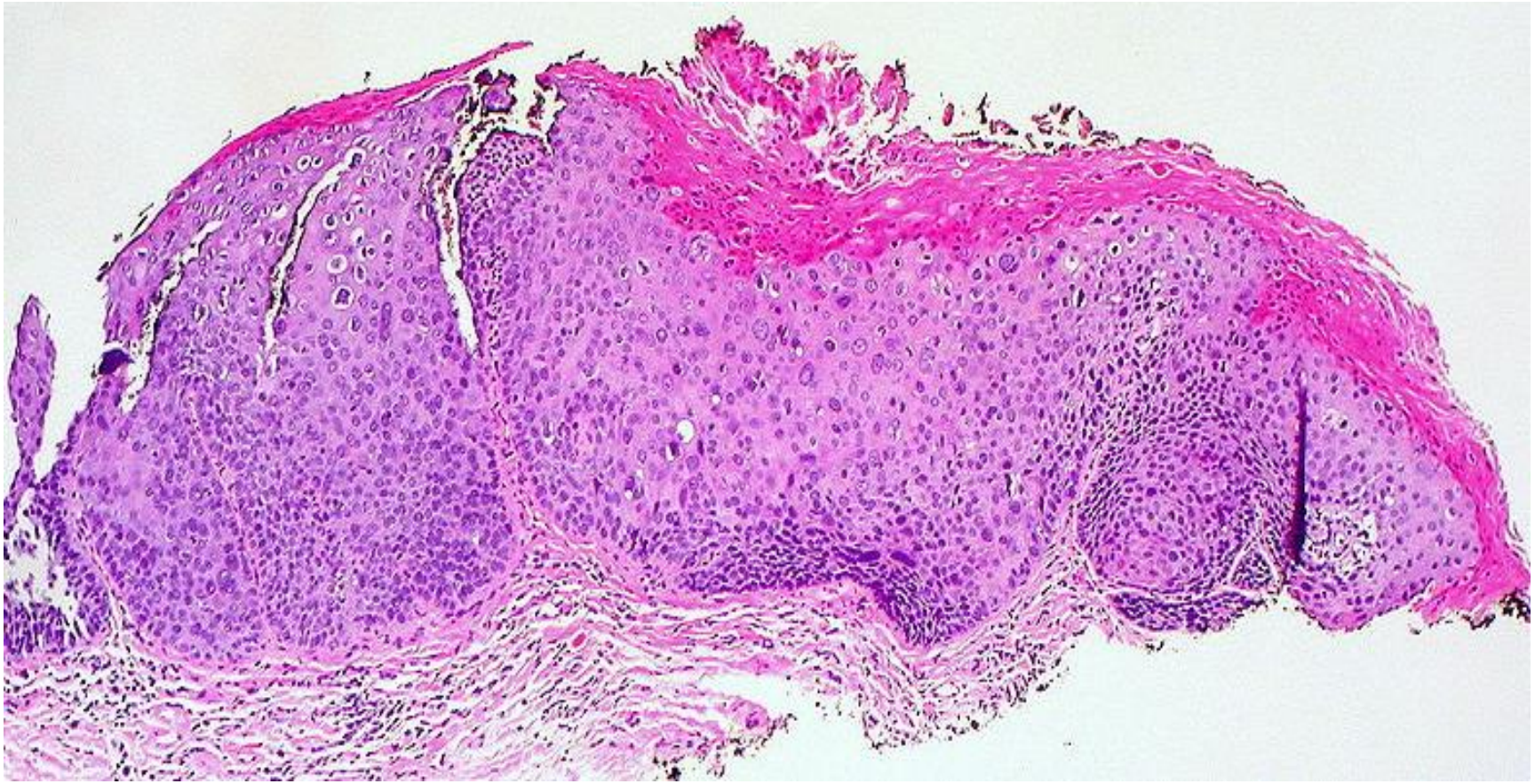
    Others are associated with lichen sclerosus

  Basal cell carcinoma

  Adenocarcinoma

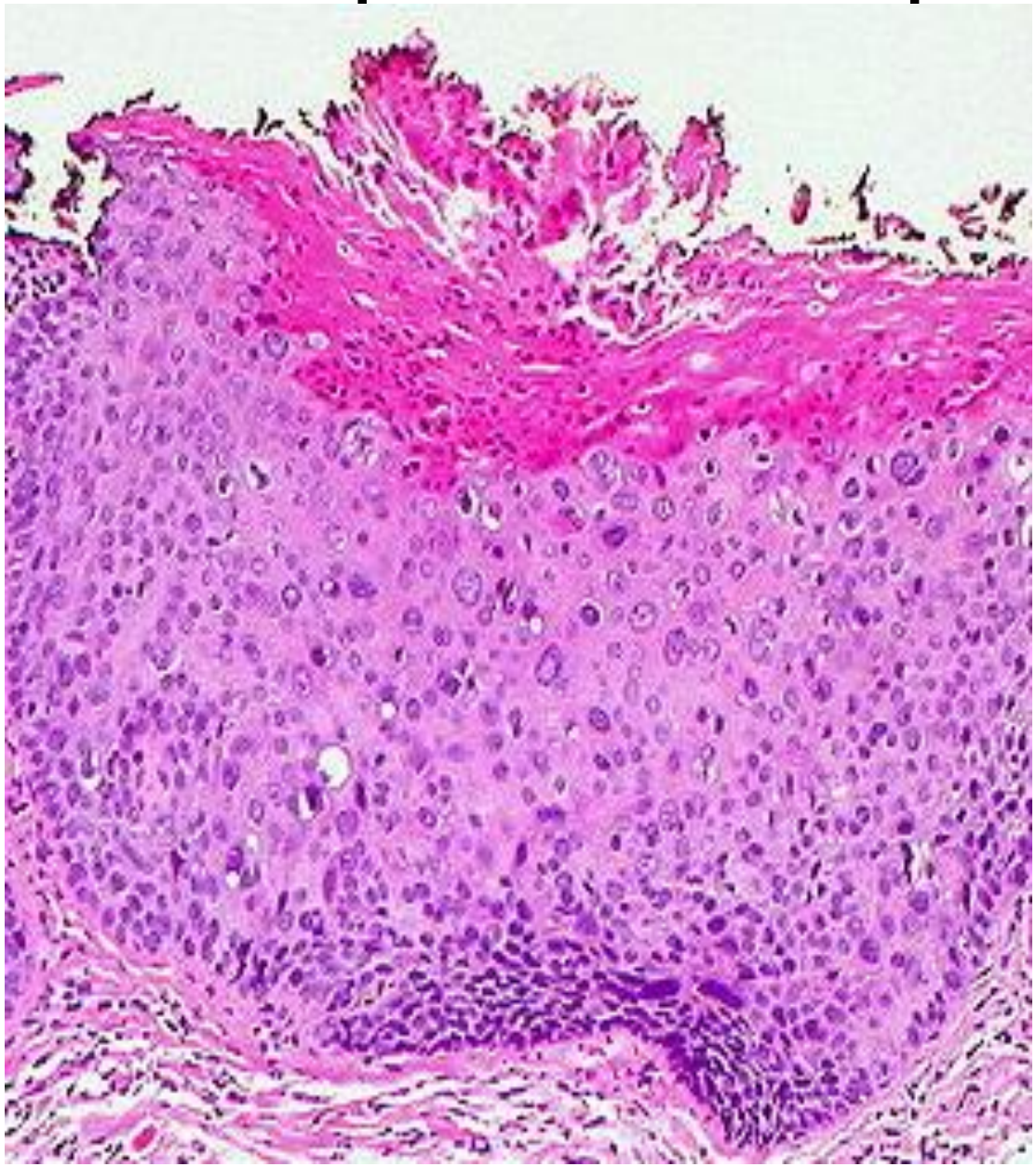
  Melanoma

Vulvar intraepithelial neoplasia (VIN)



Note: Atypical squamous epithelial cells involving the full thickness of the epithelium
loss of polarity
Cellular pleomorphism
Mitotic figures present above the basal layer
- **No stromal invasion**

Vulvar intraepithelial neoplasia (VIN)



Vagina

- Premalignant lesions

  Vaginal Intraepithelial Neoplasia

- Malignant neoplasms - Uncommon

Squamous cell carcinoma

Most are associated with high oncogenic risk HPVs

Greatest risk factor - previous CA cervix or CA vulva

Embryonal rhabdomyosarcoma (sarcoma botryoides)

Uncommon tumour

Infants and children < 5 years

Summary

Now you should be able to

- Describe the pathogenesis of human papilloma virus (HPV) related lesions of the cervix
- Describe the morphological features of intraepithelial neoplasia and carcinoma of the cervix
- Briefly describe the non-neoplastic conditions of the cervix
- Briefly describe the premalignant and malignant conditions of the vulva and vagina

Don’t forget your reading assignments! This part is as important as the lecture

- Oncogenic effects of HPV
- Vaccination against HPV