

**Approccio diagnostico alla patologia cervicale:
la colposcopia tradizionale e su strato sottile.
La classificazione Bethesda**

C. Gentili



Logo of the **Associazione Ginecologi Extra Ospedalieri** (A.G.E.O.) in the top right corner.

VI CORSO BASE A.G.E.O.

COLPOSCOPIA

Diagnostica e Operativa del Basso Tratto Genitale
8-9-10 Novembre 2018 MILANO

Presidenti: *B. Stefanon, G. Bandieramonte*

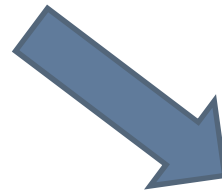
PROCEEDINGS
OF THE
Third Race Betterment Conference
January 2-6, 1928

Under the Auspices of the
Race Betterment Foundation
Battle Creek, Michigan



NEW CANCER DIAGNOSIS

Dr. George N. Papanicolaou
Cornell University Medical College



**American Journal of
Obstetrics and Gynecology**
Vol. 42 AUGUST, 1941 No. 2

Original Communications

THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN
CARCINOMA OF THE UTERUS*
GEORGE N. PAPANICOLAOU, M.D., PH.D., and HERBERT F. TRAUT, M.D.,
NEW YORK, N. Y.
*(From the Departments of Anatomic and of Gynecology and Obstetrics of the
Cornell University Medical College and the New York Hospital)*



AUREL BABES

Koss LG. Int J Gynecol Pathol. 2003, 22:101-2

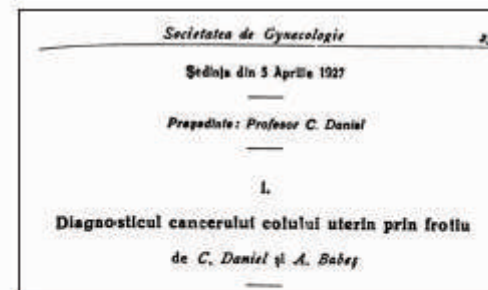


Figure 24 Title page of a paper by Professor M. Daniel and Dr. A. Babes on the diagnosis of cervical cancer from smears, presented to the Bucharest Society of Gynecology on April 5, 1927.

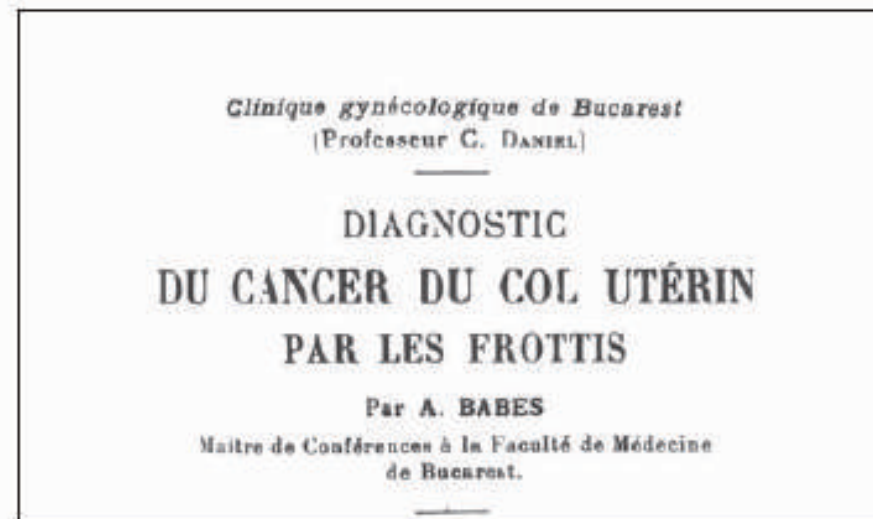


Figure 5 Title of the 1928 article by Dr. Babes in *Presse Médicale* ("Diagnosis of Cancer of the Uterine Cervix by Means of Smears").



La colorazione





The front of the 10 000-drachma note, showing George Papanicolaou (1883–1962), with his microscope and famous *Atlas of exfoliative cytology*, published in 1954.

Class I: absence of atypical or abnormal cells

Class II: atypical cytology but no evidence of malignancy (flogosis)

Class III: cytology suggestive of, but not conclusive for, malignancy;

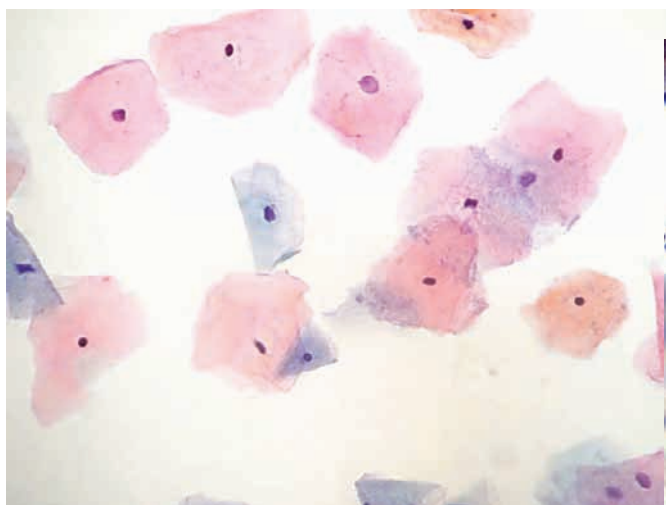
Class IV: cytology strongly suggestive of malignancy;

Class V: cytology conclusive for malignancy

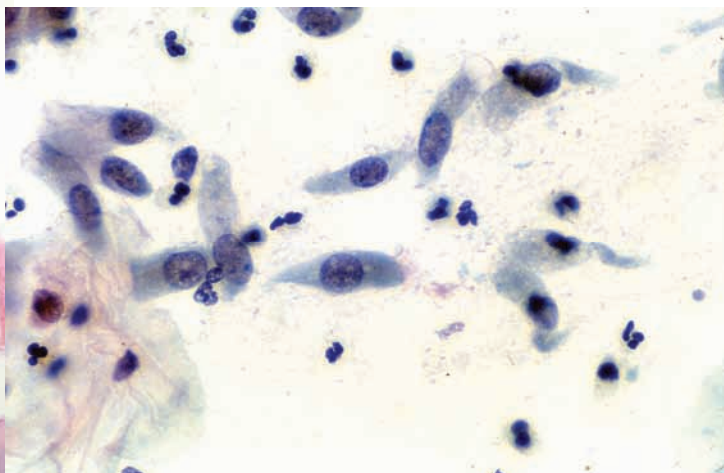
Papanicolaou GN (1954), *Atlas of Exfoliative Cytology* Cambridge, Mass: Harvard University Press 1954, pp 20-21

AIV
FEMALE GENITAL SYSTEM

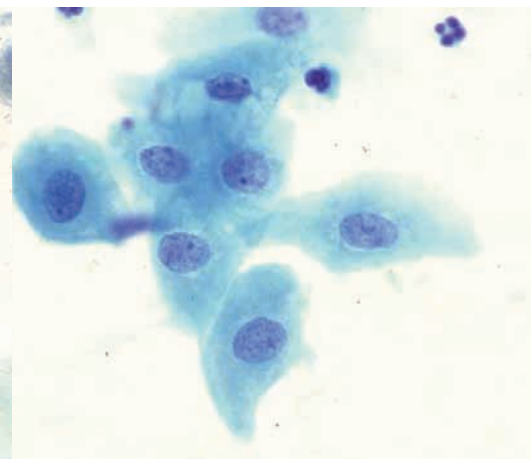




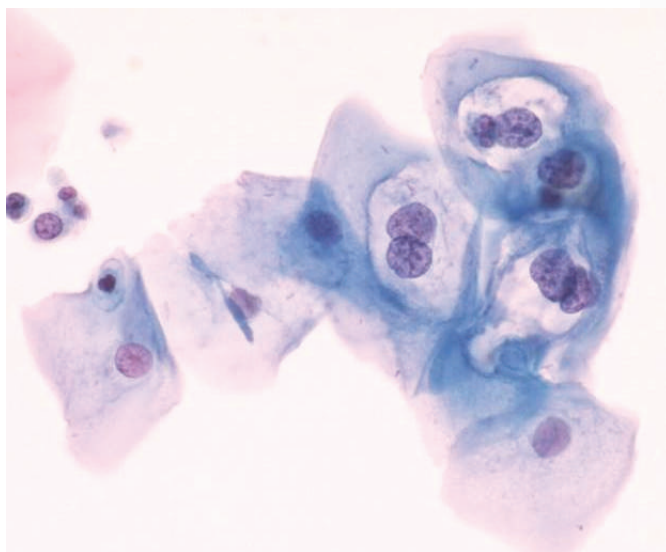
Cellule pavimentose



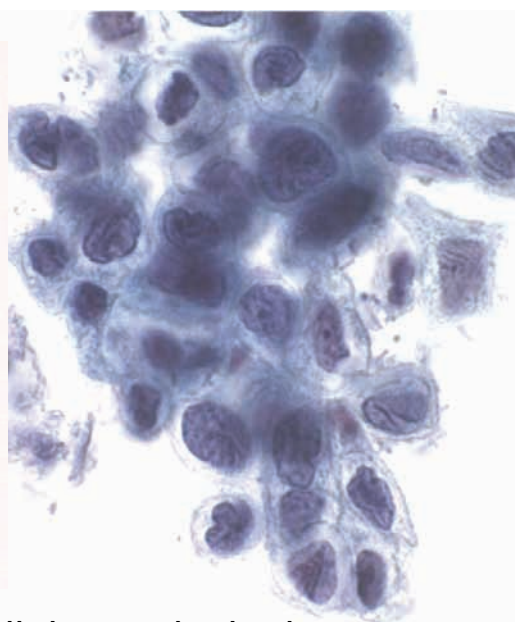
Cellule cilindriche



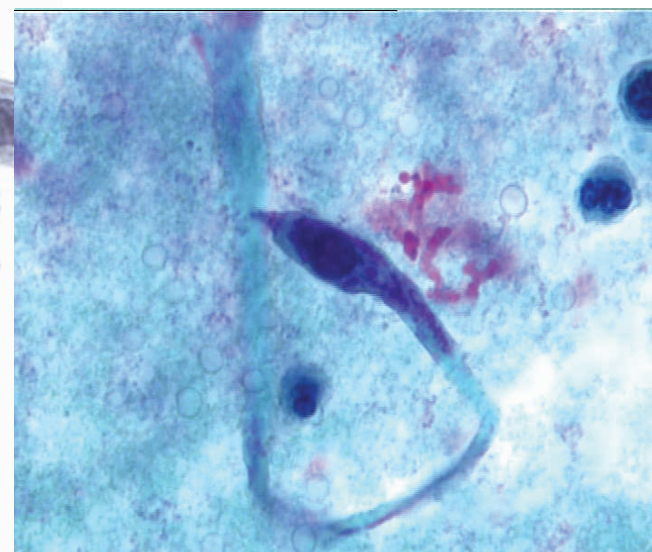
Cellule metaplastiche



Cellule con lesioni squamose di basso grado (LSIL)



Cellule con lesioni squamose di alto grado (HSIL)



Carcinoma a cellule squamose



In the 1950s, a corps of technicians at the University of Tennessee Health Sciences Center study Pap smears

Comparazione delle terminologie usate in citologia

WHO/BSCC 1960/70	CIN 1968	Bethesda System 1988	BSCC 1989	CIN Mod. 1991
Mod. borderlaine	Mod. borderlaine	ASCUS/AGUS	Mod. Bord. sq./end. Cells	Mod. borderlaine
Displasia/Discariosi Lieve	CIN1	LSIL	LG Discariosi	LG CIN
Displasia/Discariosi Moderata	CIN2	HSIL	HG Discariosi	HGCIN
Displasia/Discariosi Grave	CIN3			
Ca. in situ				
Ca. invasivo	Ca. invasivo	Ca. invasivo Gland.neopl.	Ca. invasivo Gland.neopl.	Ca. invasivo Gland.neopl.

Previous terminology (bscc 1986) new terminology

Borderline change

Borderline change in squamous cells
Borderline change in endocervical cells

Mild dyskaryosis
Borderline change with
koilocytosis

Low-grade dyskaryosis

Moderate dyskaryosis

High-grade dyskaryosis (moderate)

Severe dyskaryosis

High-grade dyskaryosis (severe)

Severe dyskaryosis ?Invasive

High-grade dyskaryosis/?invasive

Squamous carcinoma

?Glandular neoplasia

?Glandular neoplasia of endocervical type
?Glandular neoplasia (non-cervical)



Perché il Bethesda

LA TERMINOLOGIA DEVE:

1. trasmettere, dal laboratorio al clinico, informazioni chiare e pertinenti
2. essere omogenea, riproducibile, adattabile ad un'ampia gamma di settori lavorativi e di aree geografiche
3. tener conto e rispecchiare le conoscenze attuali relativamente alla neoplasia cervicale (due gradi di malattia)

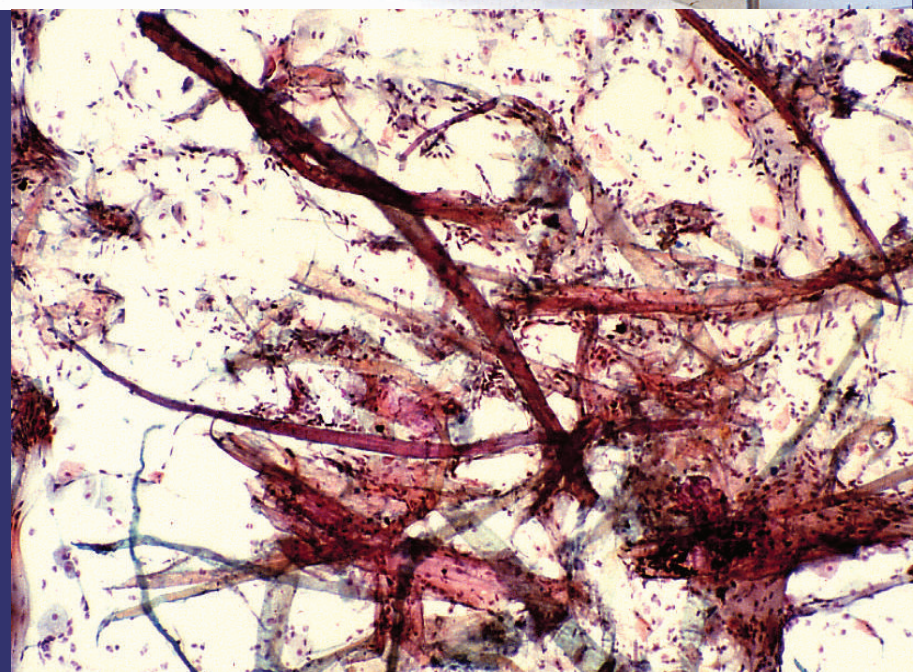
Evoluzione del Bethesda System

1988	Primo Bethesda
1991	Prima Revisione
2001	Seconda revisione
2014	Terza revisione

Oltre 400 partecipanti
45 società scientifiche
12 mesi di lavori

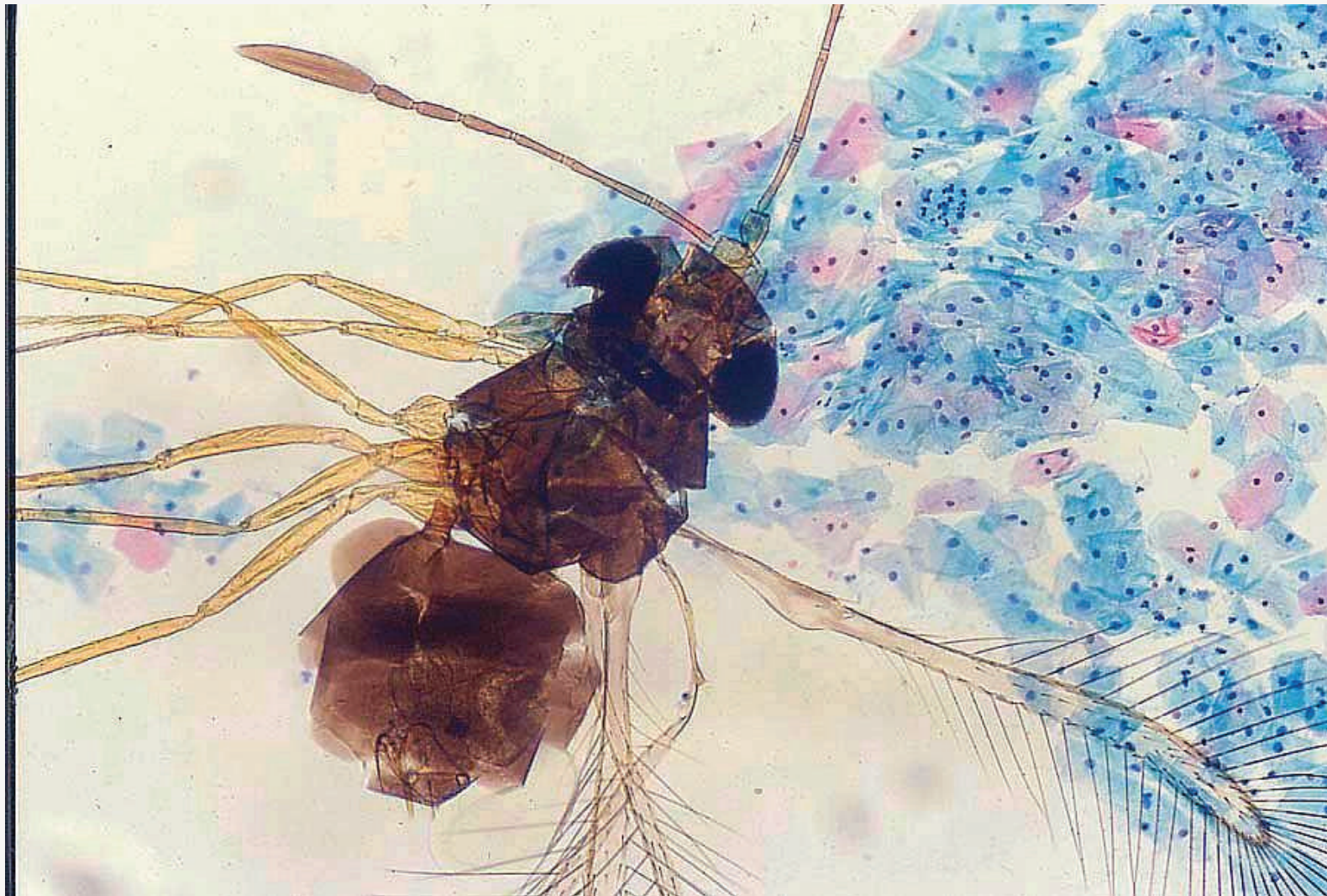


Preparato rifiutato/non processato



Valutazione dell'adeguatezza:

- Non soddisfacente per la valutazione
- Soddisfacente per la valutazione



Negative for intraepithelial lesion or malignancy

Non neoplastic findings (optional to report)

Non neoplastic cellular variations:

- ☐ Squamous metaplasia
- ☐ Keratotic changes
- ☐ Tubal metaplasia
- ☐ Atrofia
- ☐ Pregnancy associated changes

Reactive cellular changes associated with:

- ☐ Inflammation (includes typical repair)
- ☐ Radiation
- ☐ Intrauterine contraceptive device (IUD)
- ☐ Glandular cells status post hysterectomy

Organisms:

- ☐ *Trichomonas vaginalis*
- ☐ Fungal organisms morphologically consistent with *Candida spp*
- ☐ Shift in flora suggestive of bacterial vaginosis
- ☐ Bacteria morphologically consistent with *Actinomyces spp*
- ☐ Cellular changes consistent with Herpes simplex virus

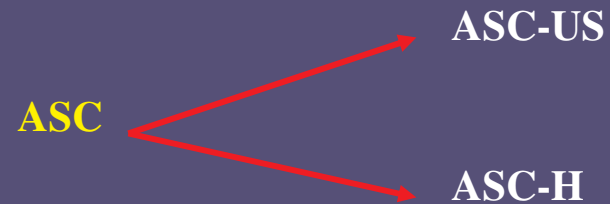
Other:

- ☐ Endometrial cells (in a woman $\geq$ 45 years of age)

Atypical squamous cells

LGSIL or LSIL (*encompassing* : HPV/ mild dysplasia /CIN1)

HGSIL or HSIL (*encompassing* : moderate and severe dysplasia /CIN 2-3-CIS)



BETHESDA 2001

Squamous cell carcinoma

Atypical Glandular Cells



Adenocarcinoma *in situ* (AIS)

Adenocarcinoma

Bethesda 2014: Time For An Update?

Ritu Nayar, MD

Professor of Pathology

Northwestern University, Feinberg School of Medicine

Chicago, USA

Risultati

Adeguatezza

- Chiarire i criteri di cellularità per i campioni post-irradiazione
- Aggiungere dati su interferenze di lubrificanti e sangue
- HPV test su campioni insoddisfacenti

Cellule epiteliali squamose

- Come affrontare il problema LSIL con poche cellule HSIL (LSIL-H)
- Non è stata creata una nuova categoria
- Conservati 2 livelli terminologici: LSIL/HSIL

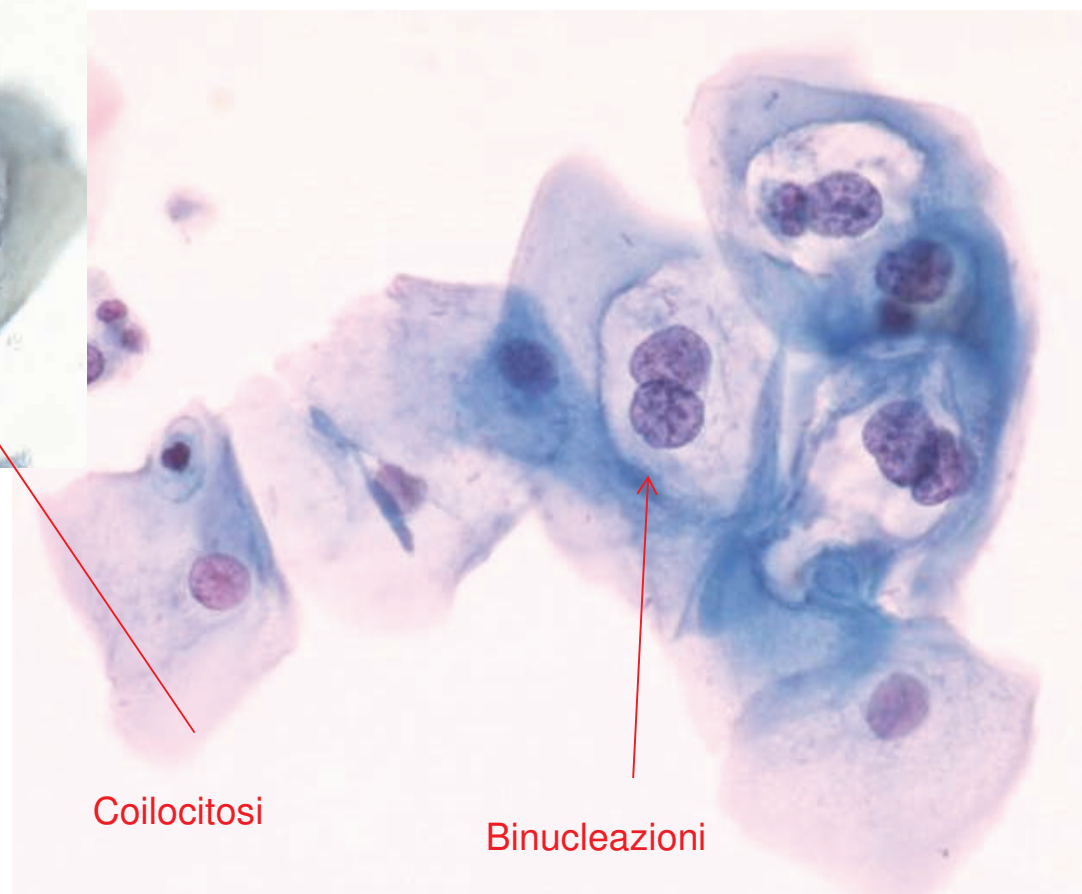
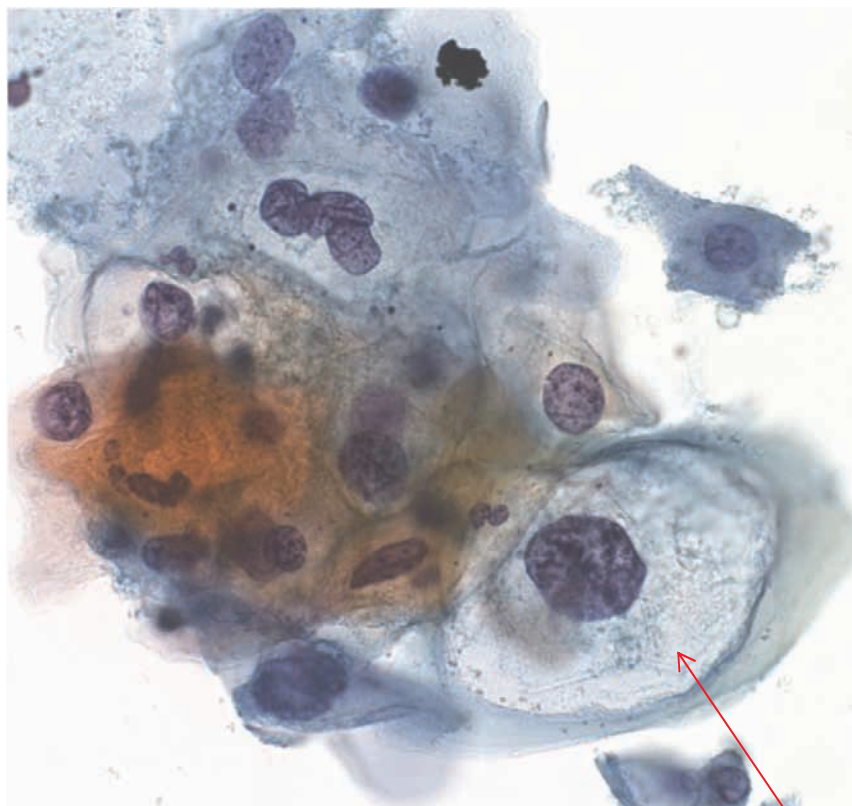
Cellule endometriali

Segnalare la presenza di cellule endometriali in donne di età ≥ 45 anni (la valutazione solo in post menopausa)

LSIL

Viareggio
La darsena



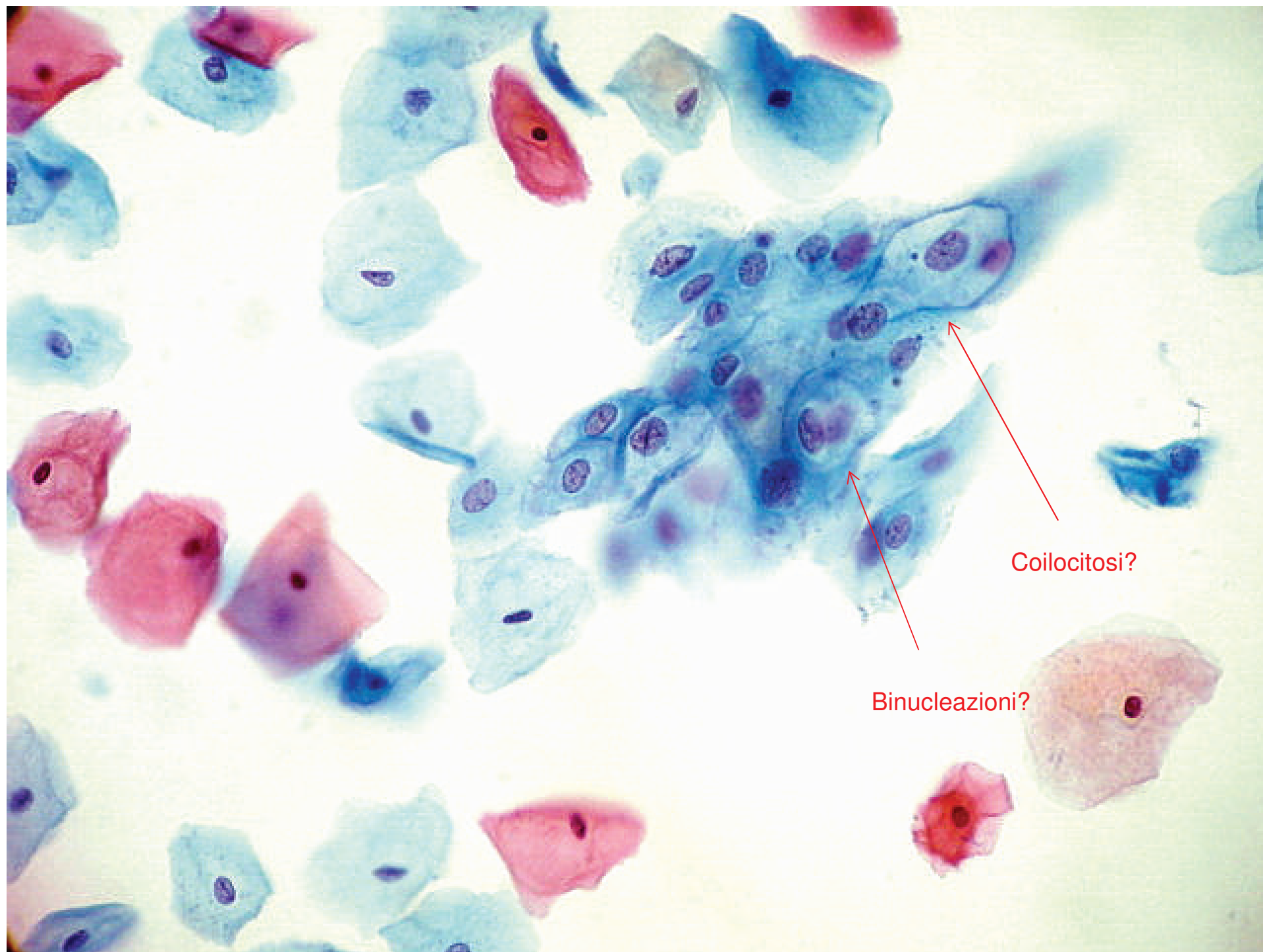


Coilocitosi

Binucleazioni

ASC-US

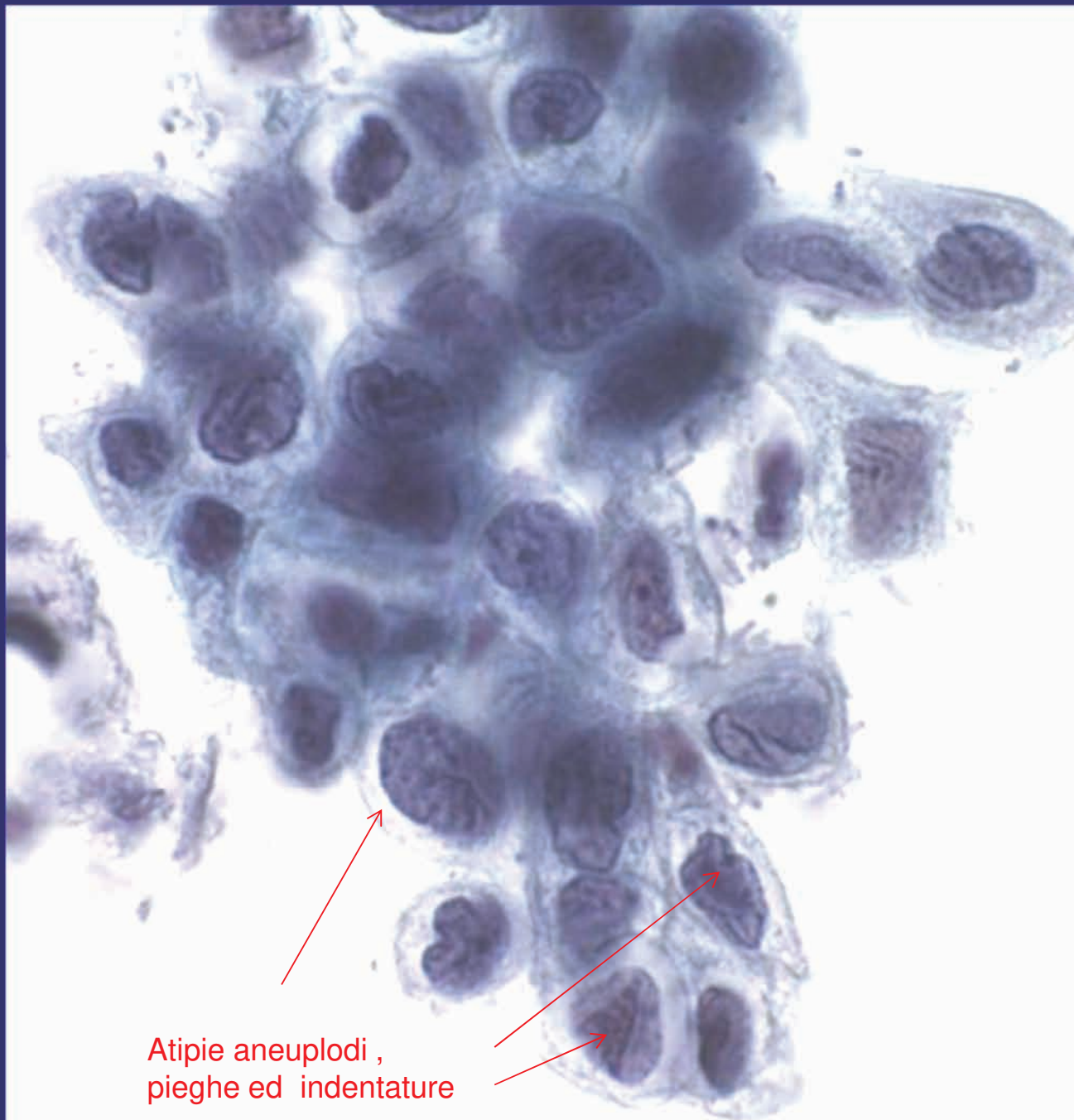




Monte Pisanino (1947m)

HSIL





Atipie aneuploidi ,
pieghe ed indentature

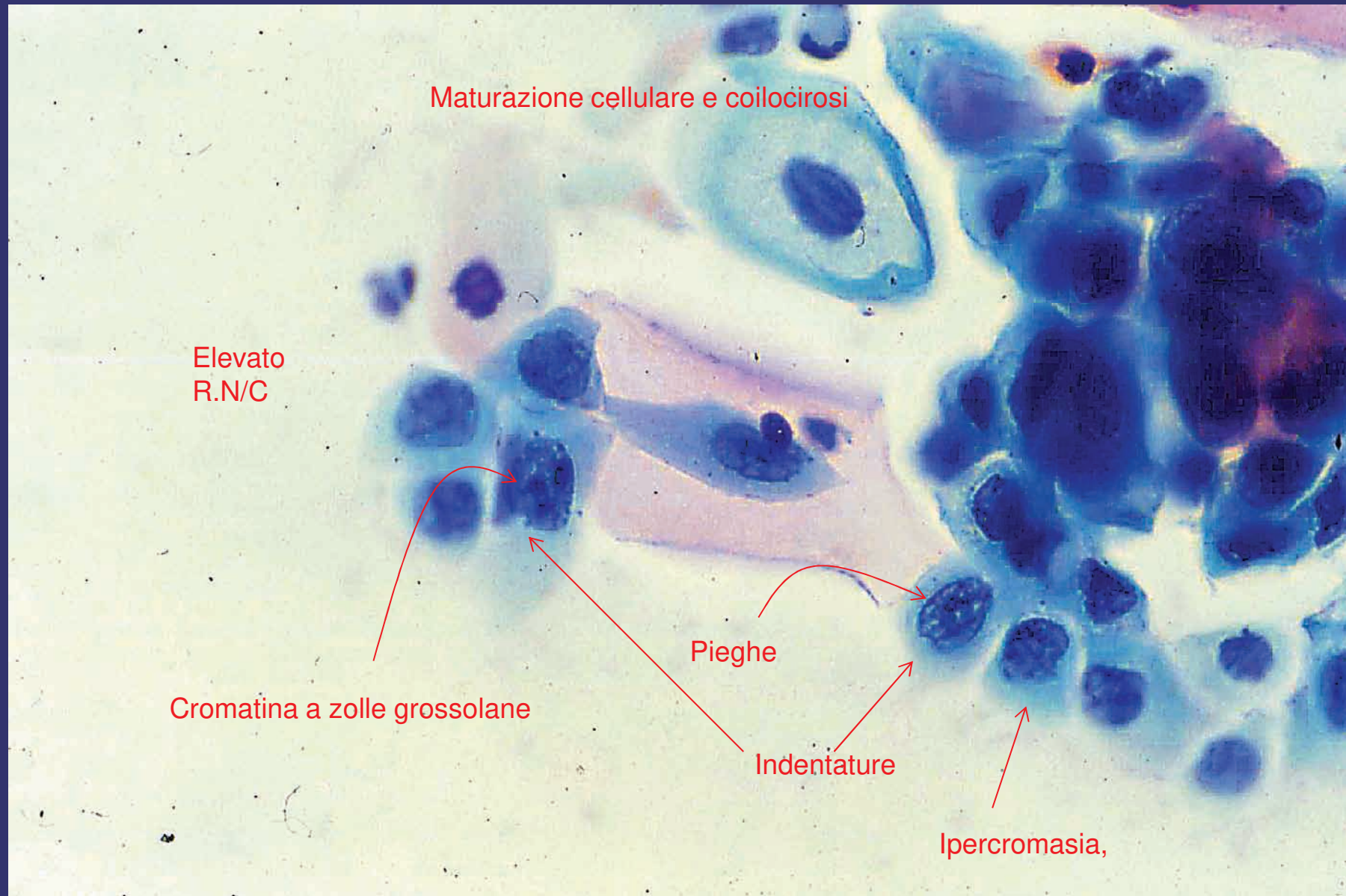
ASC-H

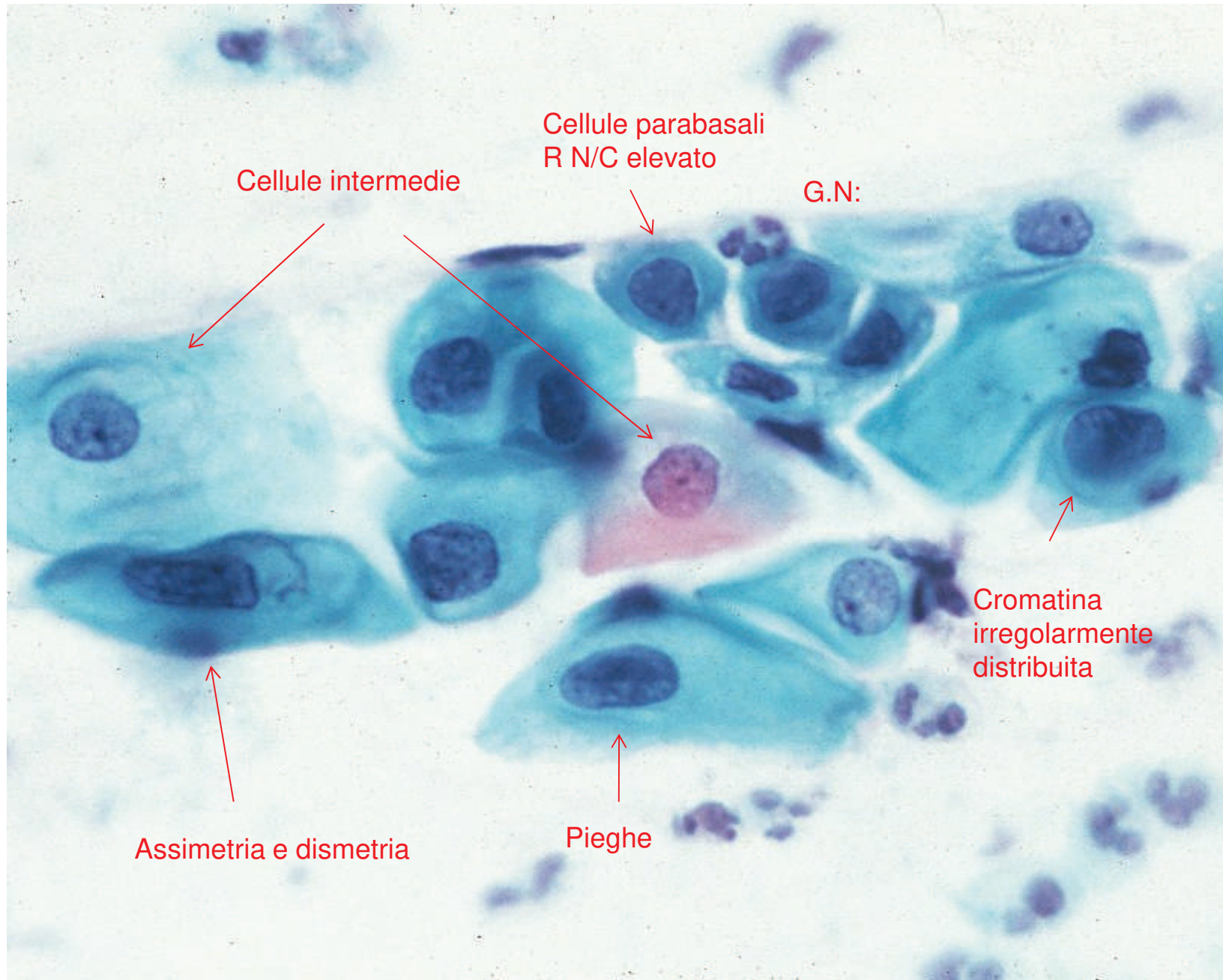
Altissimo
1589 m

Corchia
1677 m

TONFANO







Carcinoma squamoso
Adenocarcinoma in situ
Adenocarcinoma cervicale
Adenocarcinoma dell'endometrio
Altre neoplasie maligne

Pania della Croce (1859 m)

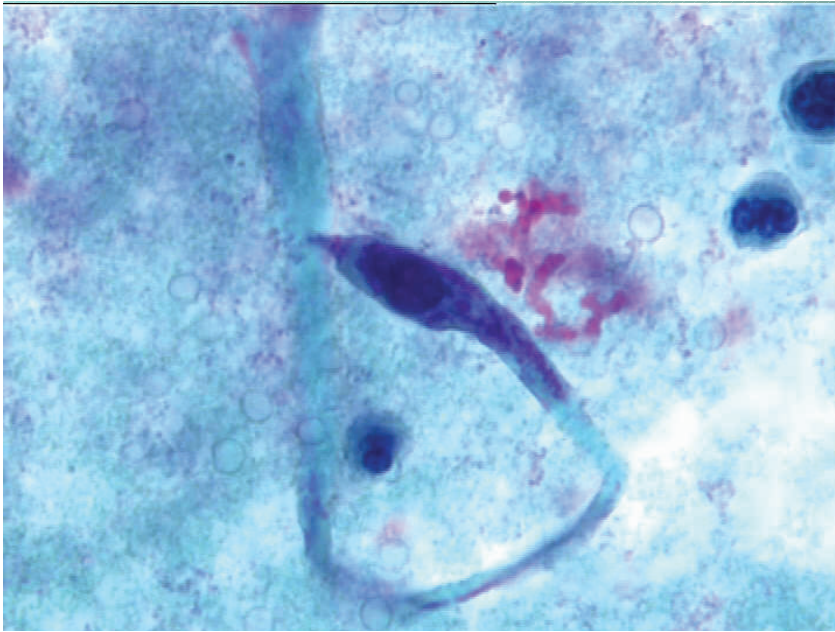
Prana

Sea

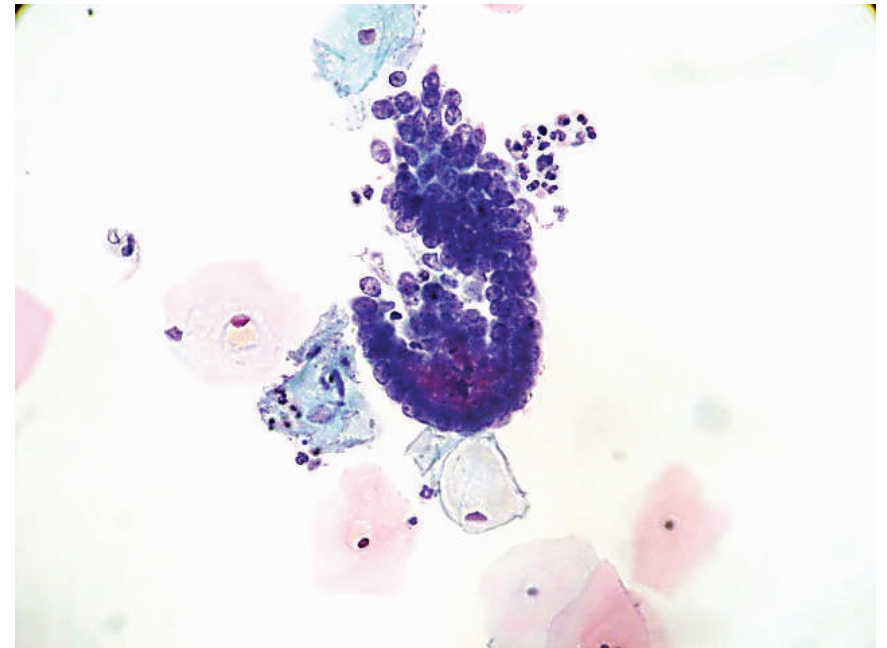
Lake of
Massaciuccoli

Matanna

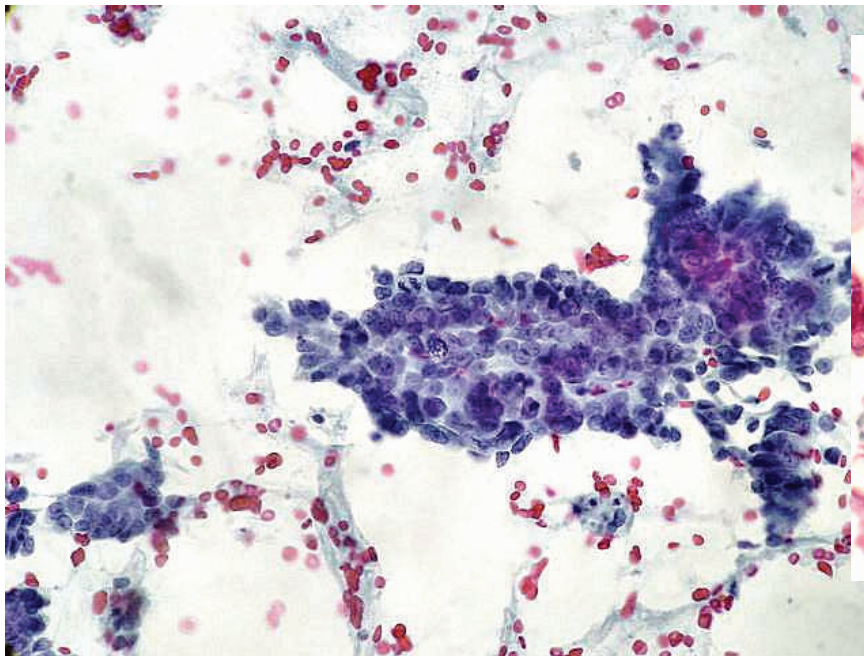




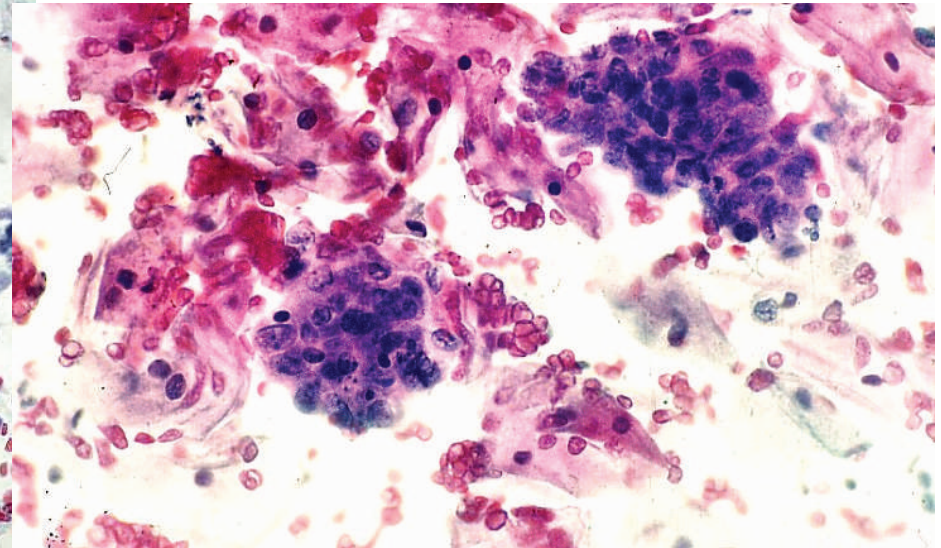
Carcinoma a cellule squamose



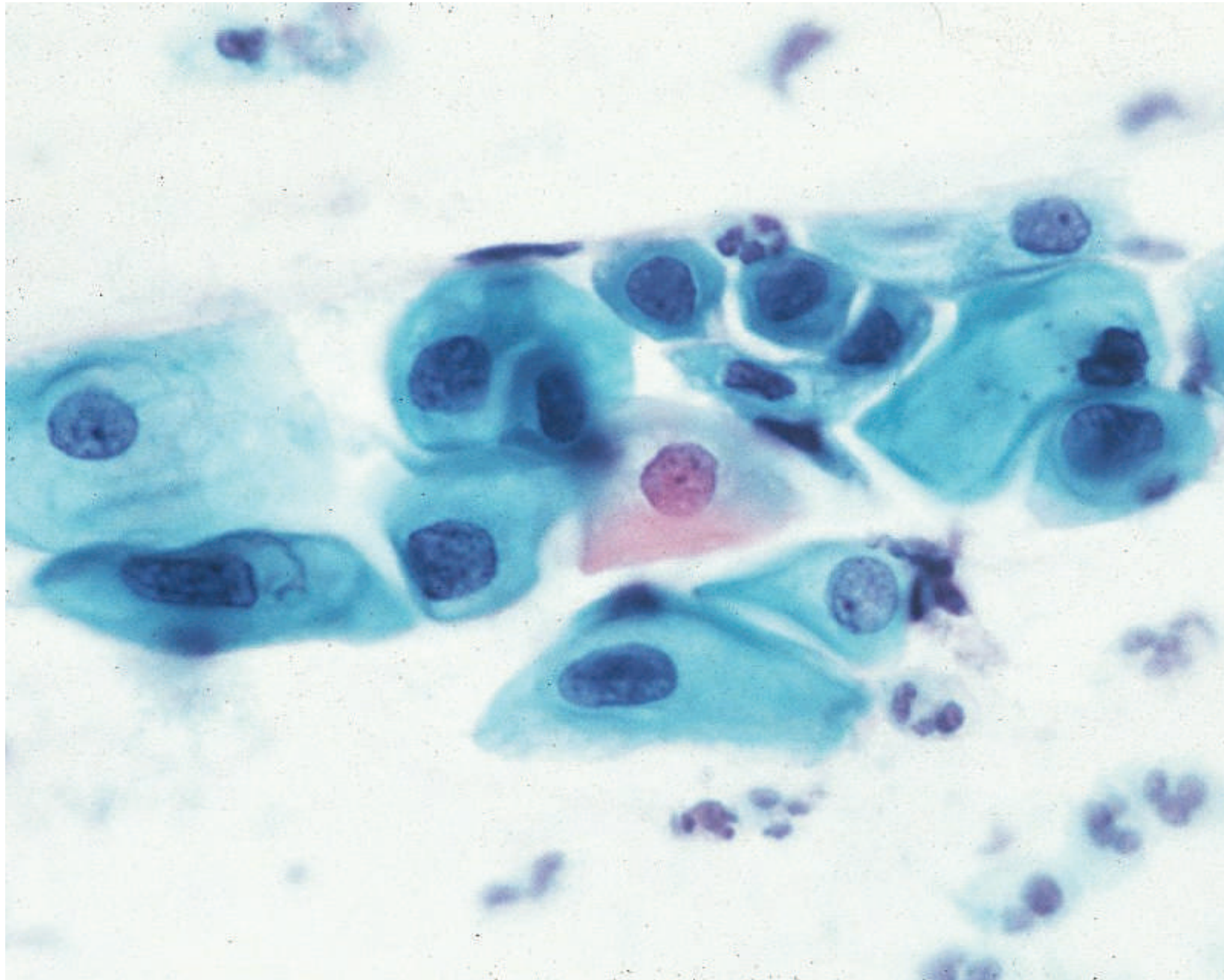
Adenocarcinoma in situ



Adenocarcinoma cervicale



Adenocarcinoma endometriale



Cellule ghiandolari atipiche AGC

Atipiche

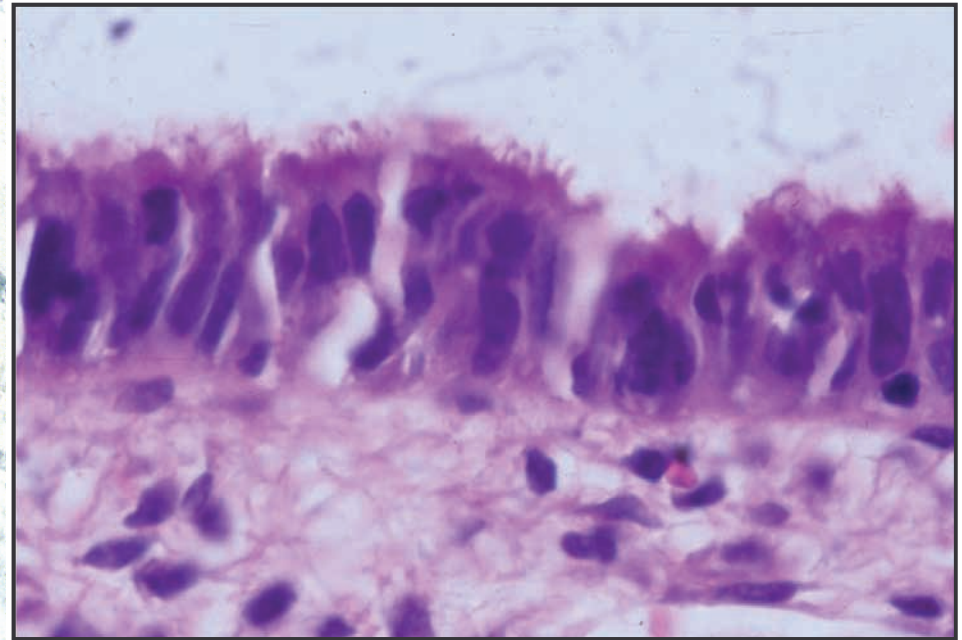
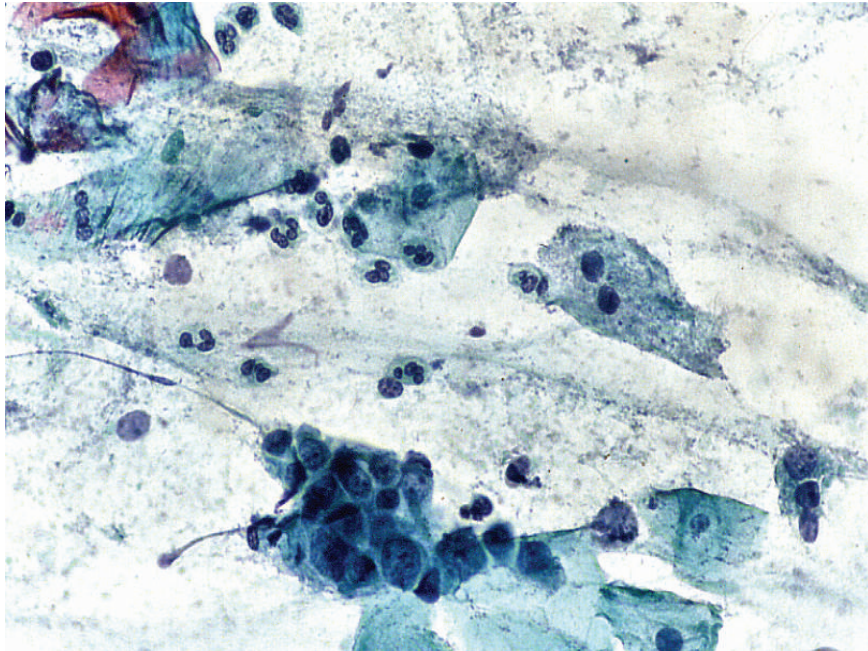
Cellule endocervicali (NAS o da specificare nel commento)

Cellule endometriali (NAS o da specificare nel commento)

Atipiche

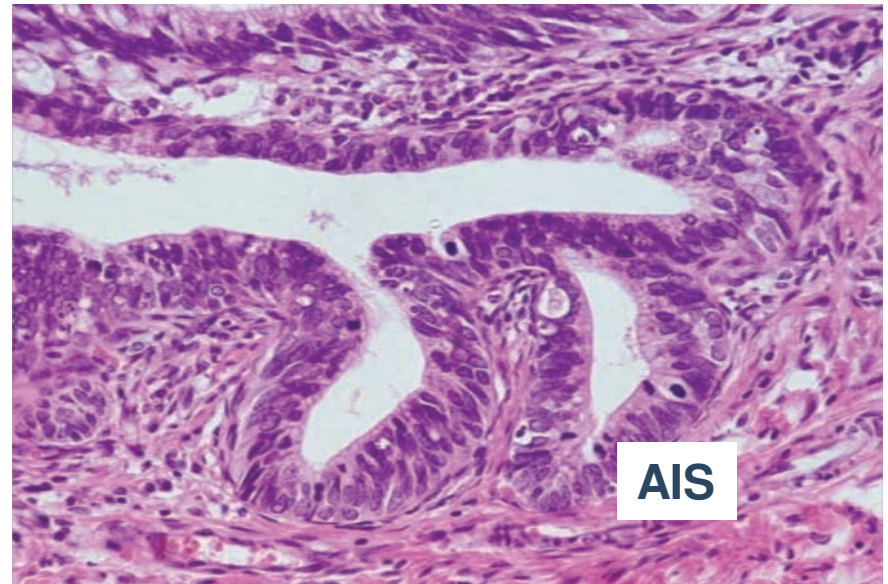
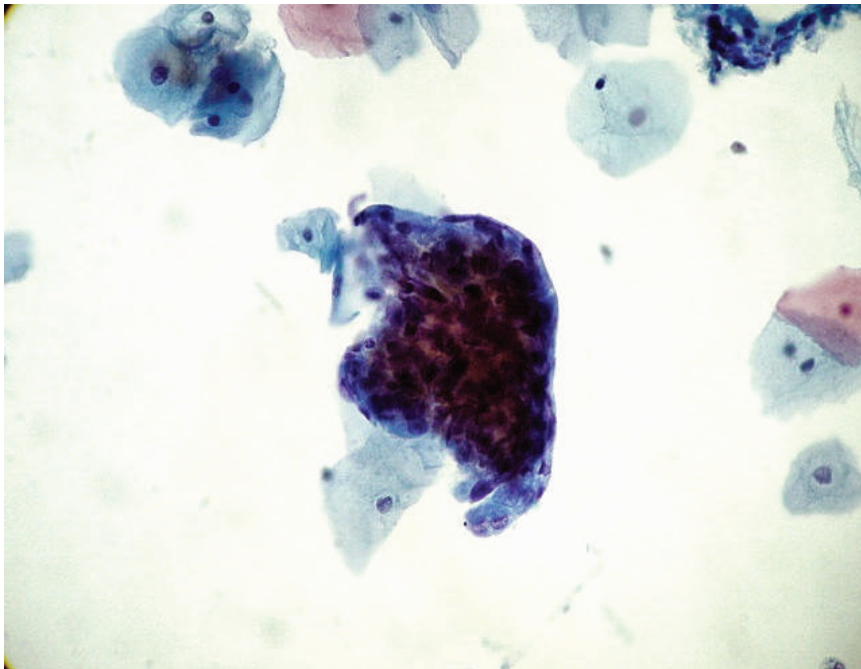
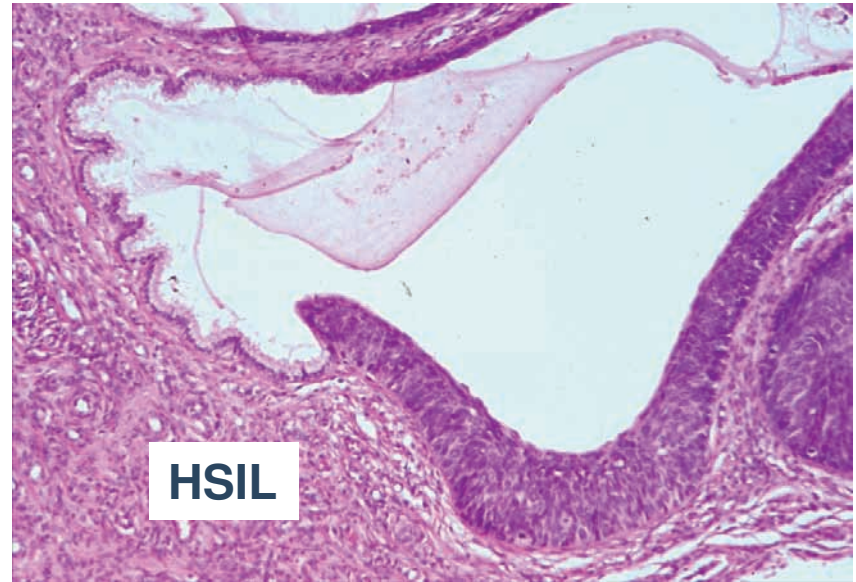
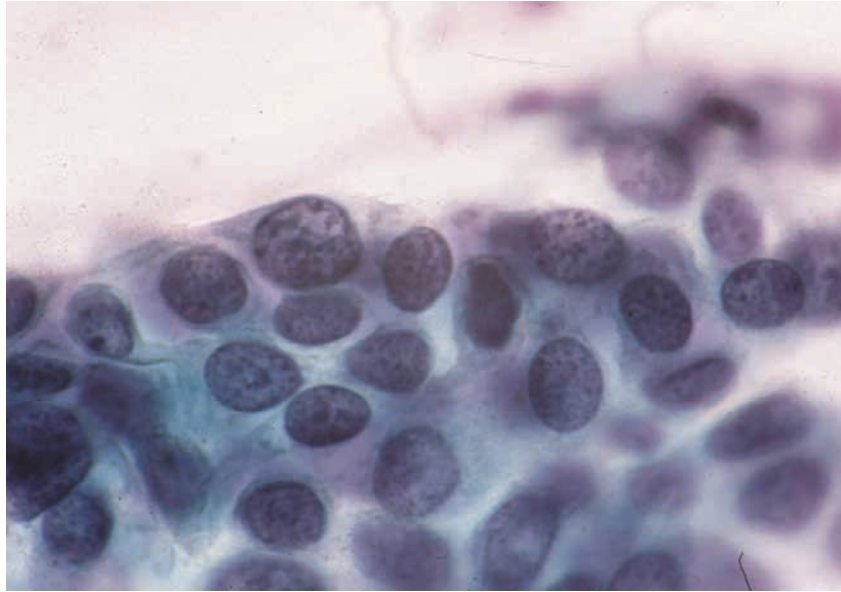
Cellule endocervicali, probabilmente neoplastiche

Cellule ghiandolari, probabilmente neoplastiche

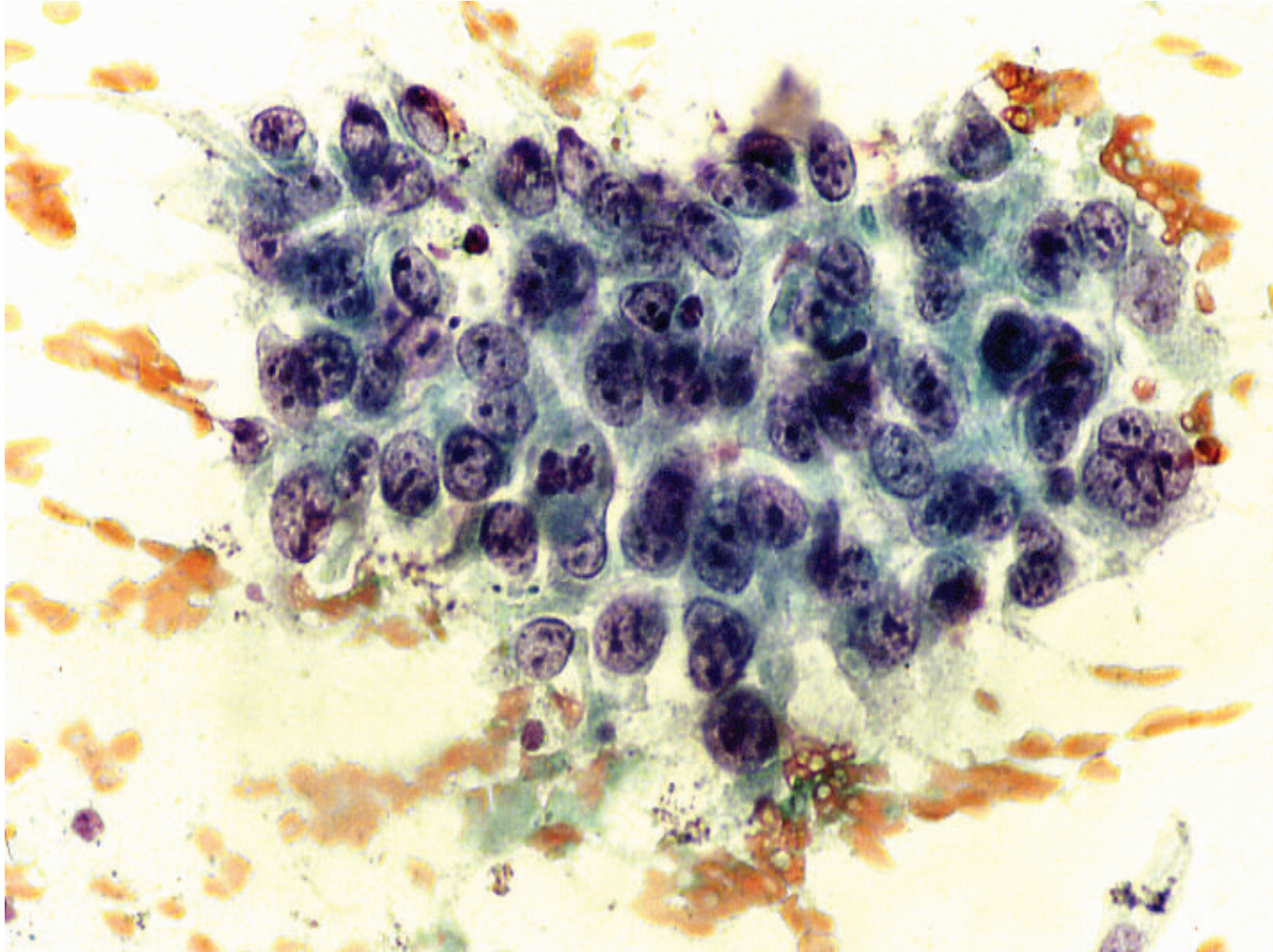


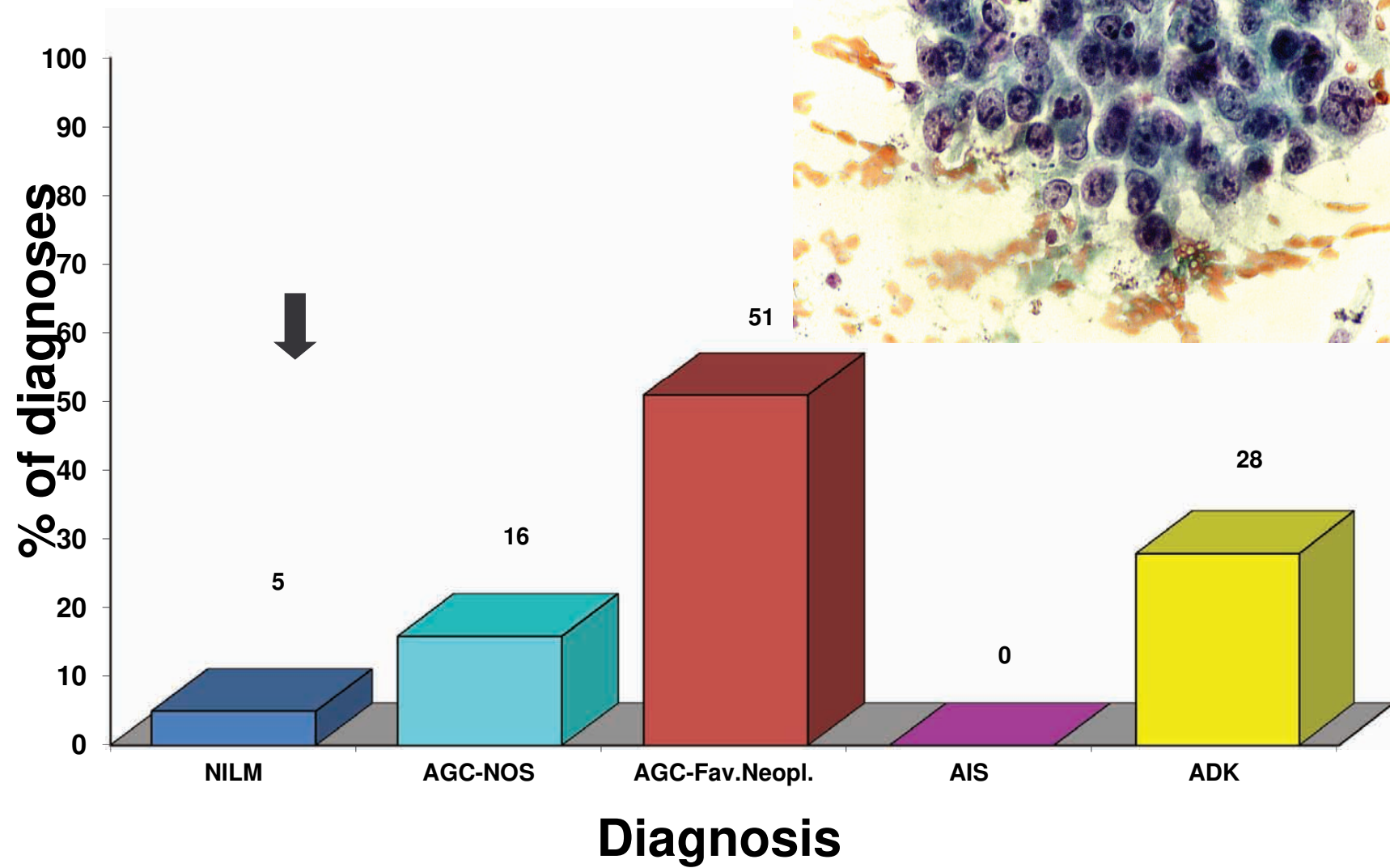
AGC

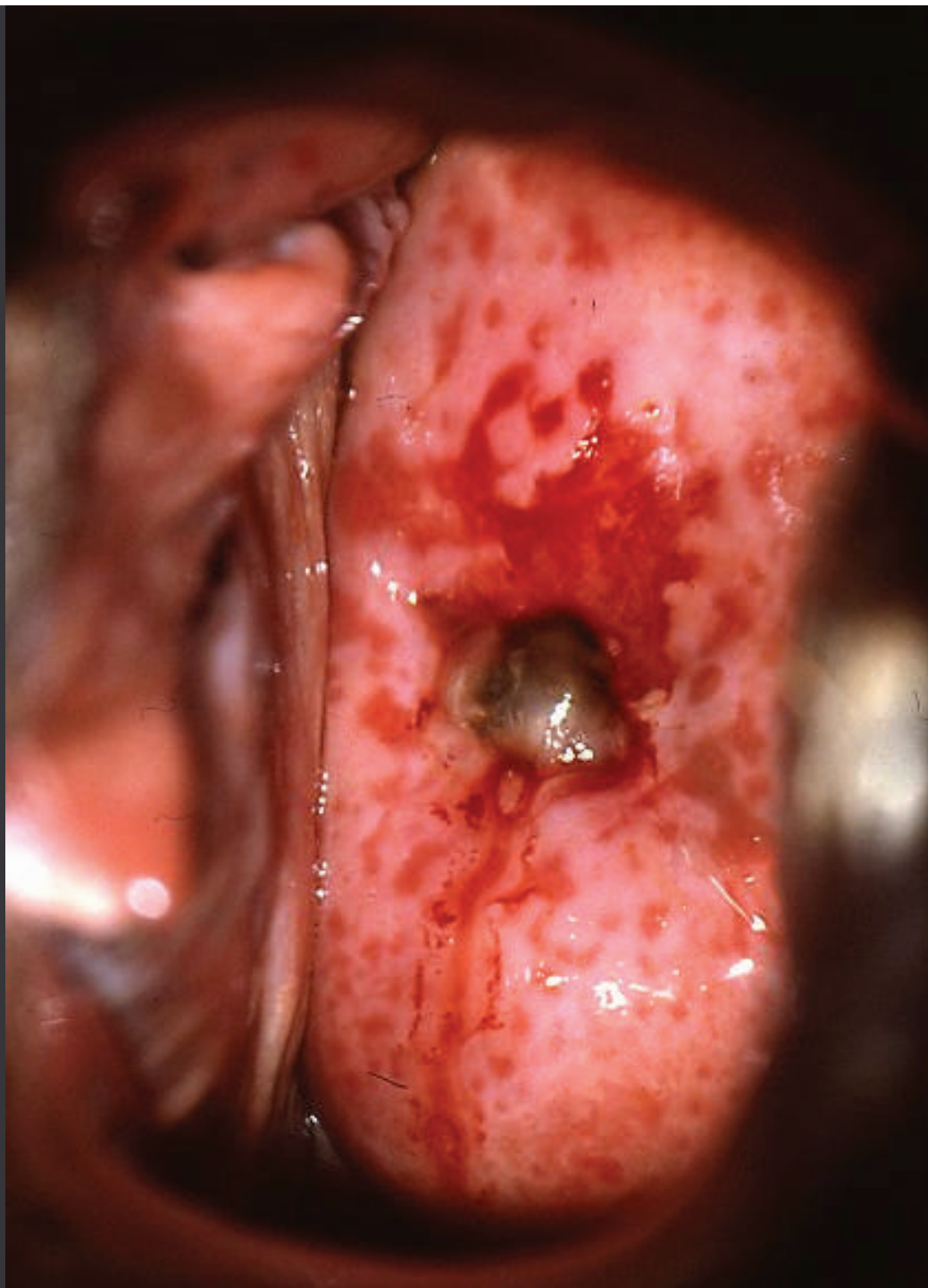
AGC probabilmente neoplasia



AGC probabilmente neoplasia







Normale

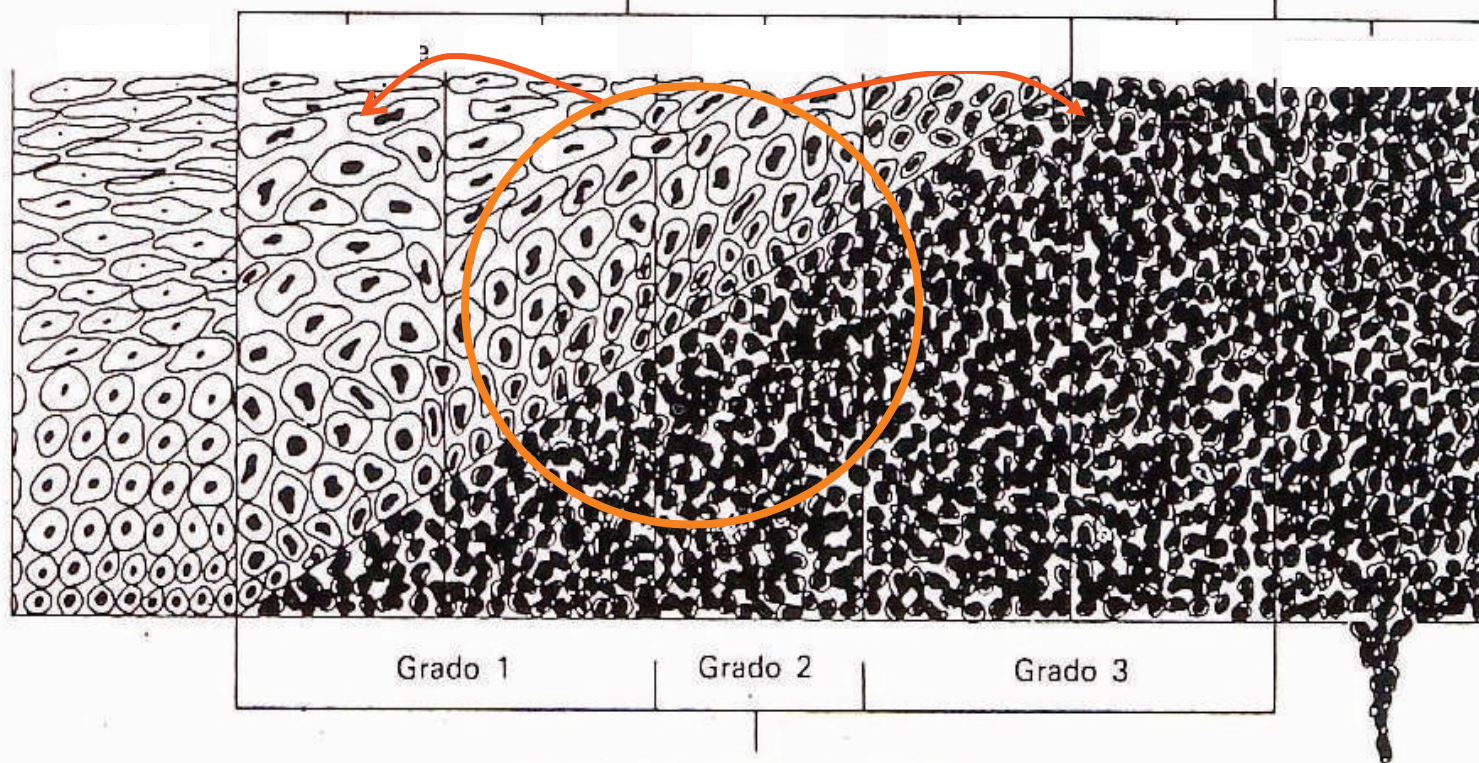
ASC-US

LSIL

ASC-H

HSIL

Carcinoma



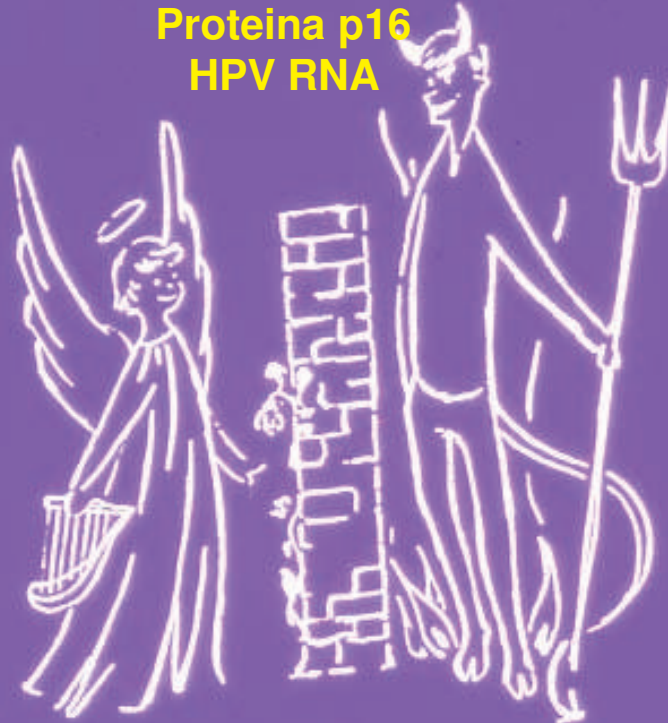
Grado 1

Grado 2

Grado 3

Neoplasia intraepiteliale cervicale

Proteína p16
HPV RNA



NEG

ASC-US

LSIL

a

ASC-H

HSIL

CAS

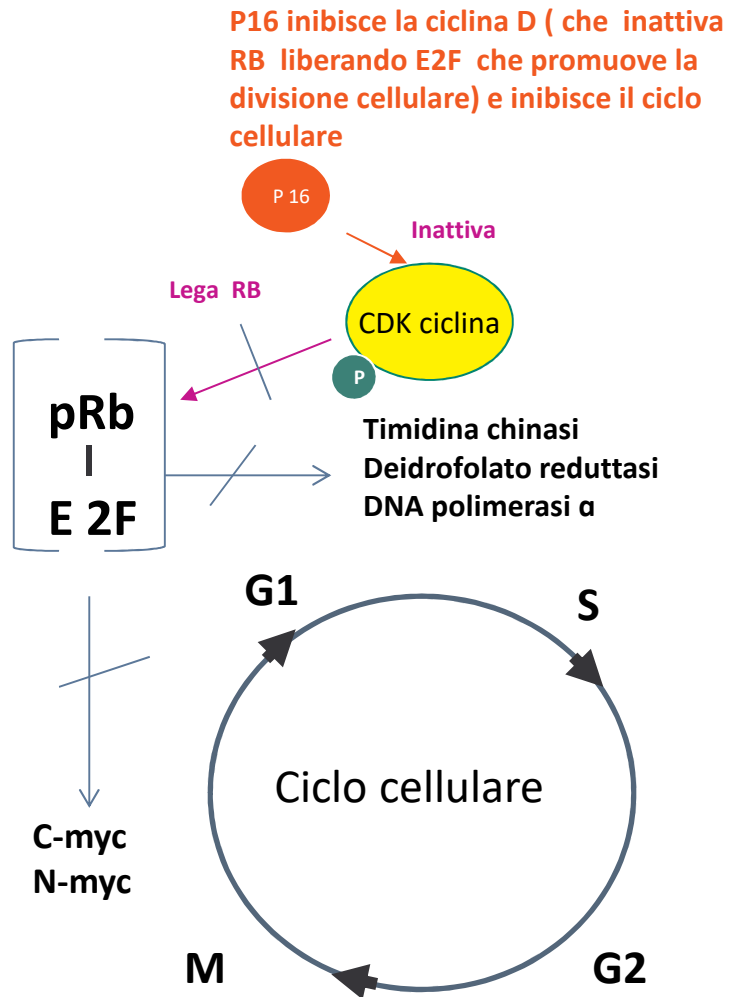


La proteina p16

Marina di Carrara



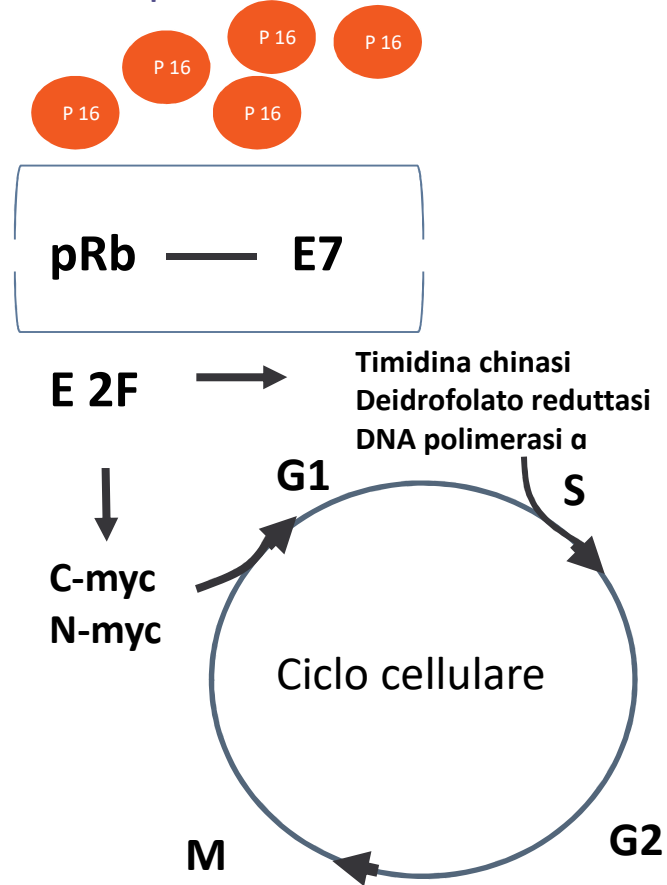
Condizioni fisiologiche



Inibizione del ciclo cellulare

Infezione da HPV ad alto rischio

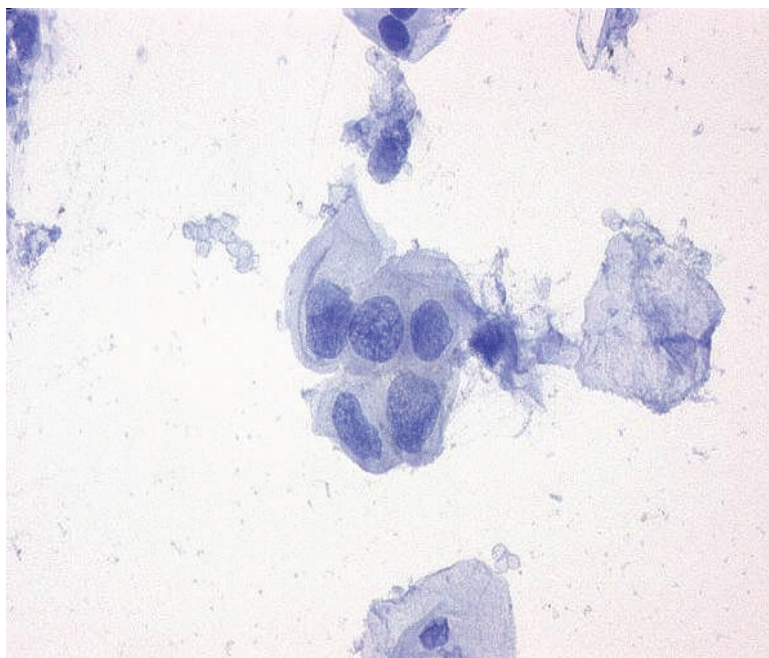
E7 si lega a pRb, liberando E2F , potente stimolatore del ciclo cellulare. La CDK ciclina non esercita più la sua azione su RB con conseguente accumulo e sovraespressione di P16



Stimolazione del ciclo cellulare

P16 inibisce il fattore Rb, evitando che le cellule con il DNA danneggiato procedano verso la fase di sintesi

P16 neg



Follow-up

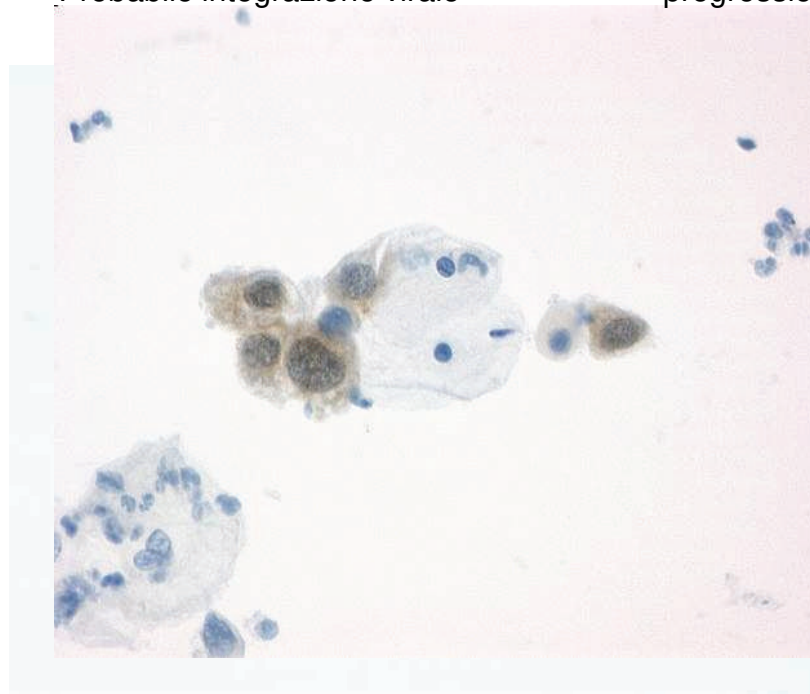
la P16, non esercitando la sua inibitoria sul fattore di Rb legato alla proteina virale E7, si accumula

P16 pos

Ki67 pos

Probabile integrazione virale

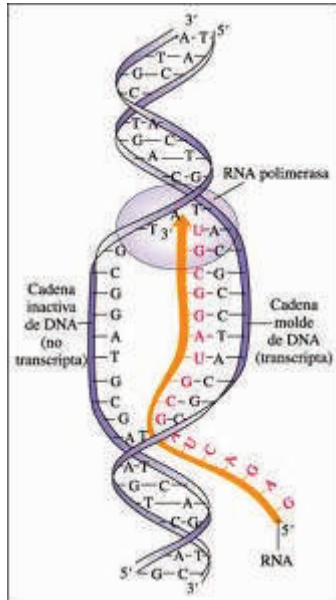
progressione



Doppia colorazione

Trattamento

HPV RNA



E6-E7
mRNA cellulare

Presenza E6-E7
Integrazione
virale

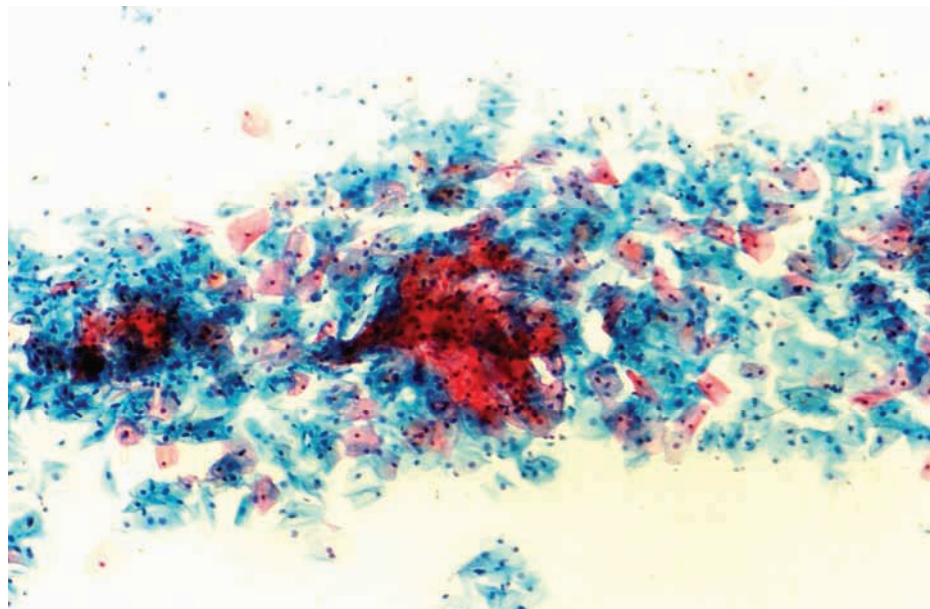
Cytology report

THE MANCHESTER CYTOLOGY CENTRE, M13 9WL		Slide No. [REDACTED].08
Patient [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] D.O.B. [REDACTED] NHS No. [REDACTED] Serial No. [REDACTED]	LMP: [REDACTED] Test Date: 11 Jan 2008 Specimen Type: LBC (SurePath) Reason for Smear: Routine call Condition: Pregnant	
Sender HOE1 Dr Elizabeth HOLT SALFORD ROYAL HOSPITAL CLAIRE DUNNE, GYNAE DEPT., * STOTT LANE SALFORD M6 8HD HOSP	Clinical Cervix appears normal Details: Pre TOP -308416	
G.P. Dr M TYRRELL ST ANDREWS MEDICAL CENTRE RUSSELL STREET ECCLES MANCHESTER M30 0NU	Cytology Report: MILD DYSKARYOSIS High risk HPV NOT DETECTED by HC2 test. Routine recall is recommended.	
HA Salford & Trafford H A PEEL HOUSE ALBERT STREET ECCLES MANCHESTER M30 0NJ	Pattern: MILD DYSKARYOSIS Infection: High risk HPV NOT DETECTED [0] Suggest: Routine recall [A]	
	Authoriser: [REDACTED] Date authorised: [REDACTED] 1st print date: 22 Jan 2008 Date: 22 Jan 2008	

Lo strato sottile



Pap test convenzionale



- Perdita di materiale nel trasferimento da campione a vetrino
- Cattiva fissazione
- Aggregazione, sovrapposizione cellulare
- Presenza di materiale oscurante

Pap test su strato liquido



- Tutto il campione viene raccolto nel contenitore
- Ottima fissazione
- Distribuzione uniforme delle cellule
- Assenza di materiale oscurante

Source: Hutchinson ML, et al. *Am J Clin Pathol.* 1994;101:215-219.



Long Island 1997

Liquid Based Cytology

The Global Situation

In the United States at least 80% percent of all Pap tests are LBC

LBC is widely used in Europe.

- LBC is the standard-of-care in England
- LBC is >60% Pap tests in Switzerland.
- LBC is >70% Pap tests in Belgium

LBC is the only screening test used in Scotland and Ireland

LBC approved for routine screening in Hong Kong and Canada

Ontario, Canada, Screening Guidelines recommend LBC

IARC / WHO (2005) approved liquid based cytology as an “effective method of cervical cancer control”

European Guidelines for Cervical cancer Screening approve LBC



Tramonto in Versilia

Dimezza i tempi di lettura

Riduce il numero degli inadeguati

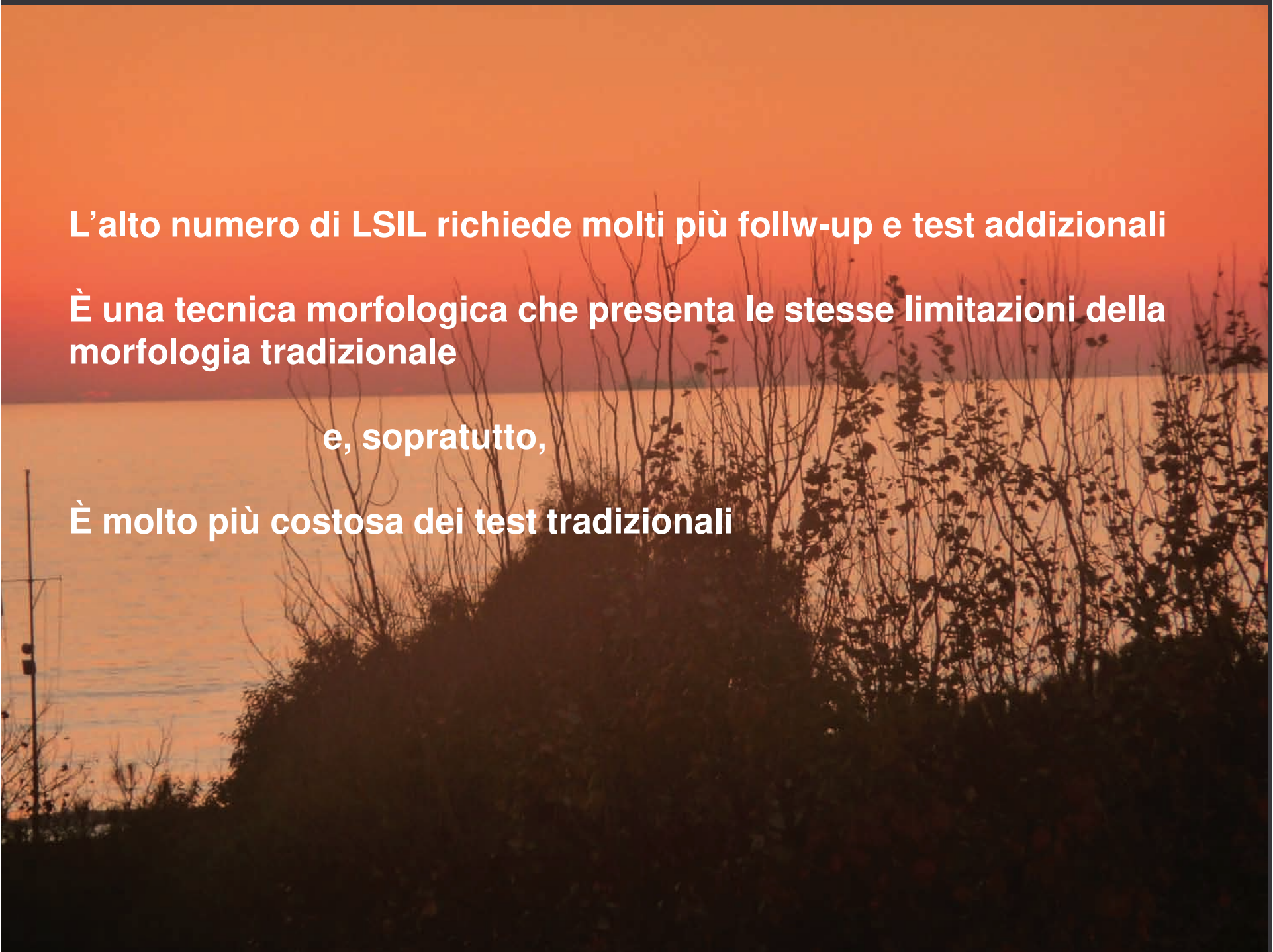
**Permette di eseguire altri test sul materiale residuo,
adatto per lo screening primario con HPV**

È il metodo più adeguato per l'automazione

Individua un numero maggiore di LSIL statisticamente significativo

Individua un numero maggiore di HSIL non statisticamente significativo

Ma



L'alto numero di LSIL richiede molti più follow-up e test aggiuntivi

È una tecnica morfologica che presenta le stesse limitazioni della morfologia tradizionale

e, soprattutto,

È molto più costosa dei test tradizionali

**Thank you
very much
for your
attention**

