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

C. Gentili

PROCEEDINGS

OF THE

Third Race Betterment Conference

January 2-6, 1928

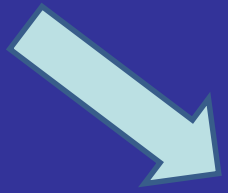
Under the Auspices of the

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

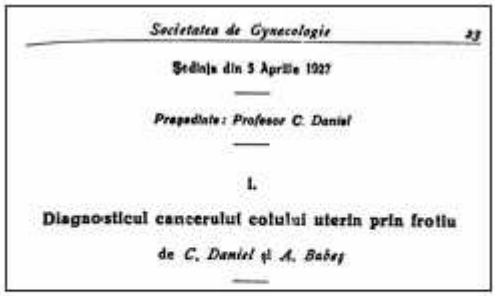
THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN CARCINOMA OF THE UTERUS*

GEORGE N. PAPANICOLAOU, M.D., PH.D., AND HERBERT F. TRAUT, M.D., NEW YORK, N. Y.

(From the Departments of Anatomy 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



Societatea de Gynecologie 23

Ședința din 5 Aprilie 1927

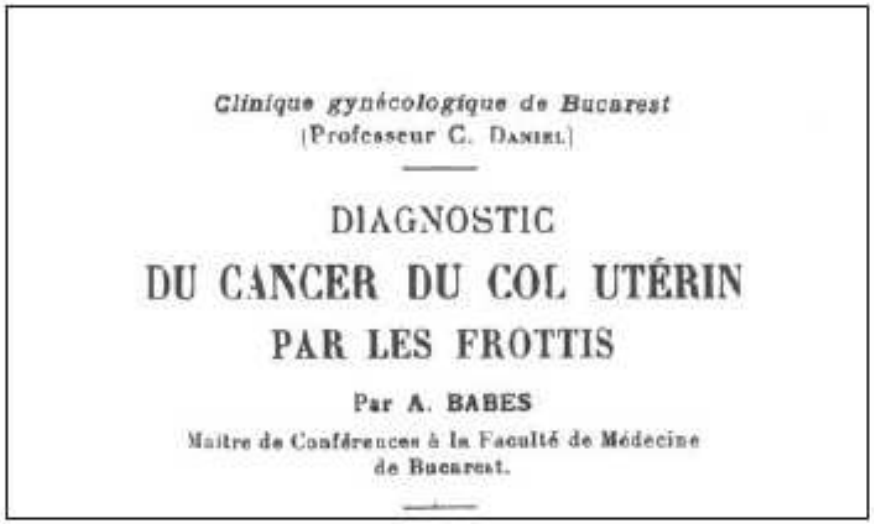
Președinte: Profesor C. Daniel

I.

Diagnosticul cancerului colului uterin prin frotiu

de *C. Daniel* și *A. Babeș*

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



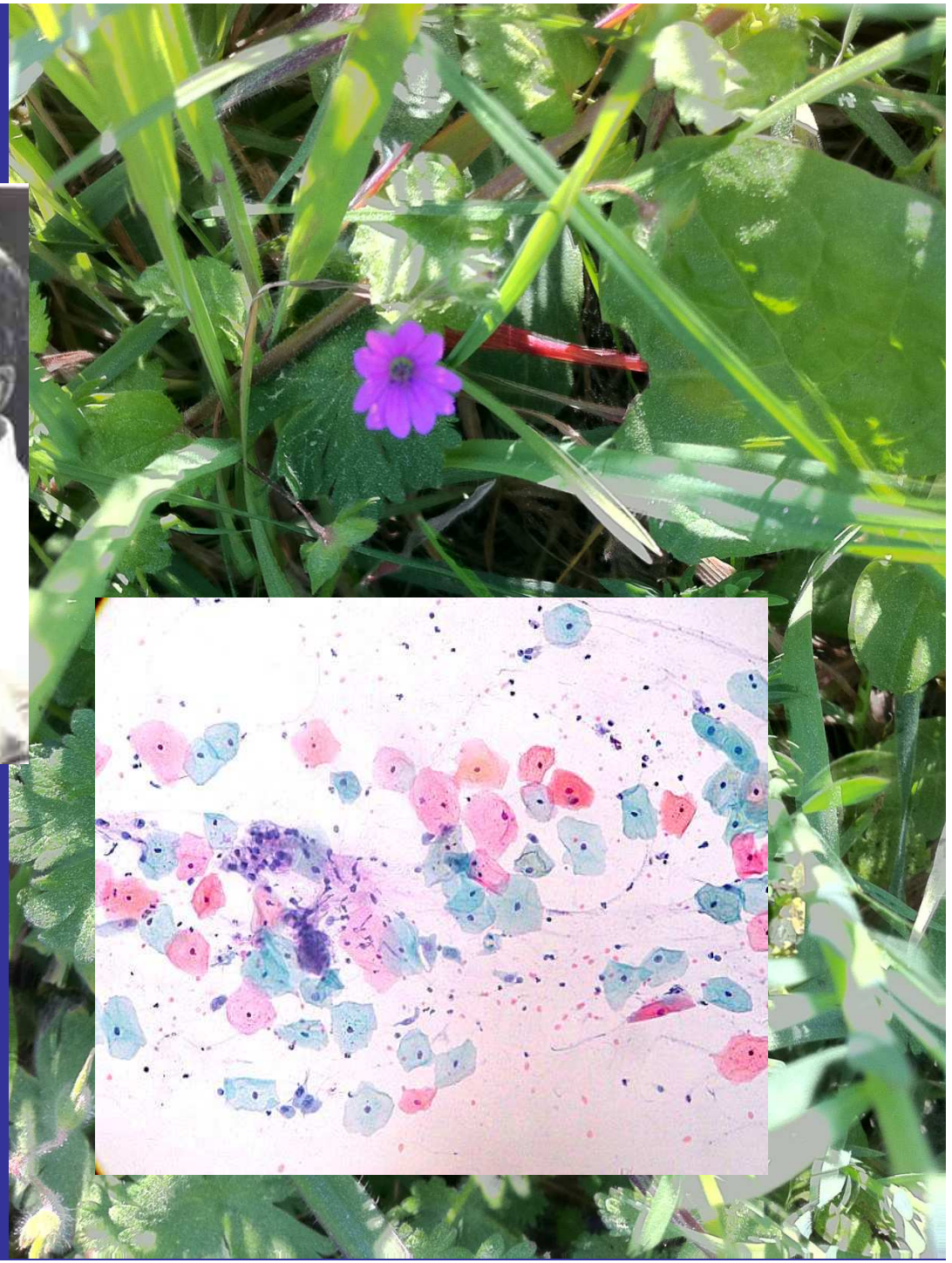
Clinique gynécologique de Bucarest
(Professeur C. DANIEL)

DIAGNOSTIC
DU CANCER DU COL UTÉRIN
PAR LES FROTTIS

Par A. BABES

Maître de Conférences à la Faculté de Médecine de Bucarest.

Figure 5 Title of the 1928 article by Dr. Babeş 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 GeorgePapanicolaou (1883–1962), with his microscope and famous *Atlas of exfoliative cytology*, published in 1954.

"Smears cannot always be judged as positive or negative.
There are cases in which cytologic findings are inconclusive.

A classification taking into consideration the relatively large group of questionable smear findings is therefore necessary. One may often experience great difficulty in classifying cells that deviate from the normal type but show no malignant characteristics.

An intermediate class between the entirely normal and the suspicious groups appears to be necessary.

A similar need for subdivision exists in the positive group. There are instances in which the results are of an overwhelmingly positive character, leaving no doubt as to their final interpretation.

On the other hand, there are cases in which there is strong but not fully convincing evidence of malignancy.

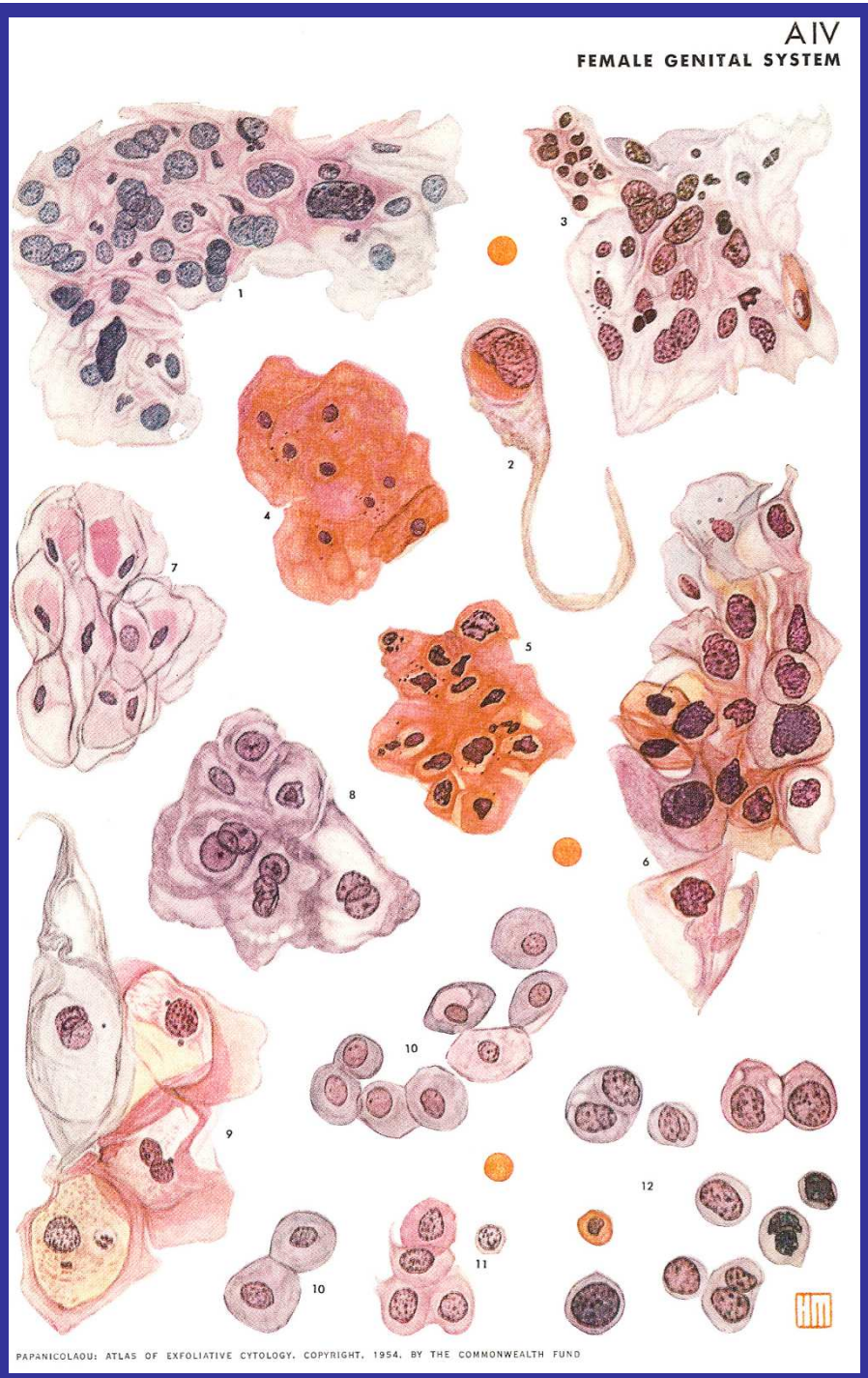
These considerations led us to the acceptance of the following system of classification for cytologic findings, consisting of five groups:

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



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

Munich Nomenclature II

		Normal	Inflammatory	Mild dysplasia	Moderate dysplasia	Severe Dysplasia	Carcinoma *in situ*	Invasive Cancer
Histological terms		Normal	Inflammatory	CIN I	CIN II	CIN III		Invasive Cancer
Cytological Terms	**Bethesda System**	Within normal limits	ASCUS	LSIL	HSIL			Invasive Cancer
	Pap-Classification (Description)	Pap I (Normal Cells)	Pap II (Inflammatory)	Pap III (Unclear)	Pap IVa (Severe Dysplasia/Carcinoma *in situ*)			Pap V (Invasive cancer)
				Pap IIId (Mild dysplasia)	Pap IVb (Potentially invasive)			

Comparazione delle terminologie usate in citologia ed istologia			
Displasia/CIS 1954	CIN 1968	Bethesda Systen 1988	CIN
Displasia lieve LGCIN(CIN1)	CIN1	LSIL	
Displasia moderata HGCIN(CIN2/3)	CIN2	HSIL	
Displasia grave Ca. in situ	CIN3		
Ca. invasivo	Ca. invasivo	Ca. invasivo	Ca. invasivo

Evoluzione nella terminologia delle lesioni squamose cervicali

Reagan JW, Seidemand IL, Saracusa Y. (1953), The cellular morphology of carcinoma in situ and dysplasia or typical hyperplasia of the uterine cervix. Cancer. 1953;6:224-235.

Richart, R.M. (1968), Natural history of cervical intraepithelial neoplasia. Clin. Obstet. Gynecol., 5, 748-784.

National Cancer Institute Workshop.The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. JAMA.1 989;262:931-934.

Terminologia displasia 1954	**Terminologia CIN 1968**	**Terminologia CIN 1990**	**Terminologia Bethesda 1988 1991**
Normale	Normale	Normale	Normale
Atipia	Atipia coilocitica condiloma piatto	CIN di basso grado	ASC-US
Displasia lieve	CIN 1	CIN di basso grado	LSIL
Displasia moderata	CIN 2	CIN di alto grado	HSIL
Displasia grave Carcinoma in situ	CIN 3	CIN di alto grado	HSIL
Carcinoma invasivo	Carcinoma invasivo	Carcinoma invasivo	Carcinoma invasivo

CLASSIFICAZIONI

PAPANICOLAOU

1°normale; 2° atipia cellulare: reperto infiammatorio; 3° atipia cellulare: sospetto di malignità; 4 ° atipia cellulare: forte sospetto di malignità; 5°cellule maligne

Classificazione rivolta principalmente ai clinici

WHO

Normale; modificazioni reattive; atipia squamosa; displasia lieve, moderata, grave; CIS; SCC; atipia ghiandolare; displasia ghiandolare; AIS; adenocarcinoma invasivo

Classificazione rivolta principalmente agli istopatologi

CIN

Neoplasia cervicale intraepitelialiale grado 1-3; carcinoma invasivo

Classificazione rivolta principalmente agli istopatologi

NHSCSP/BSCC

Normale; modificazioni reattive; discariosi lieve, moderata, grave; CIS; SCC; neoplasia ghiandolare

Classificazione rivolta principalmente ai citopatologi

BETHESDA

Normale; modificazioni reattive; ASCUS/AGUS, LSIL, HSIL, SCC, AIS, adenocarcinoma

Classificazione rivolta principalmente ai citopatologi e ai clinici

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

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

Bethesda 30 aprile - 2 maggio 2001

Bethesda System 2001

9 gruppi di lavoro: utilizzano un pannello interattivo *on line*

Bozza delle linee guida disponibili su internet per commenti

Preparato rifiutato/non processato

Valutazione dell’adeguatezza:

- Non soddisfacente per la valutazione
- Soddisfacente per la valutazione

La zona di trasformazione

Presenza di almeno due cluster di cellule cilindriche endocervicali
ben conservate e/o di cellule squamose metaplastiche (5 cellule per ogni cluster)

Studi longitudinali indicano che le lesioni epiteliali sono più comuni
quando sono presenti tali cluster.

Ma:

studi recenti non confermano il dato, per cui il Betheda 2001 non ritiene
questo parametro essenziale per valutare l'adeguatezza

Presenza o assenza devono tuttavia essere segnalate

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 =/> 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)

ASC → **ASC-US**

ASC → **ASC-H**

BETHESDA 2001

Squamous cell carcinoma

Atypical Glandular Cells

AGC → **AGC- NOS**

AGC → **AGC-neoplastic**

Adenocarcinoma *in situ* (AIS)

Adenocarcinoma

Bethesda 2014: Time For An Update?

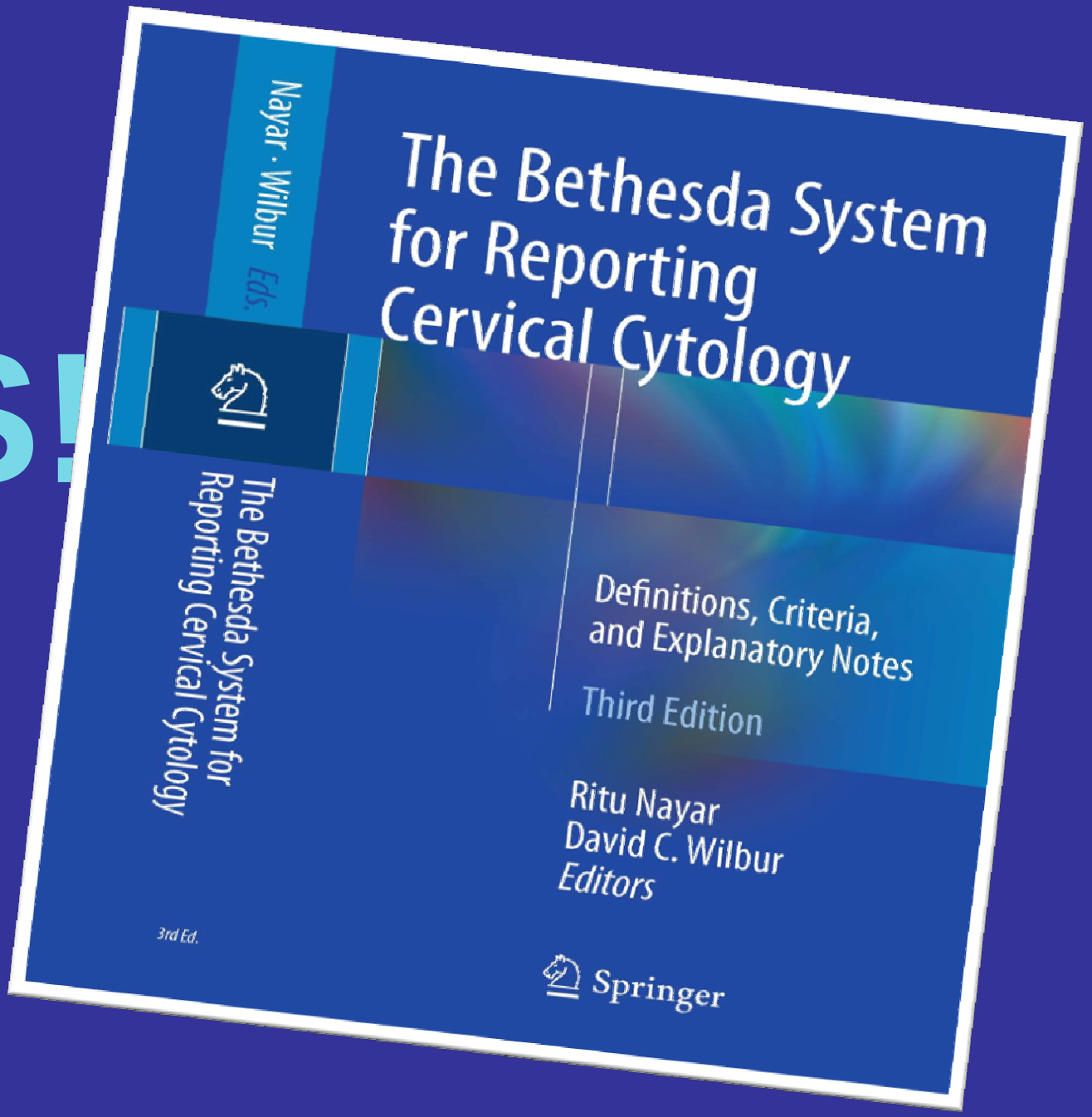
Ritu Nayar, MD

Professor of Pathology

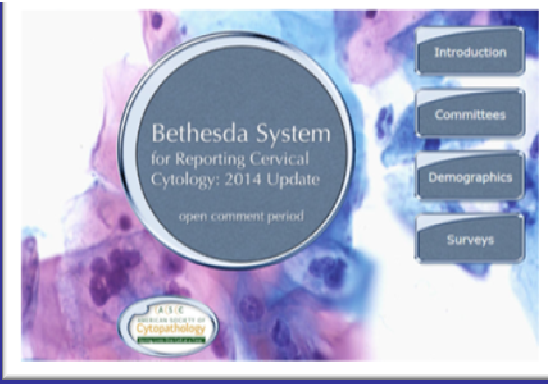
Northwestern University, Feinberg School of Medicine

Chicago, USA

YES!


Nayar · Wilbur Eds.
The Bethesda System for Reporting Cervical Cytology
3rd Ed.
The Bethesda System for Reporting Cervical Cytology
Definitions, Criteria, and Explanatory Notes
Third Edition
Ritu Nayar
David C. Wilbur
Editors
Springer

Process



- **Dr. Nayar, as President of ASC appointed a task force**
  - A smaller working group – designed for speed, expertise, and efficiency (included cytologists, clinicians and epidemiologists)
- **Development of atlas content** (*text and images*)
  - Posted proposed draft content, changes and questions on Internet bulletin board for 3.5 months

Risultati

Testo e immagini accresciuti del 30%:

Testo

13 capitoli: 6 dedicati a grandi categorie interpretative del TBS; 6 ad aree connesse; un capitolo nuovo sulla valutazione dei rischi nello screening del cancro cervicale.

Immagini

370 nell' atlante (molto più numerose nel sito web TBS 2014):

52% nuove immagini rispetto alla 2° edizione

60%: immagini di LBC, 40% di convenzionale.

Maggior numero di quadri compositi e di

Risultati

- Non cambiamenti importanti nella terminologia
- Miglioramento di alcuni criteri morfologici
- Inserimento di nuovi casi, illustrativi di possibili errori o di lesioni mimiche
- Disamina di alcune problematiche verificatesi con l'applicazione del BS 2001, propiamente rispetto ad adeguatezza e terminologia
- Aggiornamenti bibliografici e di *management*

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

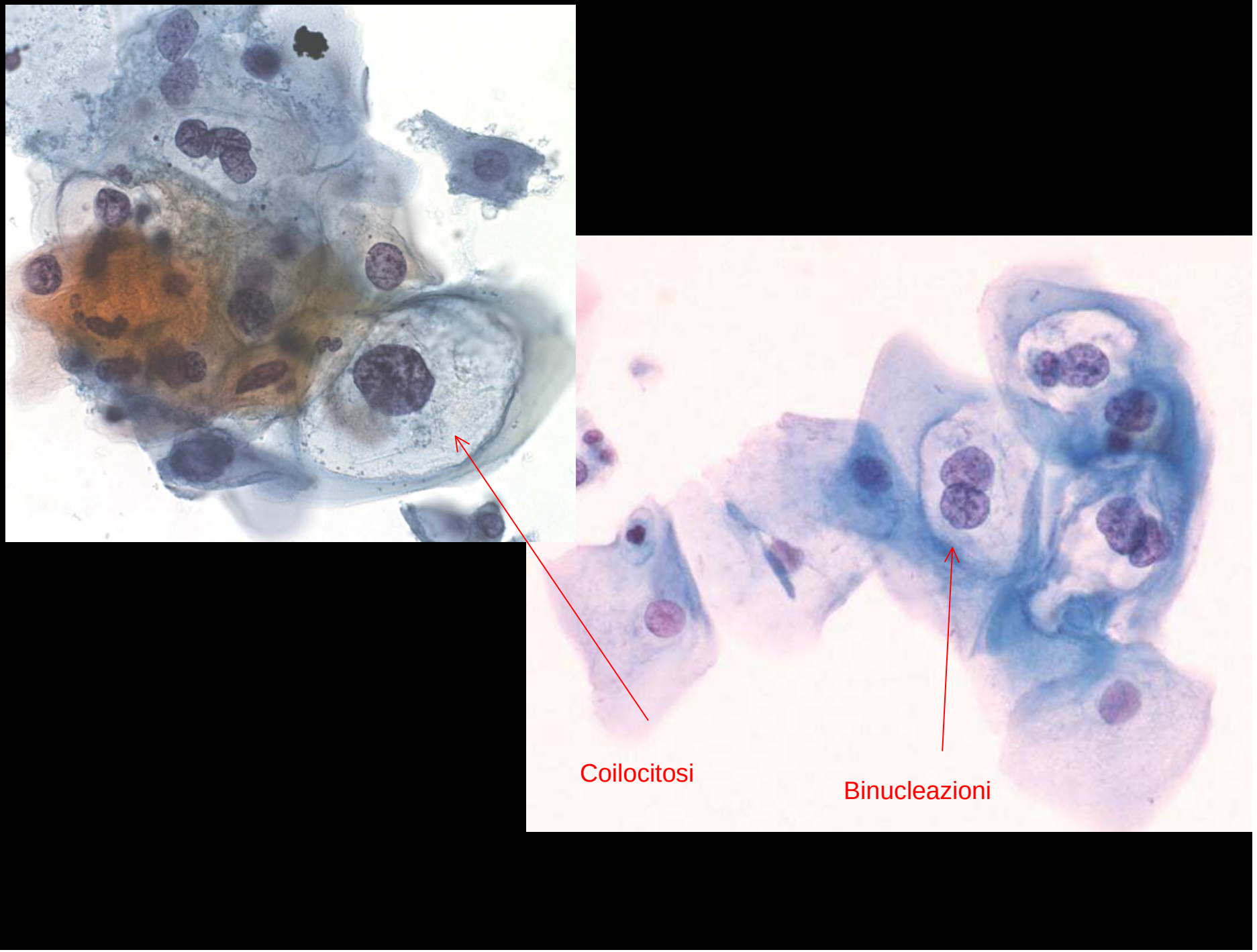
Cellule endometriali

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

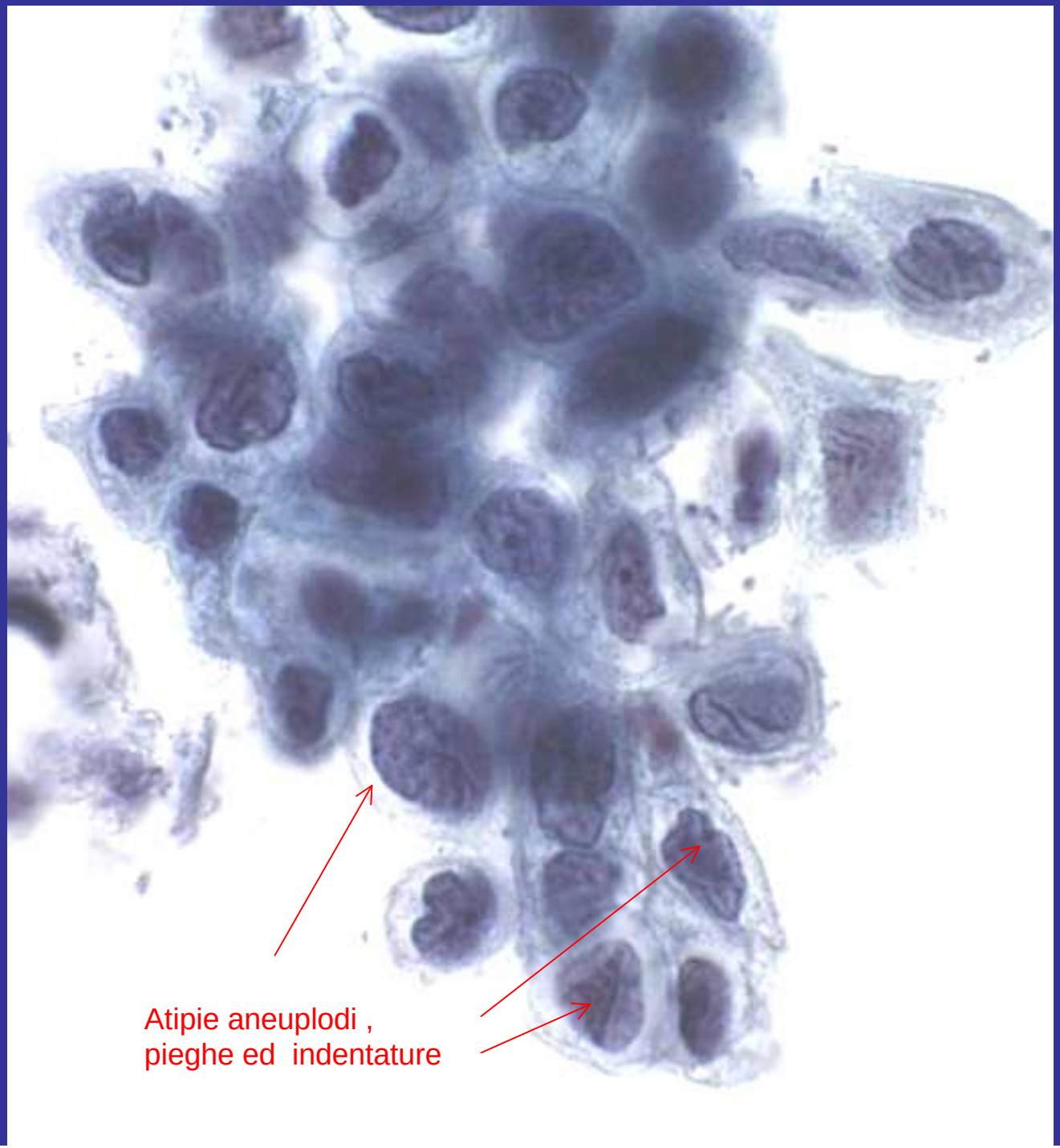
LSIL

Viareggio

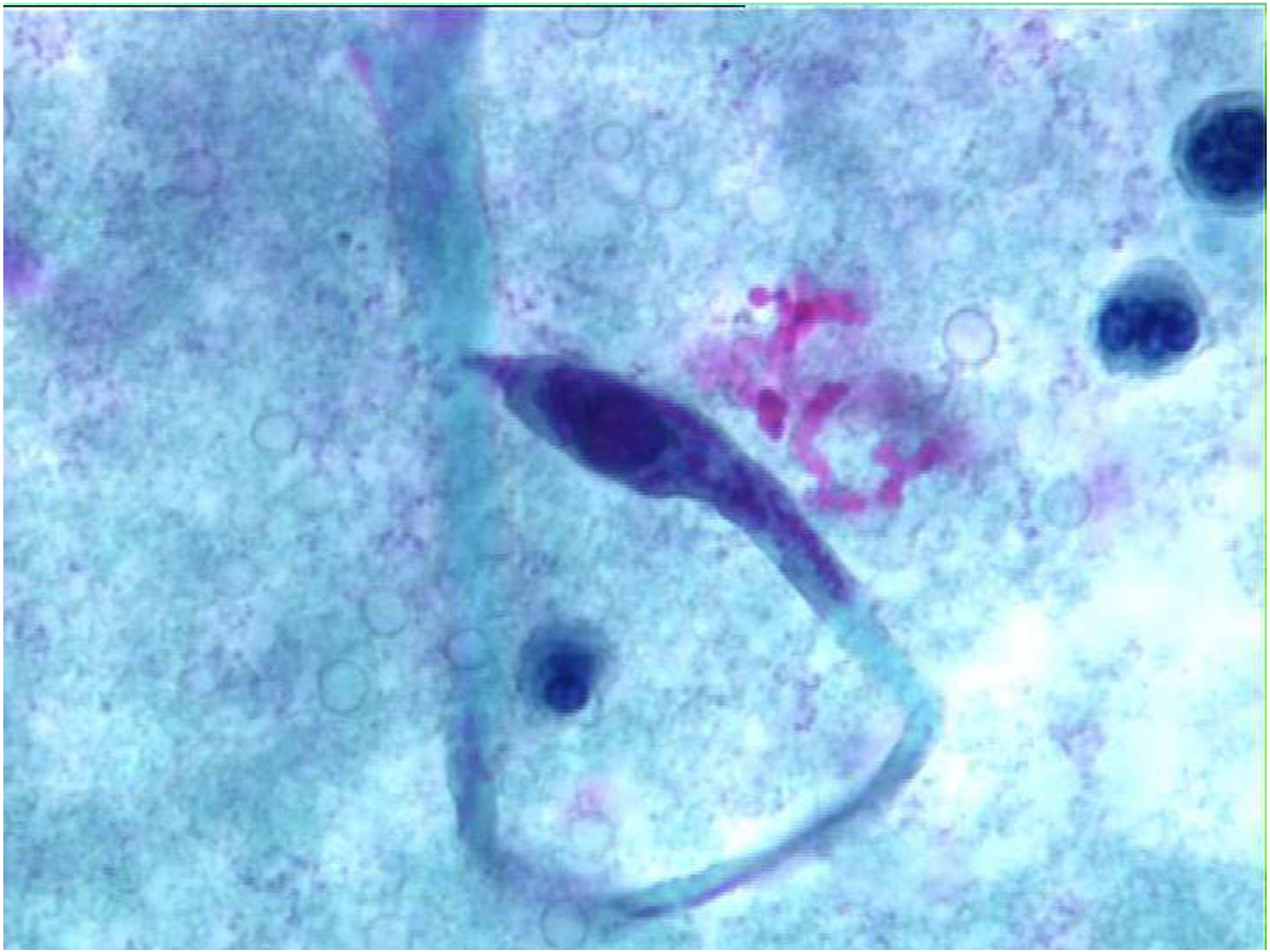
La darsena


Coilocitosi
Binucleazioni

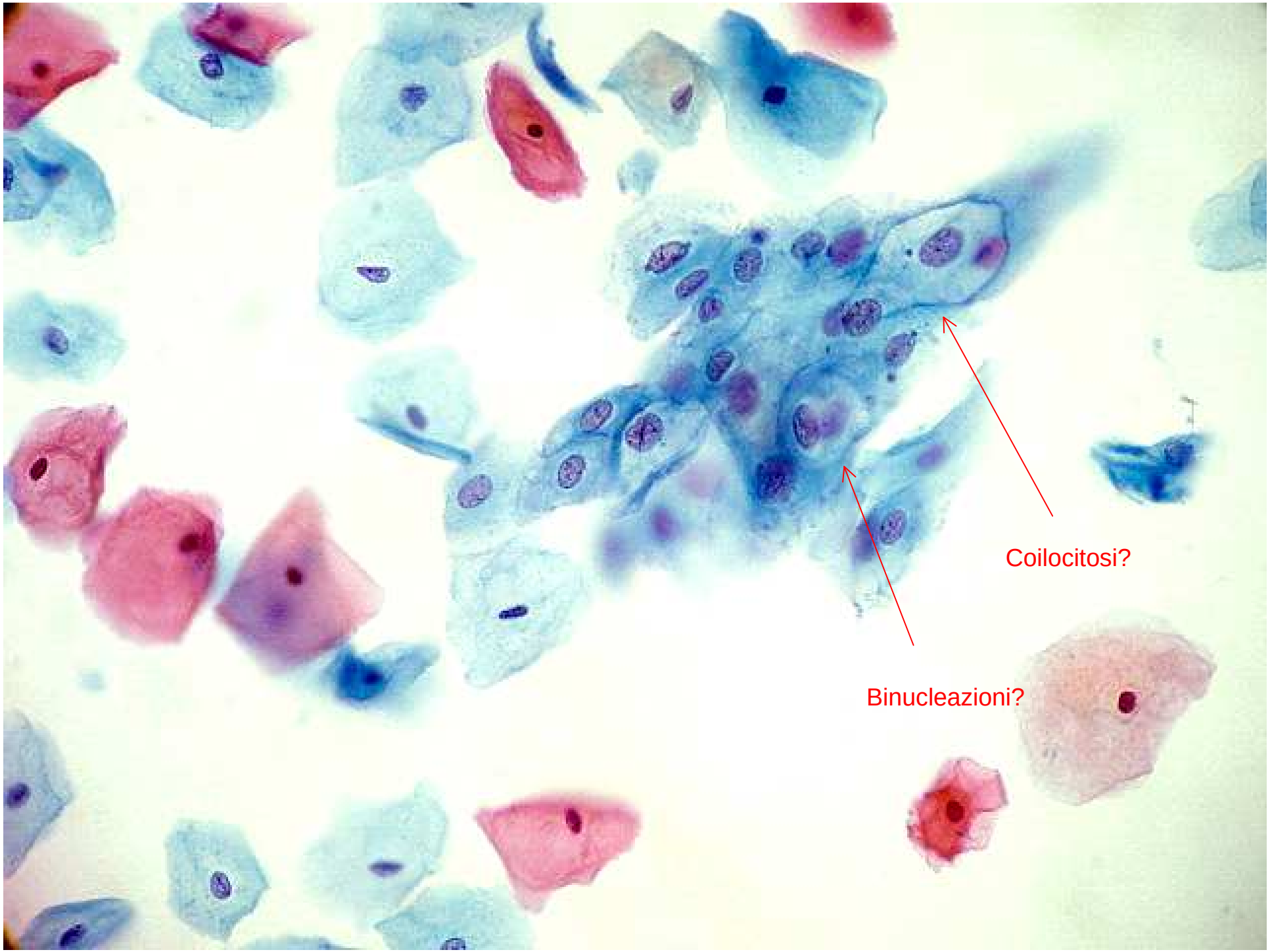

Monte Pisanino (1947m)
HSIL


Atipie aneuplodi ,
pieghe ed indentature

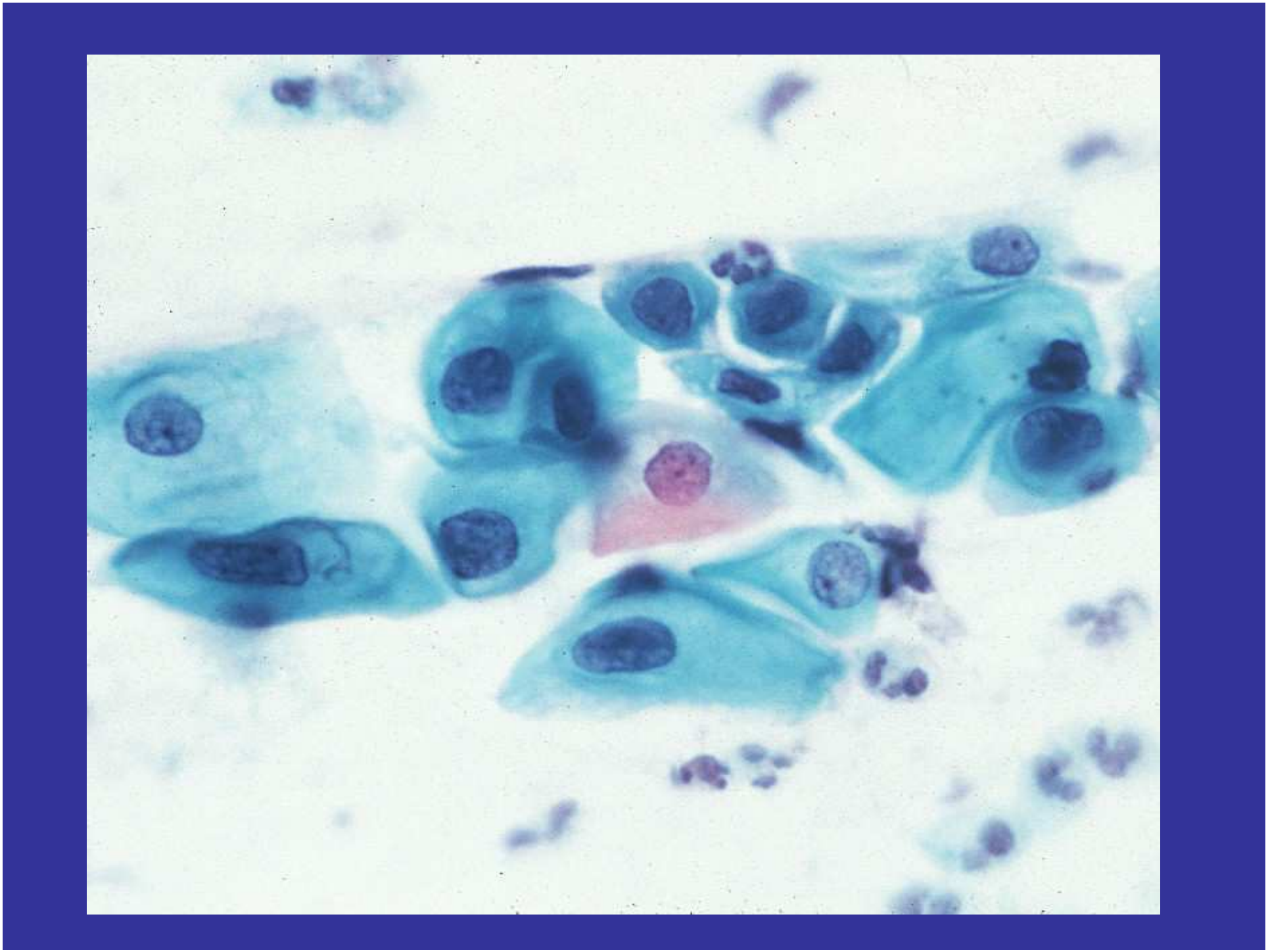

Carcinoma squamoso
Adenocarcinoma in situ
Adenocarcinoma cervicale
Adenocarcinoma dell'endometrio
Altre neoplasie maligne
Pania della Croce (1859 m)
Sea
Prana
Lake of
Massaciuccoli
Matanna

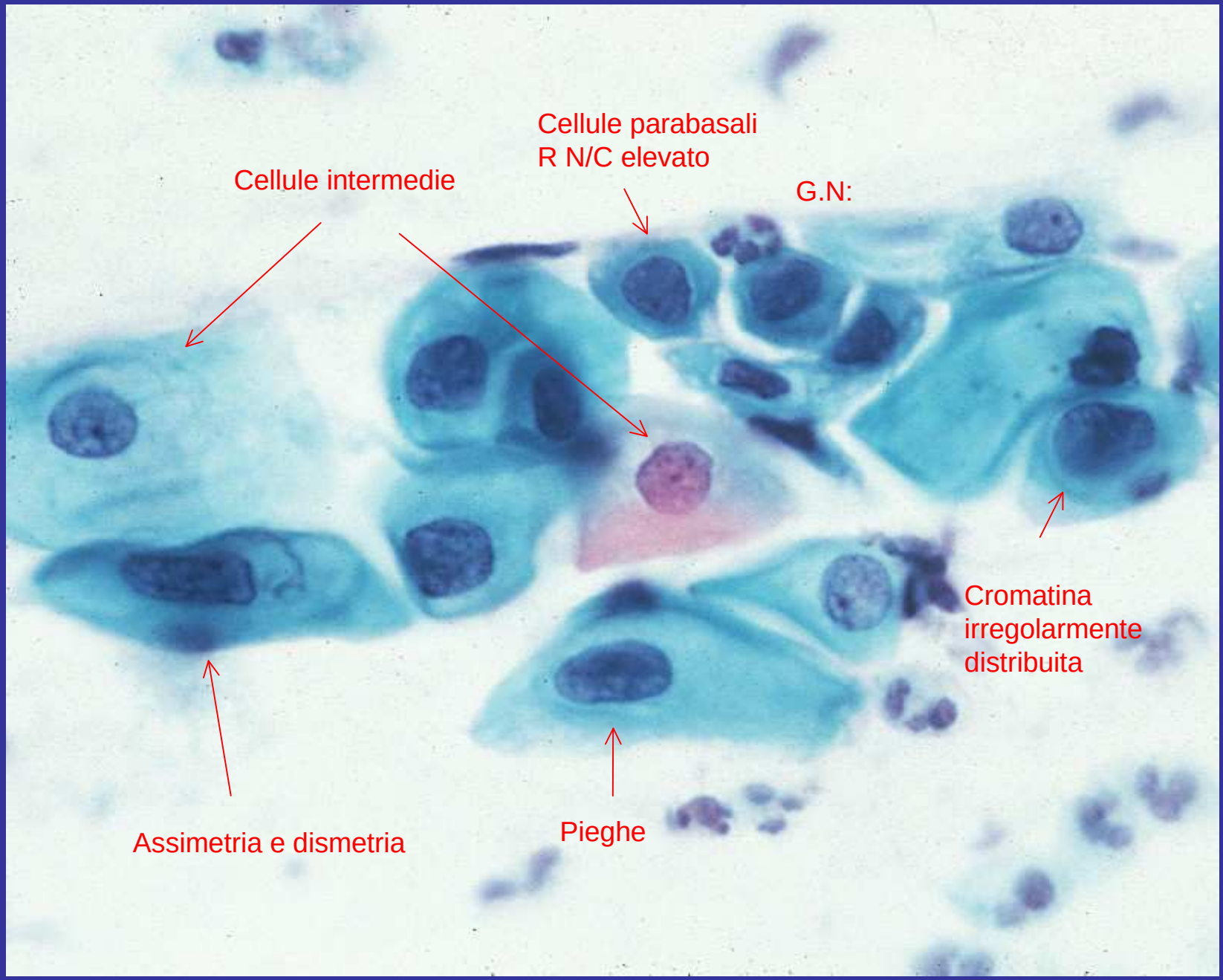


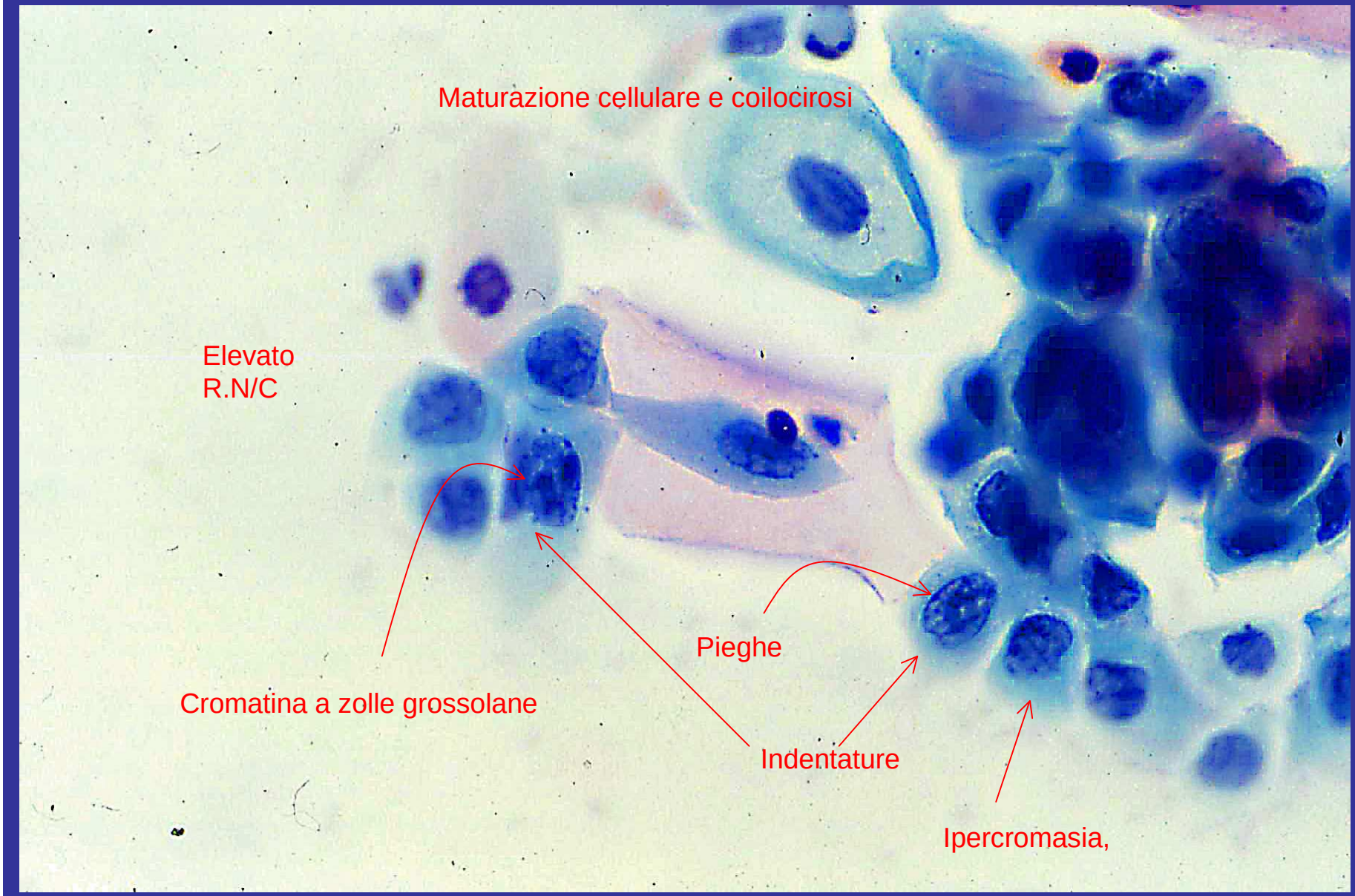

ASC-US


Coilocitosi?
Binucleazioni?


ASC-H
Altissimo
1589 m
Corchia
1677 m
TONFANO




Cellule parabasali
R N/C elevato
Cellule intermedie
G.N:
Cromatina
irregolarmente
distribuita
Assimetria e dismetria
Pieghe


Maturazione cellulare e coilocirosi
Elevato
R.N/C
Pieghe
Cromatina a zolle grossolane
Indentature
Ipercromasia,

Cellule ghiandolari atipiche

Atipiche

Cellule endocervicali (NAS o da specificare nel commento)

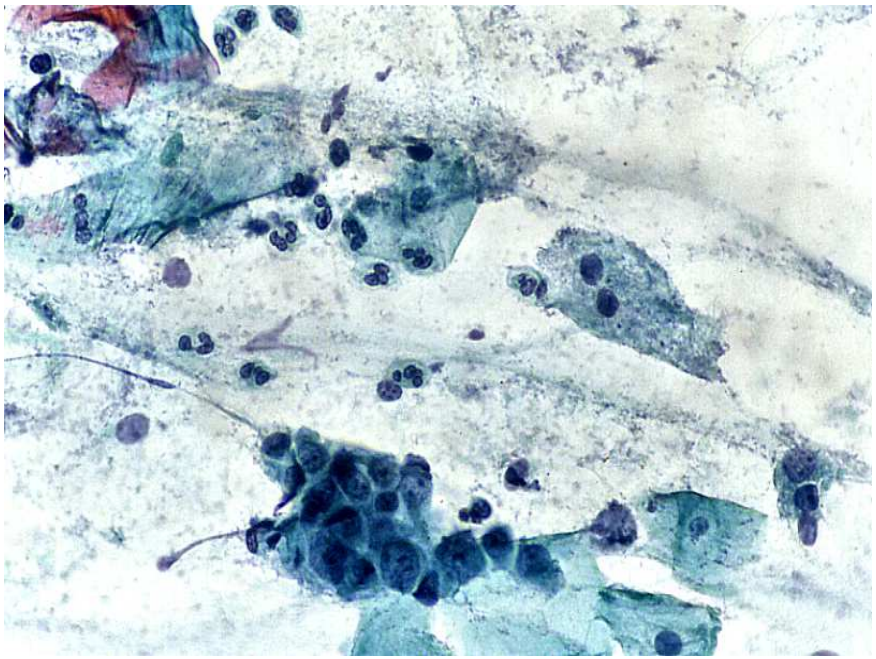
Cellule endometriali (NAS o da specificare nel commento)

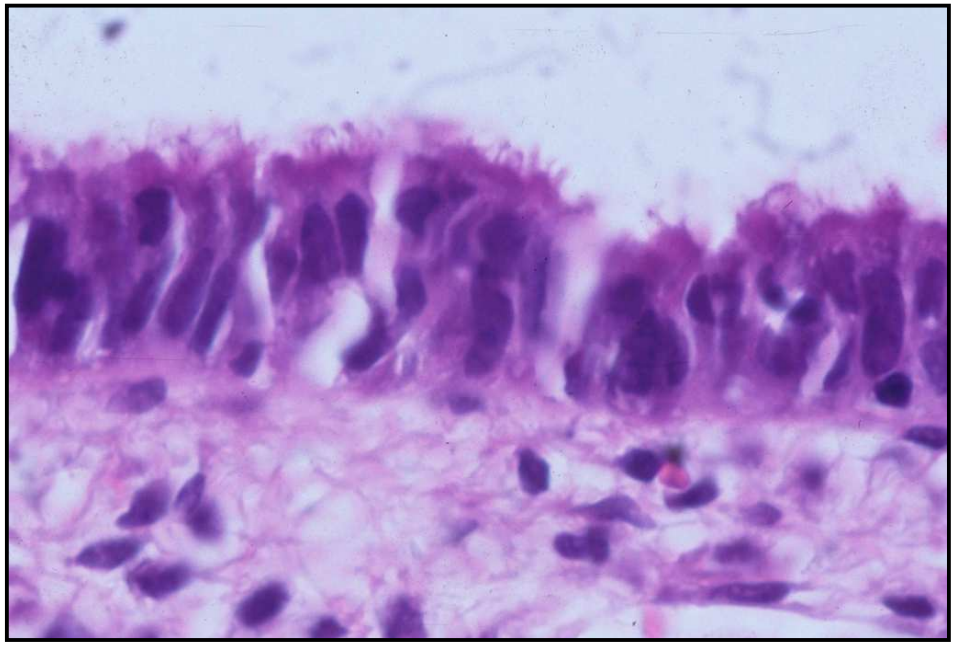
Cellule ghiandolari (NAS o da specificare nel commento)

Atipiche

Cellule endocervicali, probabilmente neoplastiche

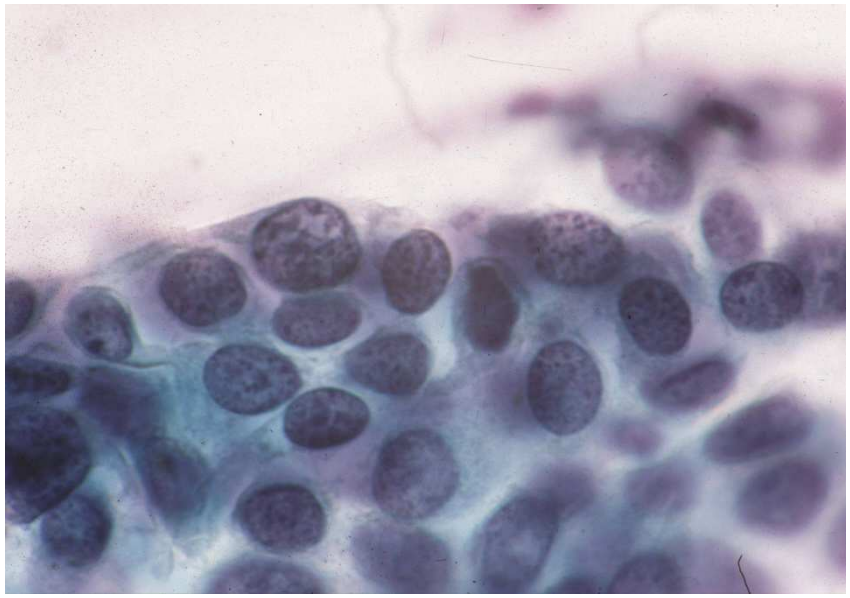
Cellule ghiandolari, probabilmente neoplastiche

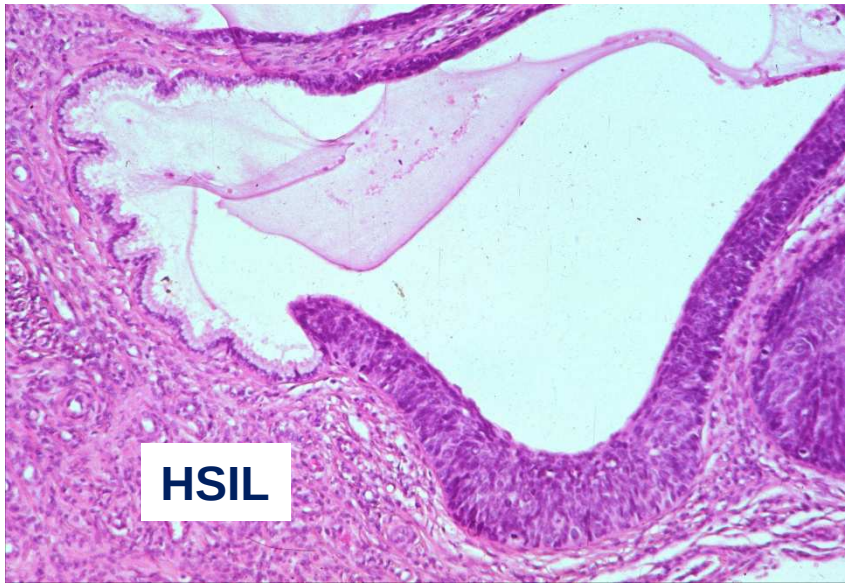


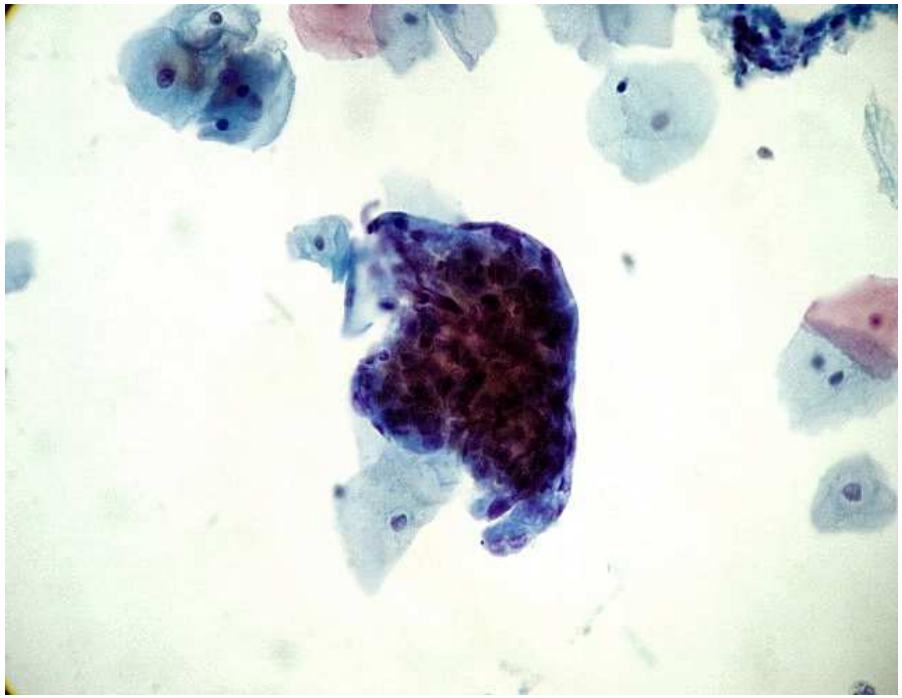


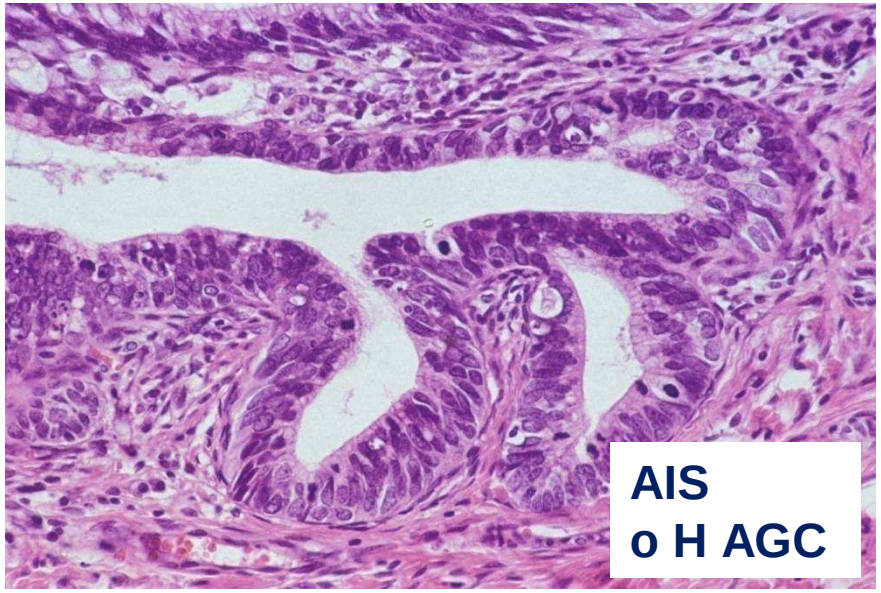
AGC

AGC verso neoplasia

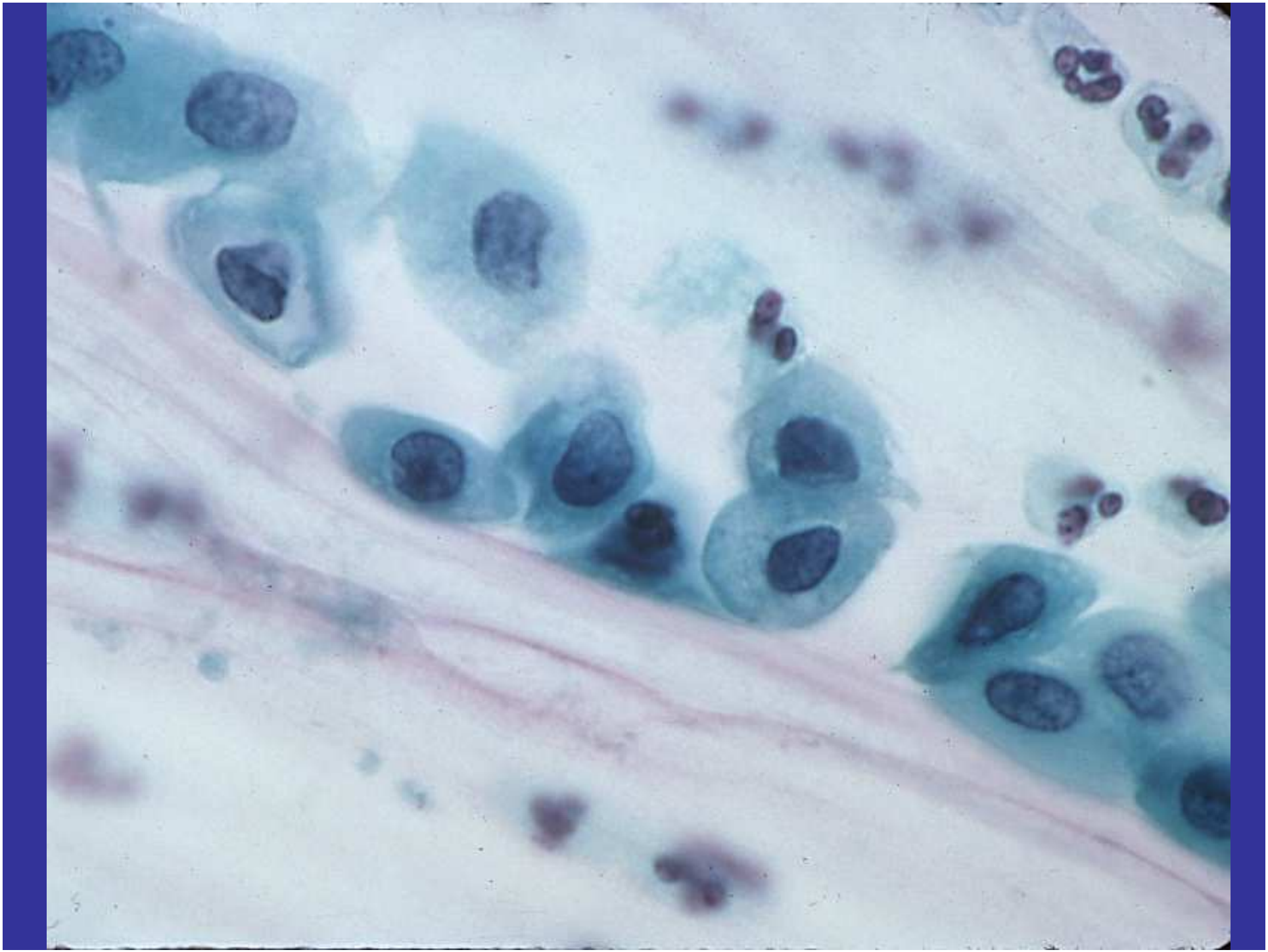


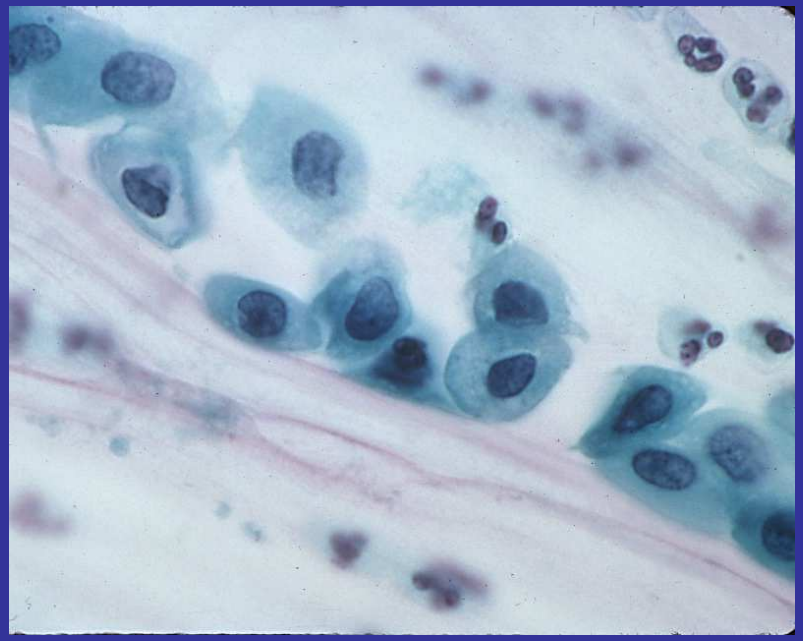


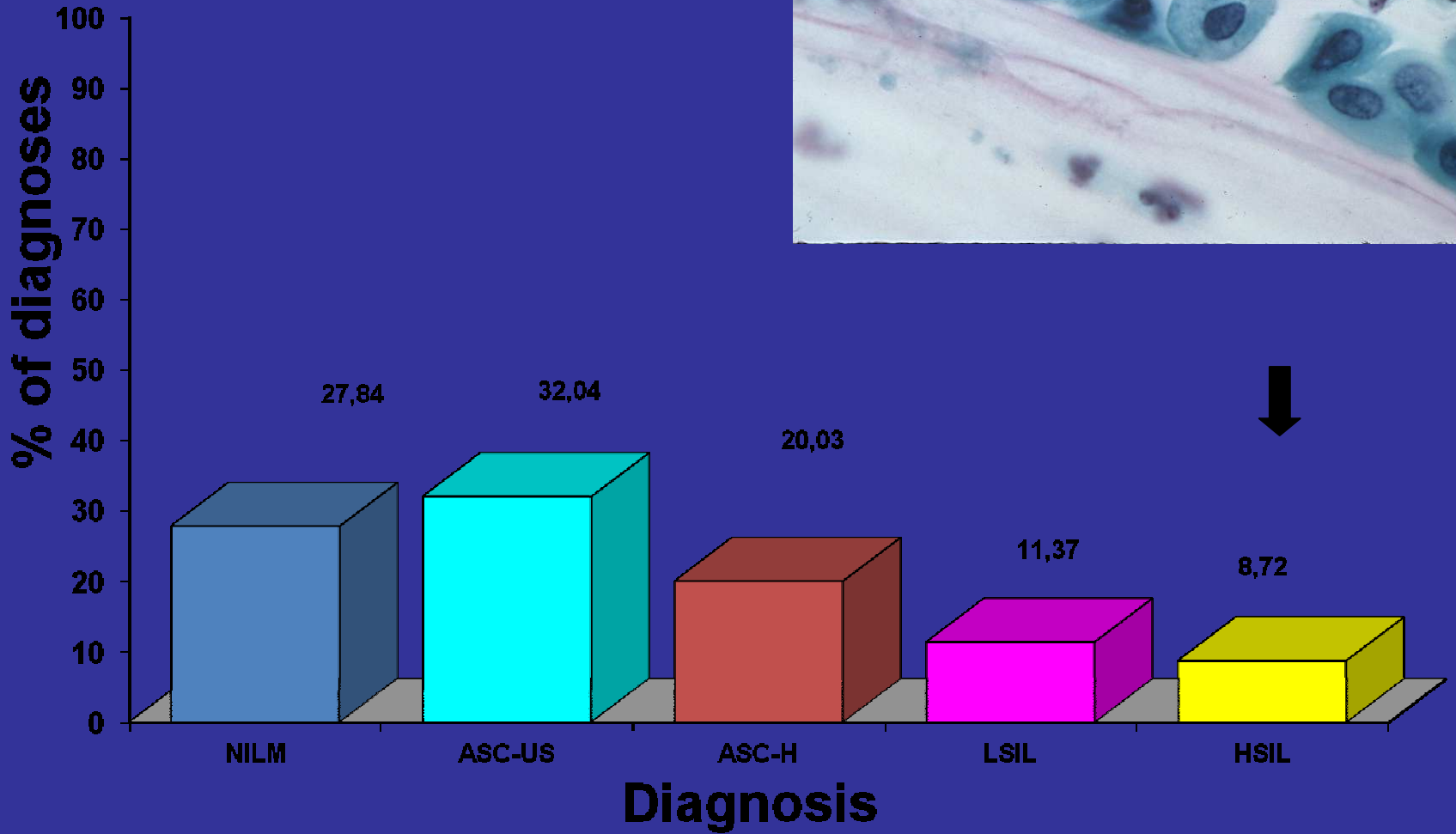


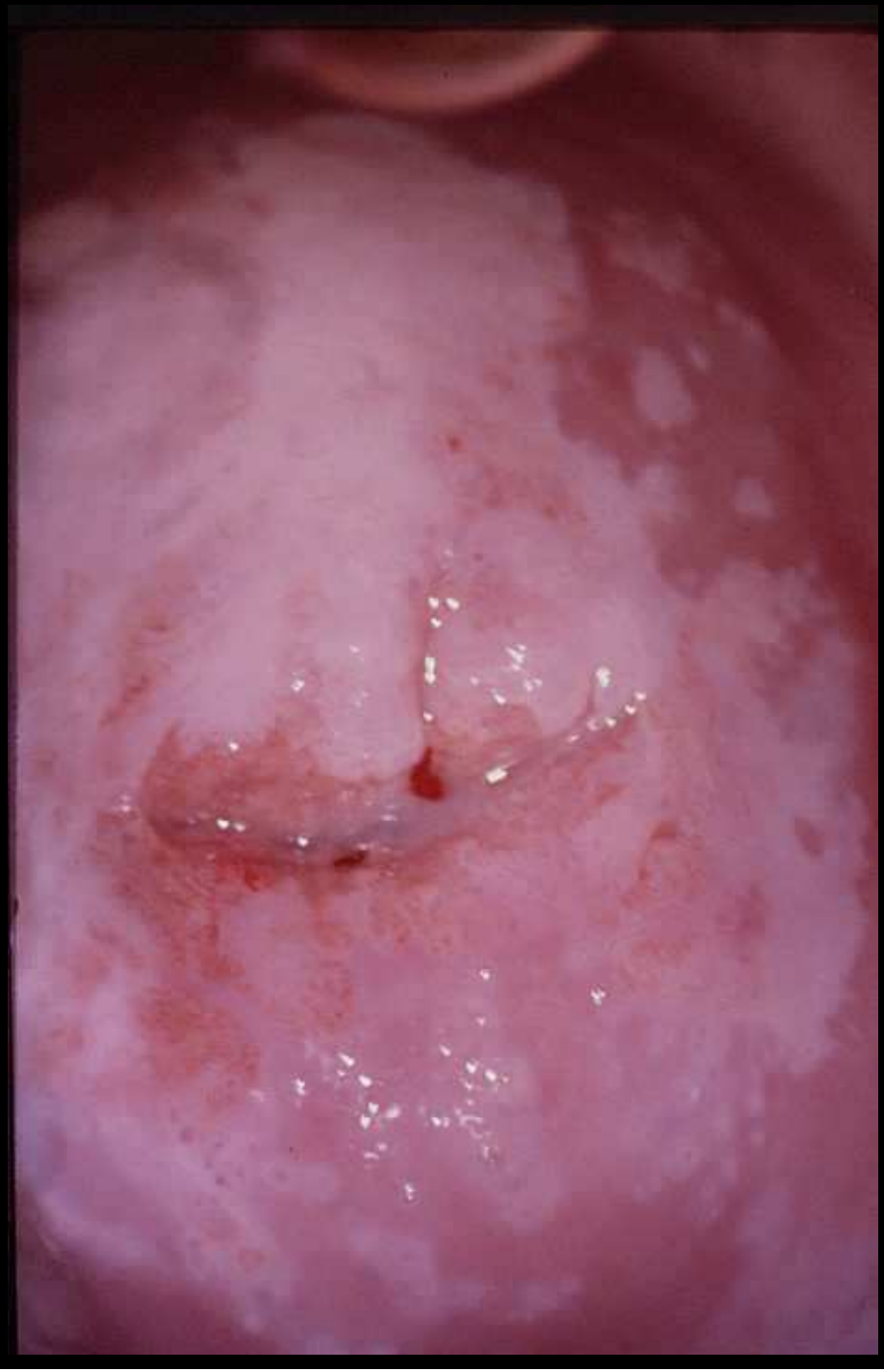


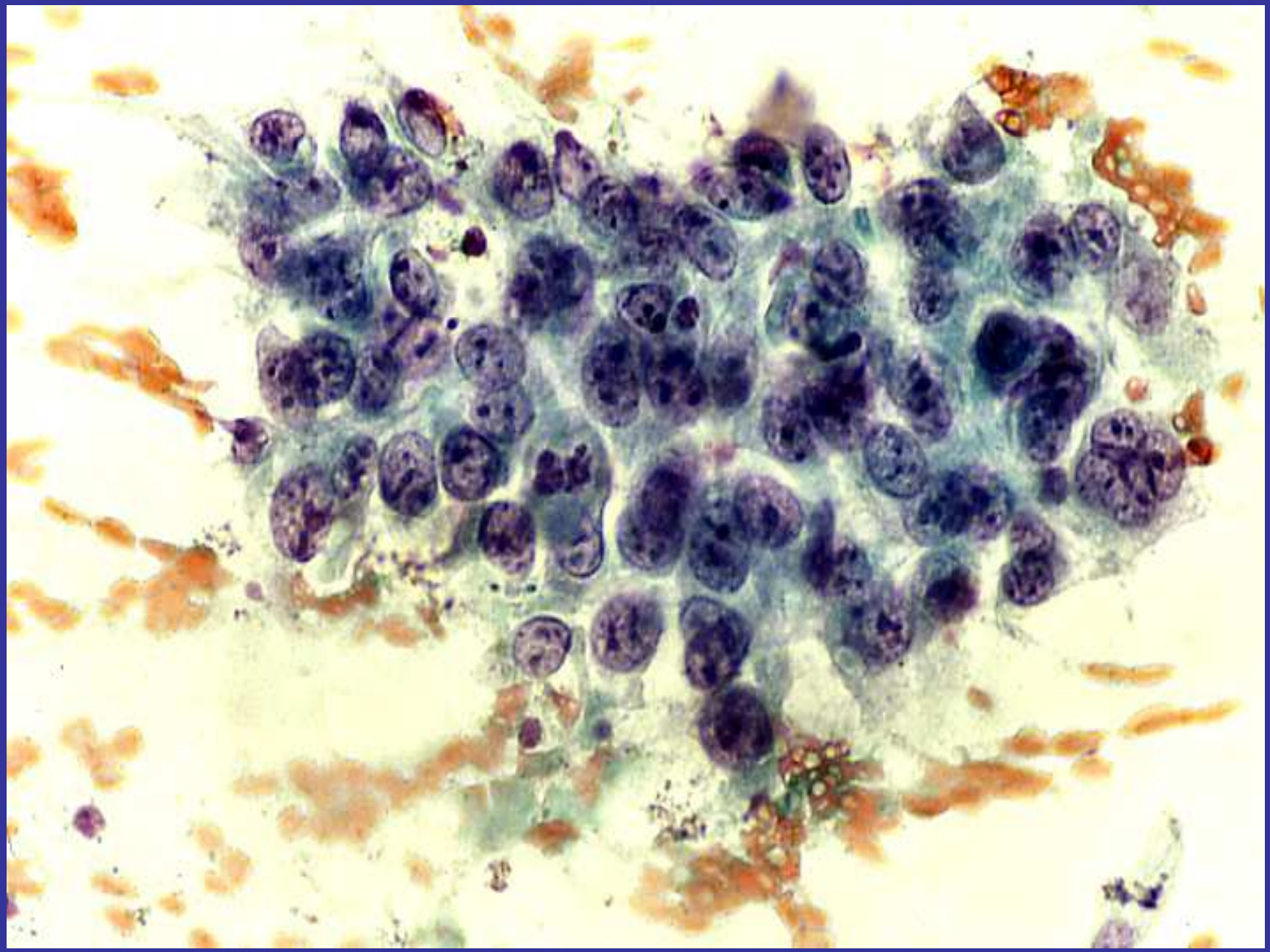
Tutto chiaro?

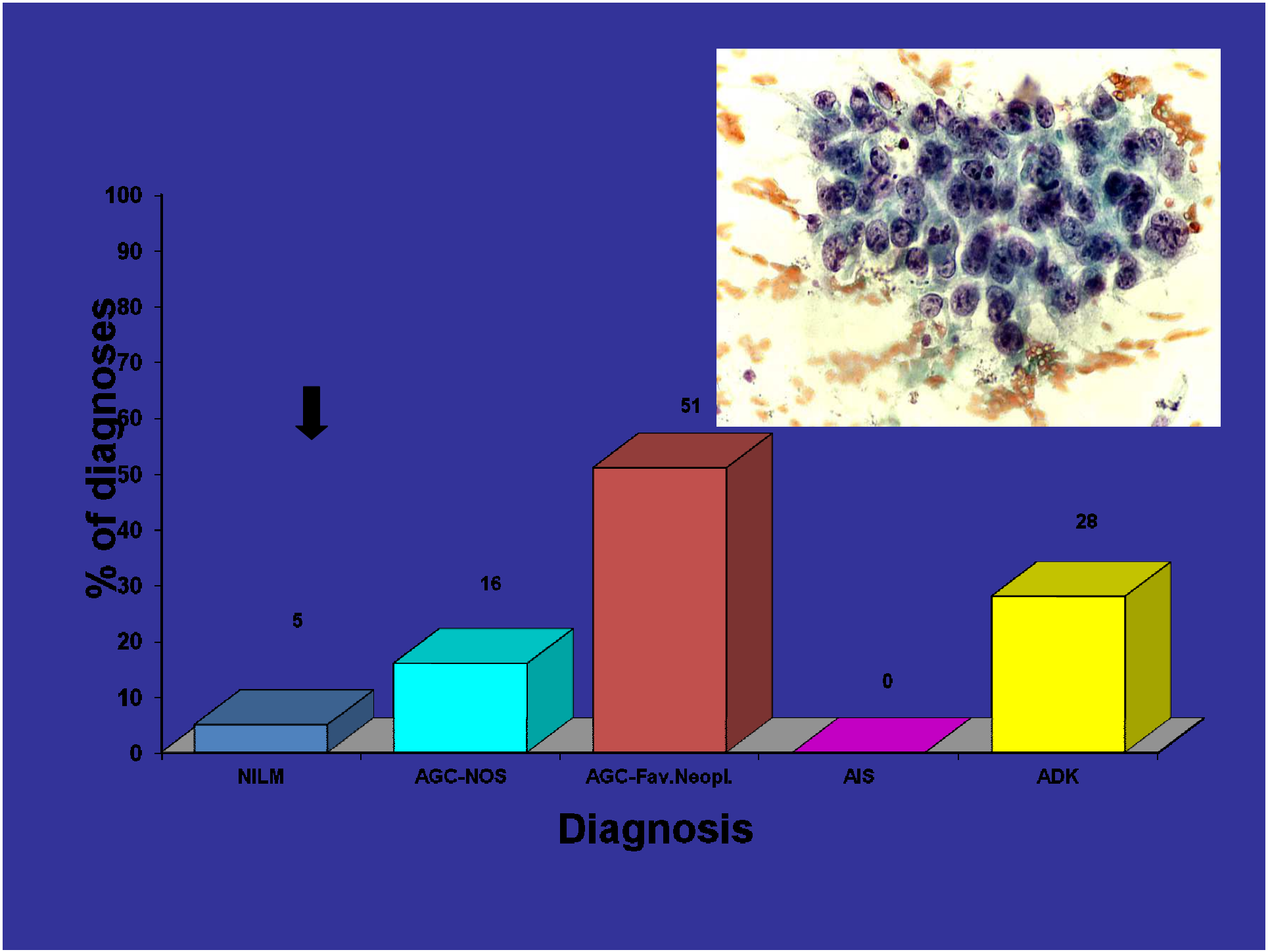


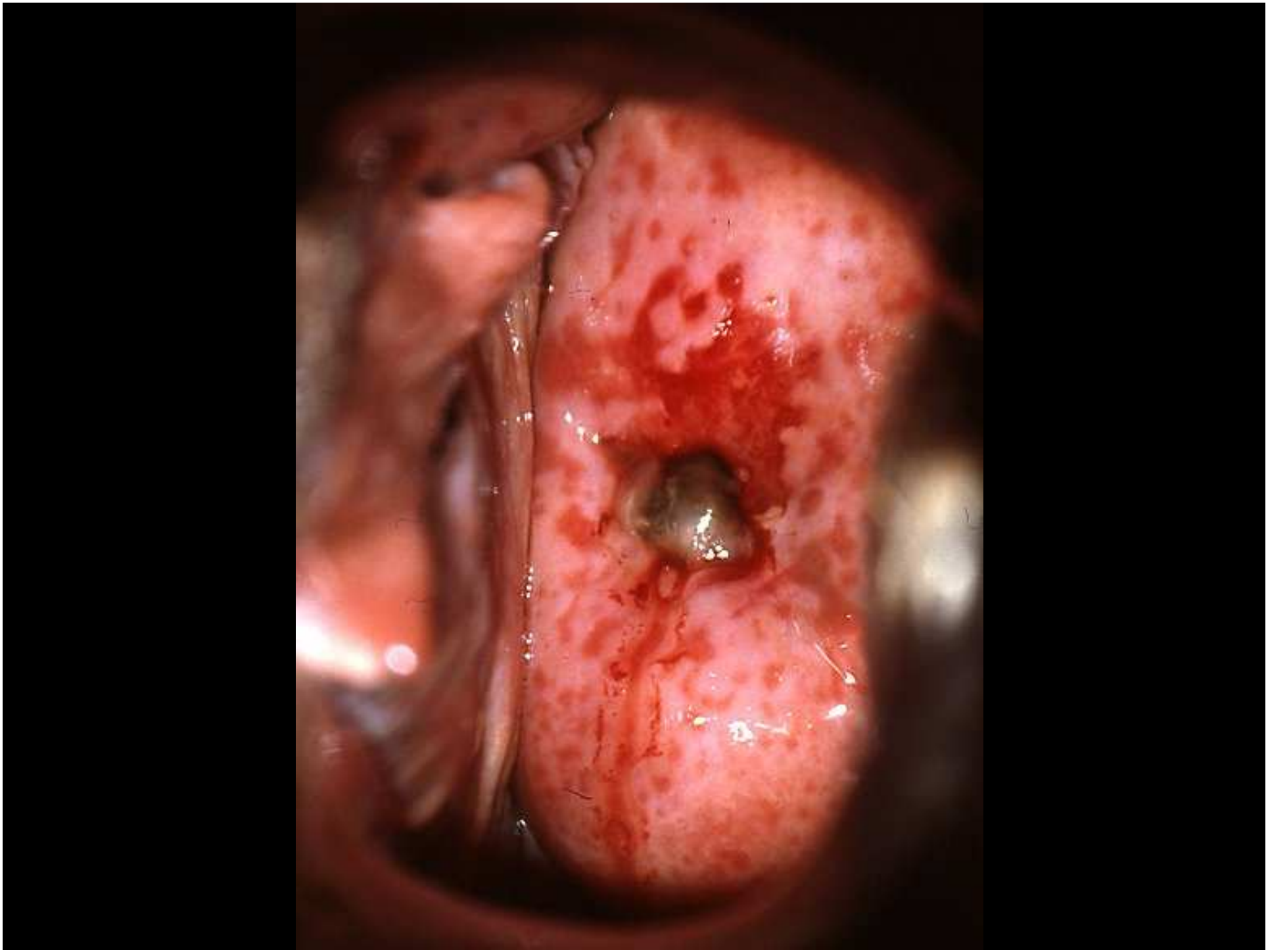


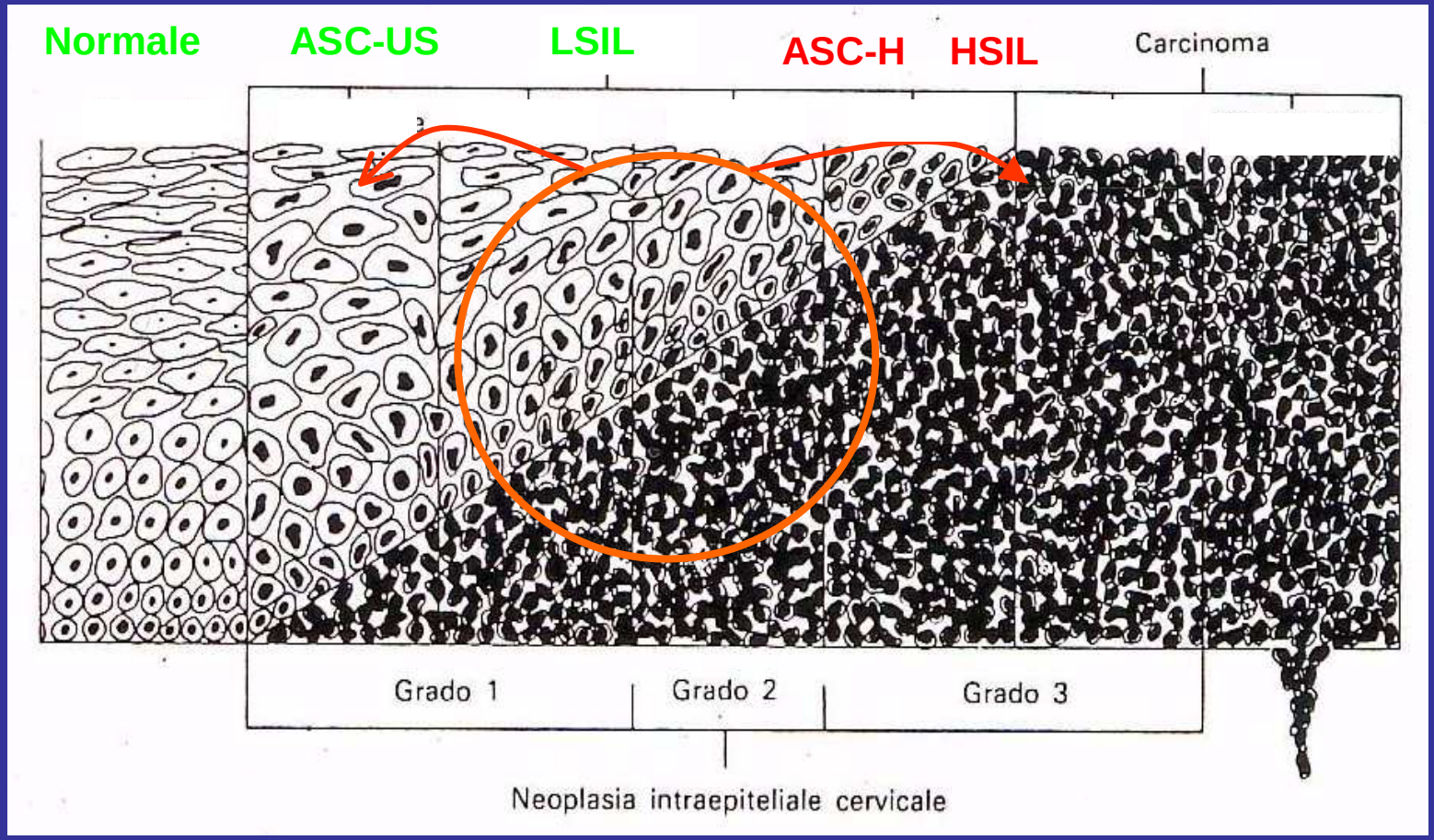

% of diagnoses
100
90
80
70
60
50
40
30
20
10
0
27,84
32,04
20,03
11,37
8,72
NILM
ASC-US
ASC-H
LSIL
HSIL
Diagnosis

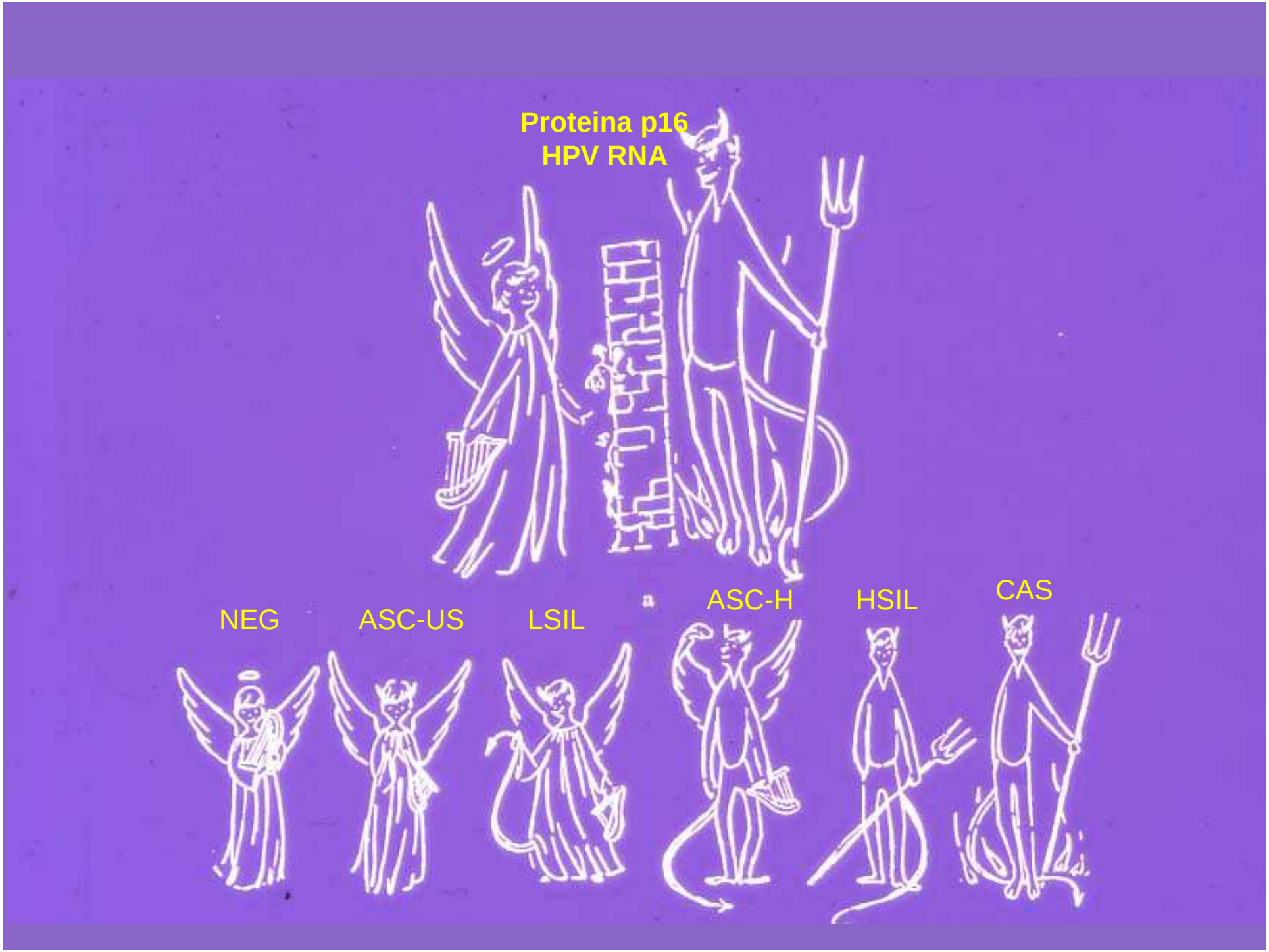





100
90
80
70
60
50
40
30
20
10
0
% of diagnoses
5
16
51
0
28
NILM
AGC-NOS
AGC-Fav.Neopl.
AIS
ADK
Diagnosis



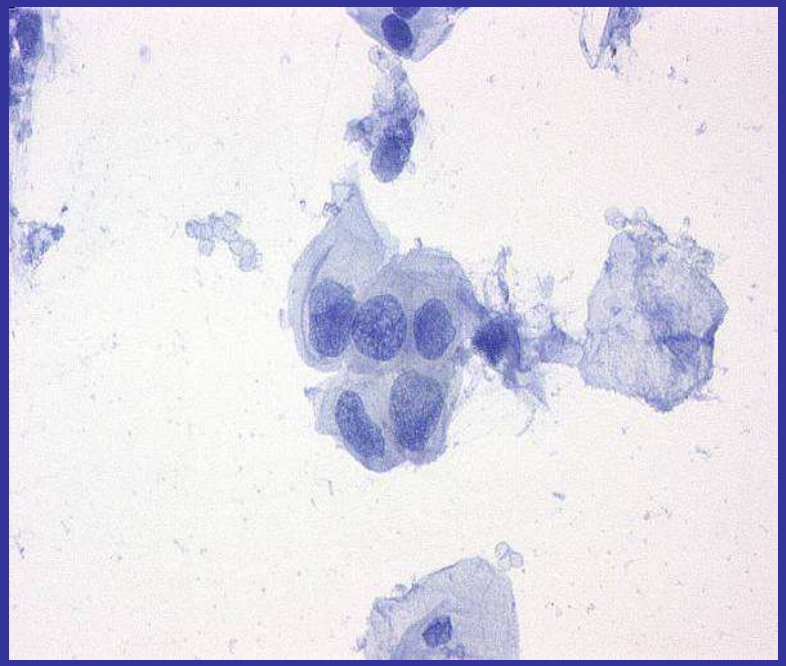

Normale
ASC-US
LSIL
ASC-H
HSIL
Carcinoma
Grado 1
Grado 2
Grado 3
Neoplasia intraepiteliale cervicale


Proteina p16
HPV RNA
NEG
ASC-US
LSIL
ASC-H
HSIL
CAS

La proteina p16

Marina di Carrara

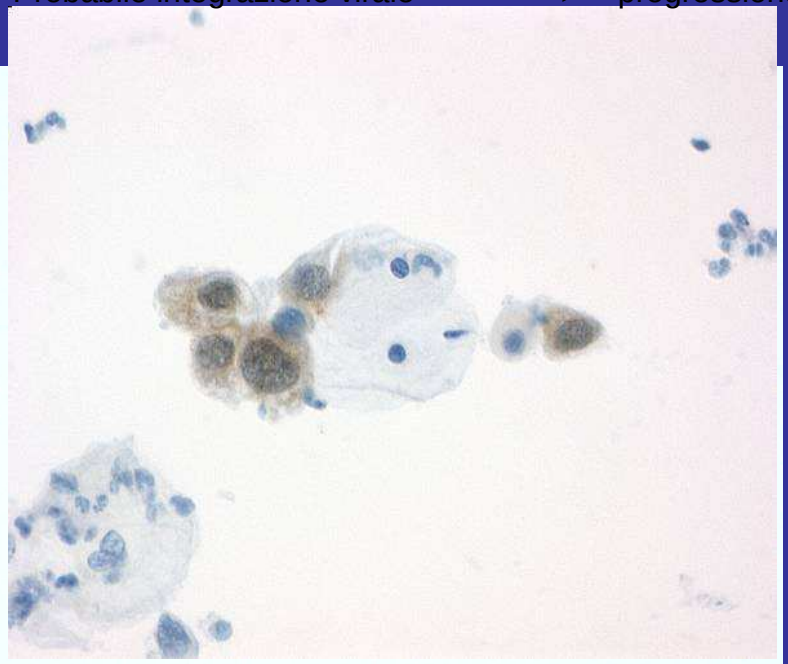
P16 neg



Follow-up

P16 pos K67 pos

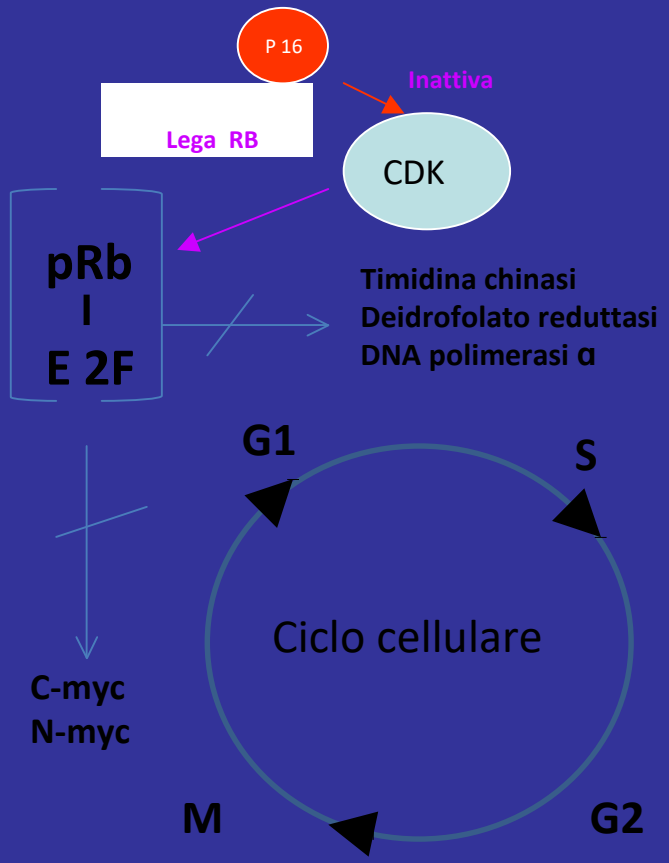
Probabile integrazione virale → progressione



Trattamento

Condizioni fisiologiche

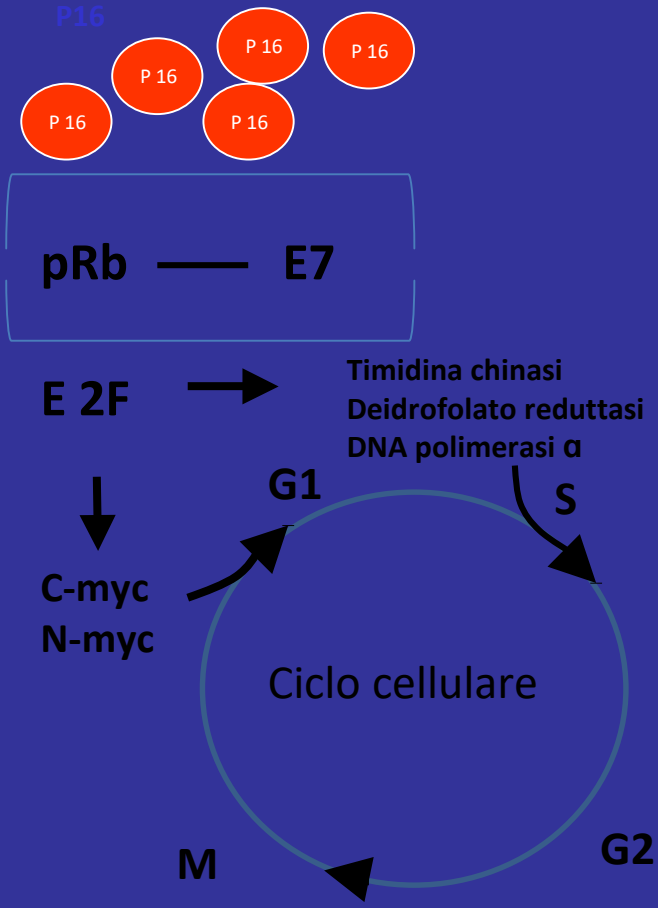
P16 inibisce la ciclina D, che lega RB liberando E2F che promuove la divisione cellulare



Inibizione del ciclo cellulare

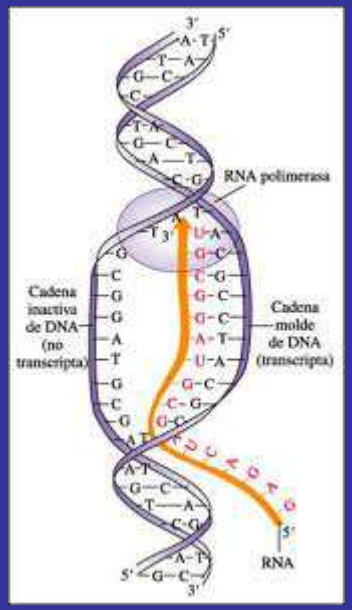
Infezione da HPV ad alto rischio

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



Stimolazione del ciclo cellulare

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]
D.O.B.
NHS No.
Serial No.

Sender HOE1
Dr Elizabeth HOLT
SALFORD ROYAL HOSPITAL
CLAIRE DUNNE,GYNAE DEPT.,
* STOTT LANE
SALFORD M6 8HD
HOSP

G.P.
Dr M TYRRELL
ST ANDREWS MEDICAL CENTRE
RUSSELL STREET
ECCLES
MANCHESTER M30 0NU

HA Salford & Trafford H A
PEEL HOUSE
ALBERT STREET
ECCLES
MANCHESTER M30 0NJ

LMP: Test Date: 11 Jan 2008

Specimen Type: LBC (SurePath)

Reason for Smear: Routine call

Condition: Pregnant

Clinical Details: Cervix appears normal
Pre TOP
-308416

Cytology Report:
MILD DYSKARYOSIS

High risk HPV NOT DETECTED by HC2 test.

Routine recall is recommended.

Pattern: MILD DYSKARYOSIS

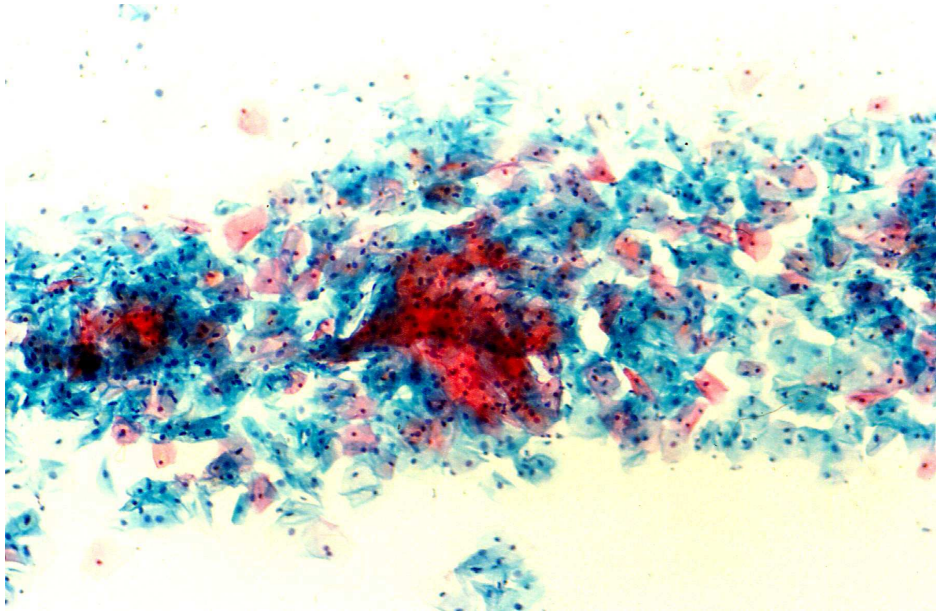
Infection:High risk HPV NOT DETECTED [0]

Suggest: Routine recall [A]

Authoriser: Date authorised:
1st print date: 22 Jan 2008 Date: 22 Jan 2008

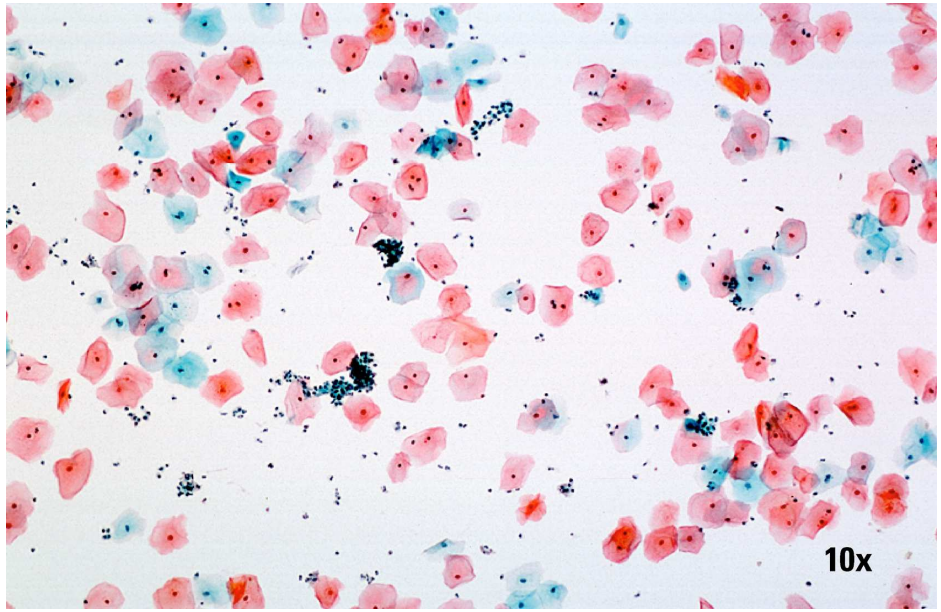
Lo strato sottile

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**

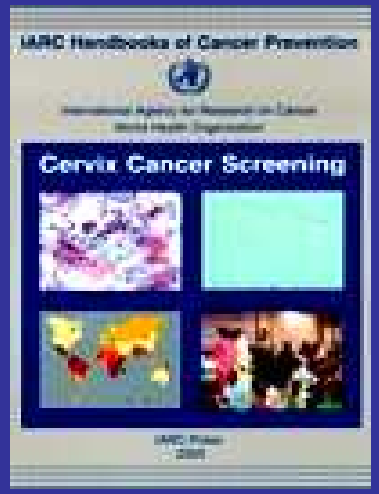
Source: Hutchinson ML, et al. *Am J Clin Pathol*. 1994;101:215-219.

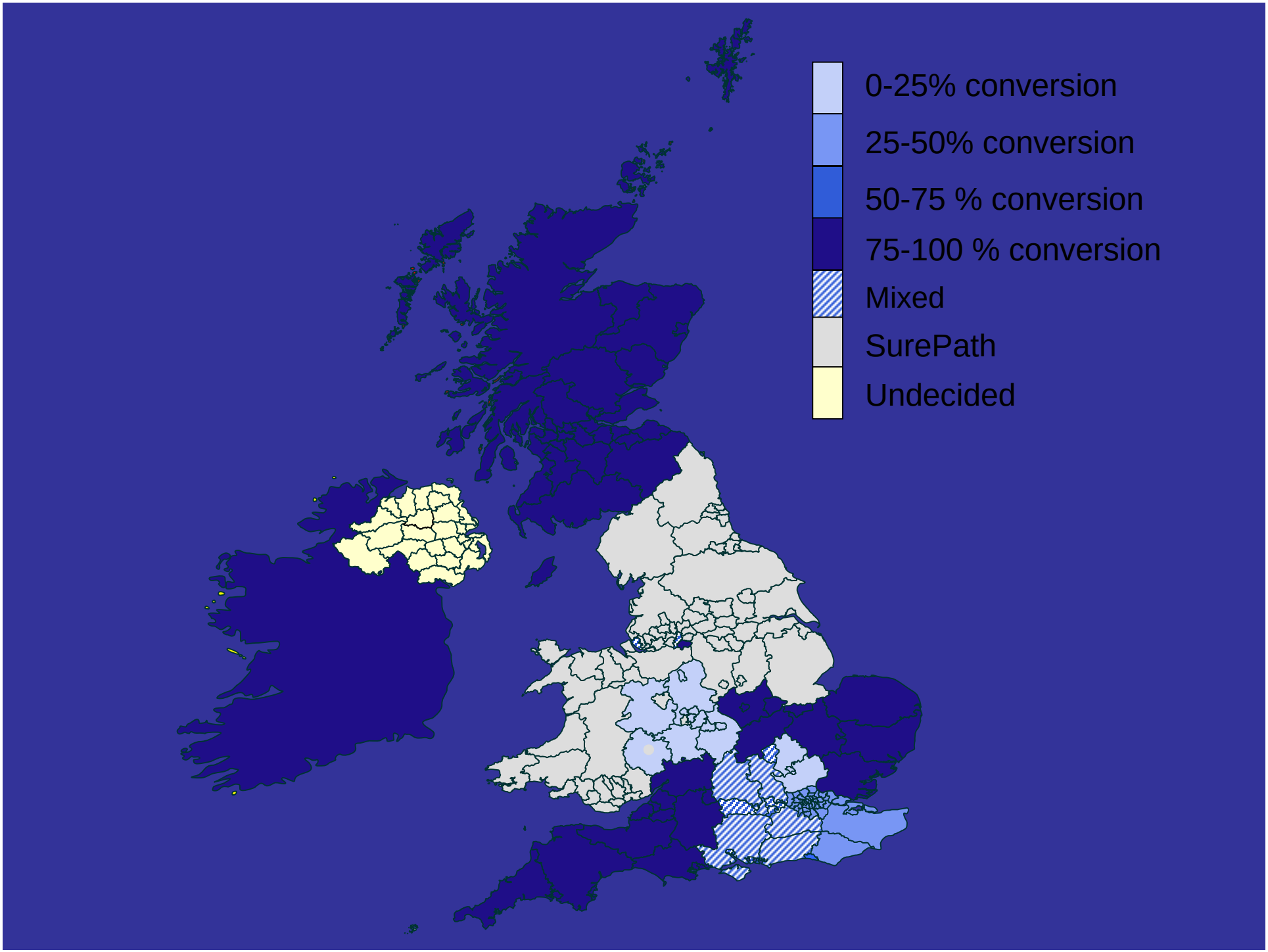
Long Island 1997

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
- LCB is the only screening test used in Scotland and Ireland
- LBC approved for routine screening in Hong Kong and Canada




0-25% conversion
25-50% conversion
50-75 % conversion
75-100 % conversion
Mixed
SurePath
Undecided

PubMed | liquid based cervical cytology | Search

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1. Immunocytochemical analysis of the **cervical** pap smear.
   Morgan TK, Berlin M.
   Methods Mol Biol. 2015;1249:203-12. doi: 10.1007/978-1-4939-2013-6_15.
   PMID: 25348308 [PubMed - in process]
   Related citations

2. Improving sensitivity of **cervical cytology** by removal of **cervical** secretions before sampling: a prospective study in Mexico.
   Curiel-Valdés J, Briones-Pimentel J, Bandala C.
   Int J Clin Exp Pathol. 2014 Aug 15;7(9):5895-901. eCollection 2014.
   PMID: 25337232 [PubMed - in process] **Free PMC Article**
   Related citations

3. CCNA1 Promoter Methylation: a Potential Marker for Grading Papanicolaou Smear **Cervical** Squamous Intraepithelial Lesions.
   Chujan S, Kitkumthorn N, Siriangkul S, Mutirangura A.
   Asian Pac J Cancer Prev. 2014;15(18):7971-5.
   PMID: 25292097 [PubMed - in process] **Free Article**
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4. **Cervical** Pathology in **Cytology**-Negative/HPV-Positive Women: Results from Lampang Cancer Hospital, Thailand.
   Paengchit K, Kietpeerakool C, Wangchai W, Pouraeng S, Lalitwongsa S.
   Asian Pac J Cancer Prev. 2014;15(18):7951-4.
   PMID: 25292093 [PubMed - in process] **Free Article**
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Results by year

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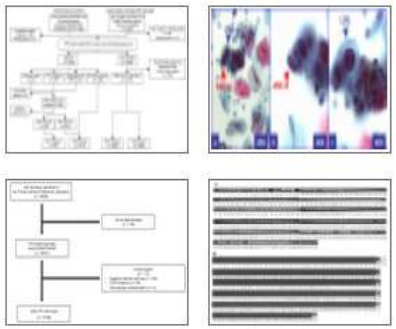
PMC Images search for *liquid based cervical cytology*



See more (24)...

Tramonto in Versilia

Dimezza i tempi di lettura

Riduce il numero degli inadeguati

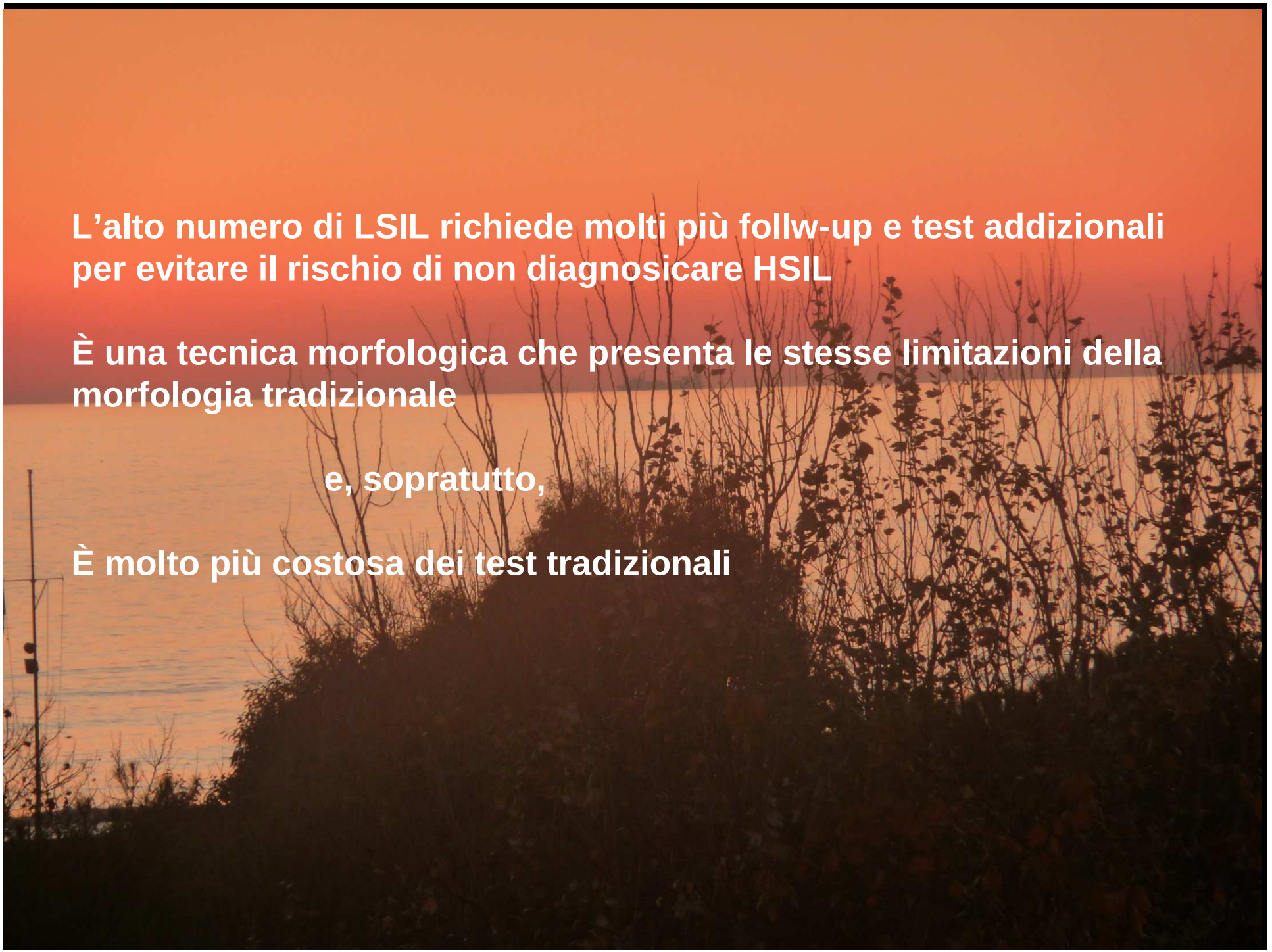
Individua un numero maggiore di LSIL statisticamente significativo

Individua un numero maggiore di HSIL non statisticamente significativo

Permette di eseguire altri test sul materiale residuo

È il metodo più adatto per l'automazione

Ma


L’alto numero di LSIL richiede molti più follw-up e test addizionali per evitare il rischio di non diagnosicare HSIL
È una tecnica morfologica che presenta le stesse limitazioni della morfologia tradizionale
e, sopratutto,
È molto più costosa dei test tradizionali

Thank you very much for your attention