

Glandular lesions of the cervix

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WHO classification v Cervical Glandular Intraepithelial Neoplasia (CGIN)

glandular atypia	glandular dysplasia	adeno- carcinoma <i>in-situ</i>
	CGIN low grade	CGIN high grade

Glandular dysplasia

“The concept that glandular dysplasia forms a biological spectrum of cervical glandular intraepithelial neoplasia remains controversial”

Wells et al 2003 Epithelial tumours and related lesions of the uterine cervix In: WHO Tumours of the breast and female genital organs

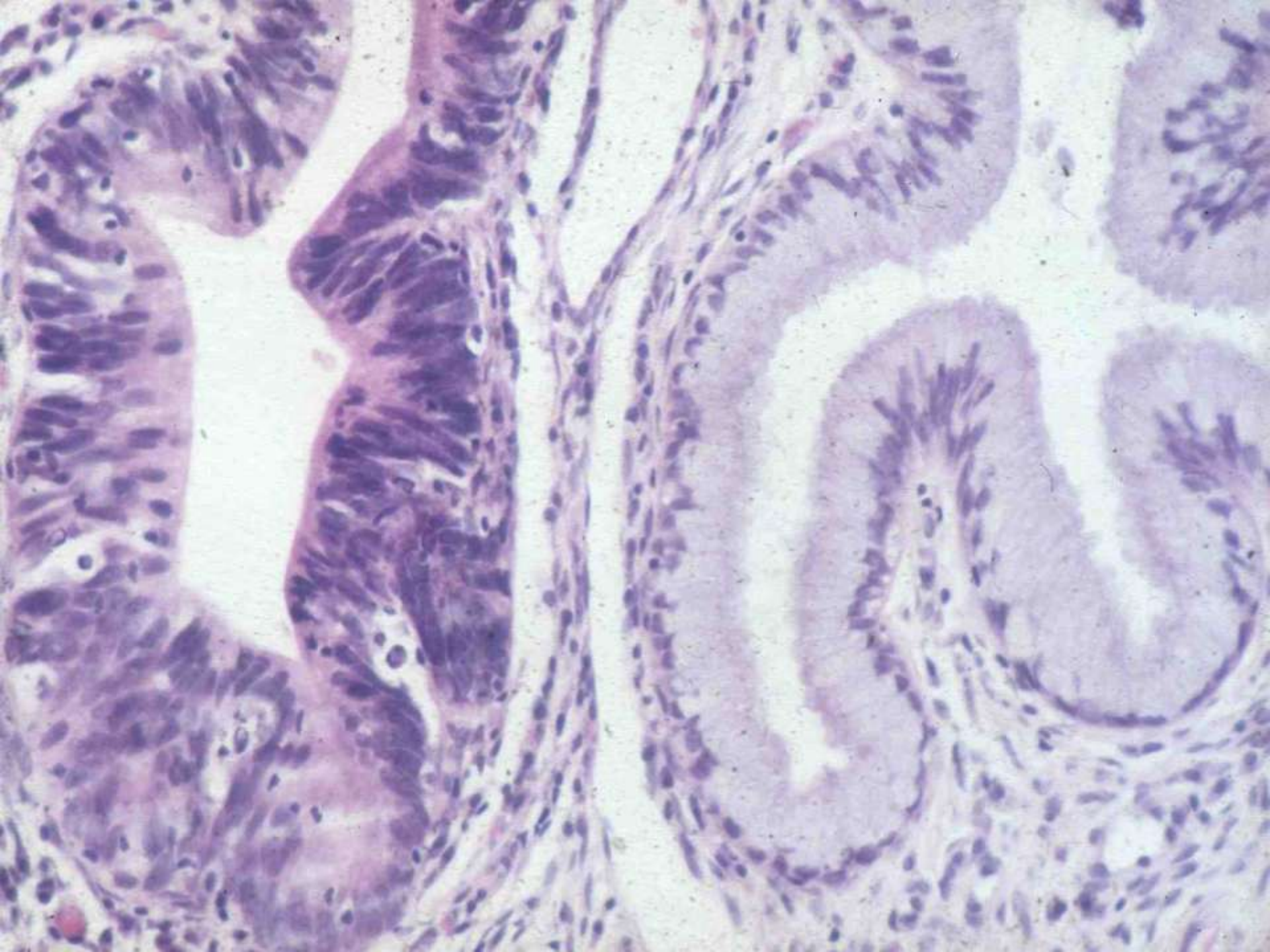
Is endocervical glandular dysplasia (EGD) a precursor of adenocarcinoma-in-situ (AIS)?

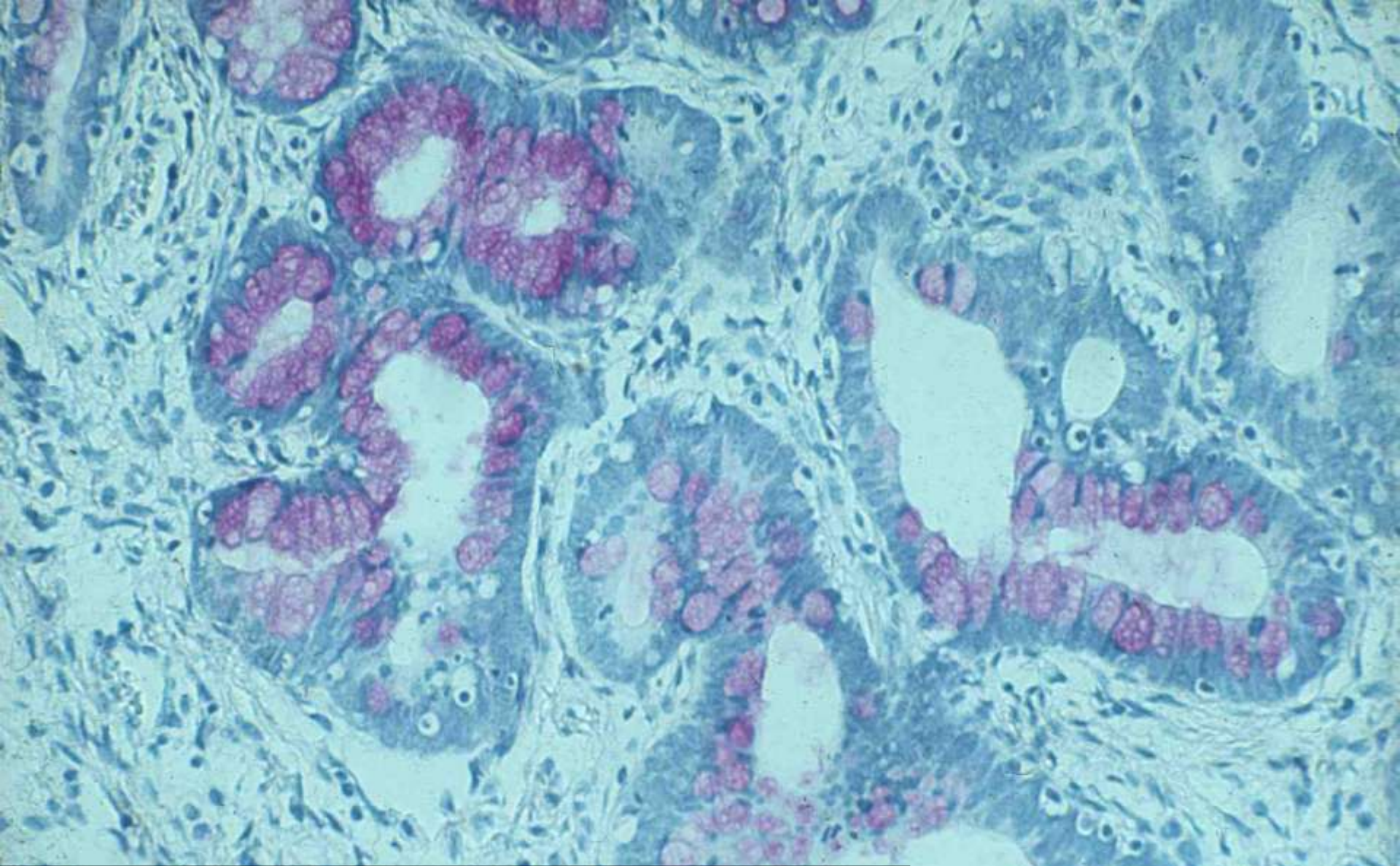
- EGD is found next to AIS
- EGD is found at a younger age than AIS or adenocarcinoma
- HPV found in both EGD and AIS
- Higher frequency of EGD than AIS

High grade CGIN

(Adenocarcinoma-in-situ/ severe glandular dysplasia)

- endocervical, intestinal, endometrioid, mixed adenosquamous types
- tubal type recently described - ? reproducible
- frequent coexistent CIN or squamous carcinoma (approx 50%)
- topography – conflicting data; most cases seem to involve surface epithelium and superficial glands near the transformation zone





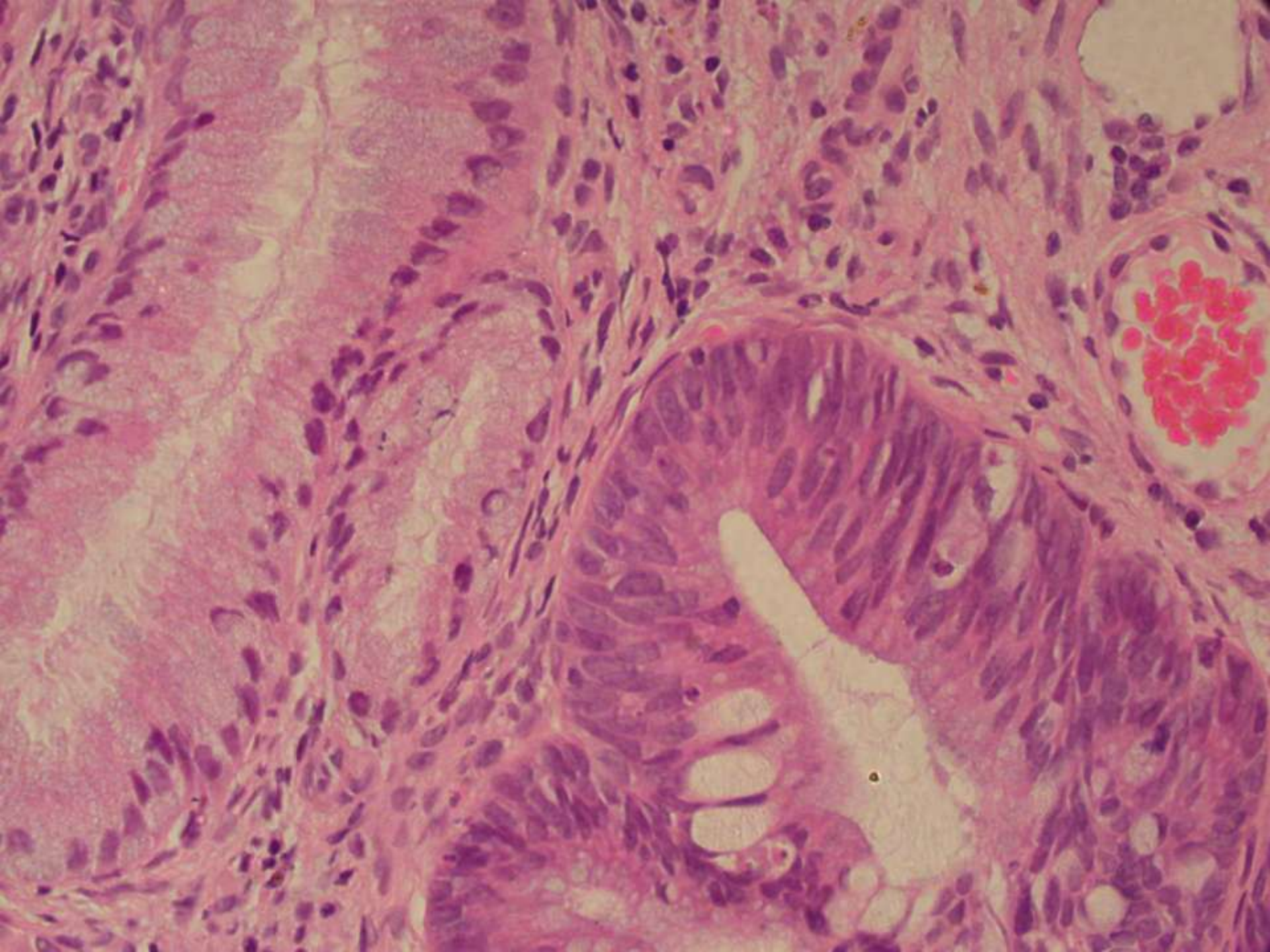
Intestinal metaplasia in high grade CGIN

Low grade CGIN

(glandular dysplasia other than severe)

- no well defined criteria – subjective
- natural history – not established
- nuclear and architectural abnormalities of a lesser degree than AIS
- reactive changes – relatively easily recognised
- some cases are HPV 16/18 +ve.
- higher mitotic index than reactive lesions
- neoplastic glycoprotein expression profile





Scoring scheme for non-invasive endocervical glandular lesions

Feature	Score
Stratification	
None	0
Mild	1
Moderate	2
Up to the luminal surface	3

Scoring scheme for non-invasive endocervical glandular lesions

Feature	Score
Nuclear atypia	
As normal	0
Normal or slightly enlarged uniform nuclei; minimal hyperchromasia or dispolarity; no nucleoli	1
Enlarged nuclei up to 3x normal; moderate anisocytosis, hyperchromasia, and dyspolarity; small nucleoli	2
Large nuclei > 3x normal; marked anisocytosis, hyperchromasia, and dyspolarity; prominent nucleoli	3

Scoring scheme for non-invasive endocervical glandular lesions

Feature	Score
Mitoses and apoptoses (average between two most active glands)	
None	0
Less than 0.5 per gland	1
0.6 – 3.0 per gland	2
> 3.0 per gland	3

Scoring scheme for non-invasive endocervical glandular lesions

Total score

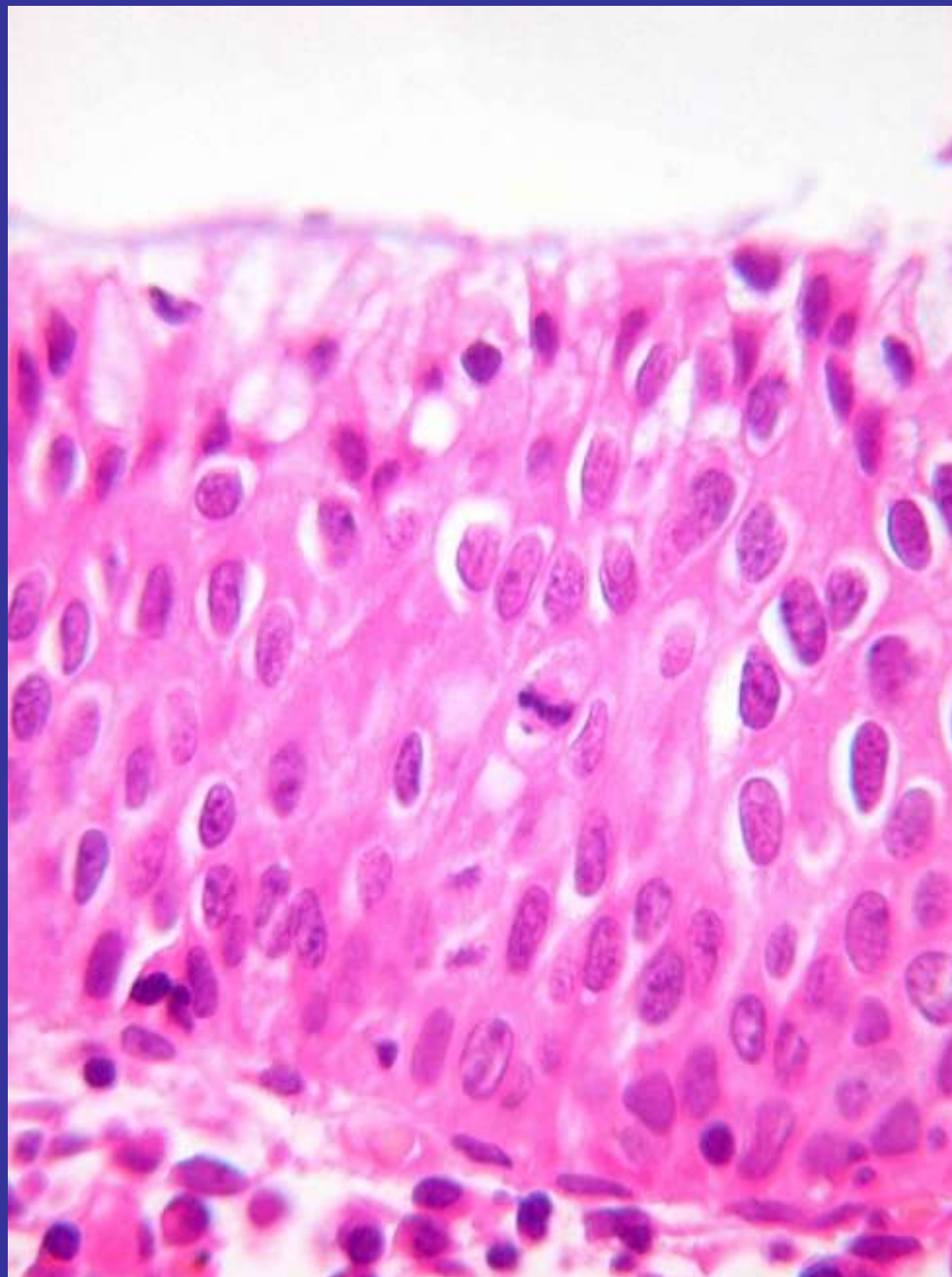
0 – 3 = benign

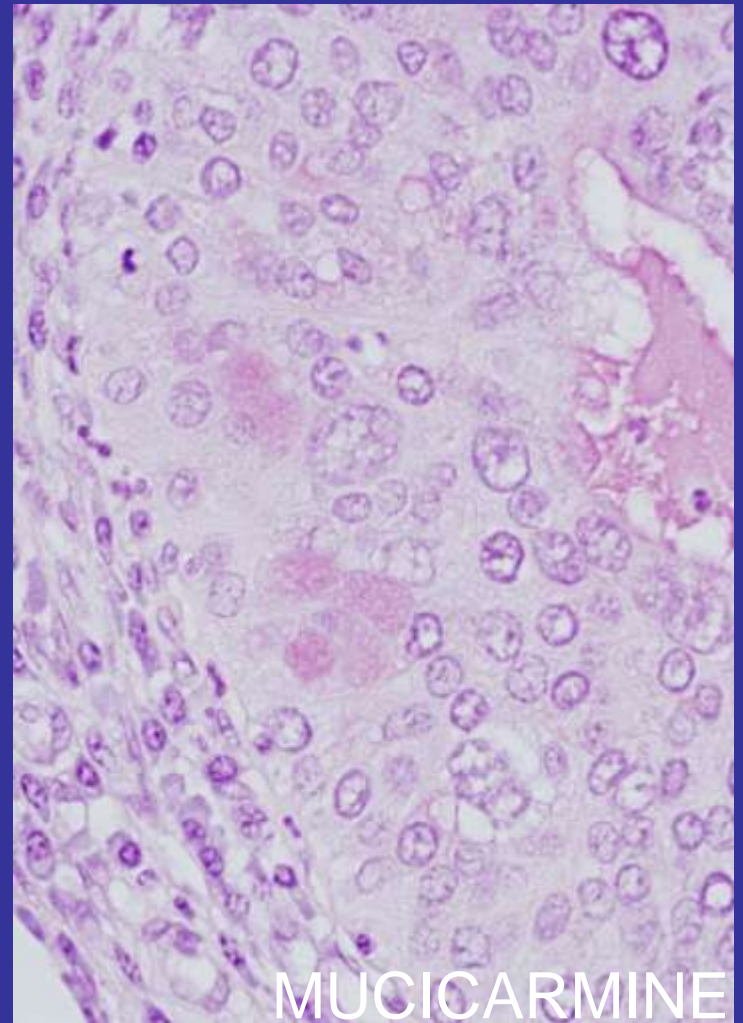
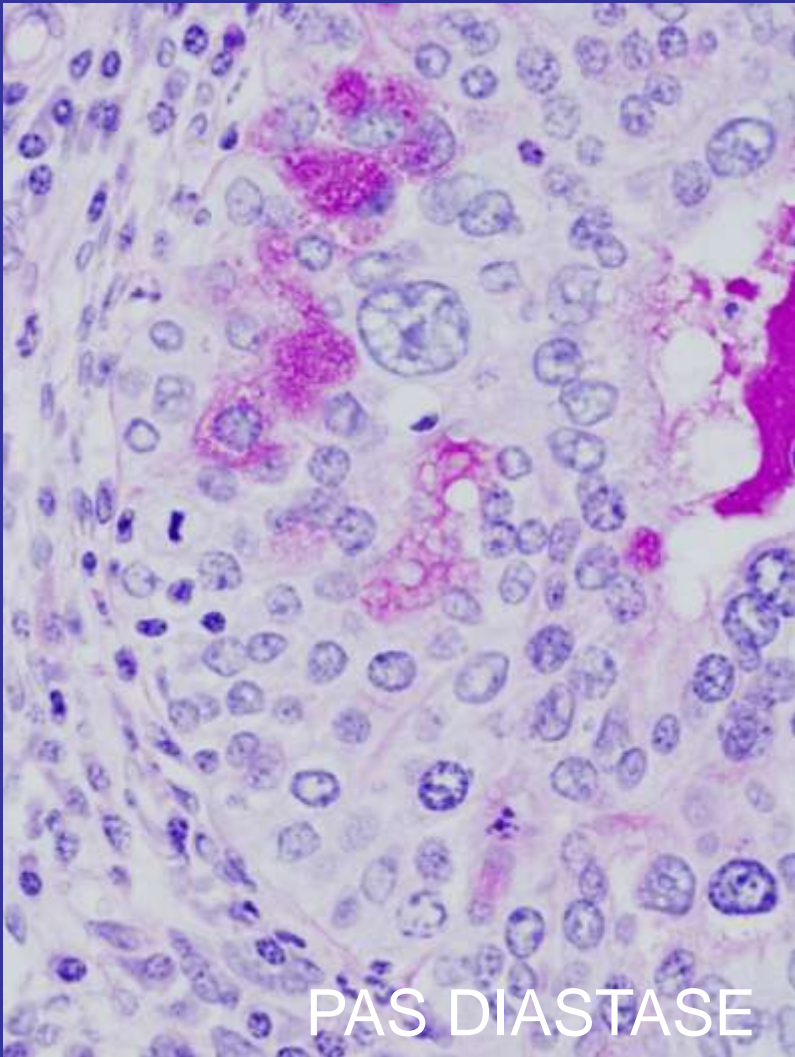
4 – 5 = endocervical glandular dysplasia

6 – 9 = adenocarcinoma in situ

Stratified Mucin-Producing Intraepithelial Lesion - SMILE

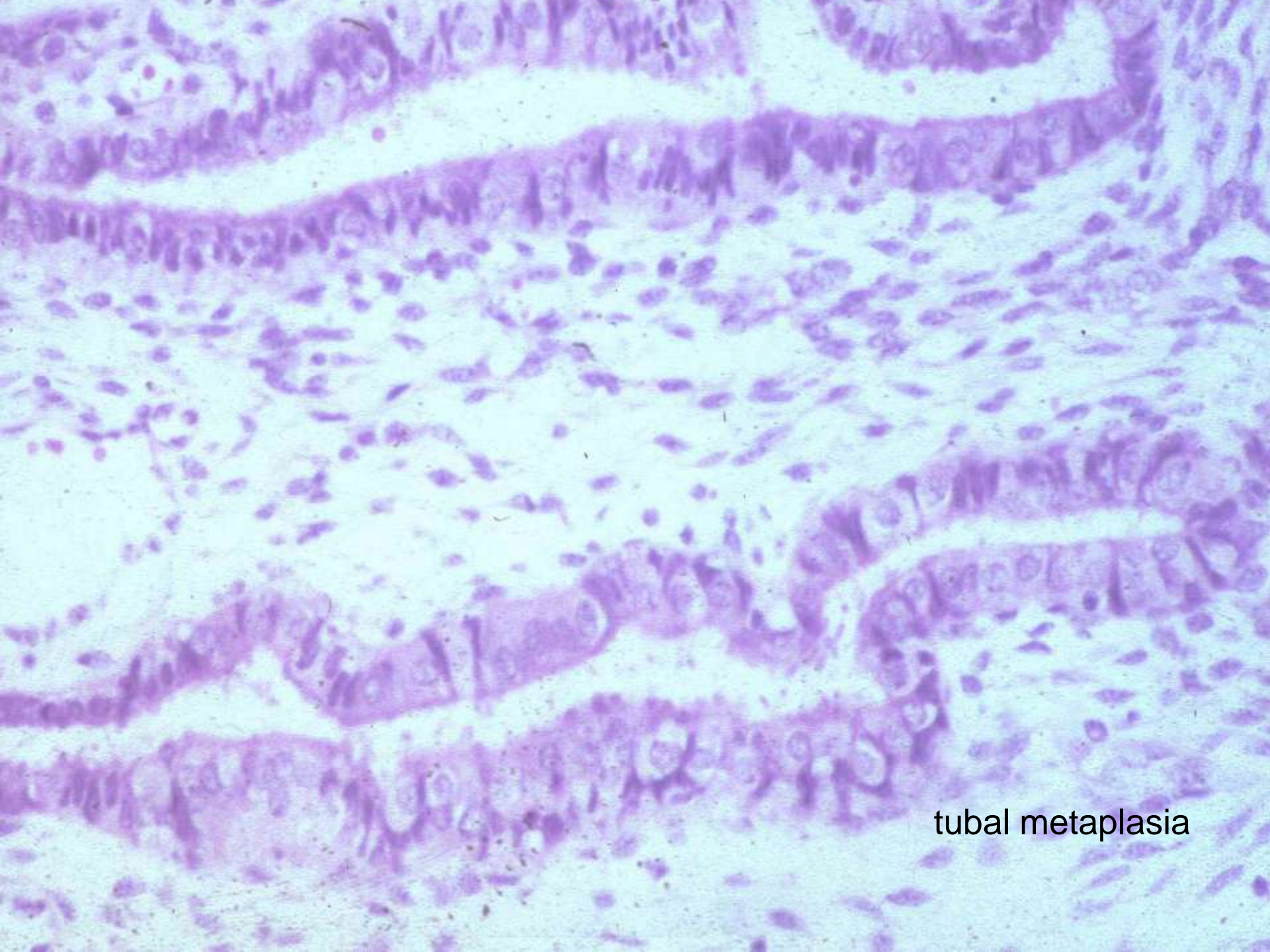
- stratified epithelium resembling CIN in which conspicuous mucin production is present
- mucin production varies from indistinct cytoplasmic clearing to discrete vacuoles
- nuclear and architectural features of neoplasia supported by extensive Ki-67 positivity
- absent keratin 14 and p63 staining consistent with columnar differentiation



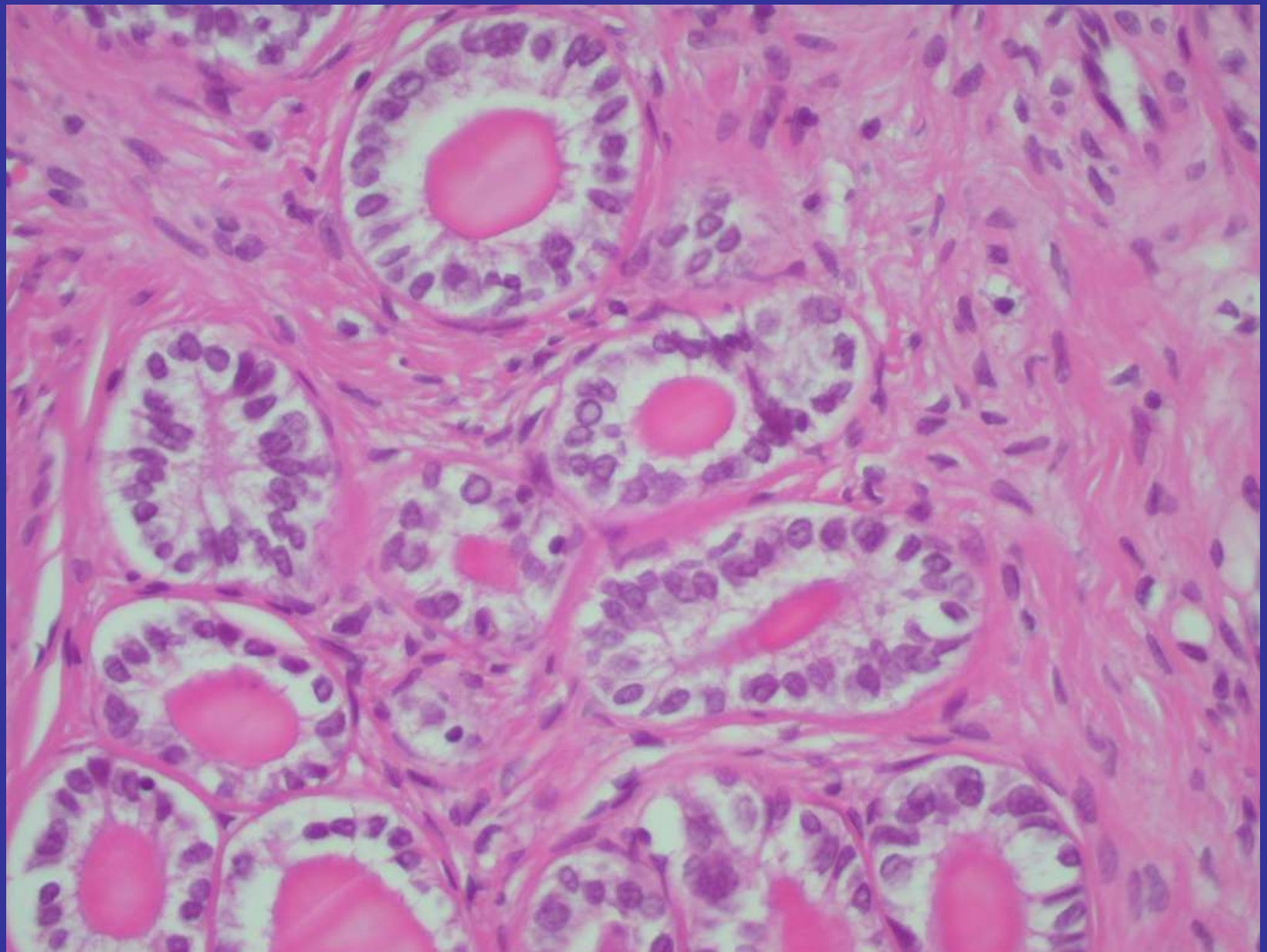


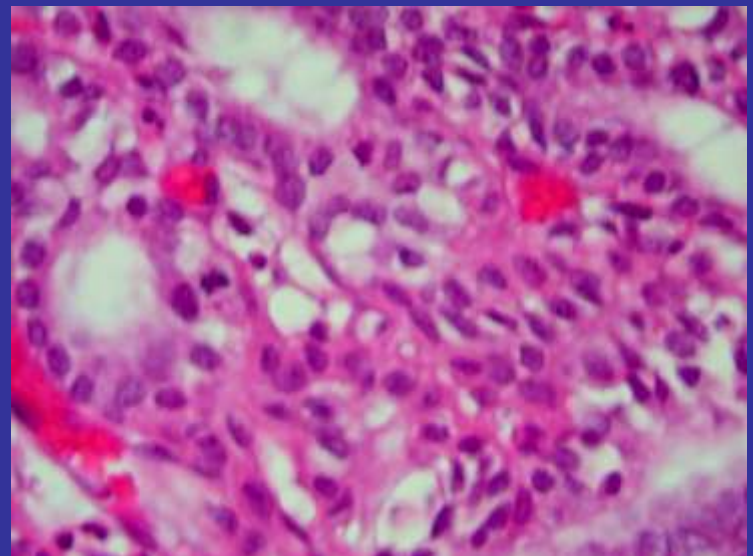
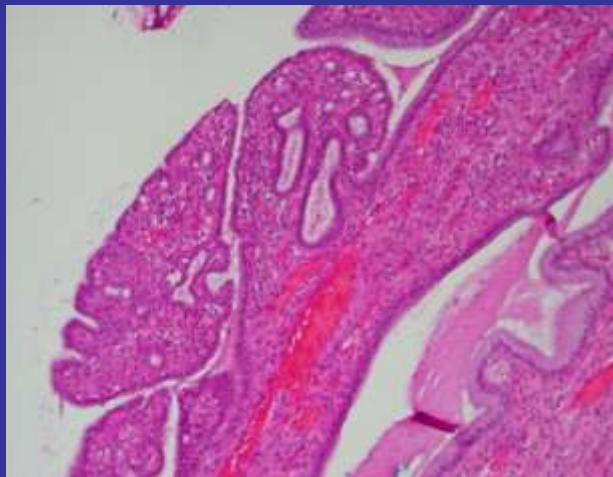
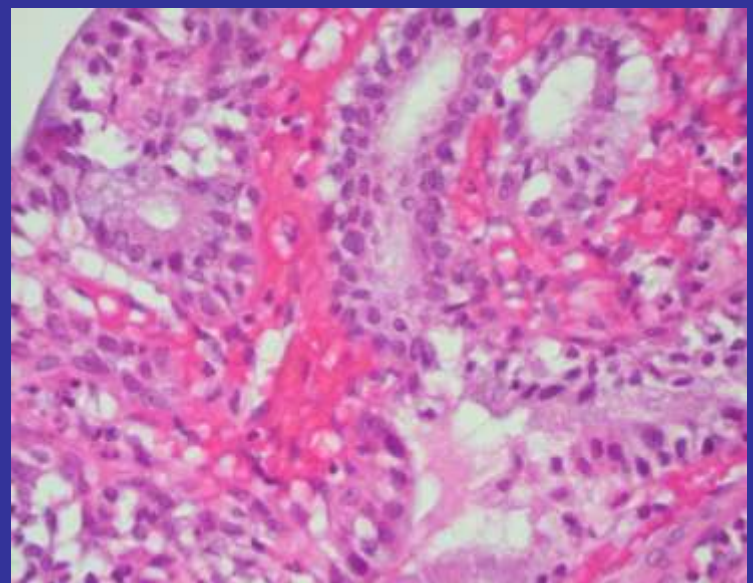
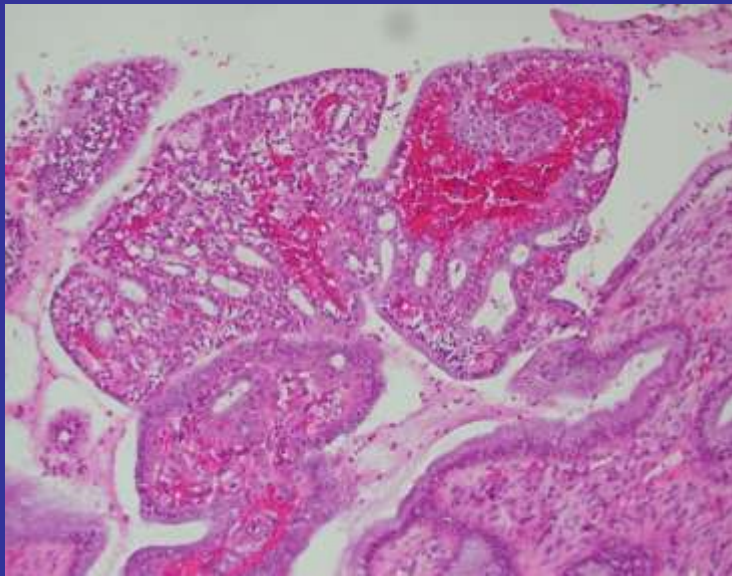
Benign Mimics of CGIN and Adenocarcinoma

- Tubo-endometrioid metaplasia
- Endometriosis
- Microglandular hyperplasia
- Inflammatory atypia
- Mesonephric remnants
- Endocervical hyperplasia
- Tunnel clusters
- Deep cervical glands
- Endocervicosis
- Atypical oxyphil metaplasia
- Adenomyoma
- Radiation effects
- Ectopic prostate
- Arias-Stella effect
- Florid cystic endosalpingiosis
- Caution artefact
- Mullerian papilloma
- Villous adenoma



tubal metaplasia

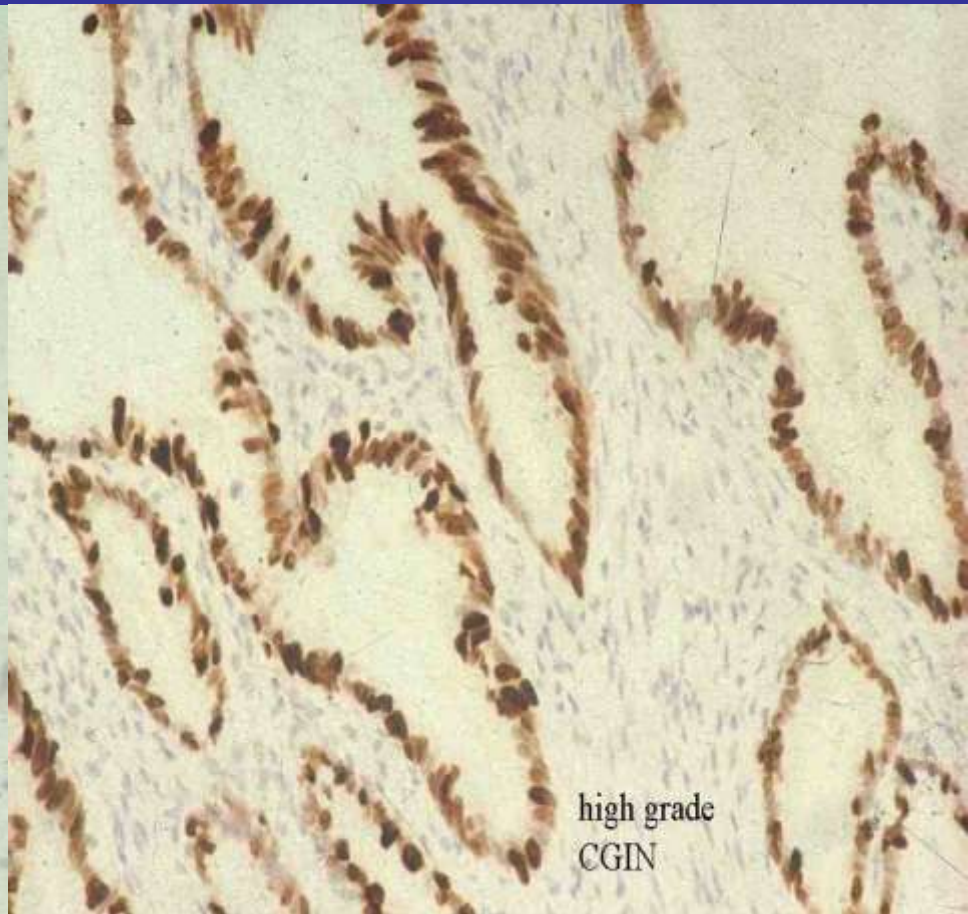
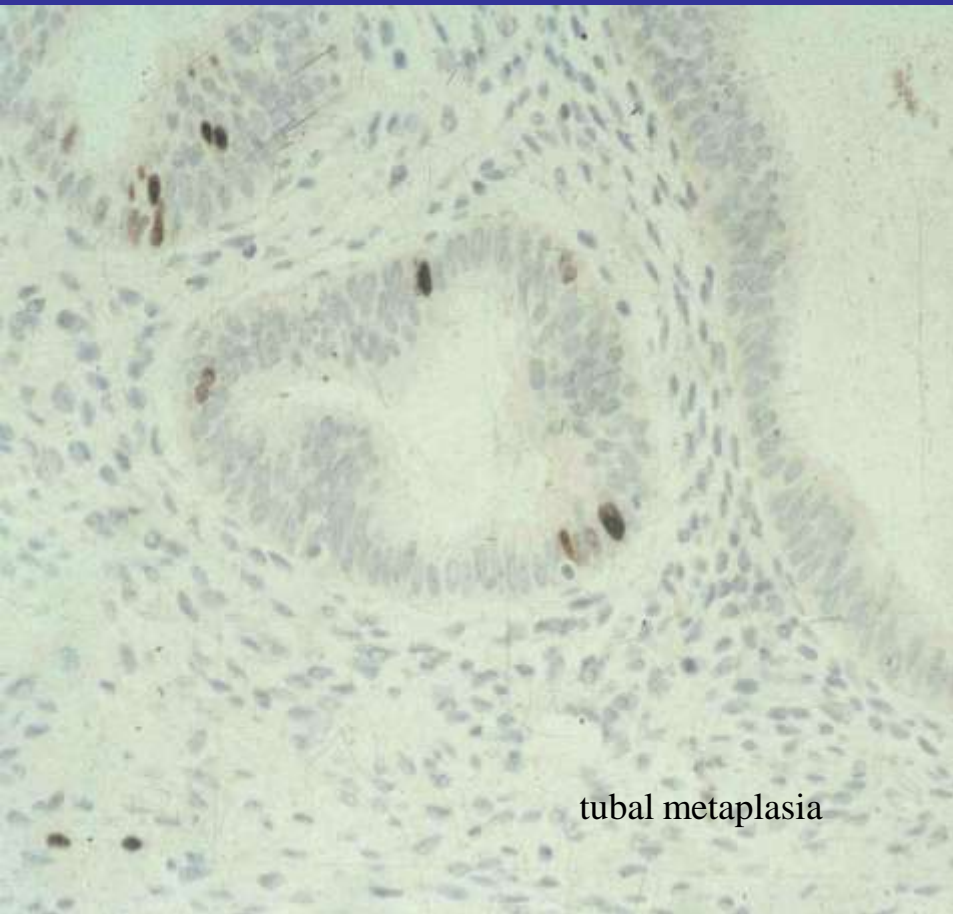




Mimics of HCGIN – special techniques

	MIB1	bcl2	p16 ^{INK4a}
TEM	<10%	+ cytoplasm	Focal +
Endometriosis	<10%	+ cytoplasm	Focal +
MEH	<10%	-	-
HCGIN	>30%	-	100% +

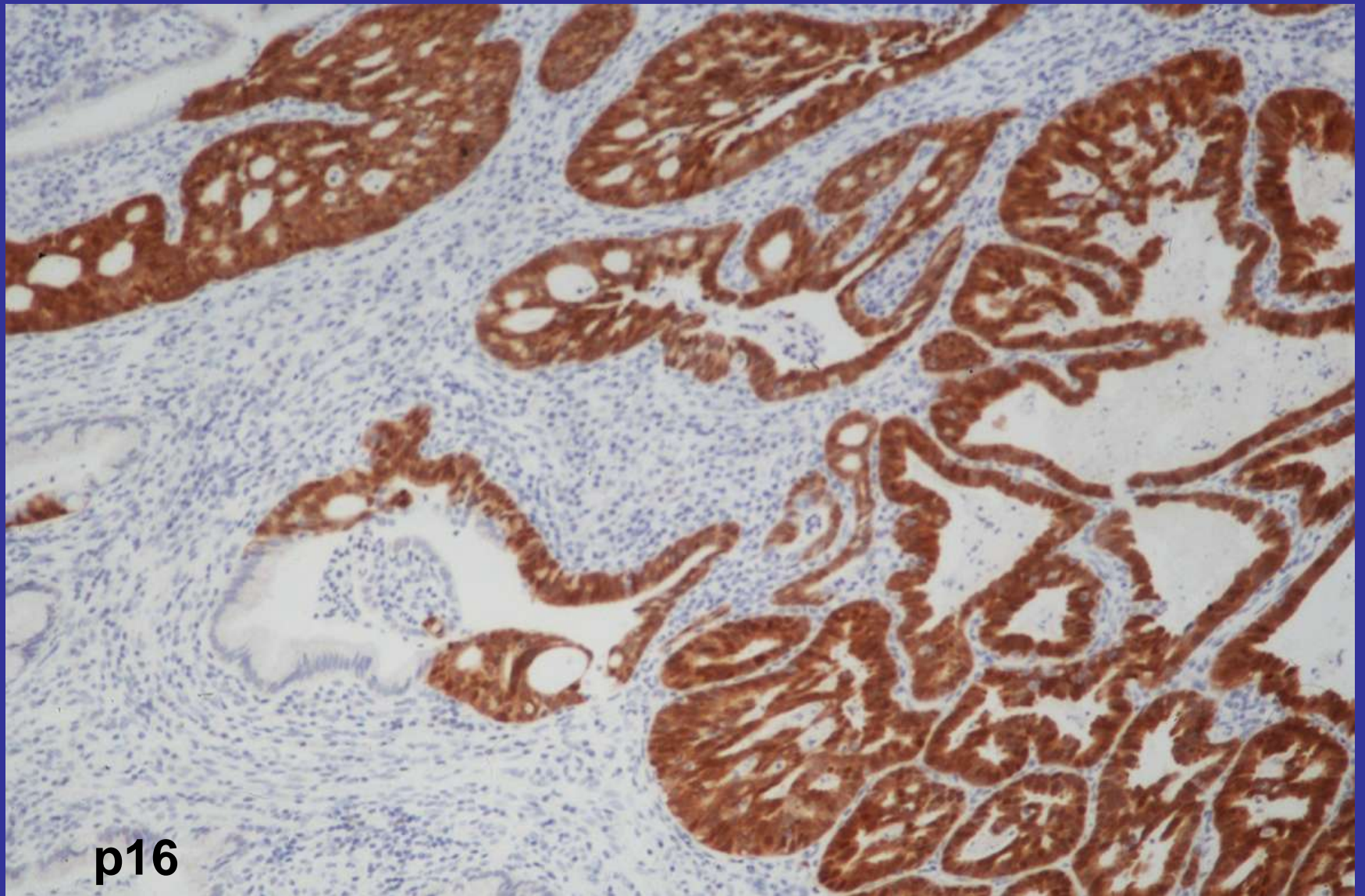
MIB1

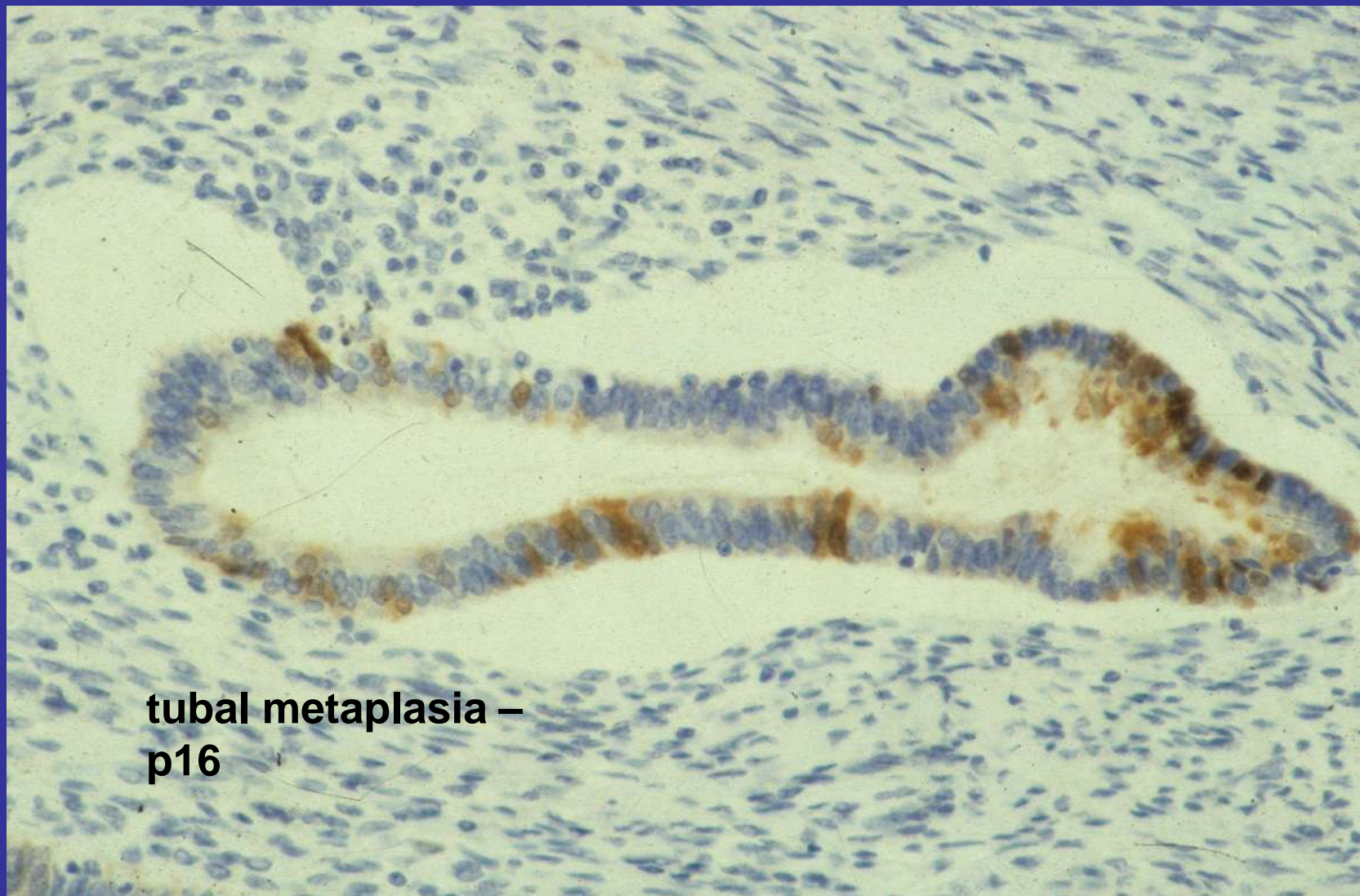


P16

in cervical glandular intraepithelial neoplasia

- encoded by CDKN2A gene on chromosome 9p21
- strong relationship between p16 expression and HPV-encoded E6/E7 transcription
- overexpression associated with presence of high-risk HPV
- all cases of CGIN – p16 positive
- tubo-endometrioid metaplasia and endometriosis may also show focal p16 immunoreactivity





tubal metaplasia –
p16

p16 immunoreactivity in cervical adenocarcinoma

- unusual types of cervical adenocarcinoma are usually HPV negative
- such tumours may be p16 positive
- p16 is not a reliable surrogate marker of HPV infection

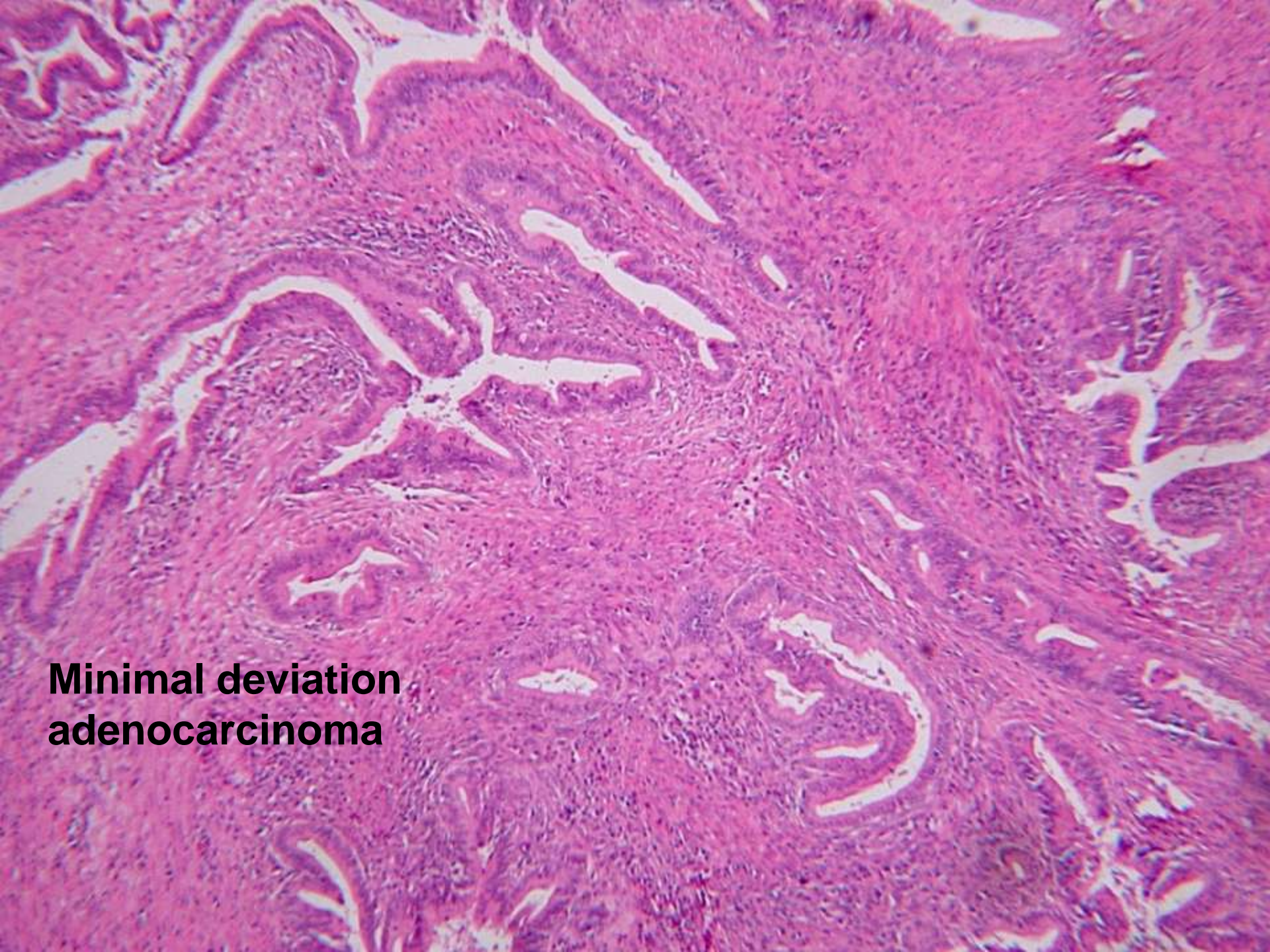
Houghton et al Histopathology 2010, 57:342-350

Lobular endocervical hyperplasia (LEGH) and cervical adenocarcinoma

- pyloric gland metaplasia
- atypical LEGH described
- HPV negative
- association with minimal deviation adenocarcinoma
- association with Peutz-Jeghers syndrome

LOBULAR ENDOCERVICAL GLANDULAR HYPERPLASIA
?pyloric gland metaplasia

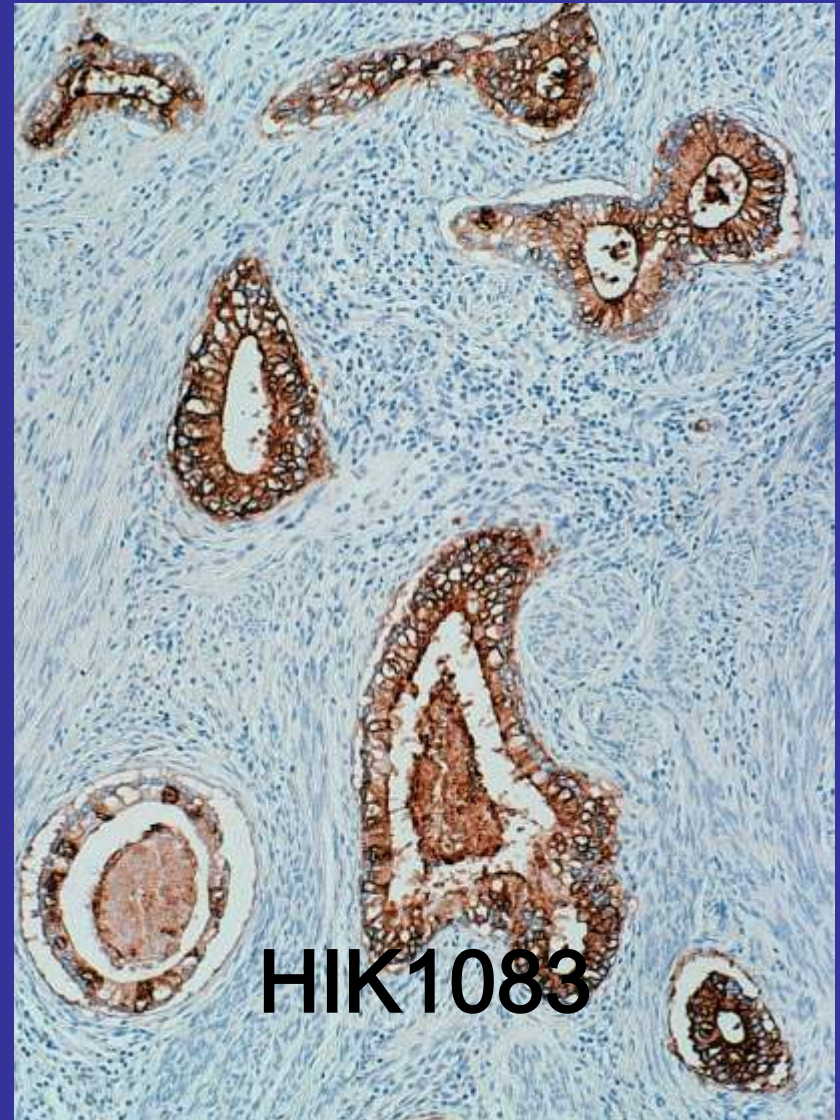




**Minimal deviation
adenocarcinoma**

Adenoma malignum

- HIK1083 – antibody against a gastric mucin-type mucin
- gastric phenotype is frequently expressed in minimal deviation adenocarcinoma (MDA)
- possible link between MDA and lobular endocervical hyperplasia

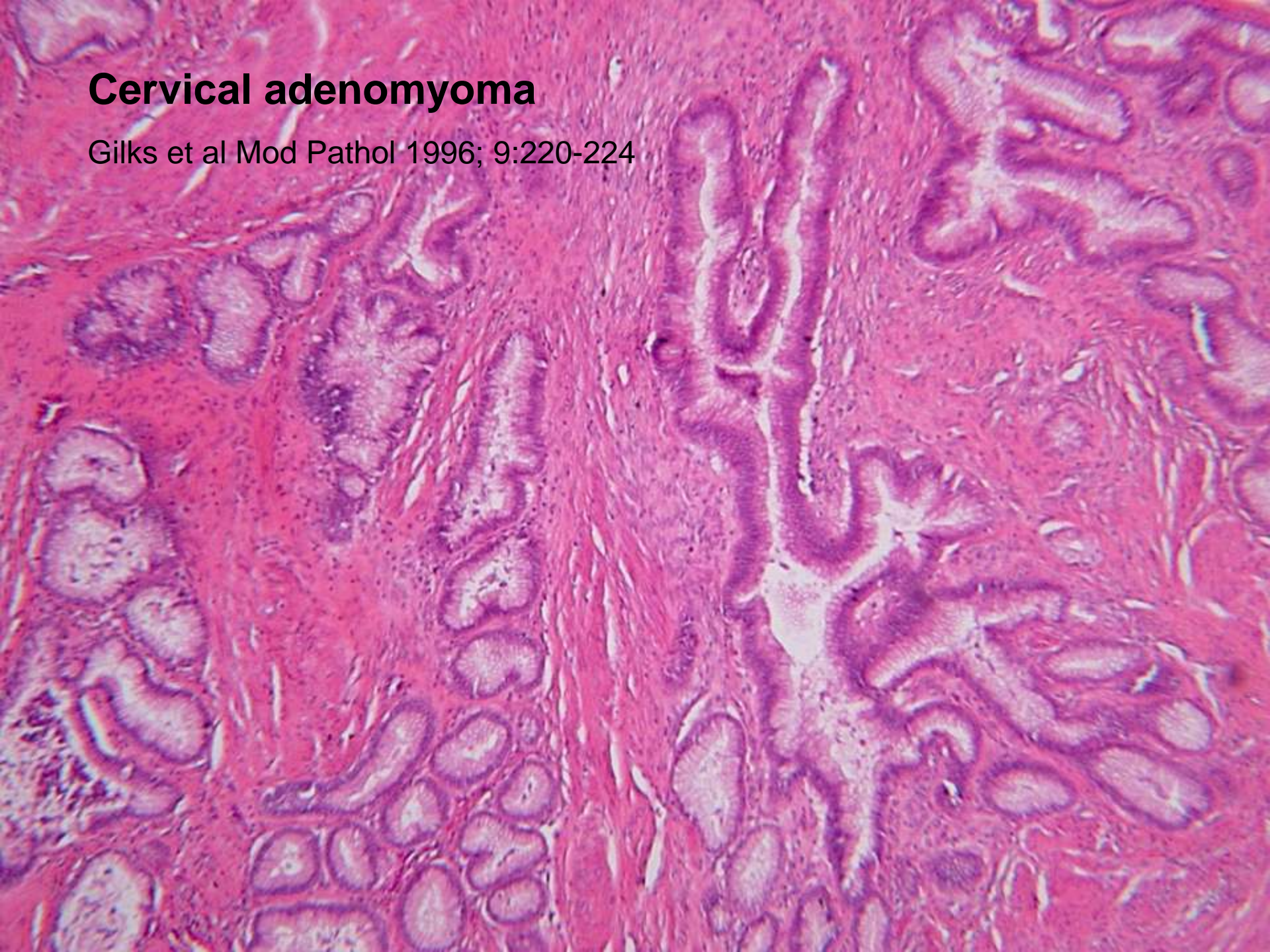


Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions

	Gastric marker		Intestinal marker	
	HIK1083	MUC6	MUC2	CD10
Adenocarcinoma NOS	7%	23%	14%	7%
Intestinal type adenocarcinoma	23%	69%	85%	15%
MDA	75%	65%	25%	0%
LEH/PGM	95%	75%	15%	0%
Atypical LEH/PGM	78%	67%	11%	0%

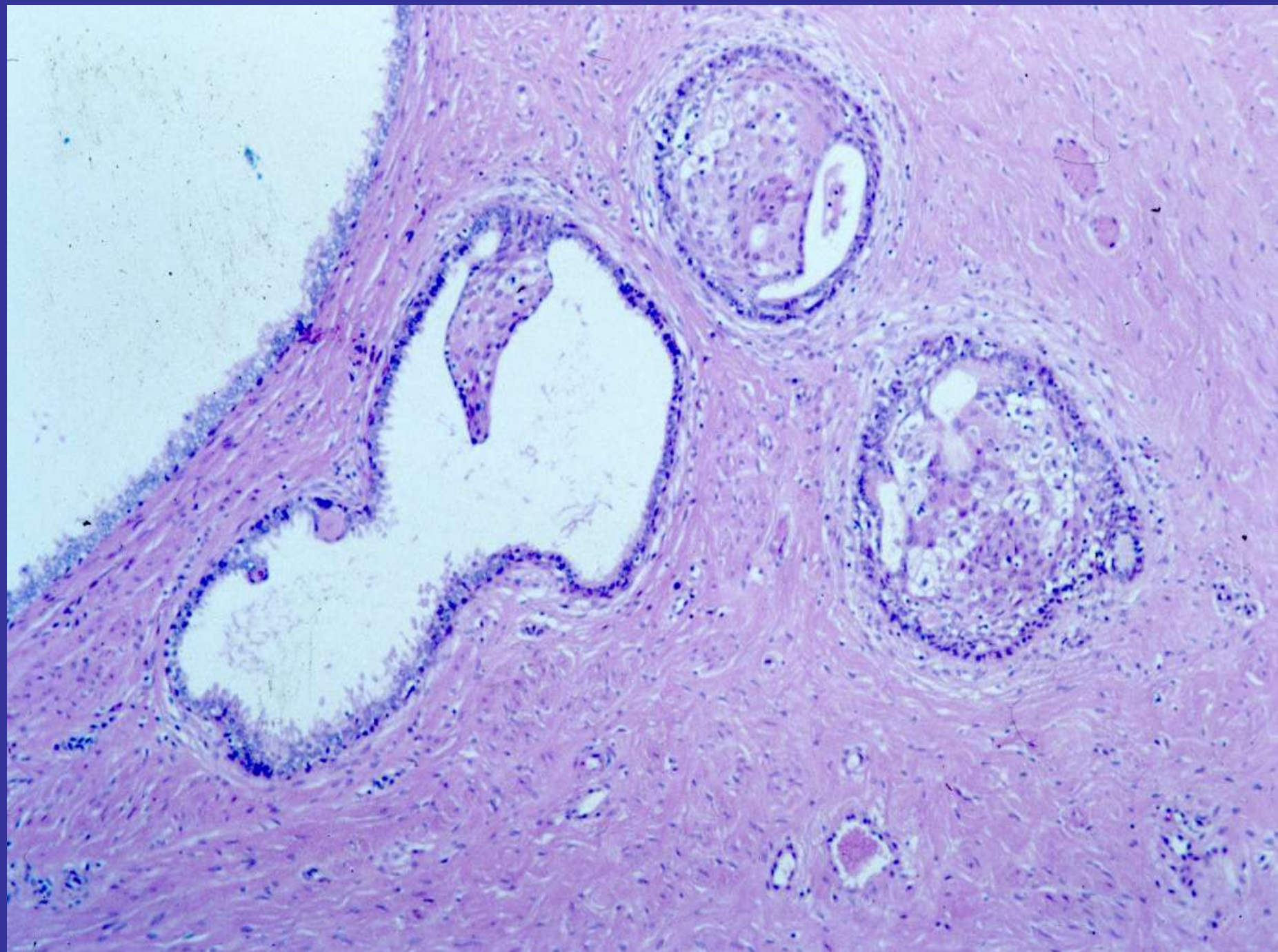
Cervical adenomyoma

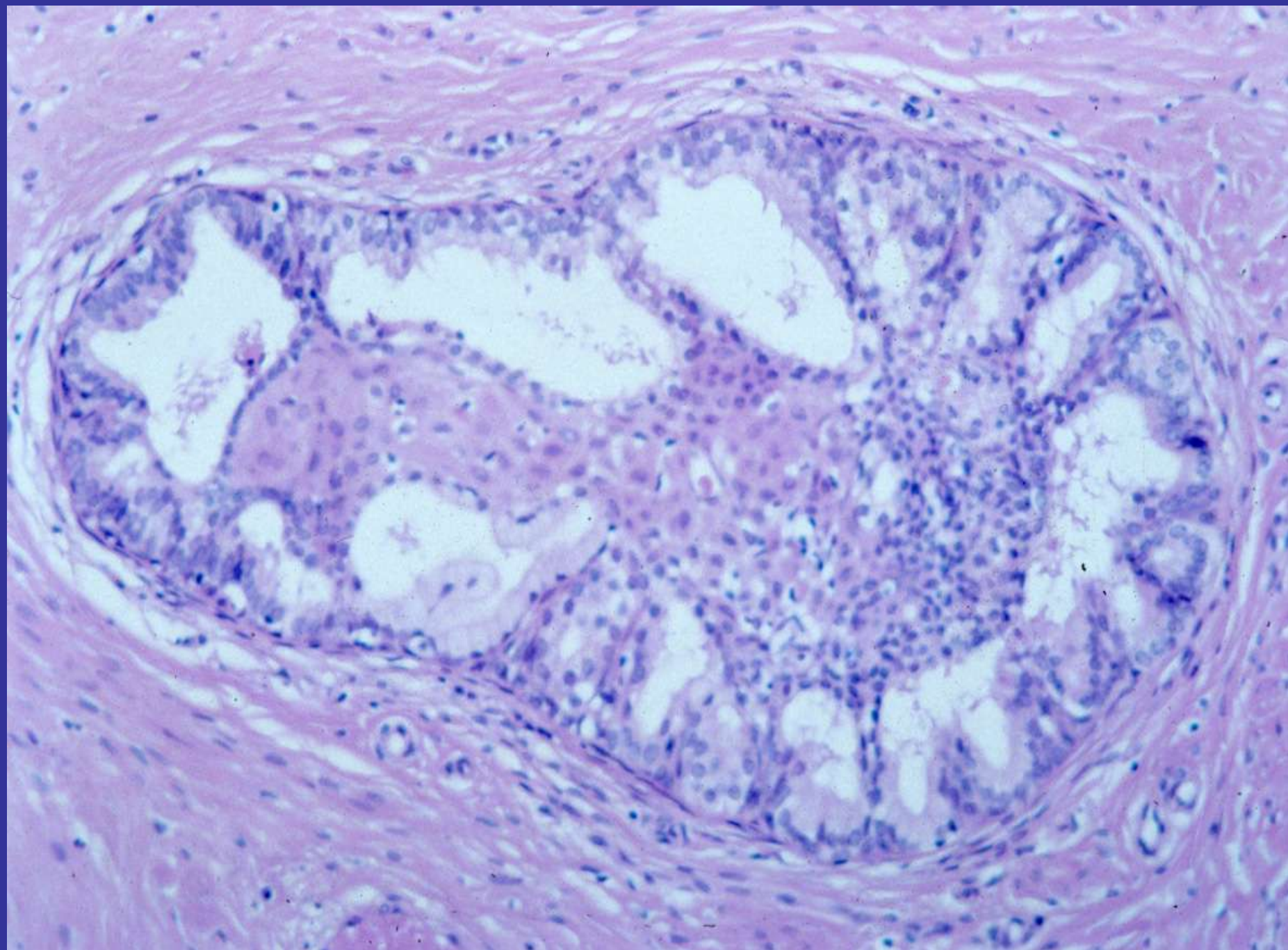
Gilks et al Mod Pathol 1996; 9:220-224

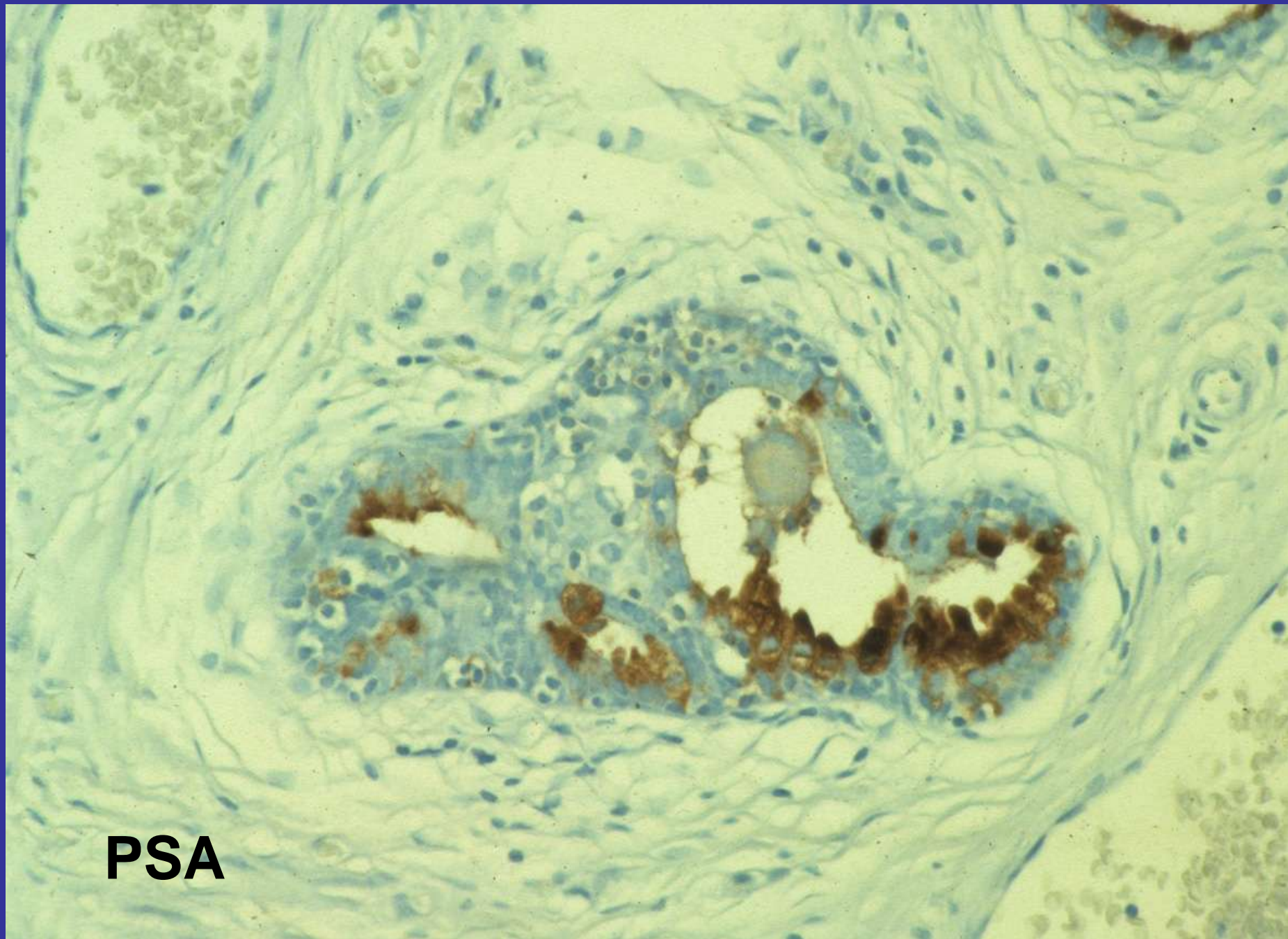


Ectopic Prostatic Tissue in Cervix

- usually incidental microscopic finding
- usually in ectocervical stroma
- ? developmental anomaly, ? metaplasia
- cribriform and papillary patterns
- usually associated squamous metaplasia
- double cell layer
- positive PSA and PrAP







PSA

PrAP

Pitfalls

- markers may be only focally positive
- identical cases which are prostate marker negative

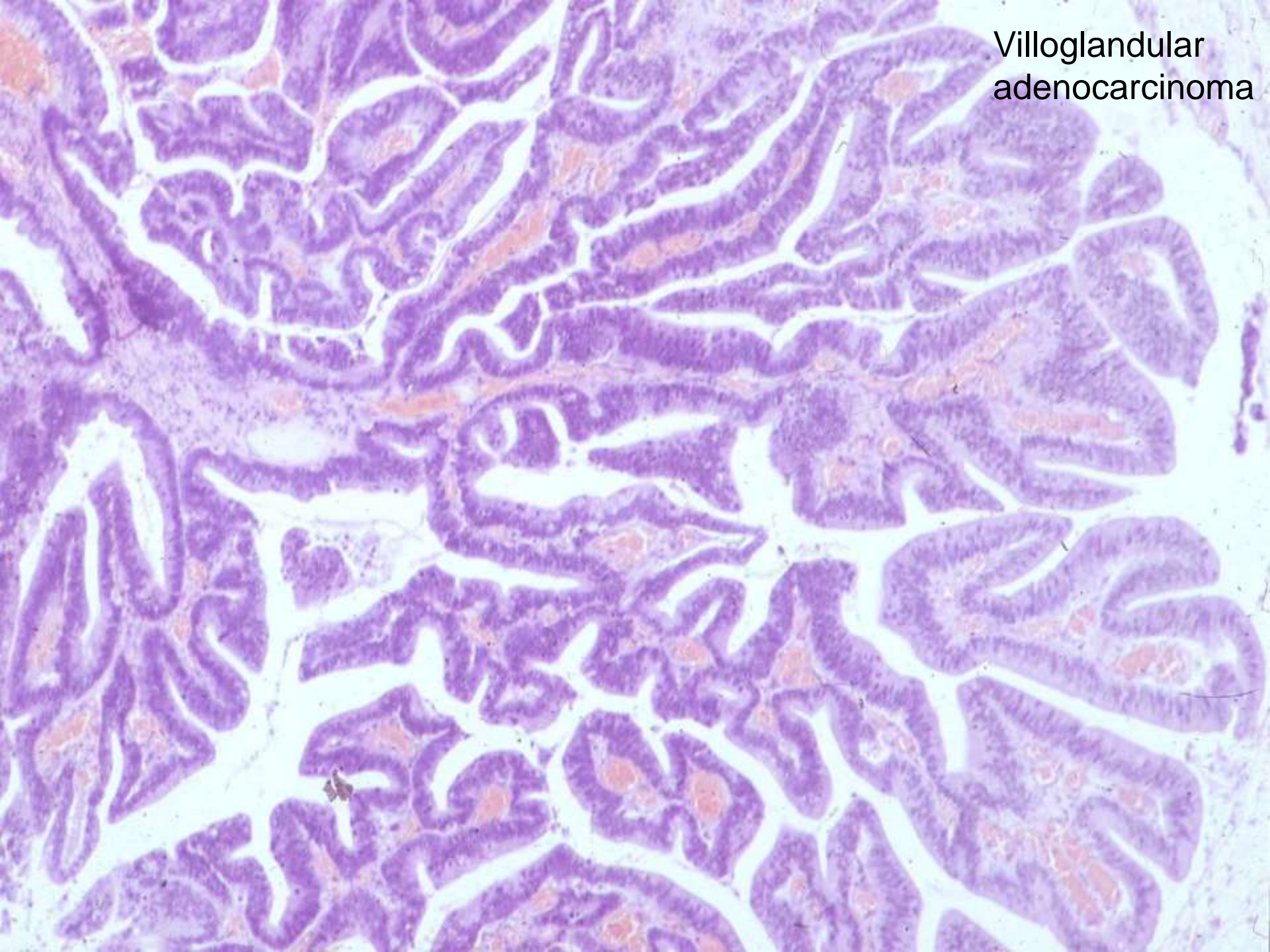
UNIFYING THEORY

- vaginal tubulosquamous polyp and ectopic prostatic tissue in cervix are same lesion
- ? derived from displaced paraurethral Skene's glands

CERVICAL ADENOCARCINOMA – histological variants

- **Adenocarcinoma NOS**
- **Mucinous**
 - endocervical**
 - intestinal**
 - signet-ring cell**
 - minimal deviation**
 - villoglandular**
- **Endometrioid**
- **Clear cell**
- **Serous**
- **Mesonephric**

Villoglandular
adenocarcinoma

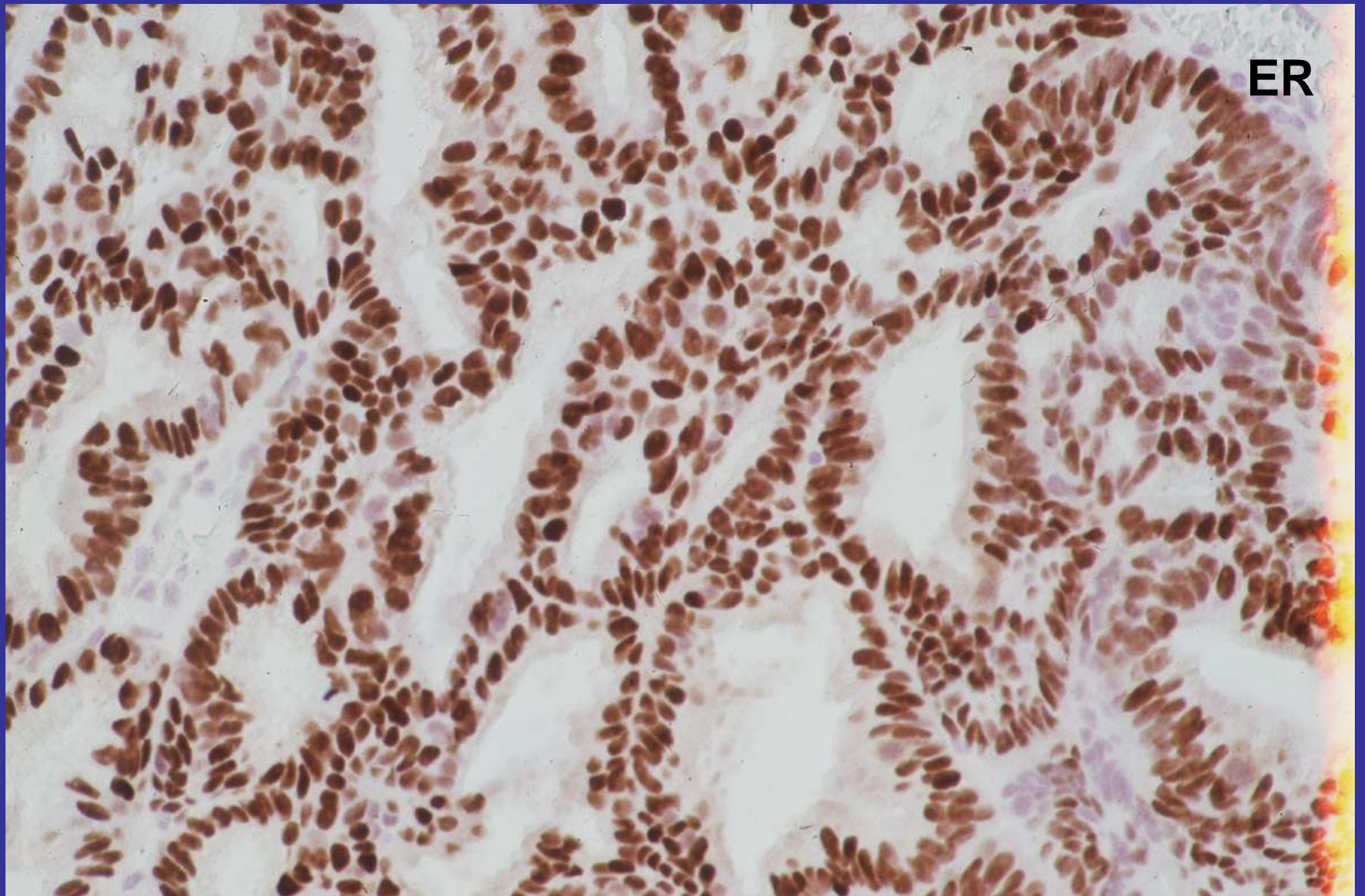


Villoglandular
adenocarcinoma

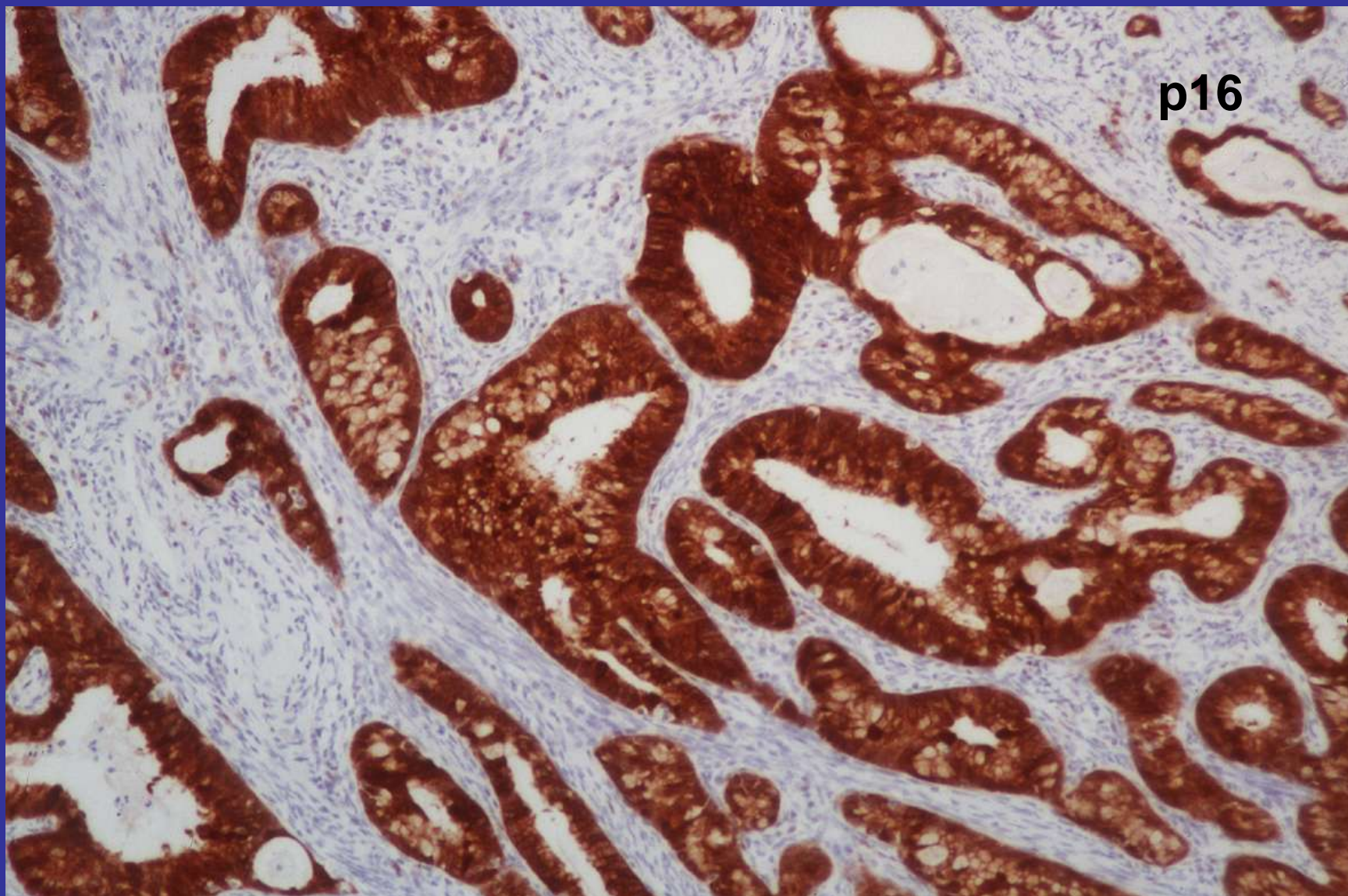


Endocervical or endometrial adenocarcinoma?

	Endocervical adenocarcinoma	Endometrial adenocarcinoma
Vimentin	-	++
Oestrogen receptor	+ Focal	++
CEA	++	+ Focal
p16	++ 100%	+ <50%
CD10	+ 33% limited luminal	77% cytoplasm,membrane or both
HPV	66%	-



ER



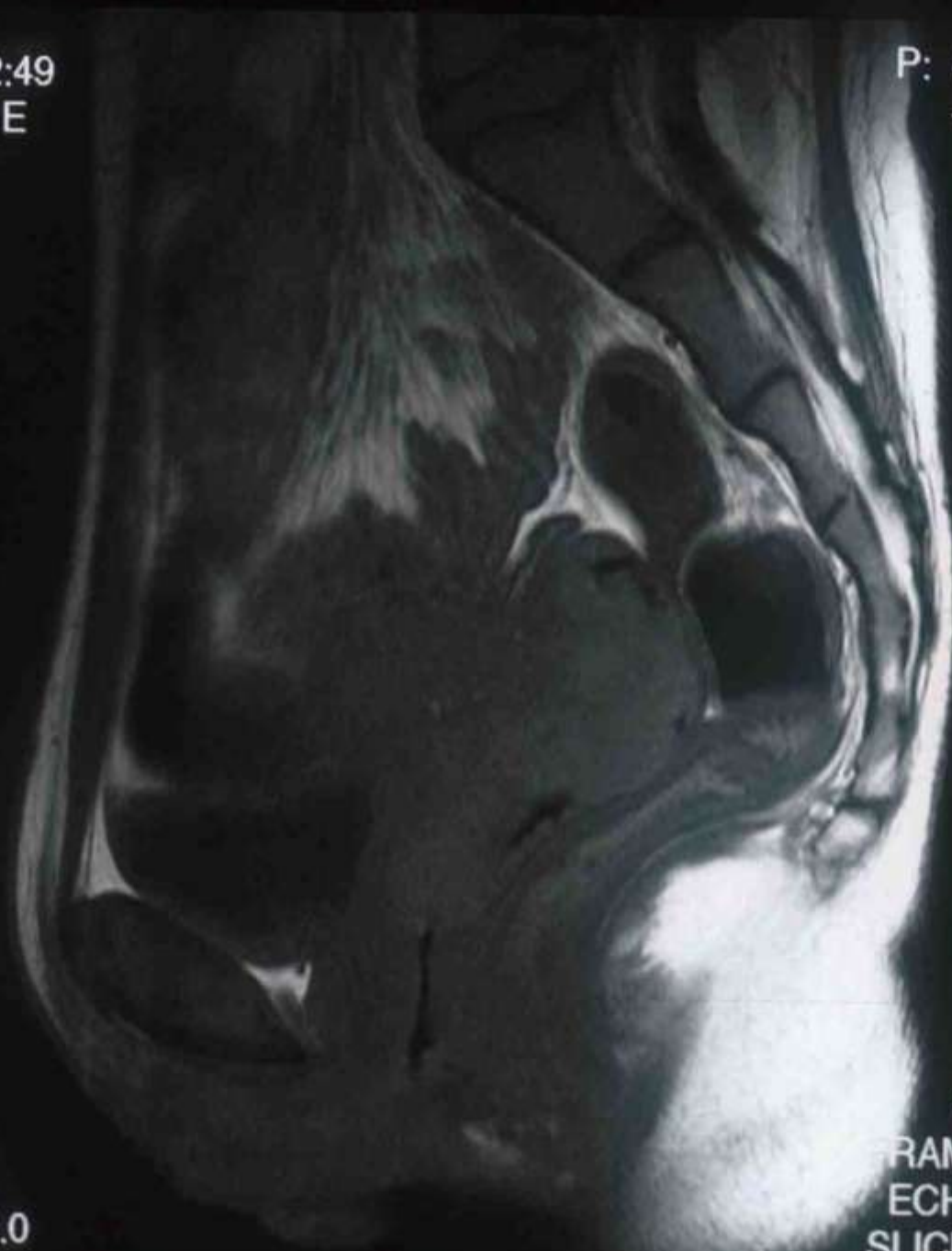
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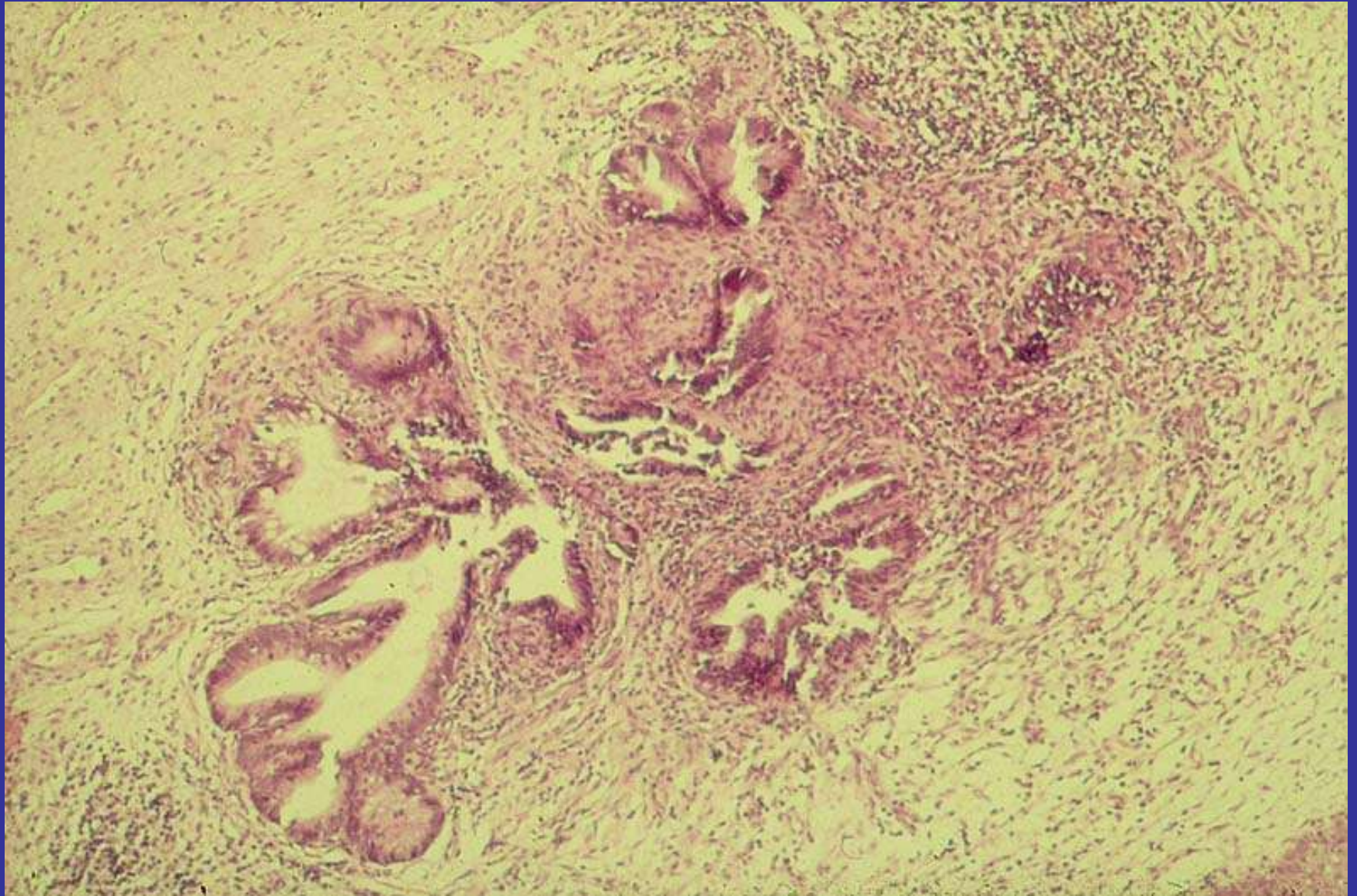
Microinvasive carcinoma

- invasive carcinoma with little or no risk of metastatic disease
- suitable for conservative treatment
- histological diagnosis
- synonymous with FIGO stage 1A1 and 1A2 (UK)

“...I do not know how to make the diagnosis of microinvasive cancer of the endocervix. I do not know where the basal lamina is and I do not know where to measure from. I do not know what depth constitutes microinvasion. We do not have the same data for endocervical invasion that we have for the lesions in the squamous epithelium”.

Richard R.





Early invasive/microinvasive adenocarcinoma

“The current 1995 FIGO staging omits specific reference to glandular lesions in stage 1A. In addition, there are practical problems in identifying microinvasive adenocarcinoma histologically. Nevertheless, it is recommended that the FIGO classification be adopted”.

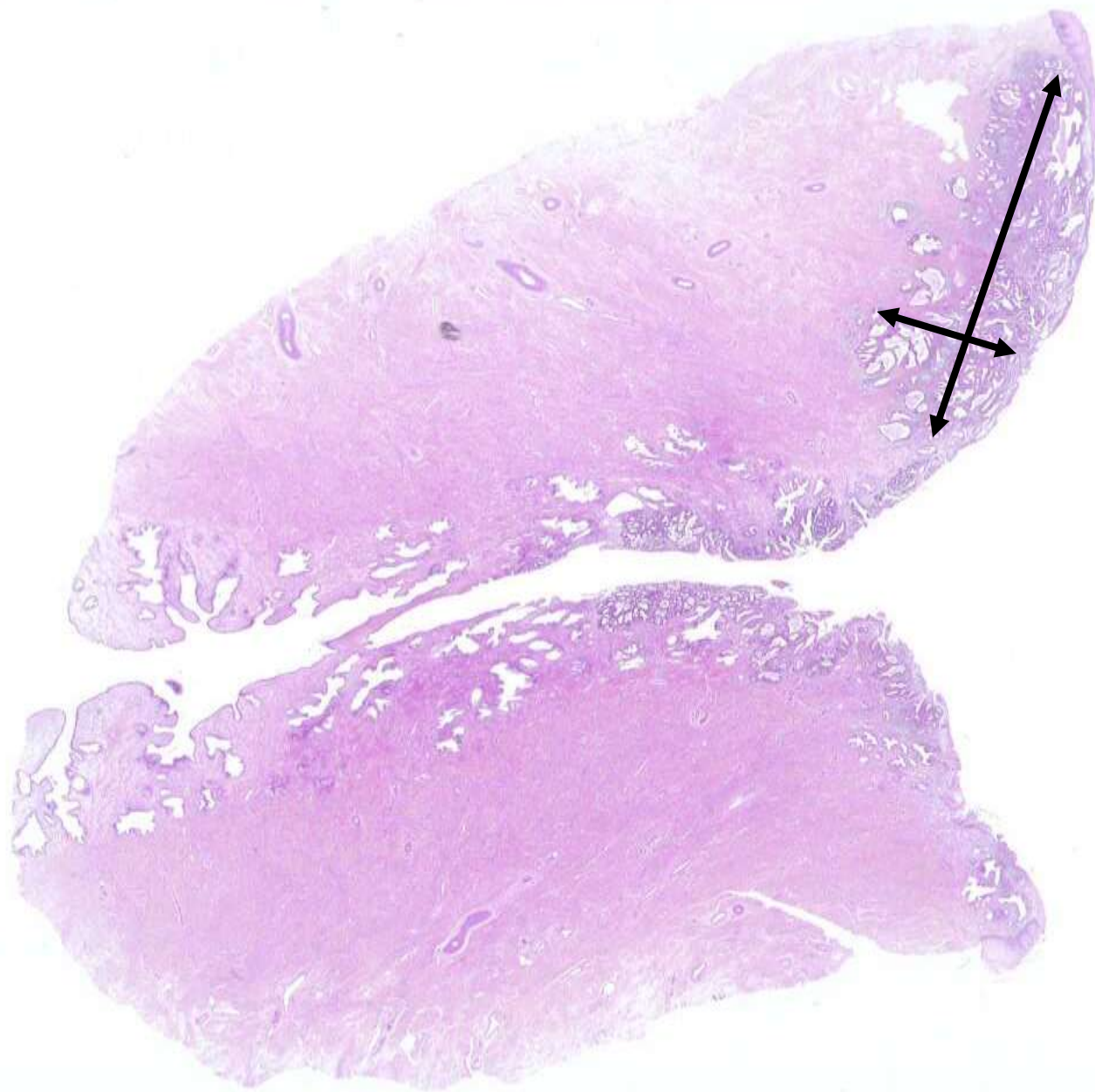
Wells et al 2003 Epithelial tumours and related lesions of the uterine cervix In: WHO Tumours of the breast and female genital organs

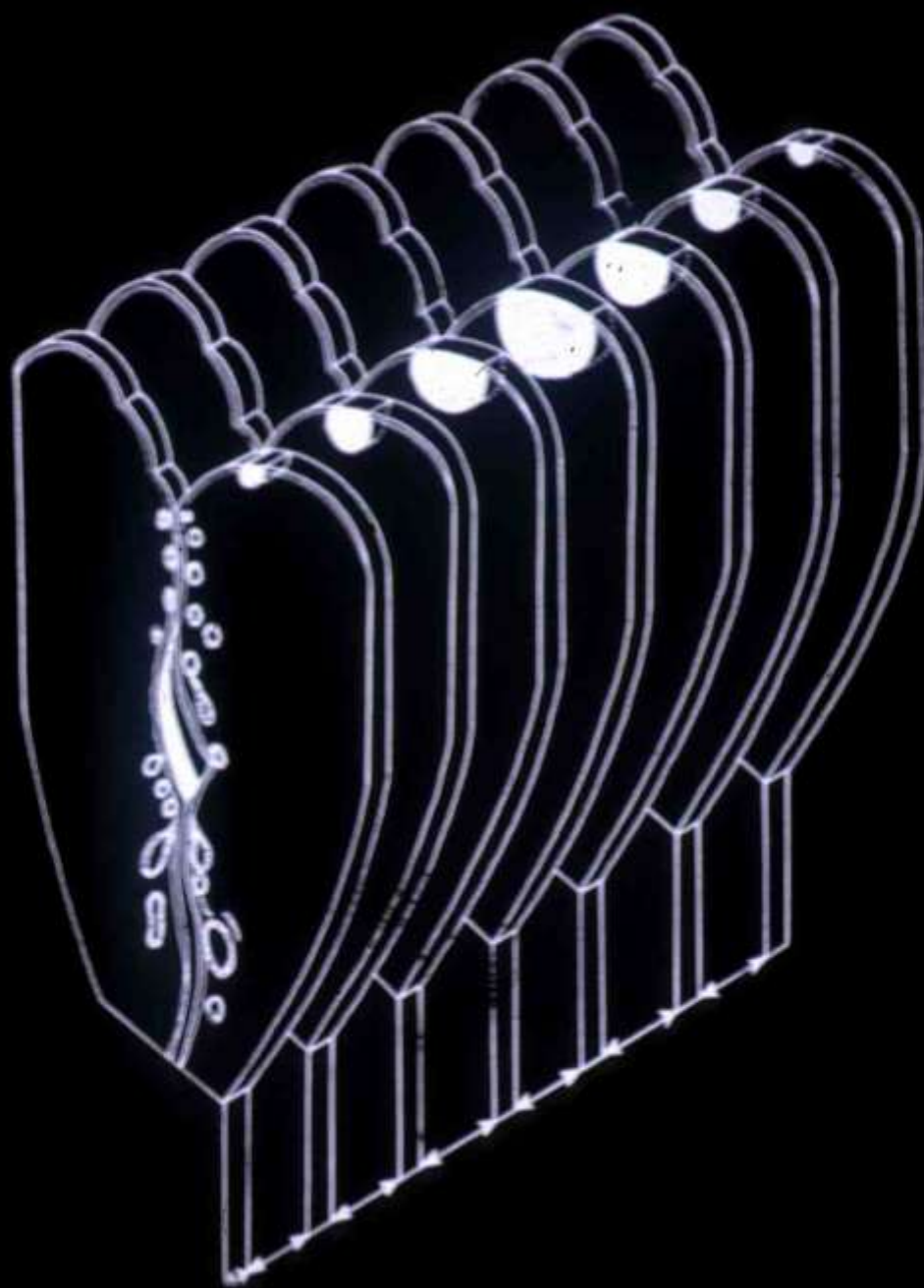


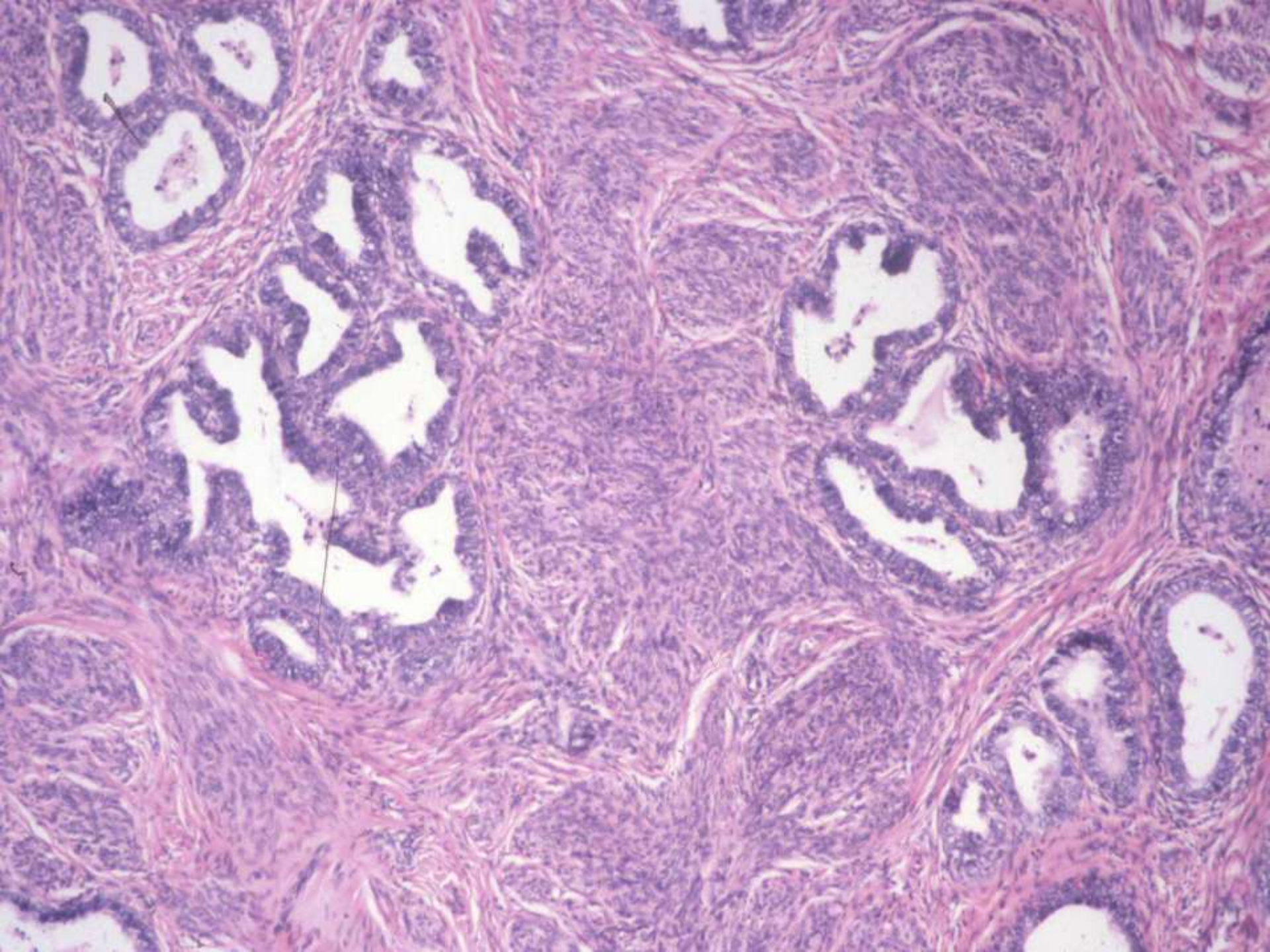
Andrew Östör 1943-2003

Criteria for Microinvasive Adenocarcinoma

- obvious invasion to 3mm or less
- usually complete obliteration of the normal endocervical crypts
- extension beyond the normal glandular field
- a stromal response typical of invasive carcinoma







Early invasive adenocarcinoma

- 0/126 patients treated by radical hysterectomy had parametrial spread
- 5/219 (2.3%) had pelvic lymph node metastases
- 15/436 (3.5%) had recurrence
- 6/436 (1.4%) tumour related deaths

Early invasive adenocarcinoma

- no recurrence in 21 treated by cone alone
- cold knife conisation acceptable treatment if:
 - adequately sampled
 - margins free of disease
- loop excision not acceptable for diagnosis or treatment