NCPTS

Cervical Histopathology for Cytoscientists

Pre-invasive and Invasive lesions of the Cervix

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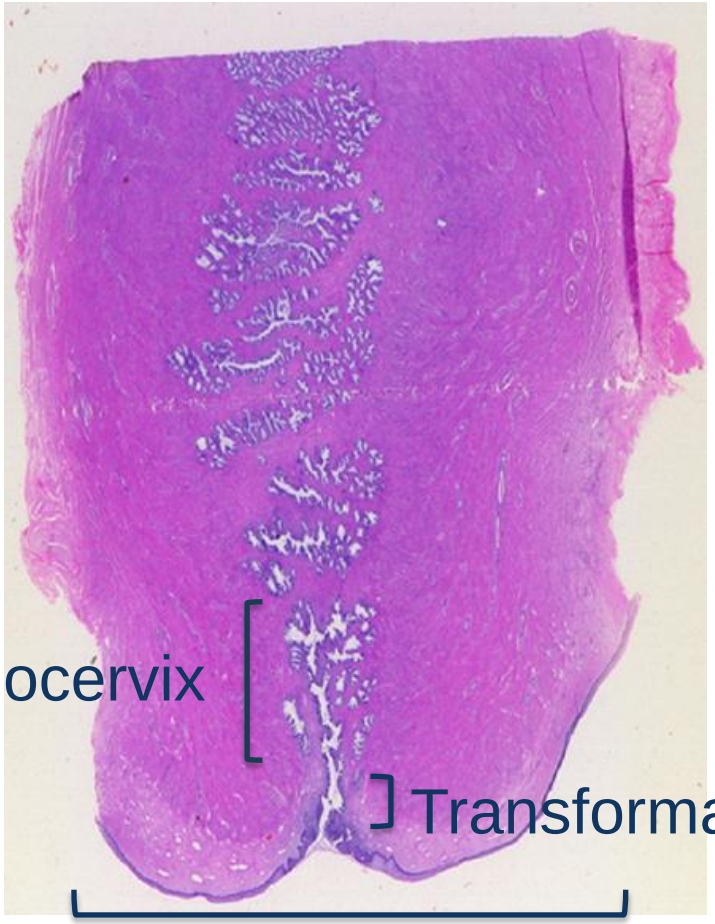
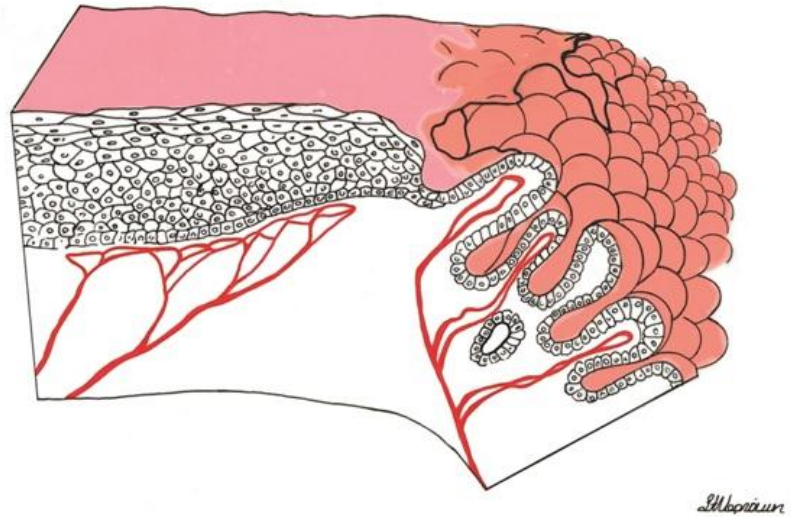
Topics overview

1. Histology of the normal cervix and physiological changes
2. Squamous lesions
   - Pre-invasive lesions
   - Invasive cancer
3. Glandular lesions
   - Pre-invasive lesions
   - Invasive cancer

1. The structure of the cervix





The Transformation Zone (TZ)

Figure 3. Cervical Squamocolumnar Junction (SCJ) and Transformation Zone

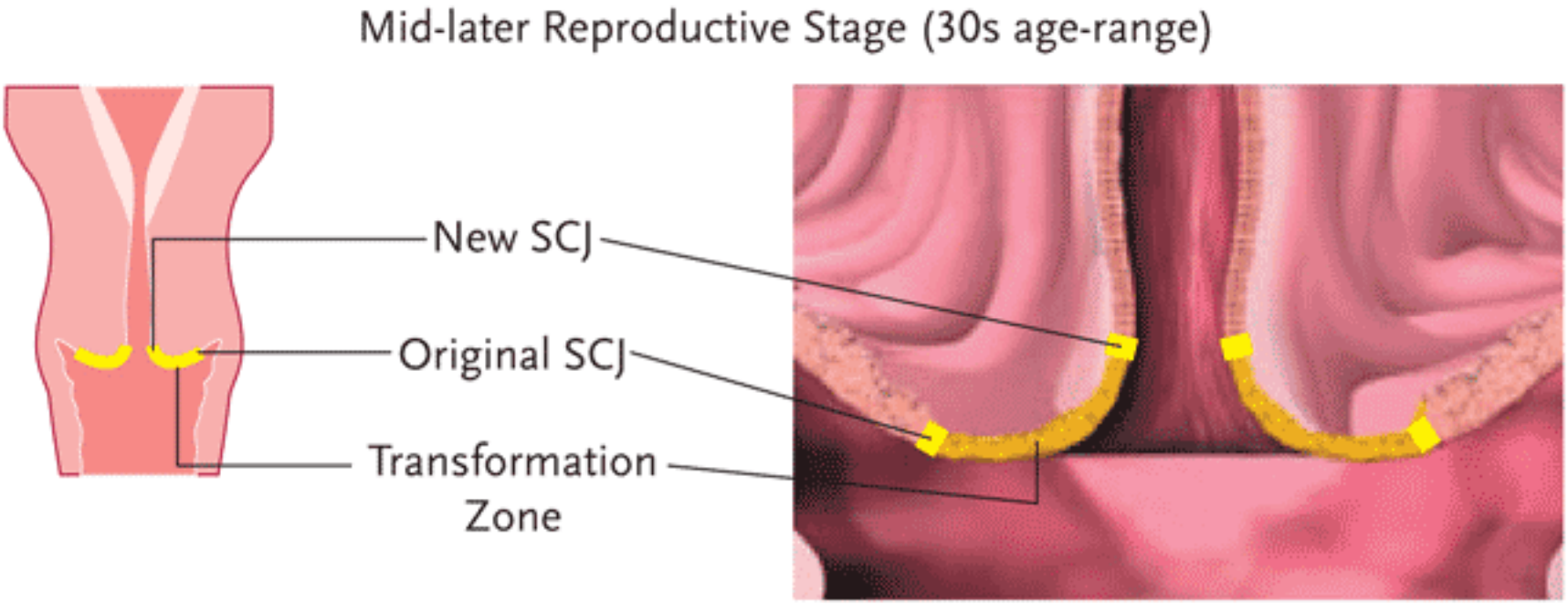
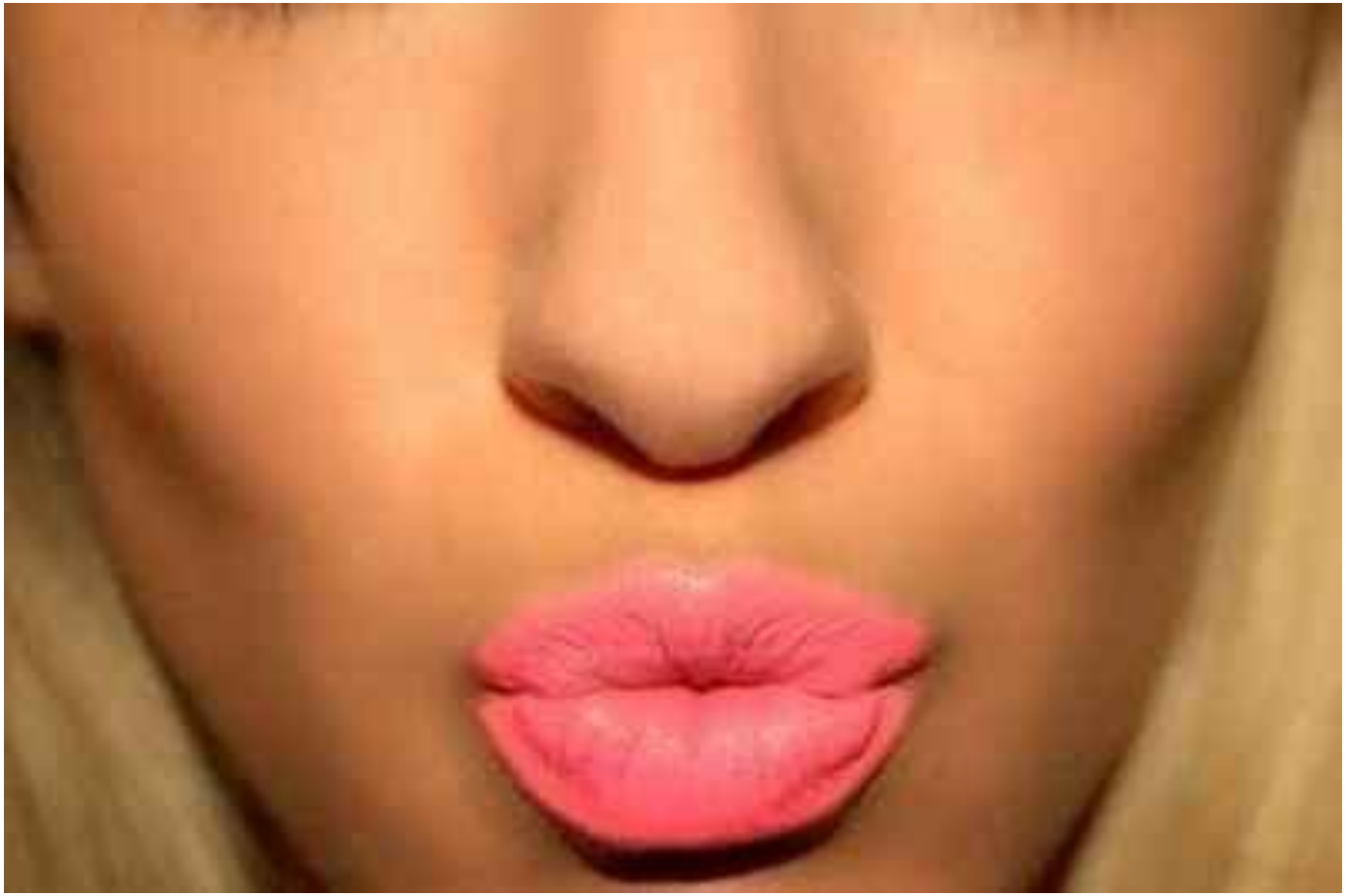


Figure from: *Human Papillomavirus, Monographs in Medicine.* Whitehouse Station, NJ: Merck and Co; 2008.

The pout

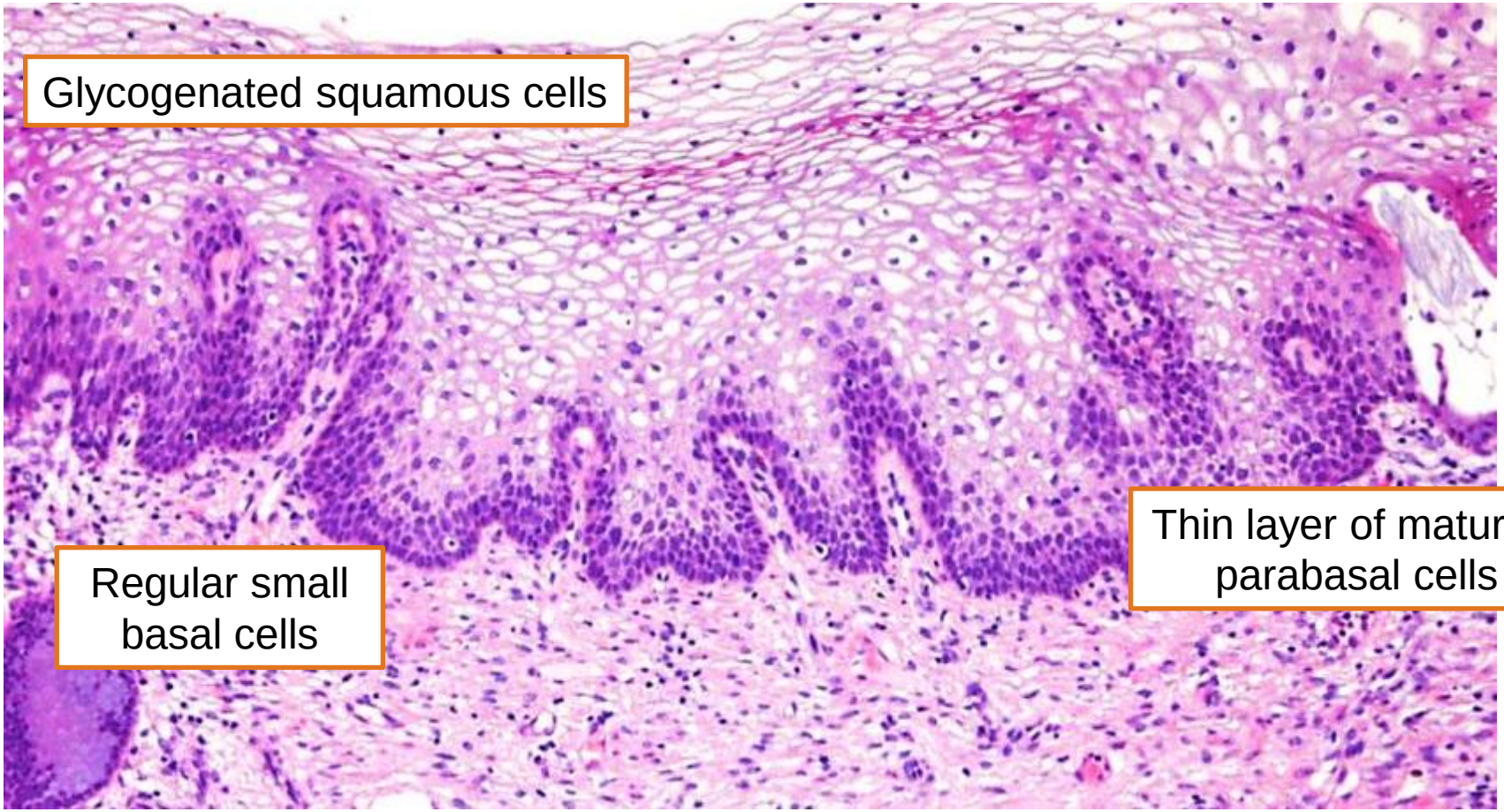


From http://www.avonconnects.co.uk/message/1286446

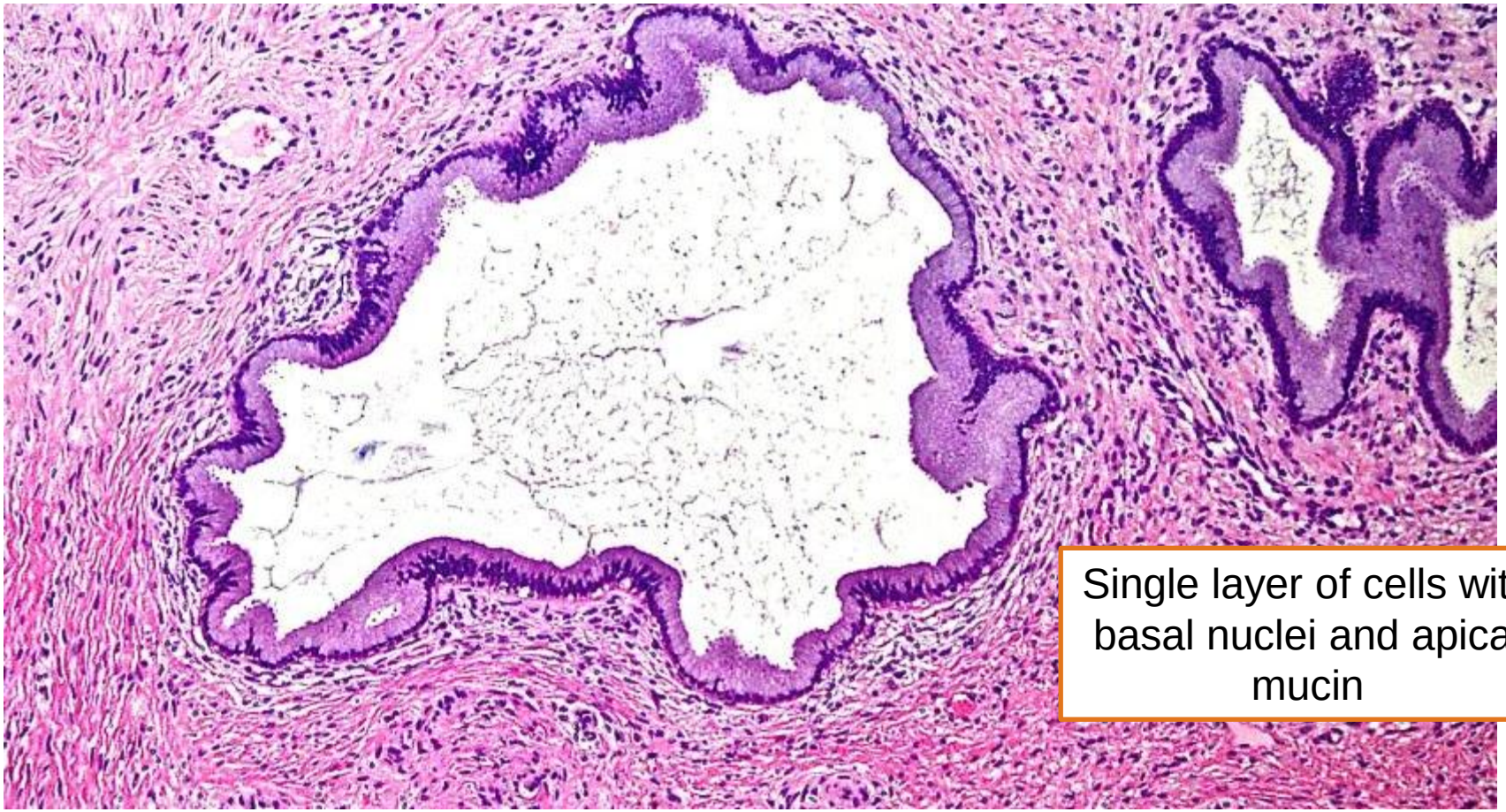
Cervical ectropion

- Central columnar epithelium extends out through and around the external os
- More commonly seen in teenagers, during pregnancy and in women on the oral contraceptive pill

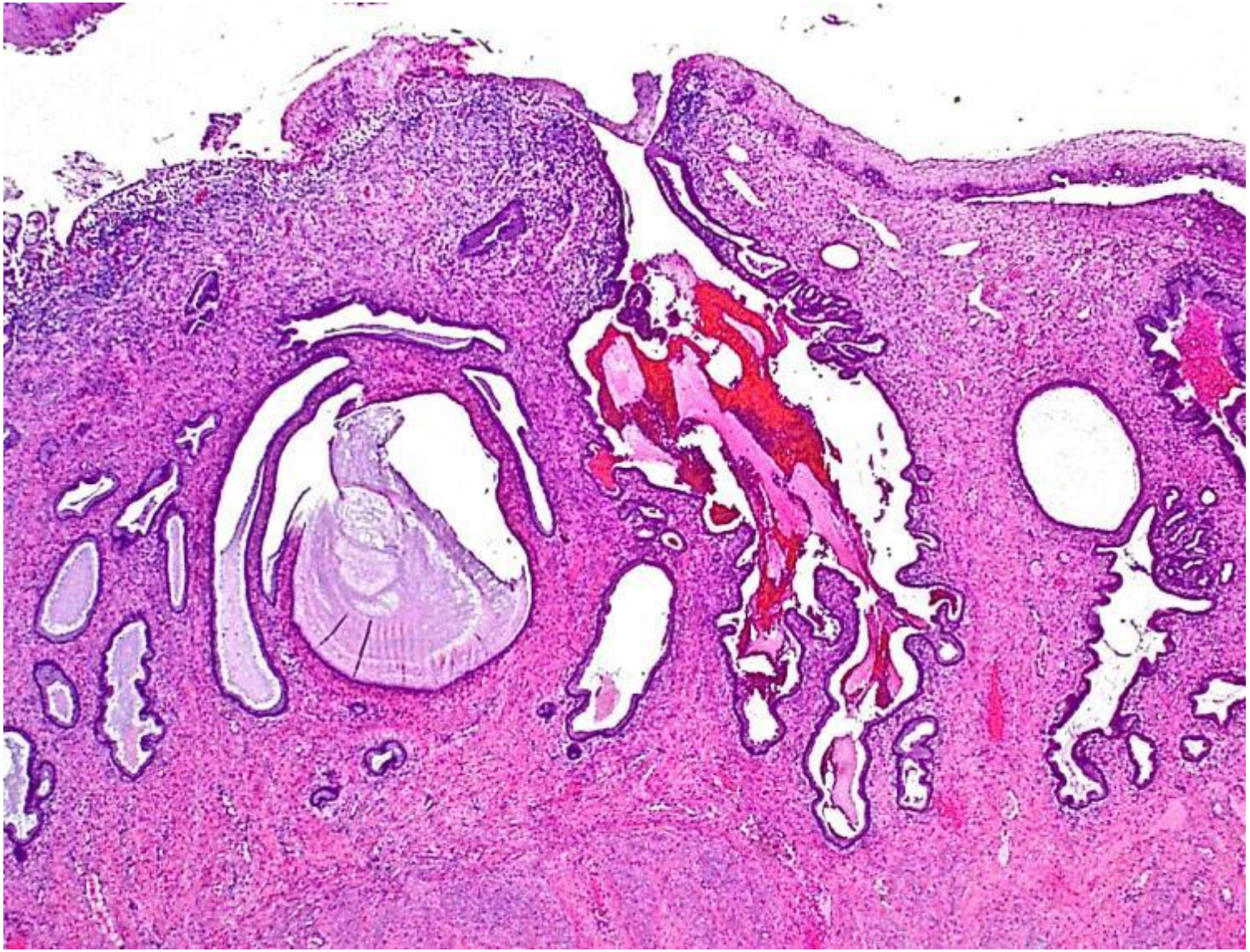
Normal squamous epithelium



Normal endocervical glands



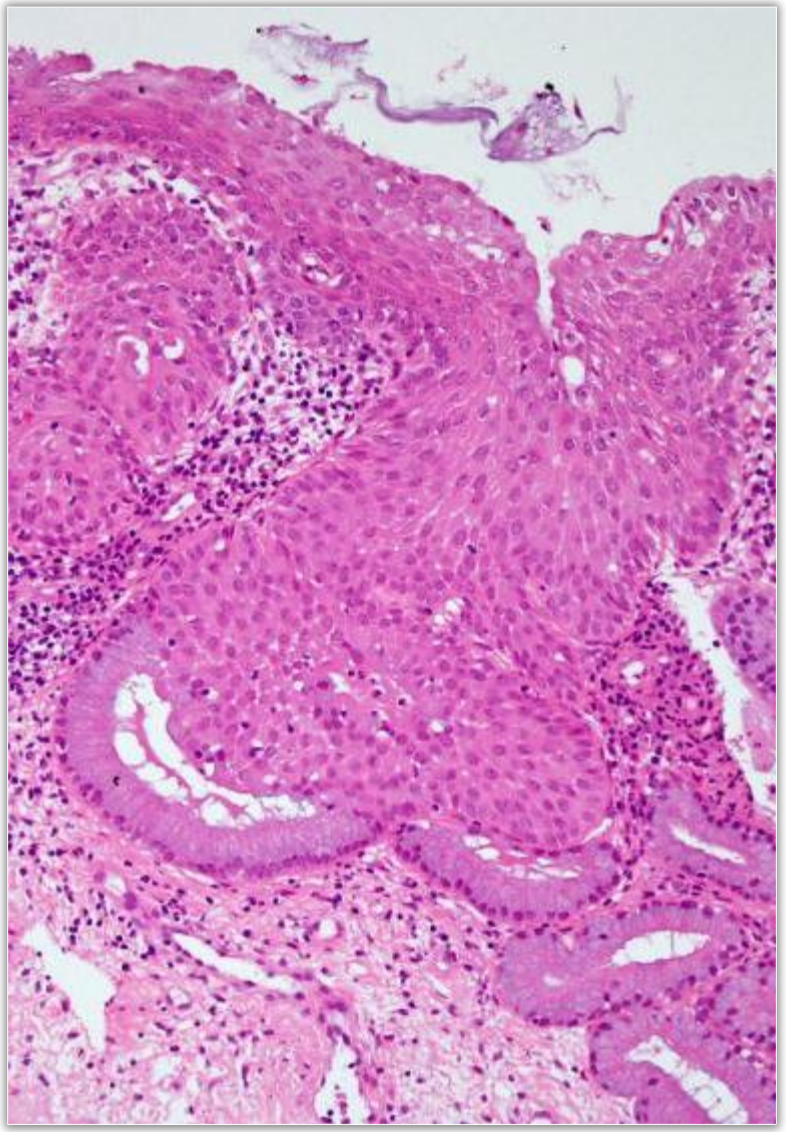
Not really glands – crypts



TZ- squamous epithelium overlying cervical glands

Squamous metaplasia: Gland extension

As part of the physiologic squamous metaplasia, squamous epithelium can extend into glands.



2. SQUAMOUS LESIONS

HPV Pathogenesis

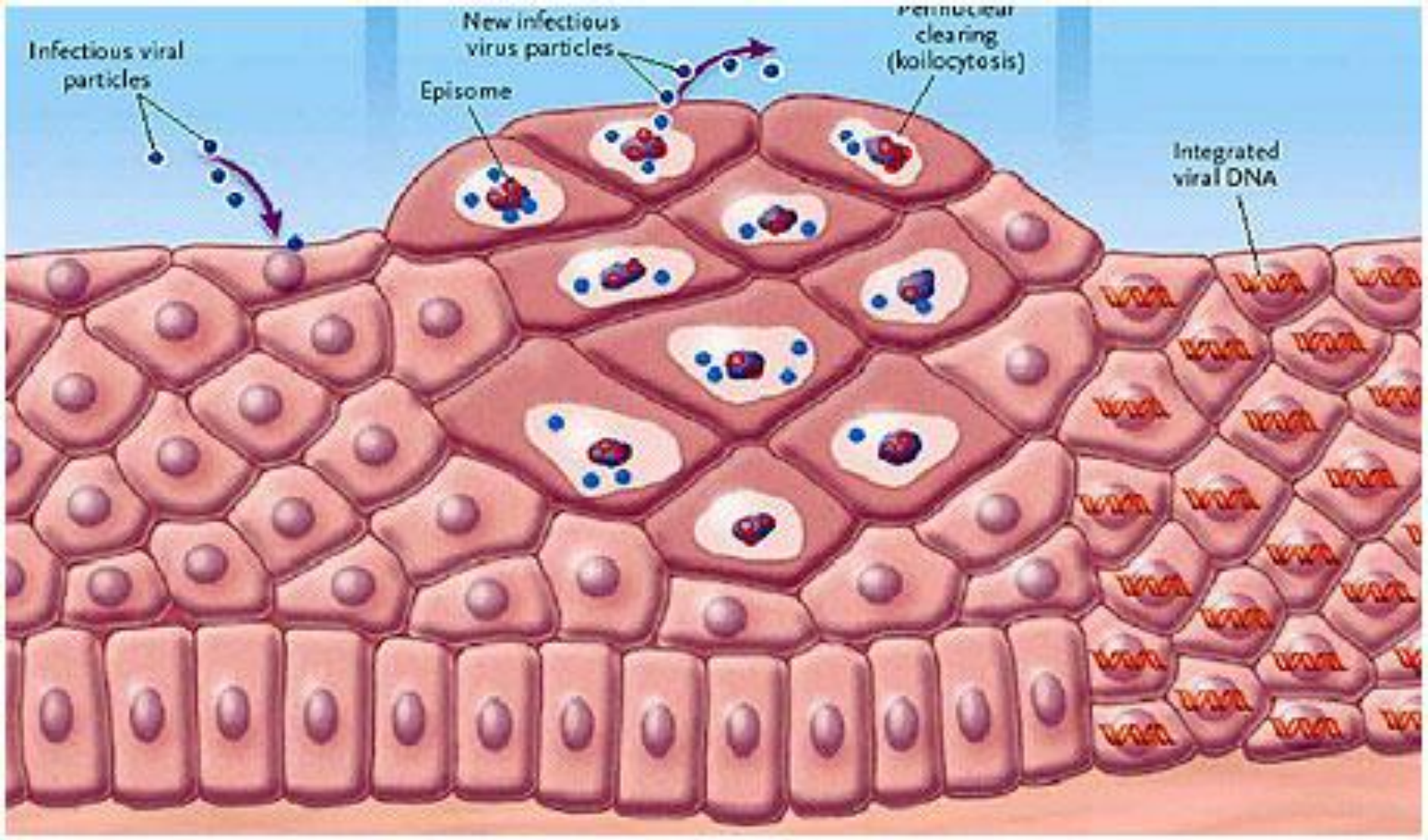
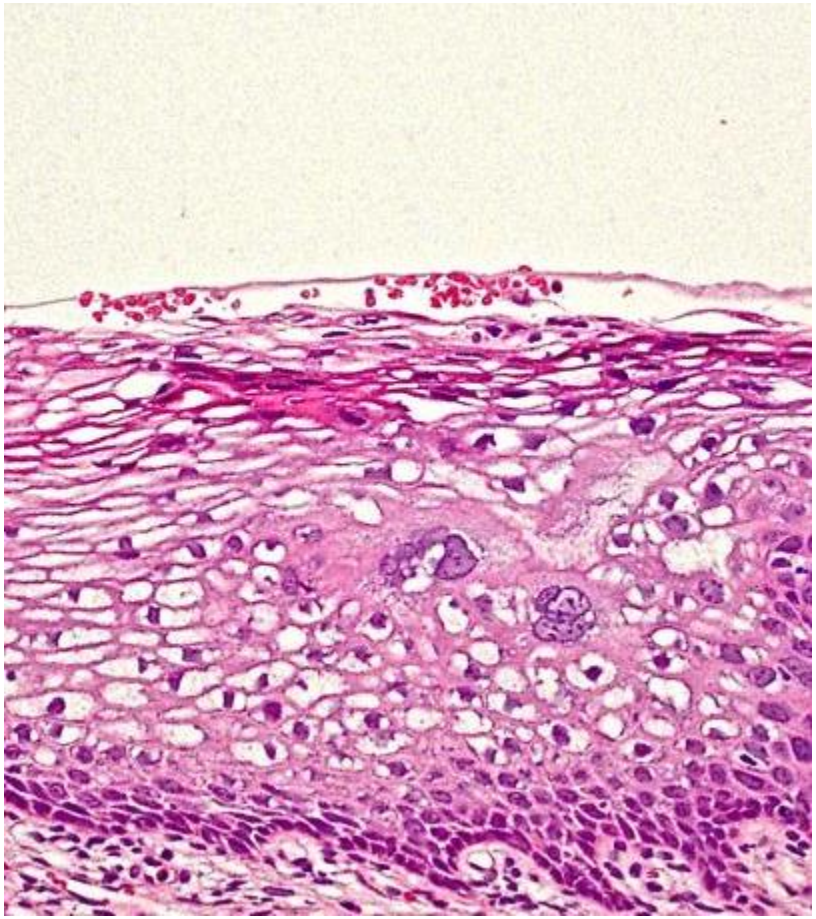


Diagram courtesy of research.leidenuniv.nl/index.php3?c=243



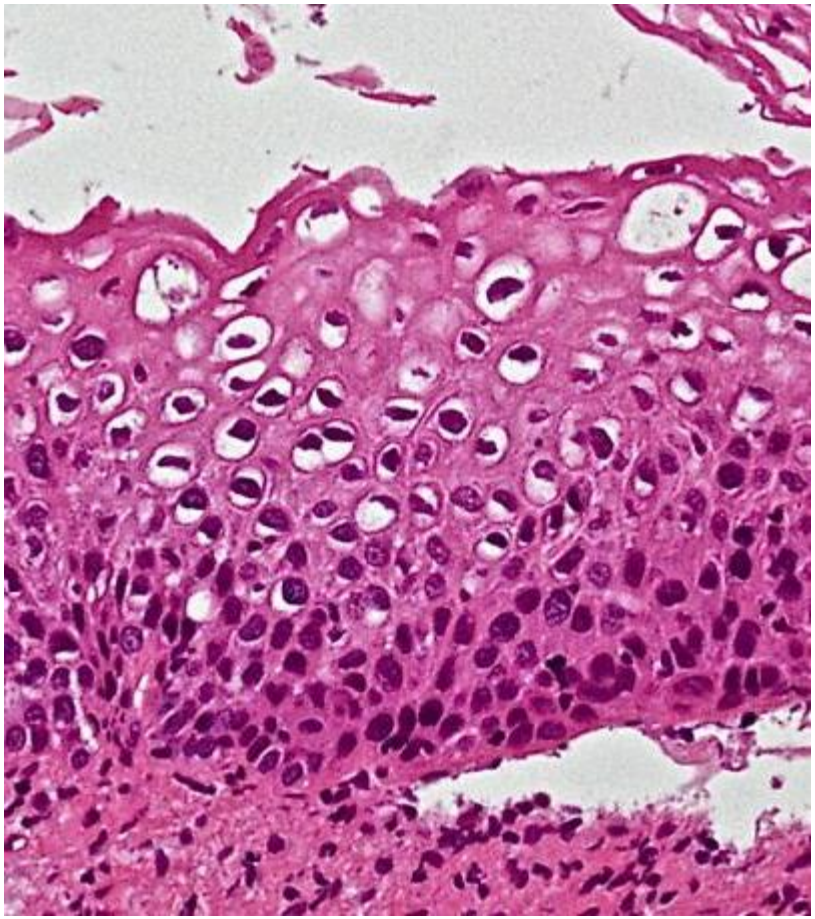
HPV cytopathic effect

- Cellular enlargement
- Multinucleation
- Nuclear hyperchromasia
- Nuclear irregularity
- Peri-nuclear halos

Abnormalities persist to the surface layers so can be detected by cytology

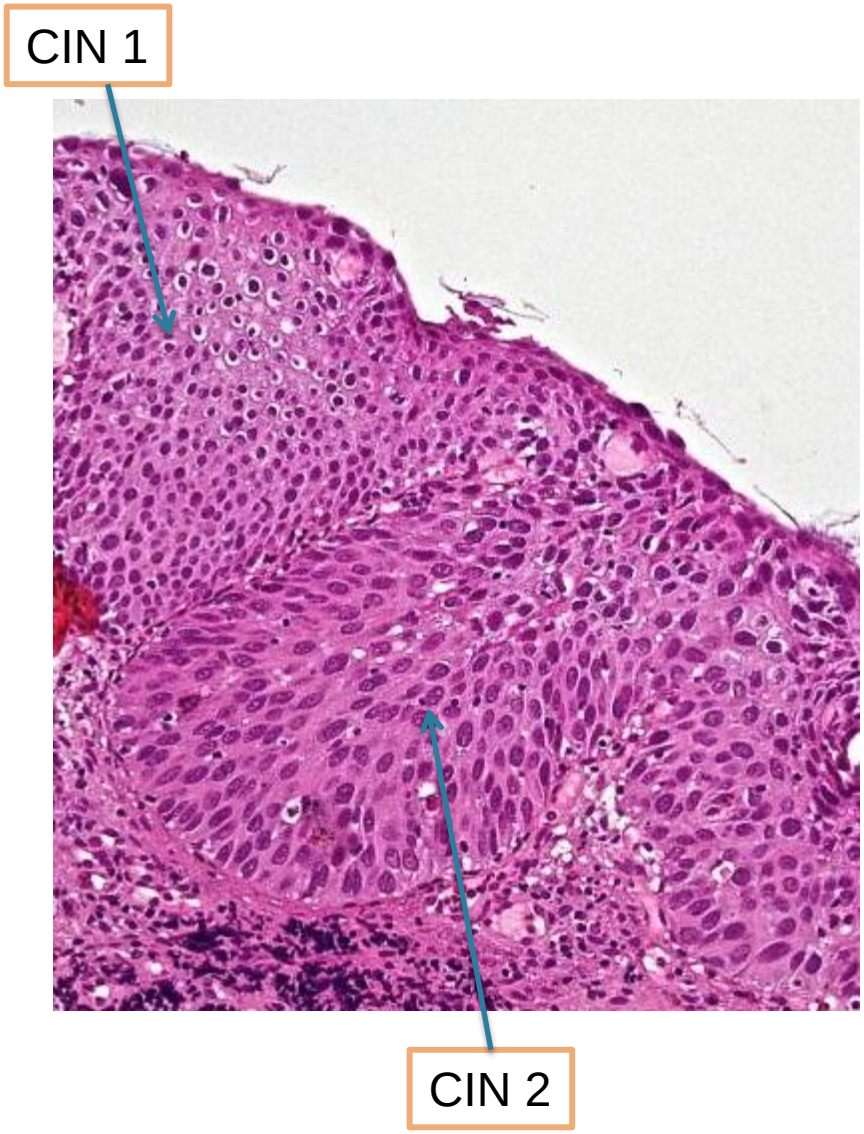
- Histopathologists make a distinction in cervical biopsy reports between HPV cytopathic effect alone, and lesions where CIN1 is also present.
- In contrast, The Bethesda System used for cytology reporting includes all HPV +/-CIN 1 lesions under LSIL.

CIN 1



- Cell enlargement
- Multinucleation
- Nuclear hyperchromasia
- Nuclear irregularity
- Perinuclear halos

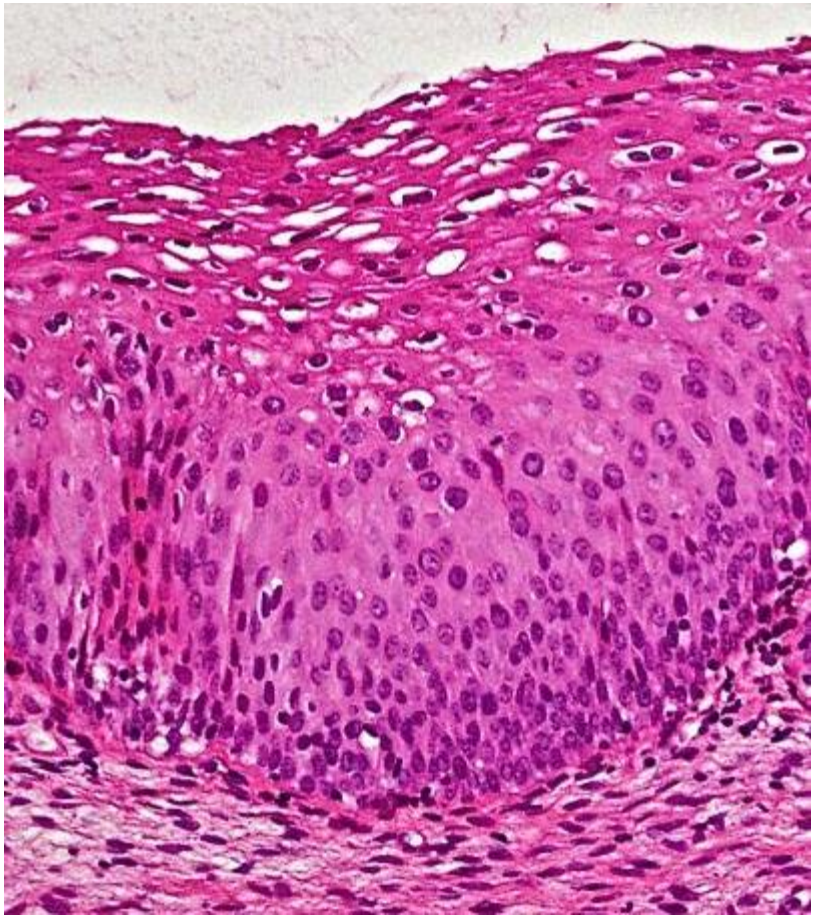
CIN1 vs CIN 2



In CIN 2:

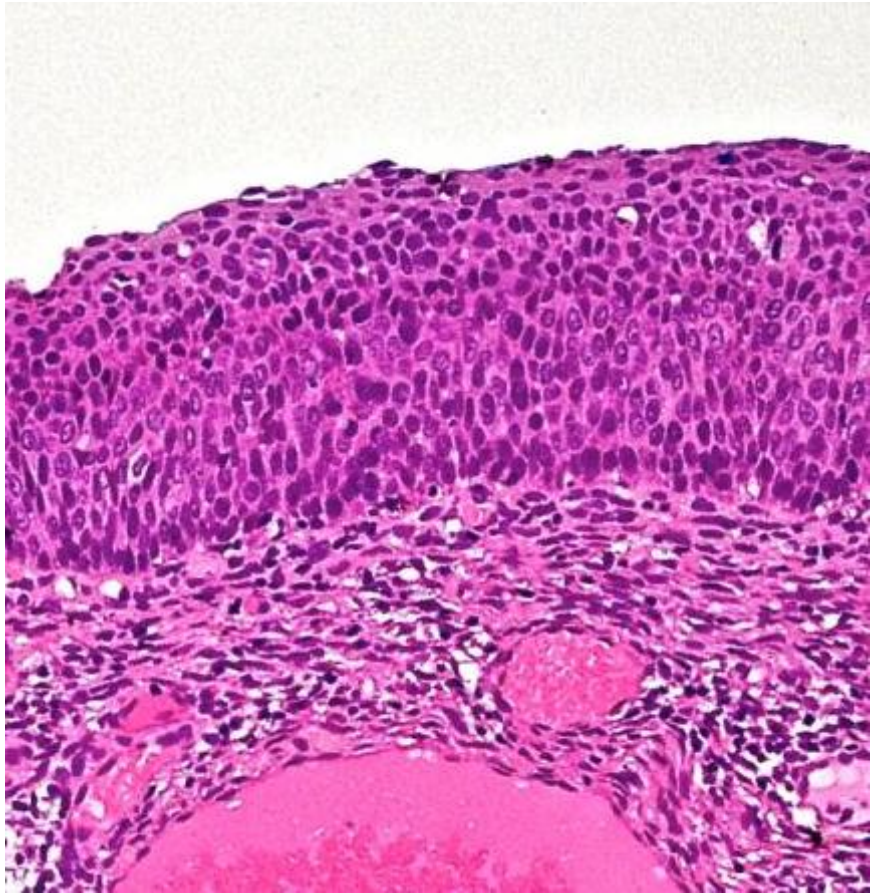
- HPV DNA is integrated
- The nuclei are larger and more pleomorphic

CIN 2



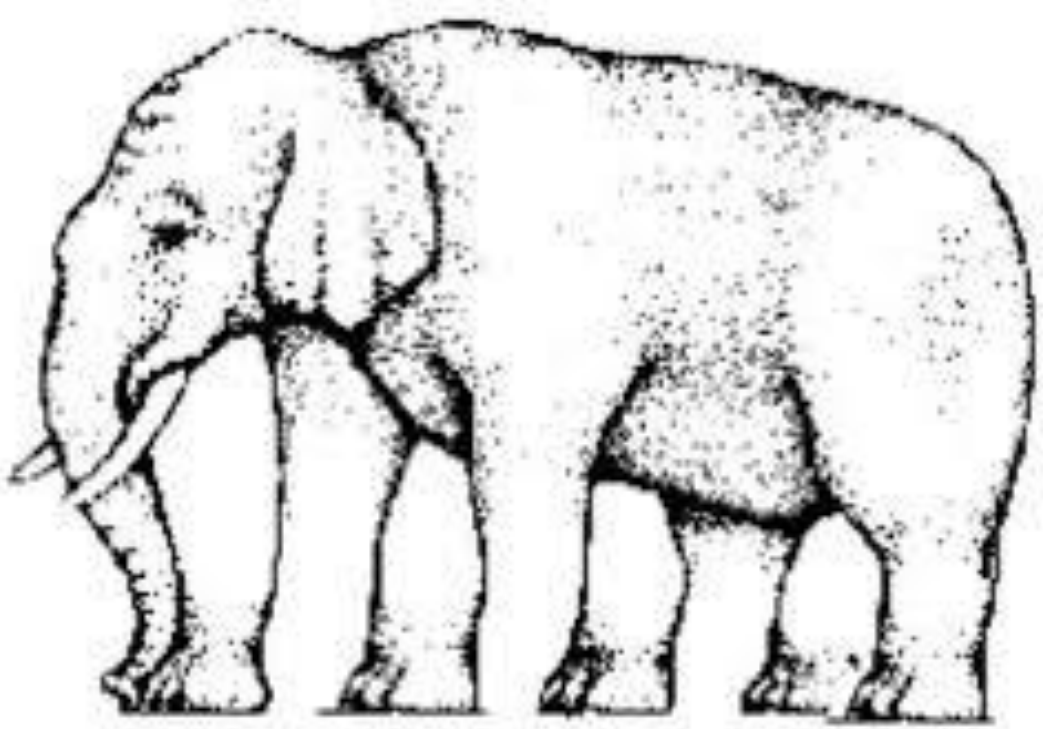
- Immature basaloid-type cells with high nucleus to cytoplasm (N:C) ratios
- Immature basaloid-type cells in the middle 1/3 of the epithelium
- Mitoses occur in the mid 1/3 of the epithelium
- Irregular, hyperchromatic nuclei
- Abnormal mitotic figures

CIN 3



- Immature basaloid-type cells with high N:C ratios
- Immature basaloid-type cells in the upper 1/3 of the epithelium
- Mitoses occurring in the upper 1/3 of the epithelium
- Irregular, hyperchromatic nuclei
- Abnormal mitotic figures

When things aren't easily seen… Problems with histology interpretation

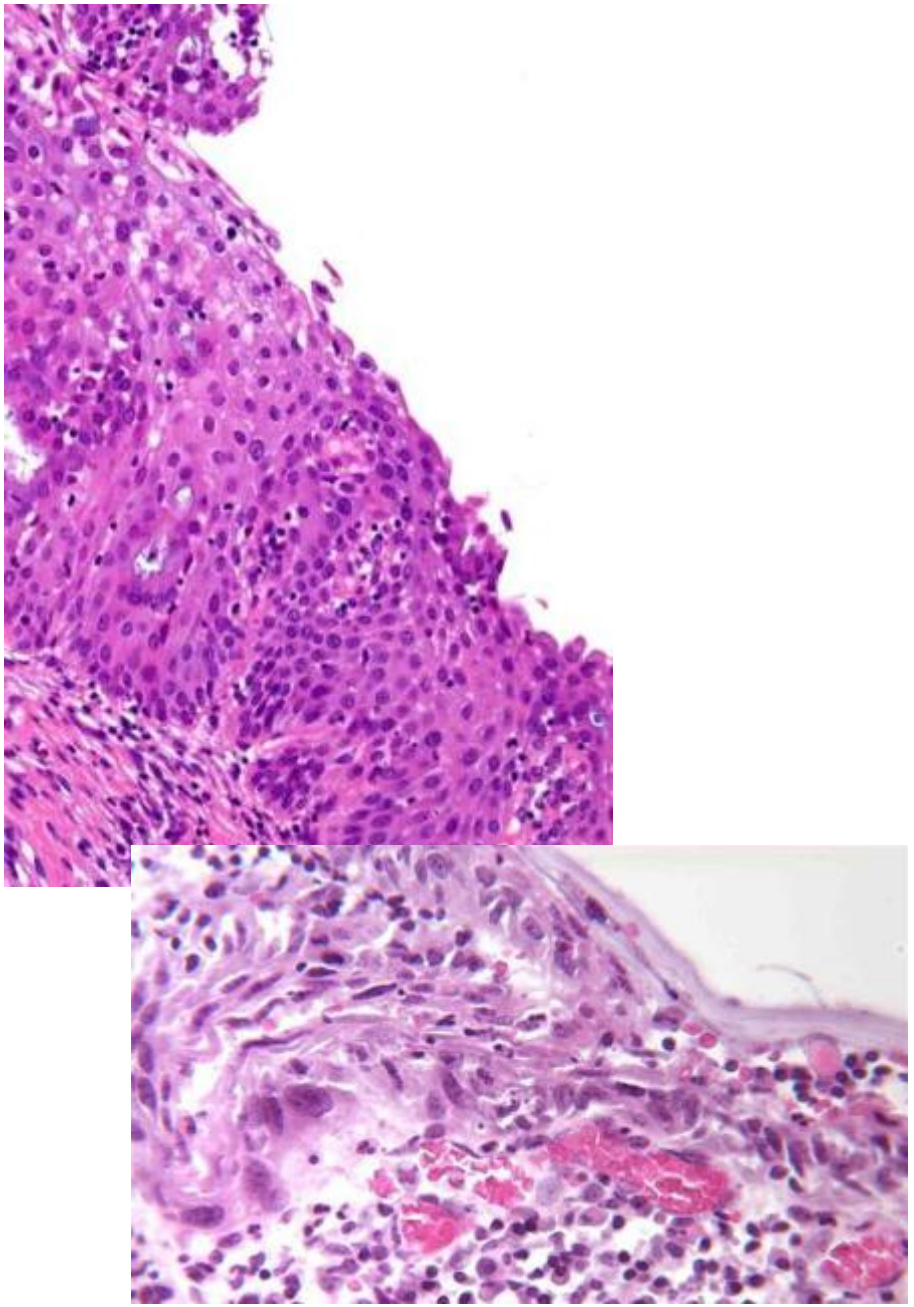


How many legs does this elephant have?

1. Inflammation

Cervicitis causes problems for histologists as well as cytologists

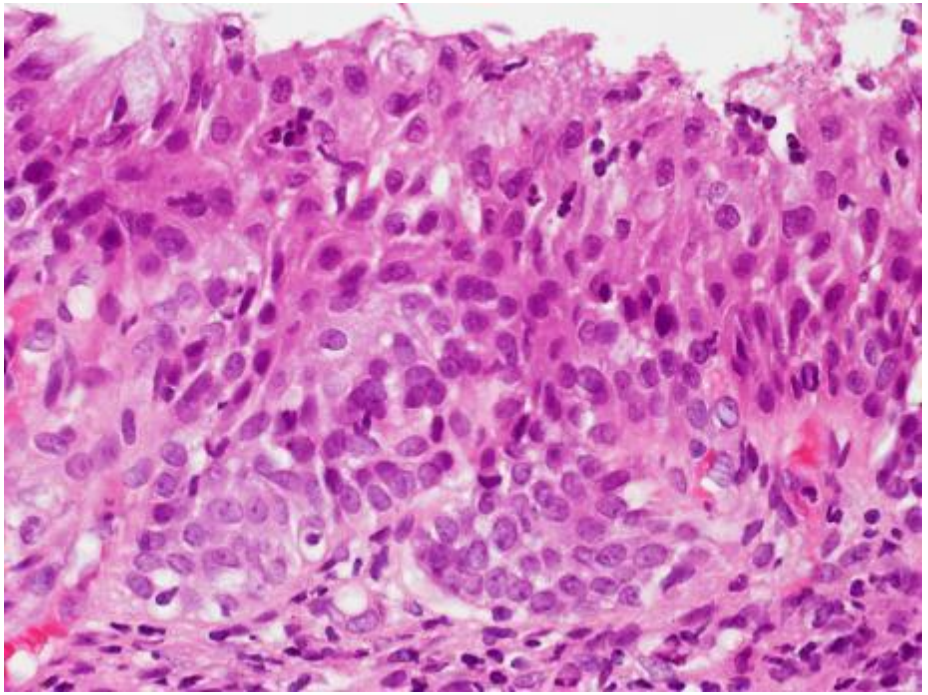
- Causes nuclei to enlarge
- Mimics CIN
- Particularly difficult in immature squamous epithelium



2. Immature squamous metaplasia

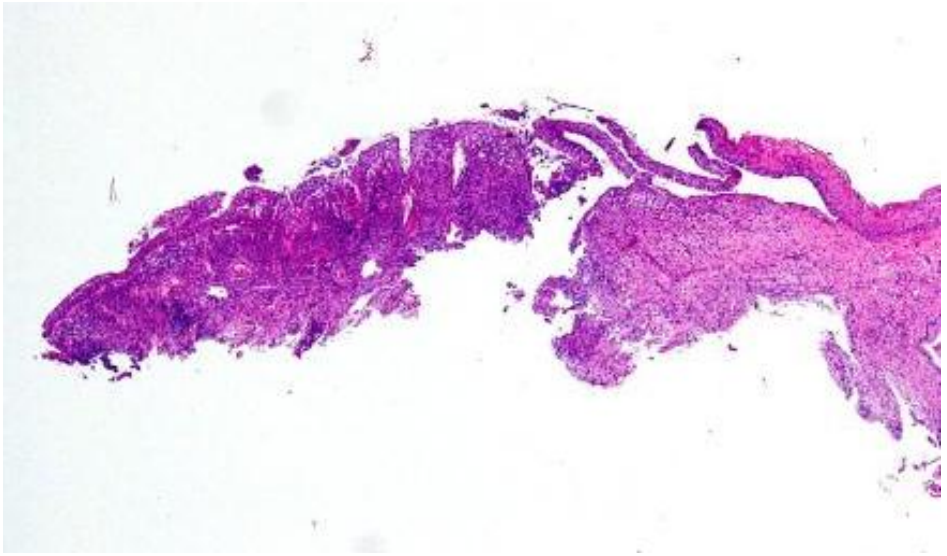
Can be difficult to distinguish from HSIL on cytology, at colposcopy and also on histology

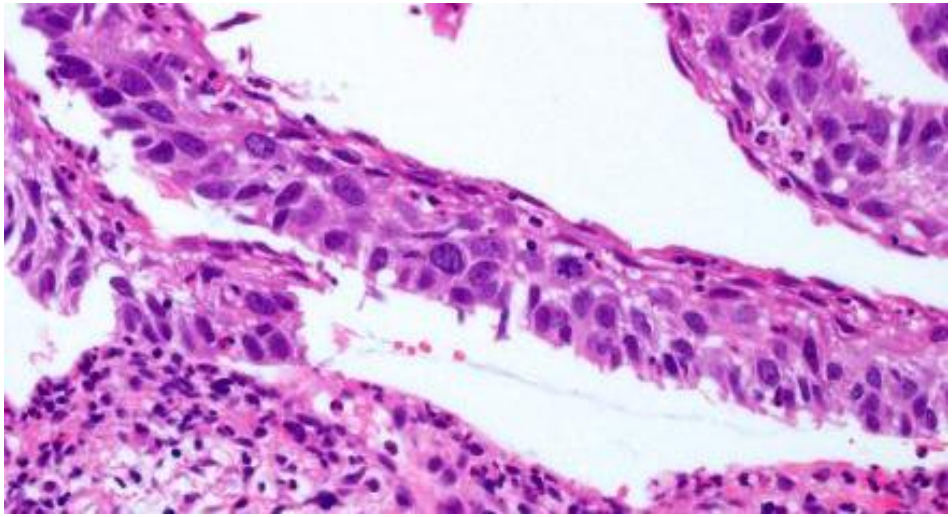
- Increased N:C ratios
- Nuclei are metabolically active



3. Thin epithelium

- HPV infection makes it look abnormal
- Difficult to grade as too thin to see maturation.
- Some biopsies will be reported as “CIN NOS”
- Others are reported as “at least CIN1”
  (or “at least CIN 2”)



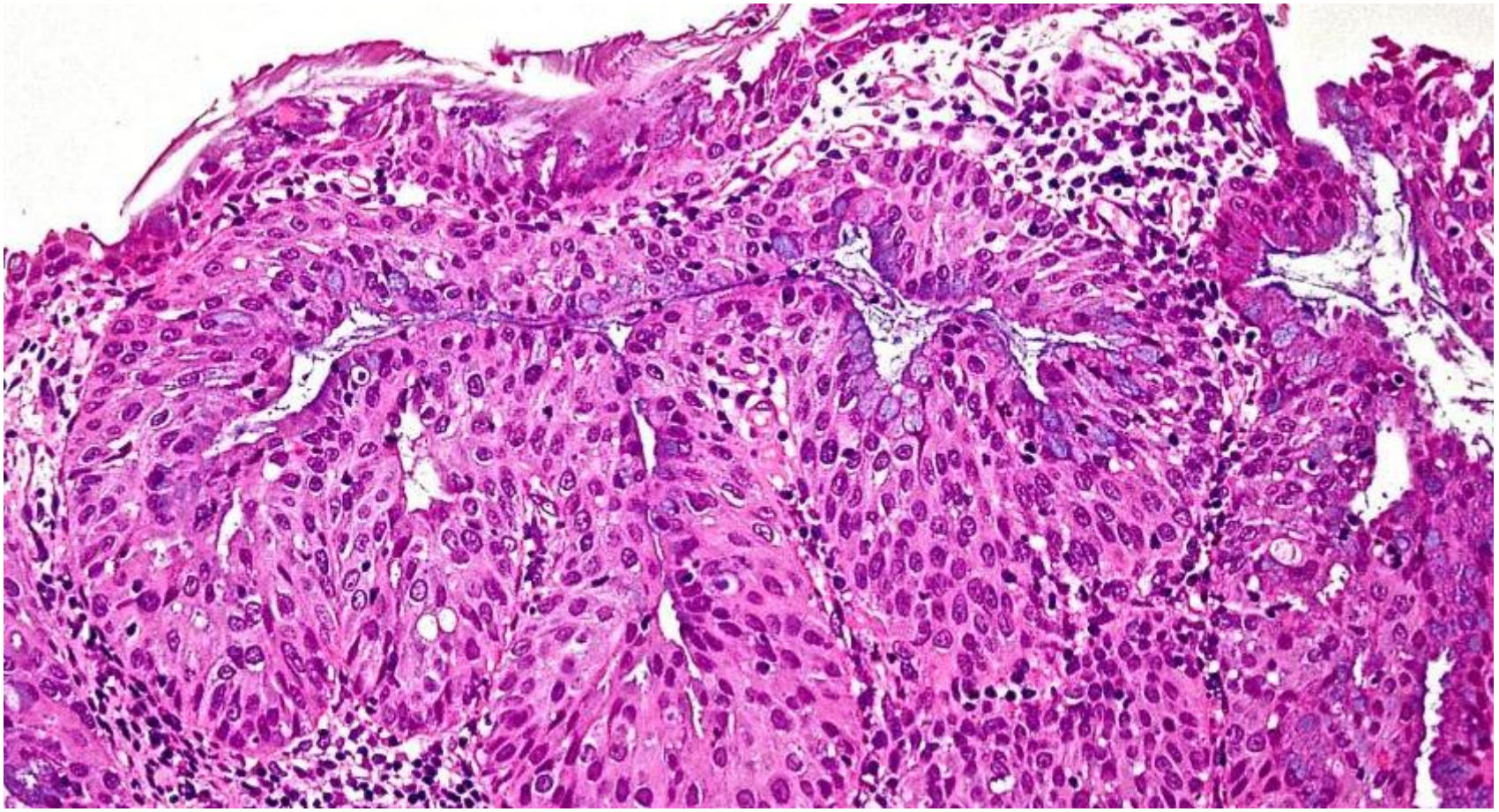


4. Poor visualisation

- Ectocervix only (no endocervical glands) so the TZ isn't seen
- Histo block needs more trimming to see if there are glands deeper in the tissue

Loss of surface epithelium by stripping or destruction by diathermy artefact can also cause poor visualisation

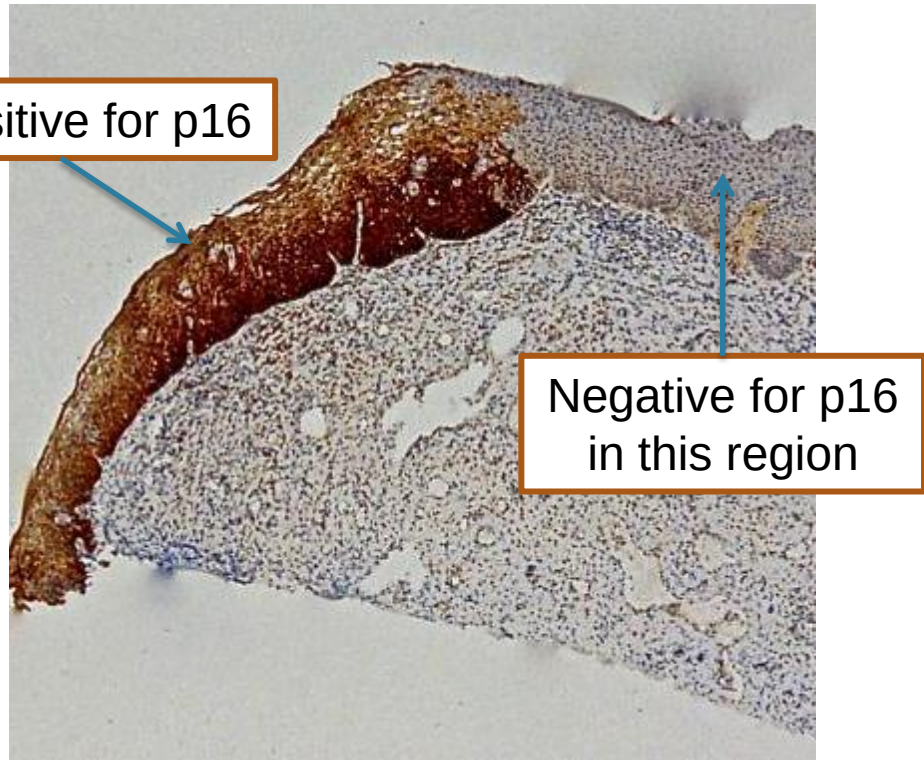
Immature, inflamed, atypical TZ epithelium: difficult to interpret!



What now?

Immunohistochemistry: p16

- p16 is a normal cell protein that regulates the cell cycle by turning off cell proliferation.
- When present, the HrHPV oncogene E7 disrupts the binding of retinoblastoma protein to E2F in the host cell. This binding usually stops inappropriate cell proliferation
- When the binding is disrupted, the cell can proliferate at an abnormally high rate: p16 levels increase dramatically.

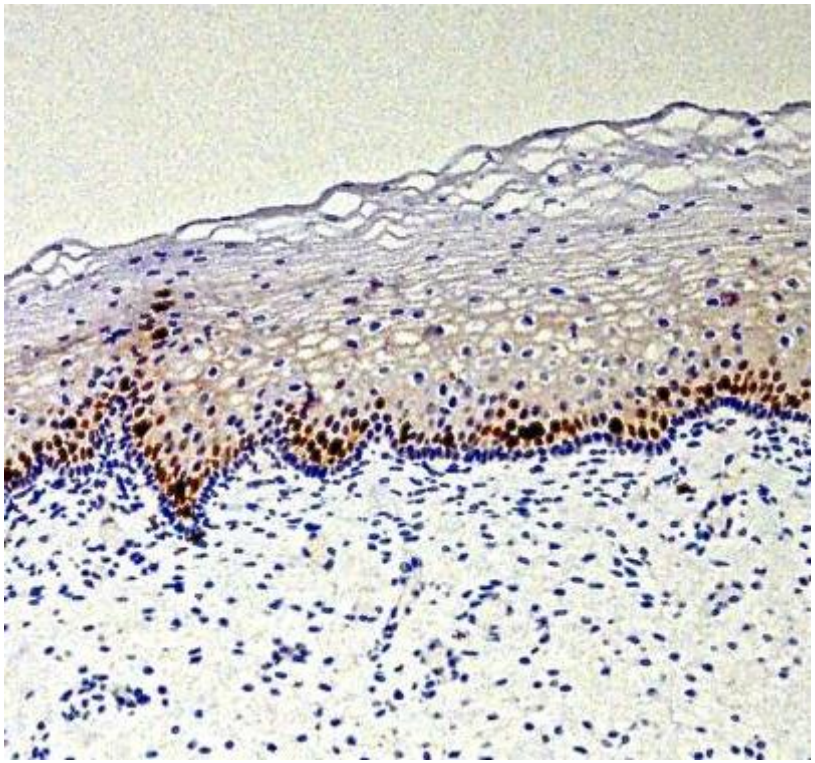


Solid dense band-like full thickness staining
- positive pattern for high-grade CIN
- HrHPV is present and integrated

Immunohistochemistry:Ki-67

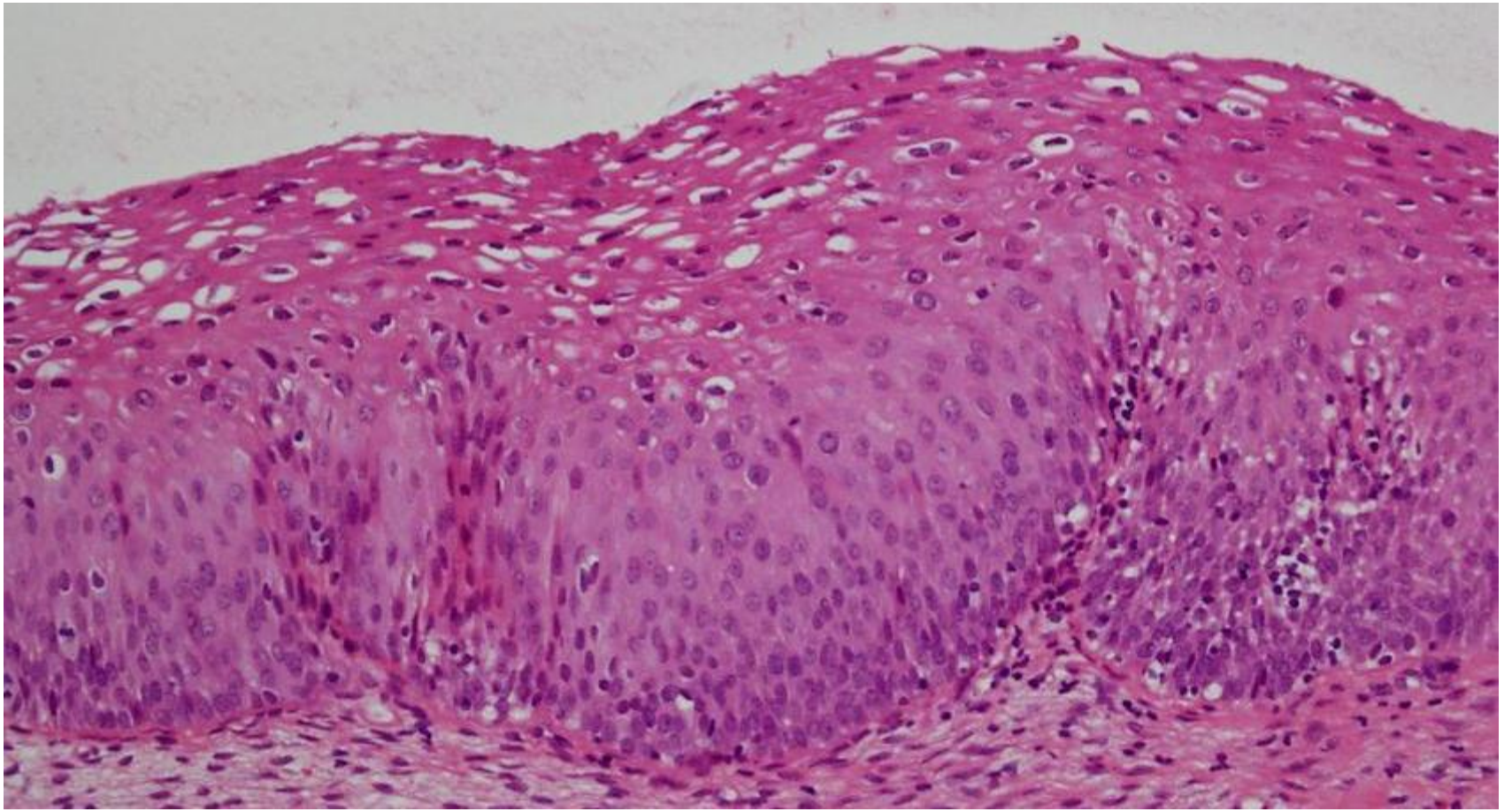
Ki67 is a marker of cell proliferation.

- Normal basal epithelial cells proliferate to maintain the epithelium
- Epithelial cells higher up in the epithelium are not normally proliferating

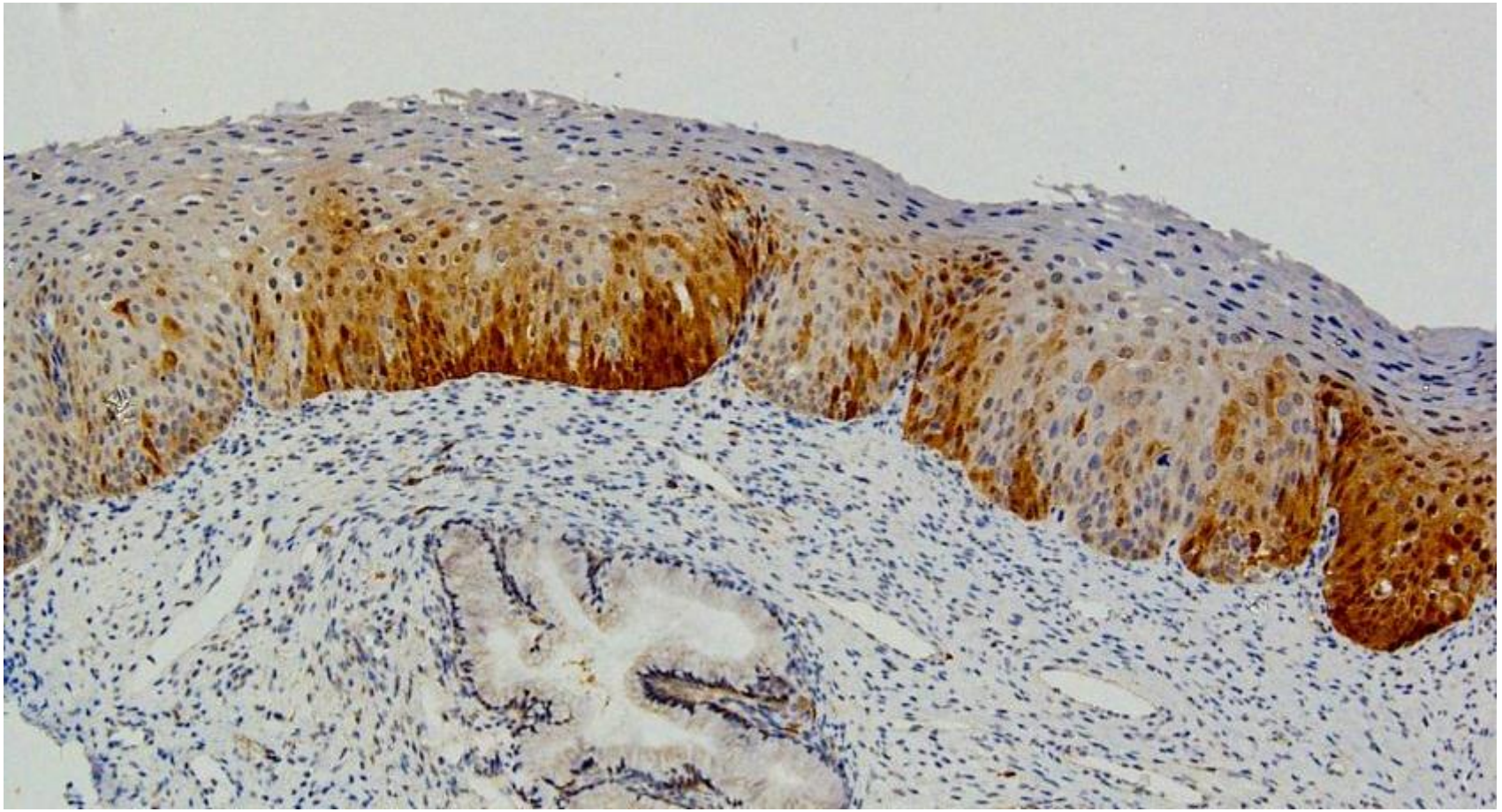


Normal parabasal staining
- No increase in proliferation
- HrHPV not present

How can immunohistochemistry help sort out what this is?

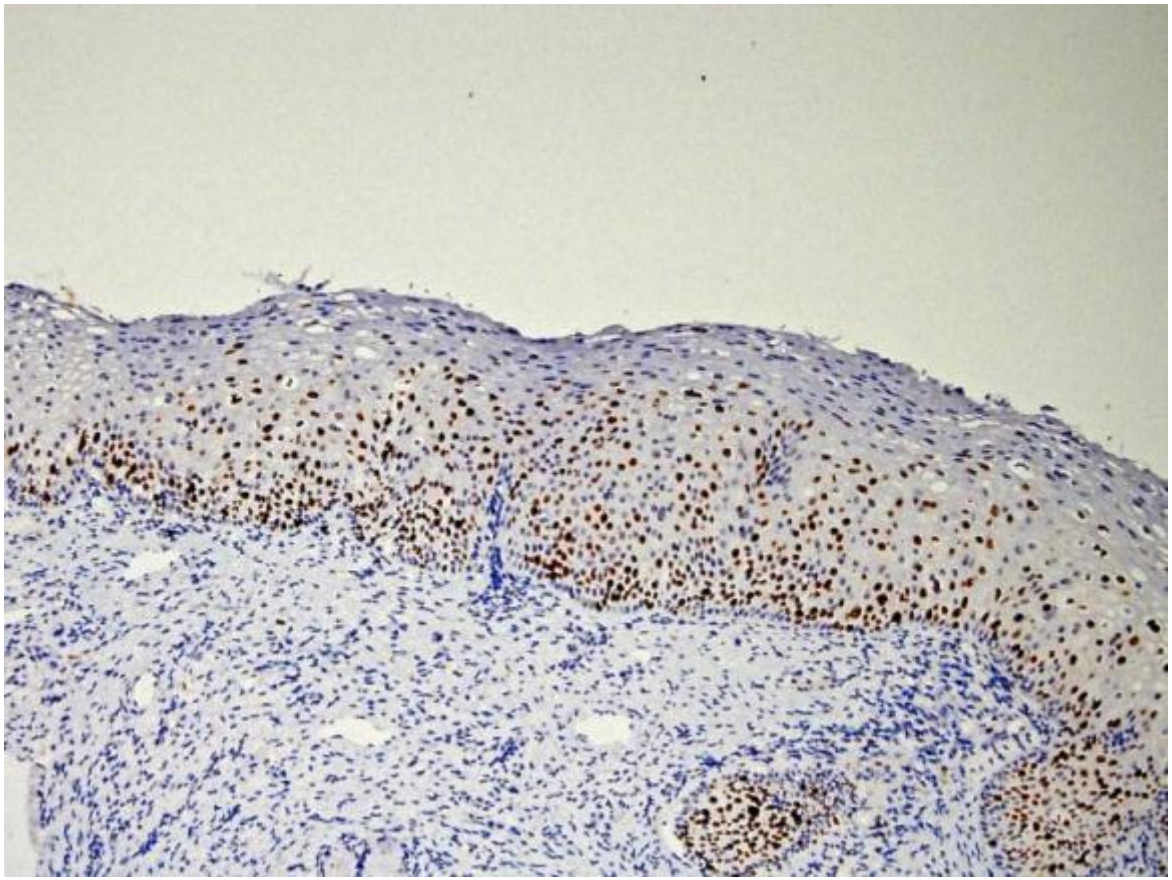


p16



Patchy staining indicates the presence of HPV but it is not integrated.
Both low-risk and high-risk viruses can give this pattern.

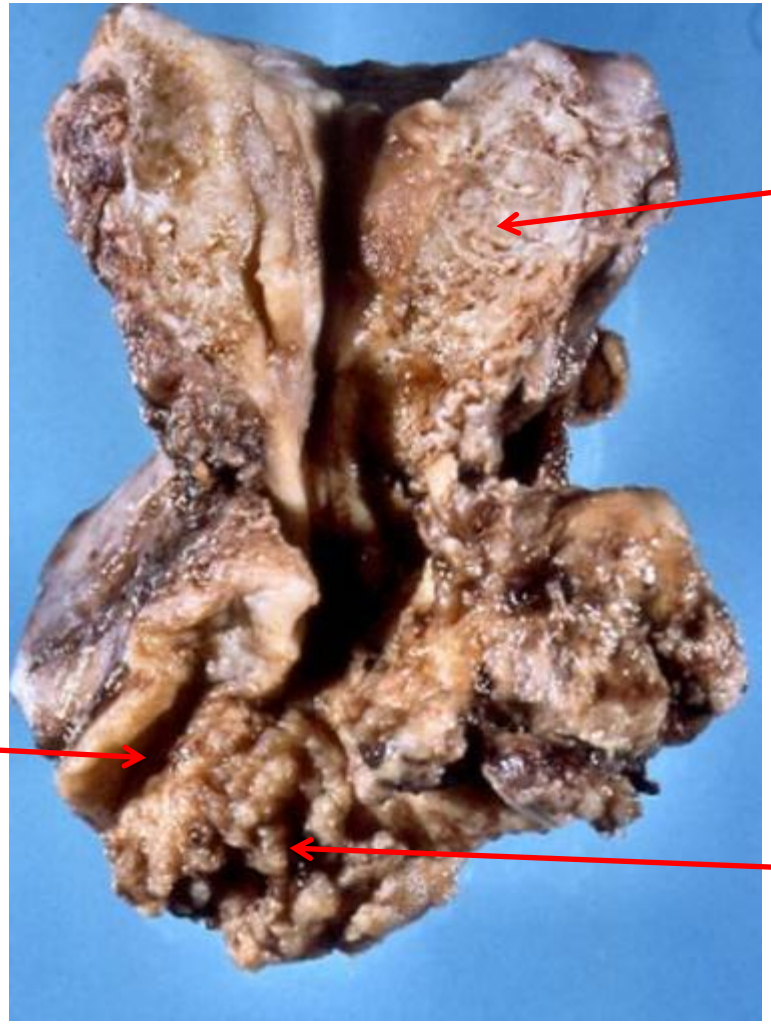
Ki-67



Proliferation is increased, with positive staining in 40-50% of cells in the lower 2/3^{rds} of the epithelium

- This pattern could be CIN 1 or 2. Need to interpret in conjunction with the H&E and p16 appearances to reach a diagnosis.

Invasive Cervical Cancer

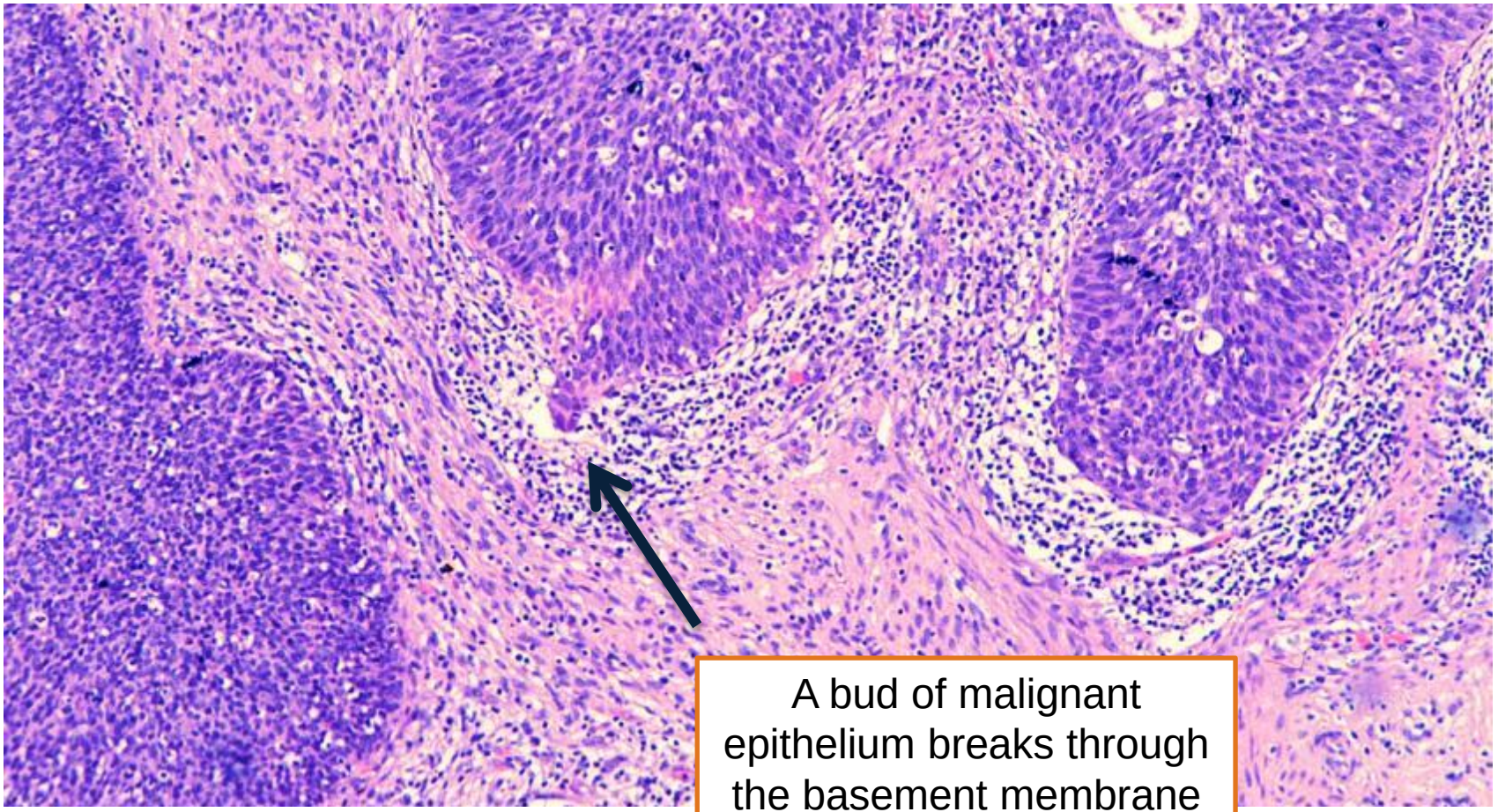


Uterus

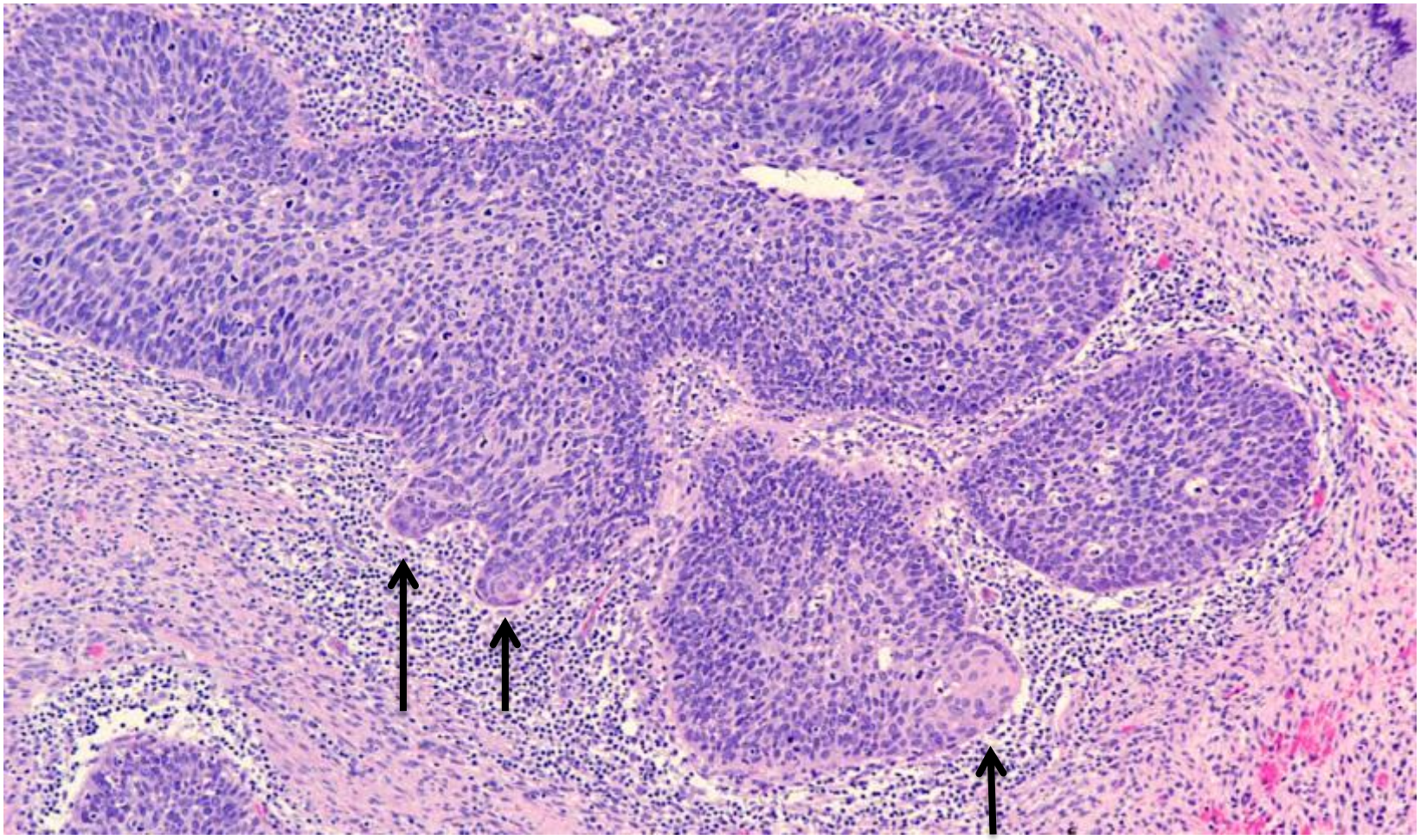
Endocervical canal

Fungating mass arising from the cervix

Squamous Cell Carcinoma (SCC) - very early invasion

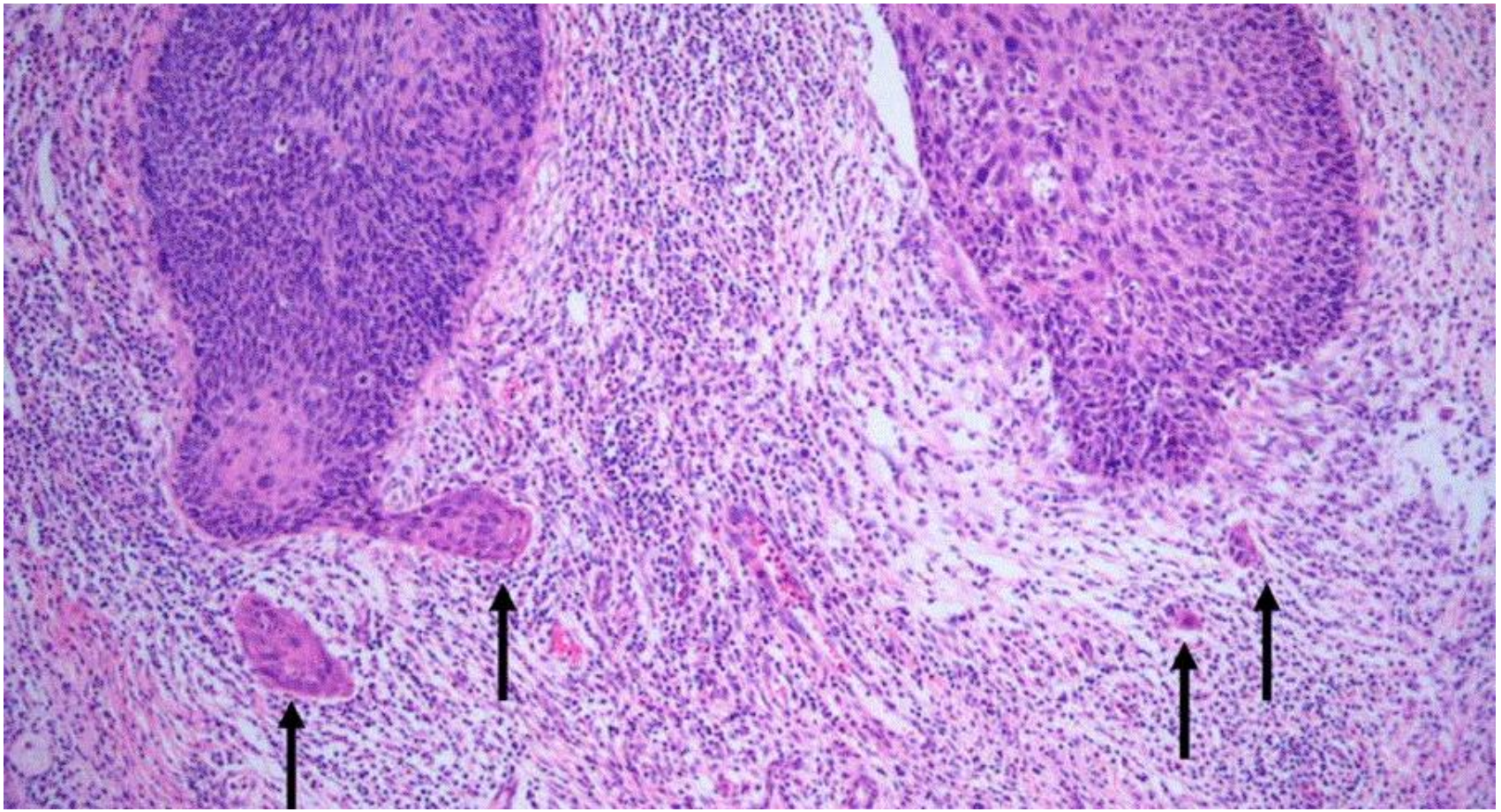


Several small foci of invasion



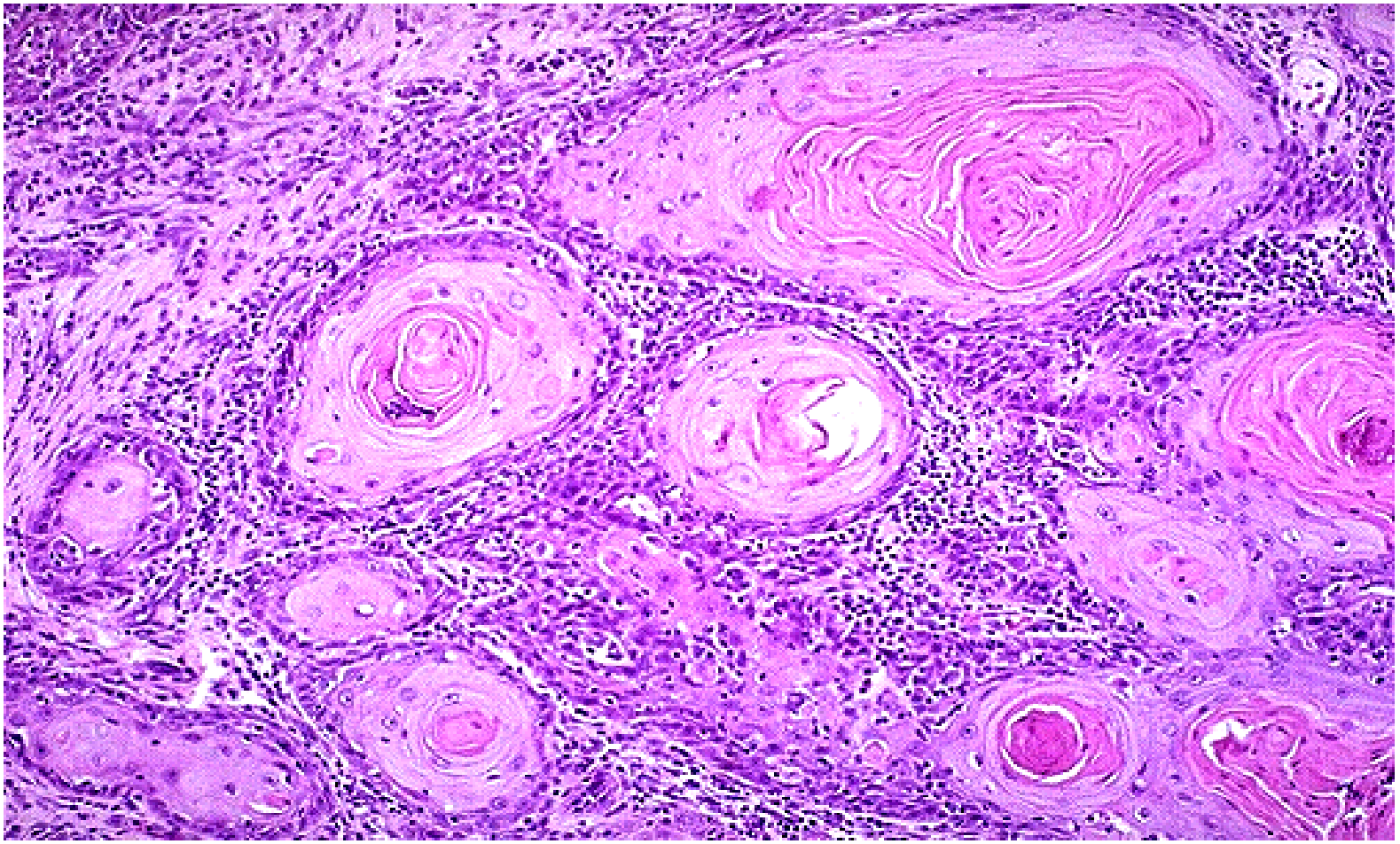
Buds and islands of SCC invading inflamed cervical stroma

“Spray” pattern of invasion

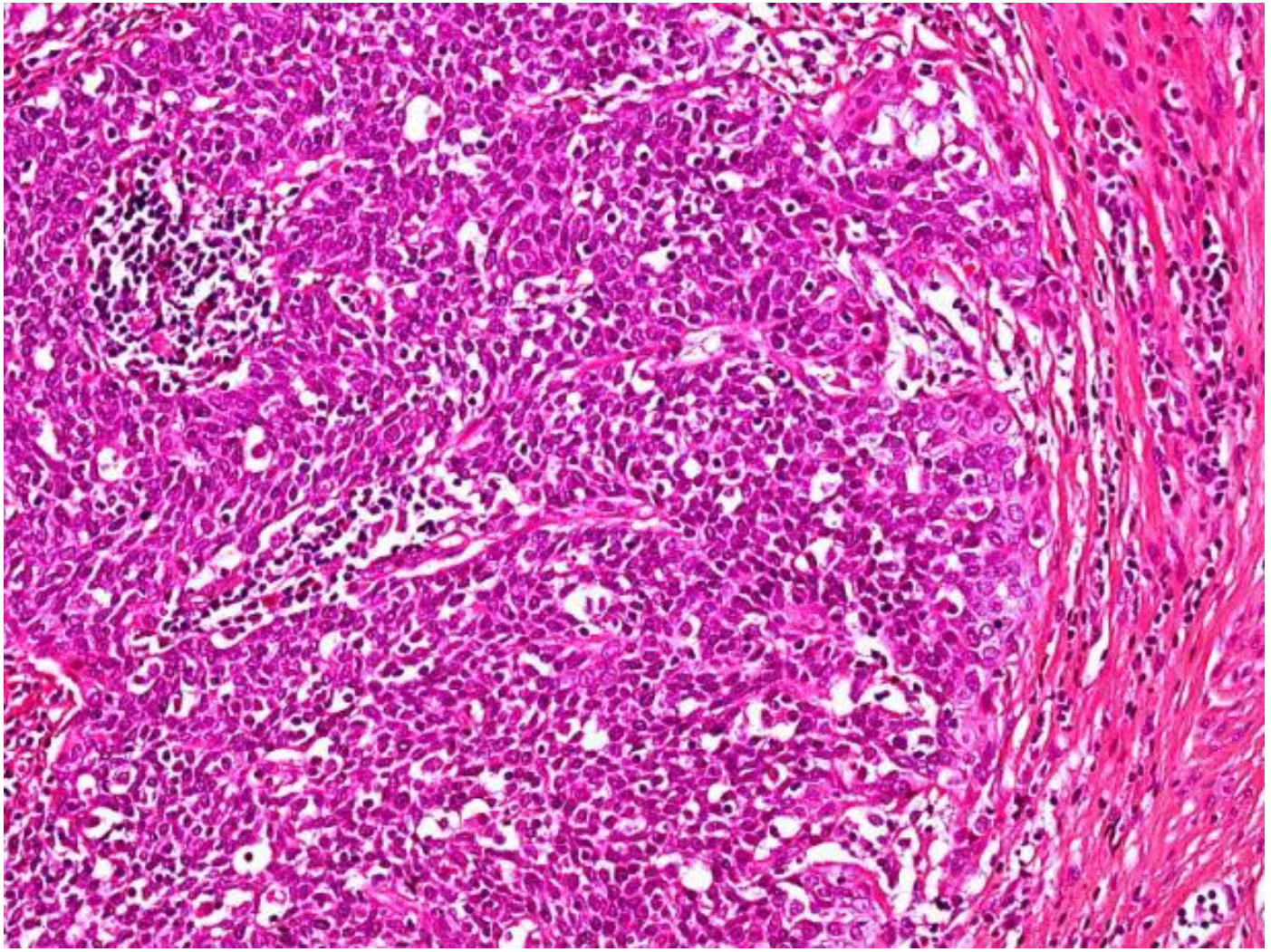


Increased amounts of cytoplasm, increased cytoplasmic eosinophilia, larger more pleomorphic nuclei and the presence of nucleoli: seen in invasive lesions in histology and cytology

Invasive keratinising SCC

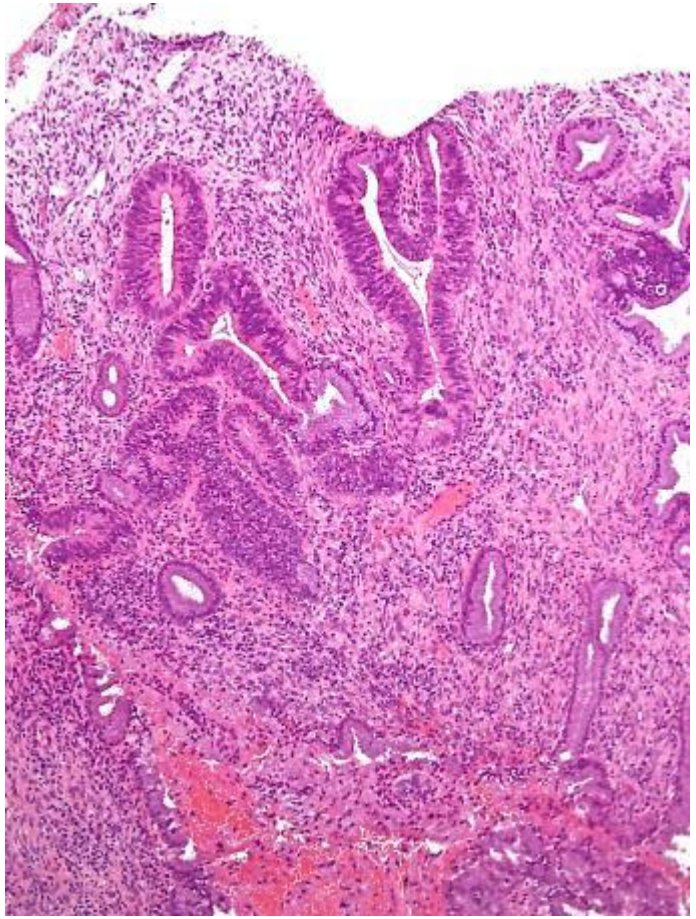


Invasive non-keratinising SCC



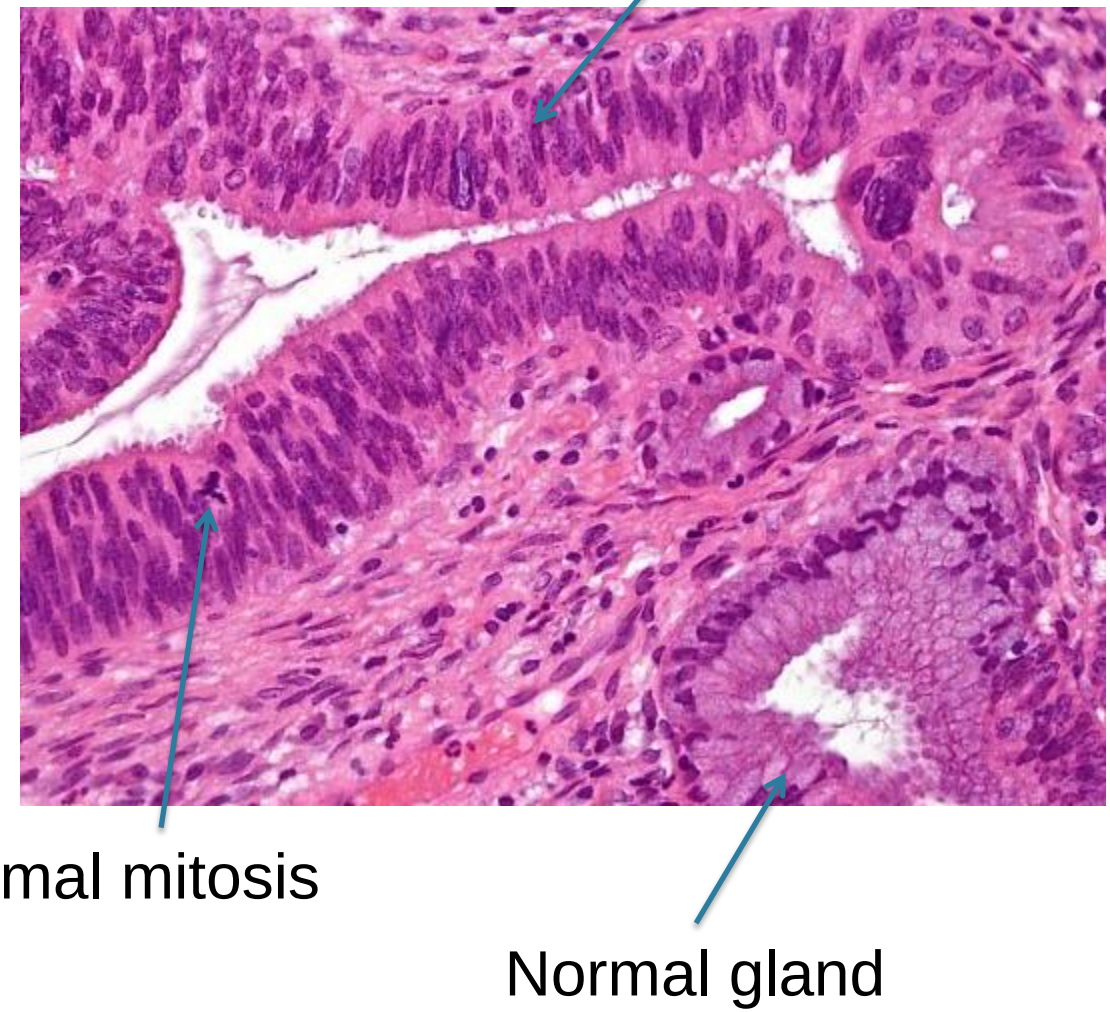
3. GLANDULAR LESIONS

Glandular dysplasia

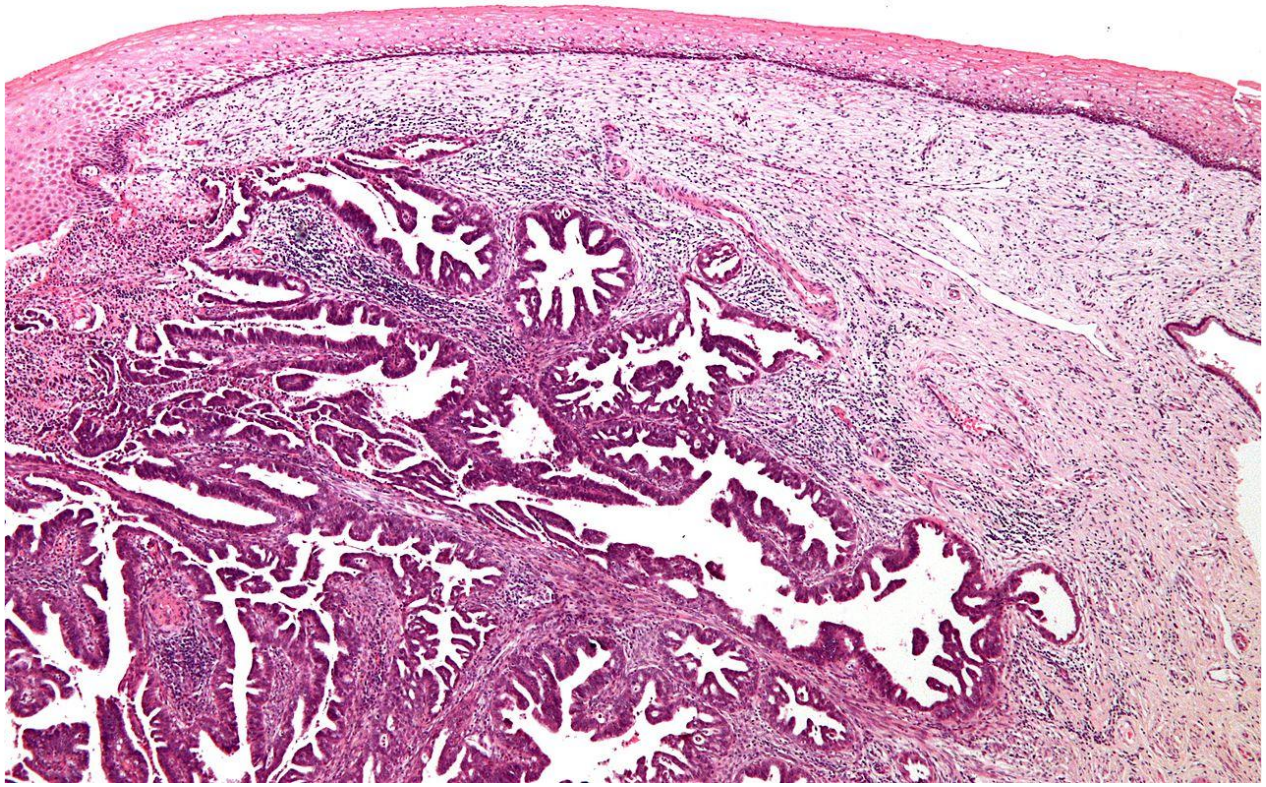


Adenocarcinoma in situ (AIS)

- Hyperchromatic atypical nuclei
- Mitotically active
- Pseudostratified epithelium
- Mucin loss



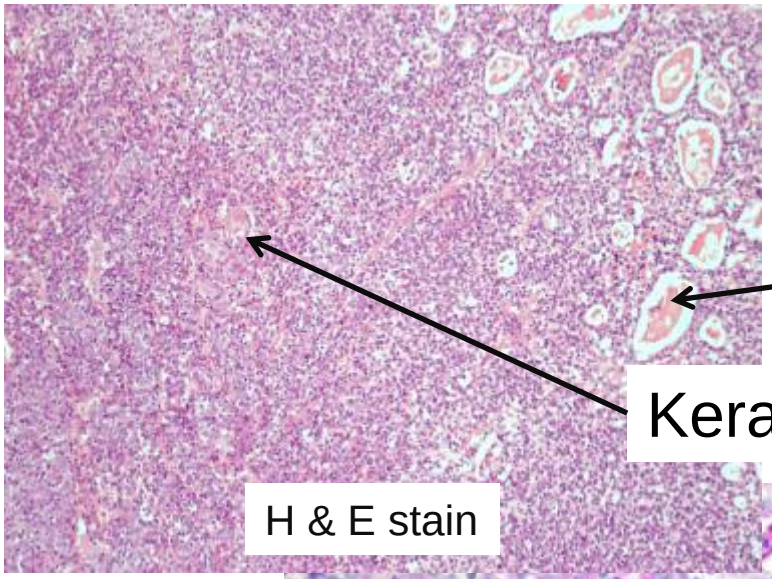
Invasive endocervical adenocarcinoma

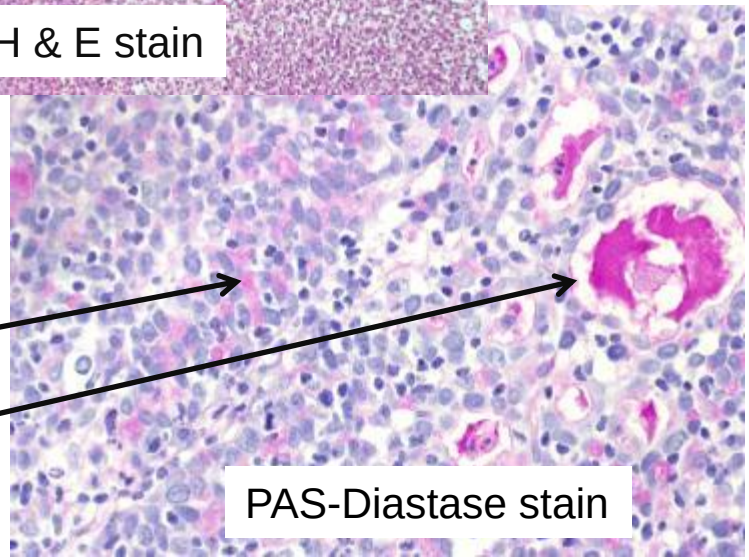


- glands invading cervical stroma lined by pleomorphic cells
- arises from AIS

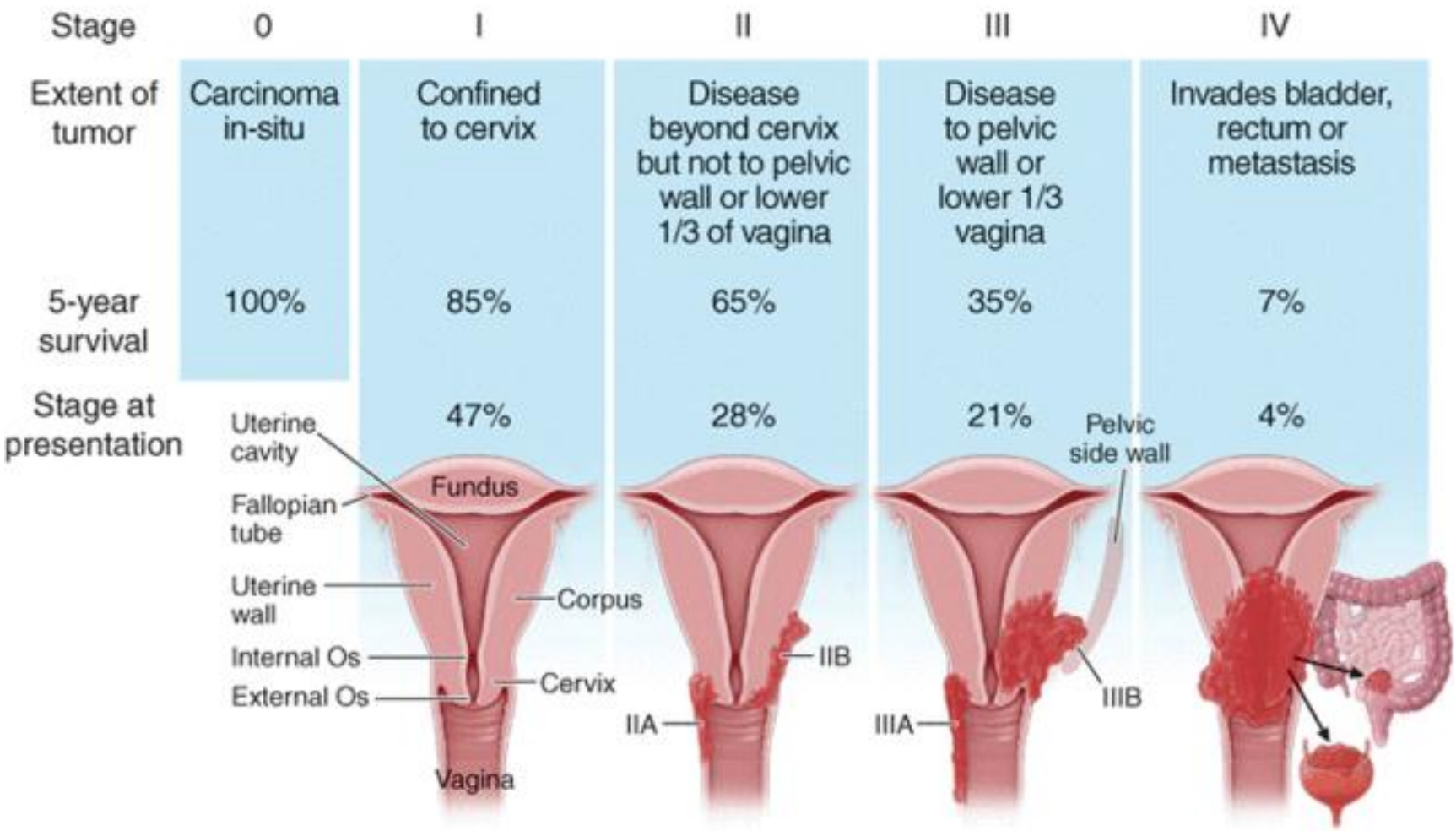
Adenosquamous carcinoma

Poorly differentiated carcinoma showing both squamous and glandular differentiation





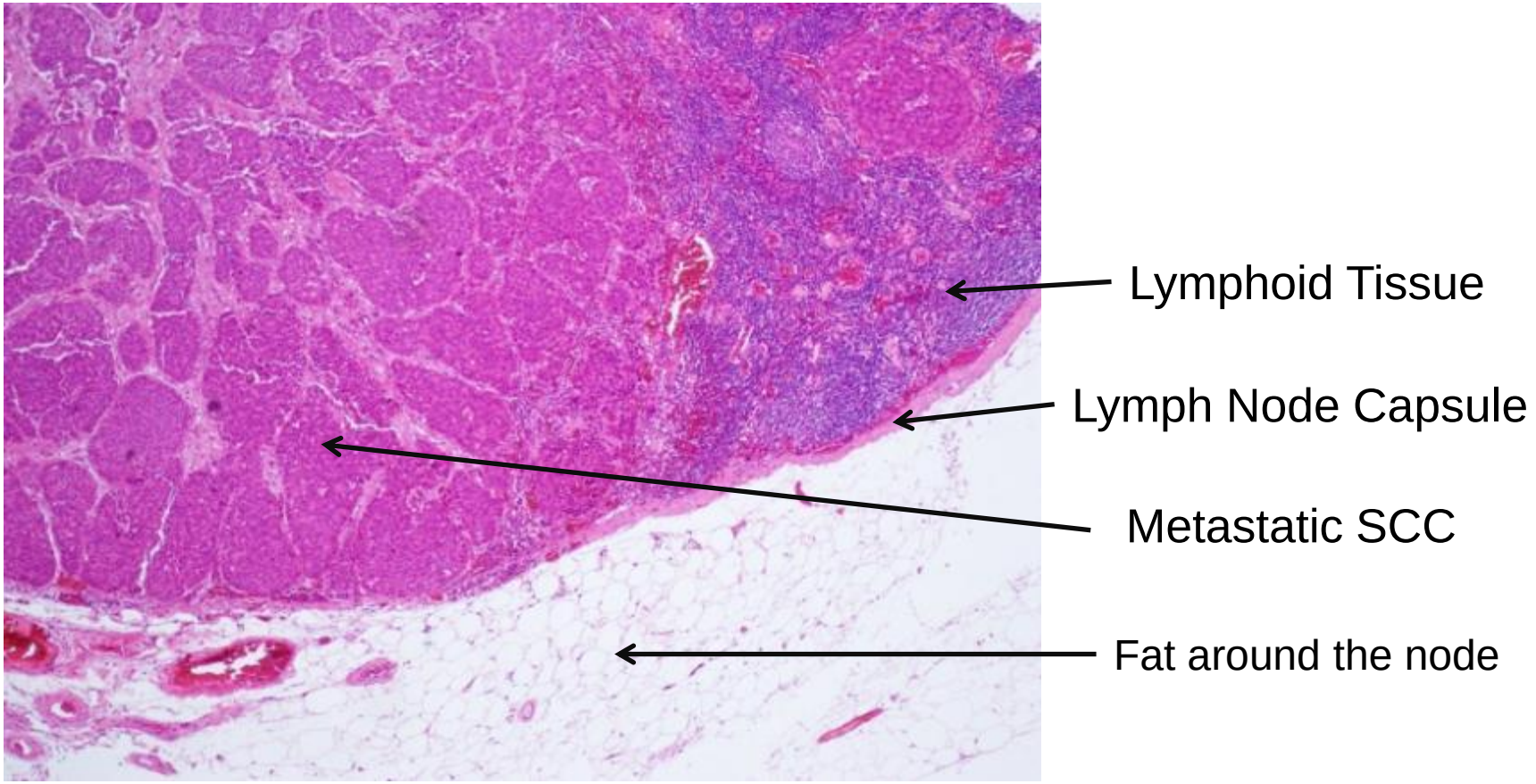
CLINICAL STAGING OF CERVICAL CANCER



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

HISTOLOGIC CONFIRMATION OF SPREAD

Metastatic Squamous Cell Carcinoma invading a lymph node



Reasons for discordance between cytology and histology

Cytology

- Abnormal cells not present on the cytology slide
- The cytology was difficult / the cytologist got it wrong

Colposcopy

- The colposcopist didn't see the lesion so biopsy not targeted adequately
- The lesion was too high up the endocervical canal e.g. older women
- The lesion was very difficult to see e.g. small lesion, atrophic cervix, inflamed cervix, it looked like squamous metaplasia
- The colposcopist biopsied the wrong area

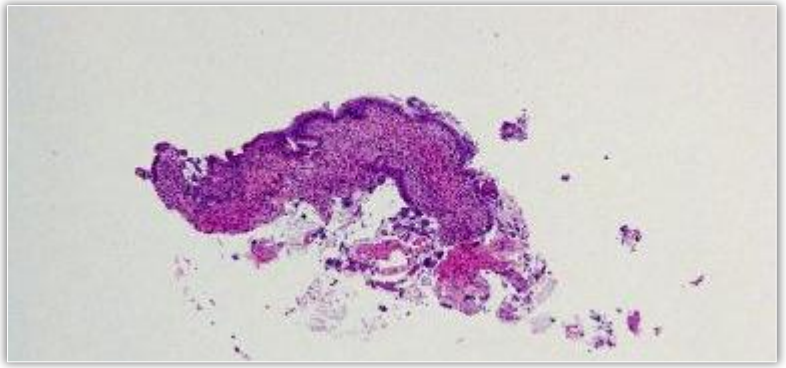
Histology

- The lesion was biopsied but the abnormal area wasn't present in the tissue sections seen by the histopathologist
- The biopsy was difficult to interpret / the histopathologist got it wrong

When things don't add up, we need to do reviews

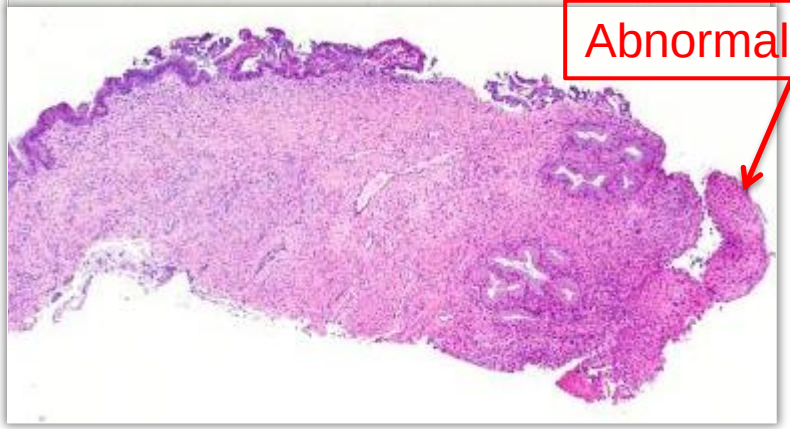
The value of levels on histologic blocks

Level 1

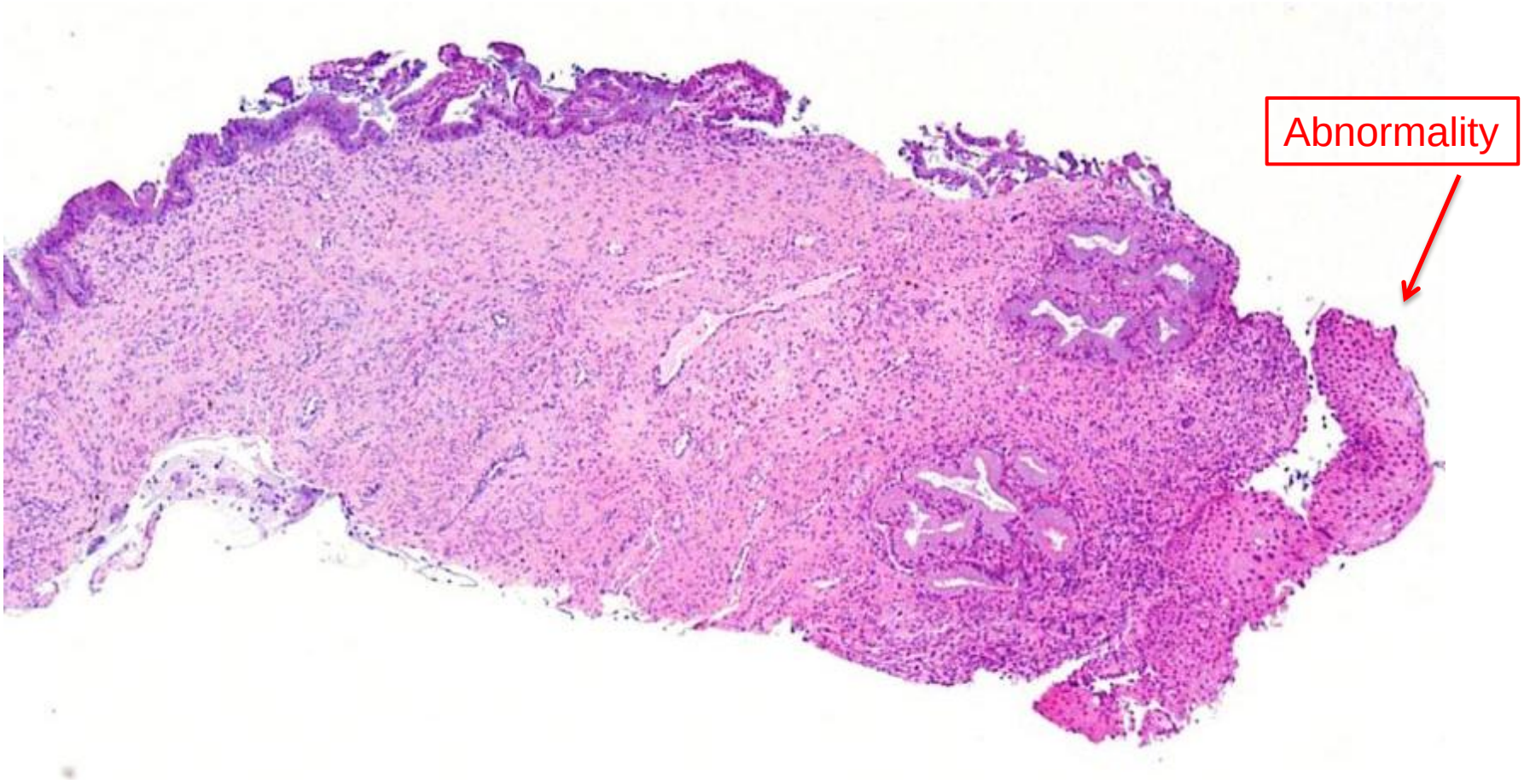


Level 6

Level 12



Level 12



Cytology and Histopathology of the Cervix

- Cytology aims to accurately predict histology
- Histology defines the pathology but some cases are very difficult and errors in histopathology can occur
- The best outcome is achieved when cytology, colposcopy and histology work together