Physiology and Colposcopy of Normal and Abnormal cervical epithelium

G. Miniello

DISTANCE LEARNING PROGRAMME

COLPOSCOPY AND CERVICAL PATHOLOGY

A collaboration between

The African Organisation for Research and Training in Cancer

The International Federation of Cervical Pathology and Colposcopy

and

The International Agency for Research on Cancer

Programme

Introduction *Walter Prendiville*

Colposcopy, the equipment *Walter Prendiville*

Colposcopic examination of the normal cervix *Patrick Walker*

The Biology of Human Papilloma Virus cervical infection *John Doorbar*

Cervical cytology screening, principles, utility and future perspectives *Christine Bergeron*

Colposcopy of the abnormal cervical transformation zone *Lynette Denny*

Clinical Utility of HPV Testing *Jack Cuzick*

Screening Initiatives in the Developing World *R Sankaranarayanan*

Colposcopic nomenclature and useful scoring systems *Bjorn Strander*

The anatomy, physiology and colposcopy of normal and abnormal cervical epithelium *Giovanni Miniello*

Intraepithelial neoplasia of the lower genital tract *John Tidy*

Difficult colposcopic circumstances and physiological Variations (Previous treatments, Atrophy, Infection, Menopause, DES) *Patrick Walker*

The treatment of Cervical Intra-epithelial Neoplasia excision practical aspects. *Walter Prendiville*

Excision of the TZ Morbidity and Safety *Walter Prendiville*

HPV and Cervical Disease *Amanda Tristram*

The management of women with minor smear abnormalities *Grainne Flannelly*

The treatment of CIN using ablative methods *Patrick Walker*

HIV and CIN *Lynettte Denny*

Multifocal disease: Diagnostic and management issues *Silvio Tatti*

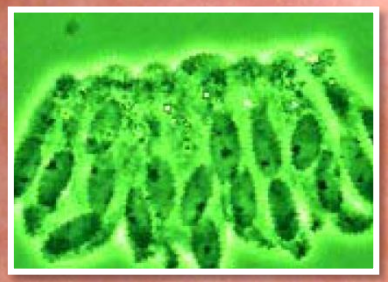
Cervico-vaginal infections – Colposcopic recognition and management *Lynette Denny*

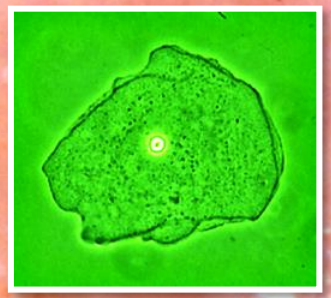
Video

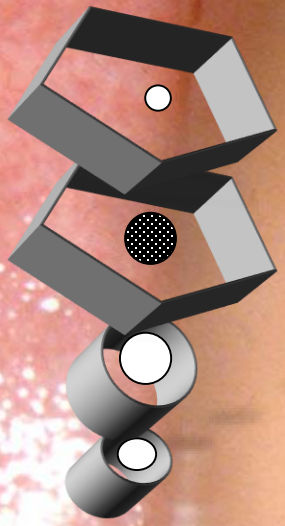
How best to follow up women after treatment for CIN *Pierre Martin-Hirsch*

Colpsocopic Management of women with abnormal cytology *Pierre Martin-Hirsch*

Glandular lesions of the cervix *John Cullimore*







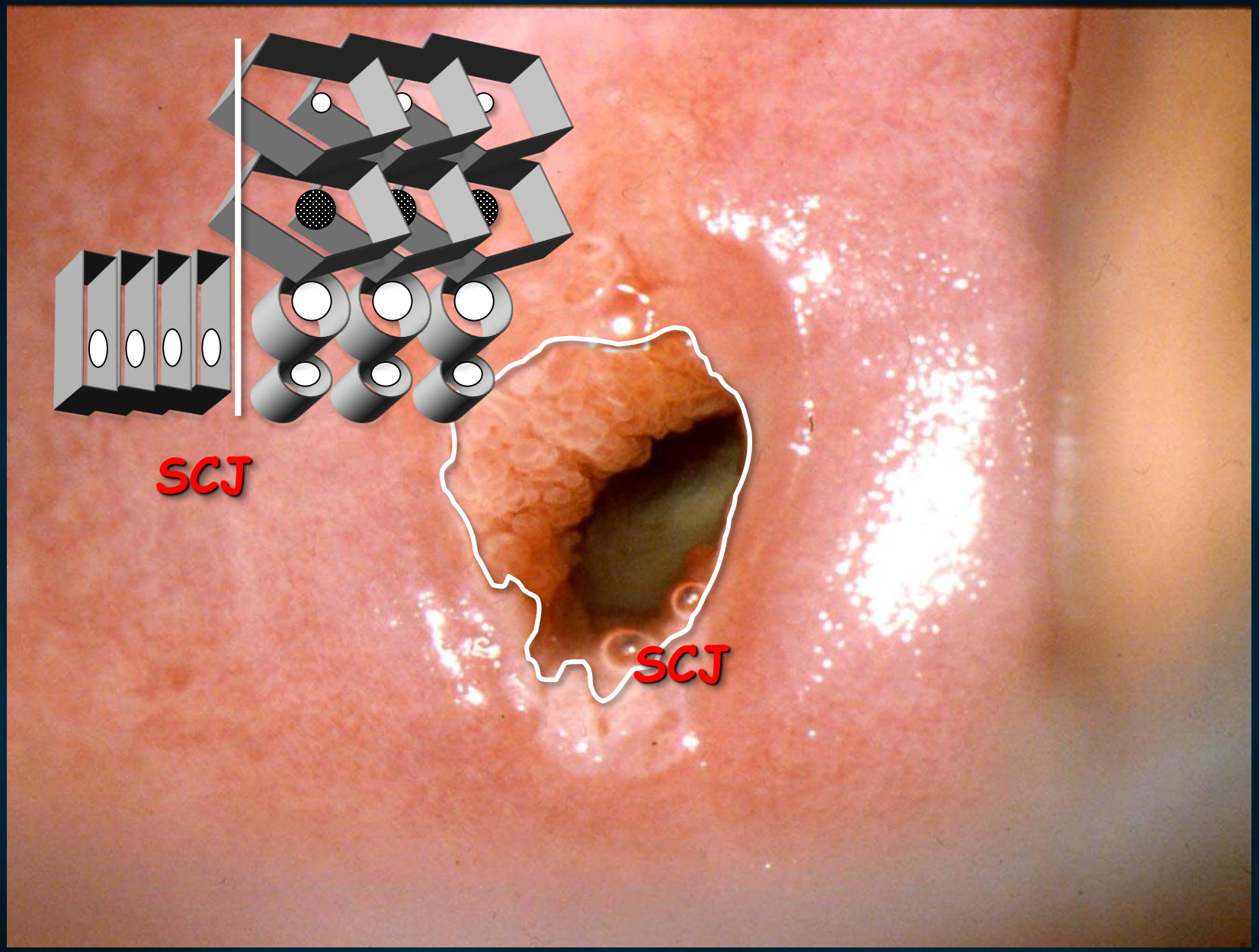
endocervix

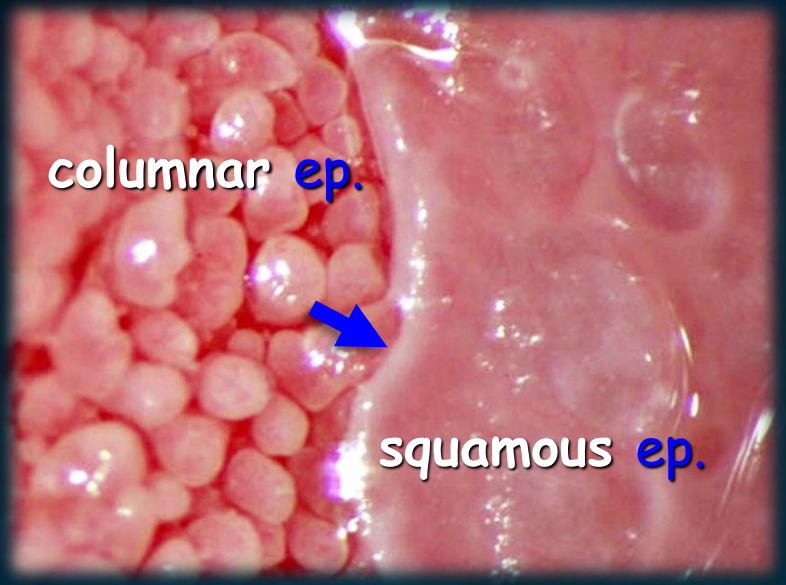
monolayered
columnar ep.

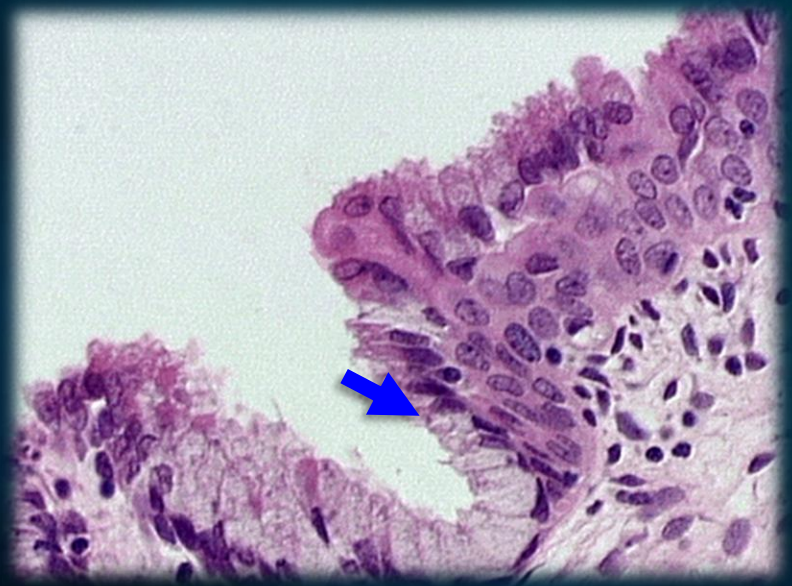
stratified
squamous ep.

SCJ

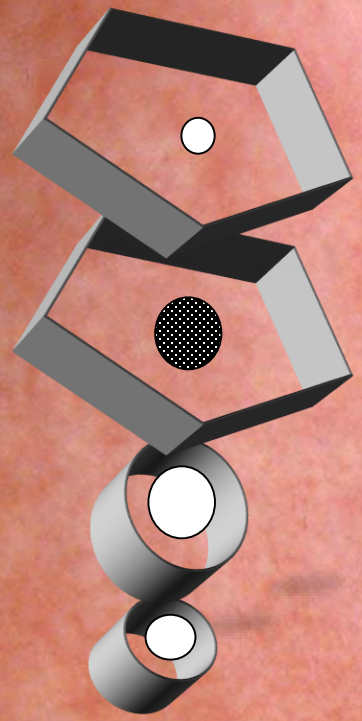
ectocervix


SCJ
SCJ

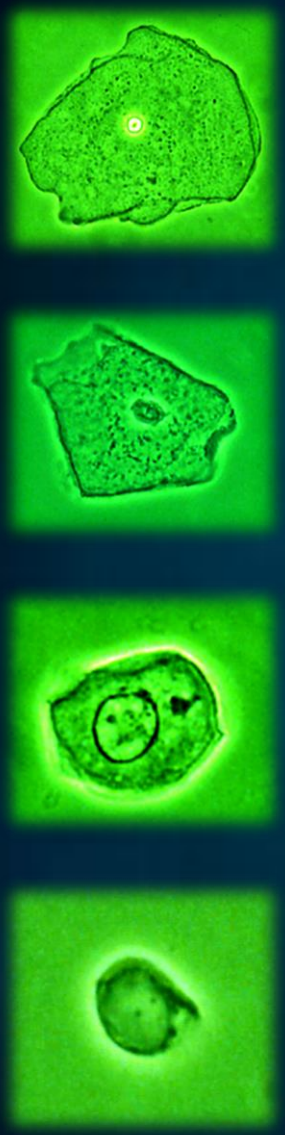




Squamo-Columnar Junction



stratified
squamous ep.

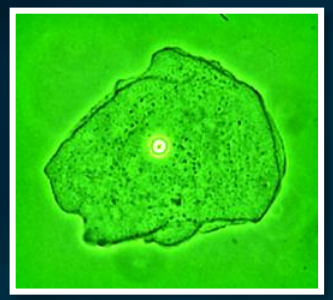


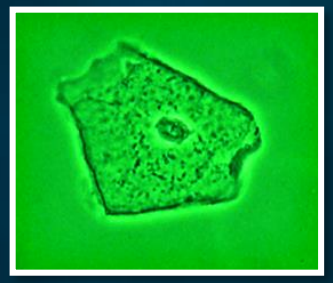
The hormonal stimulation on the vaginal epithelium is responsible for the prevalence of different types of cells in the vaginal smear

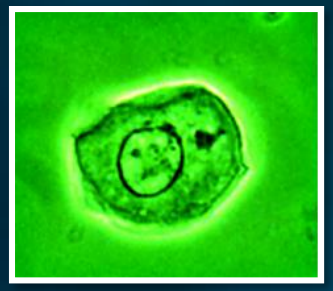
SQUAMOUS EPITHELIUM

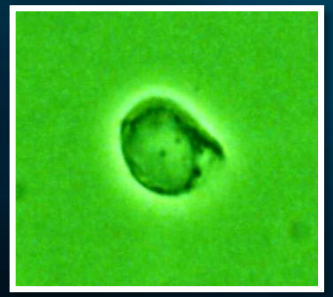
squamous cells

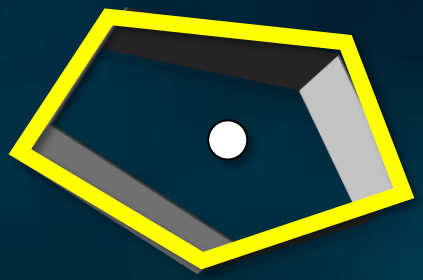
roundish cells





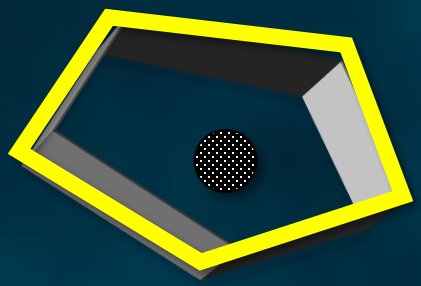






superficial cell

predominant cytoplasm



intermediate cell

parabasal cell

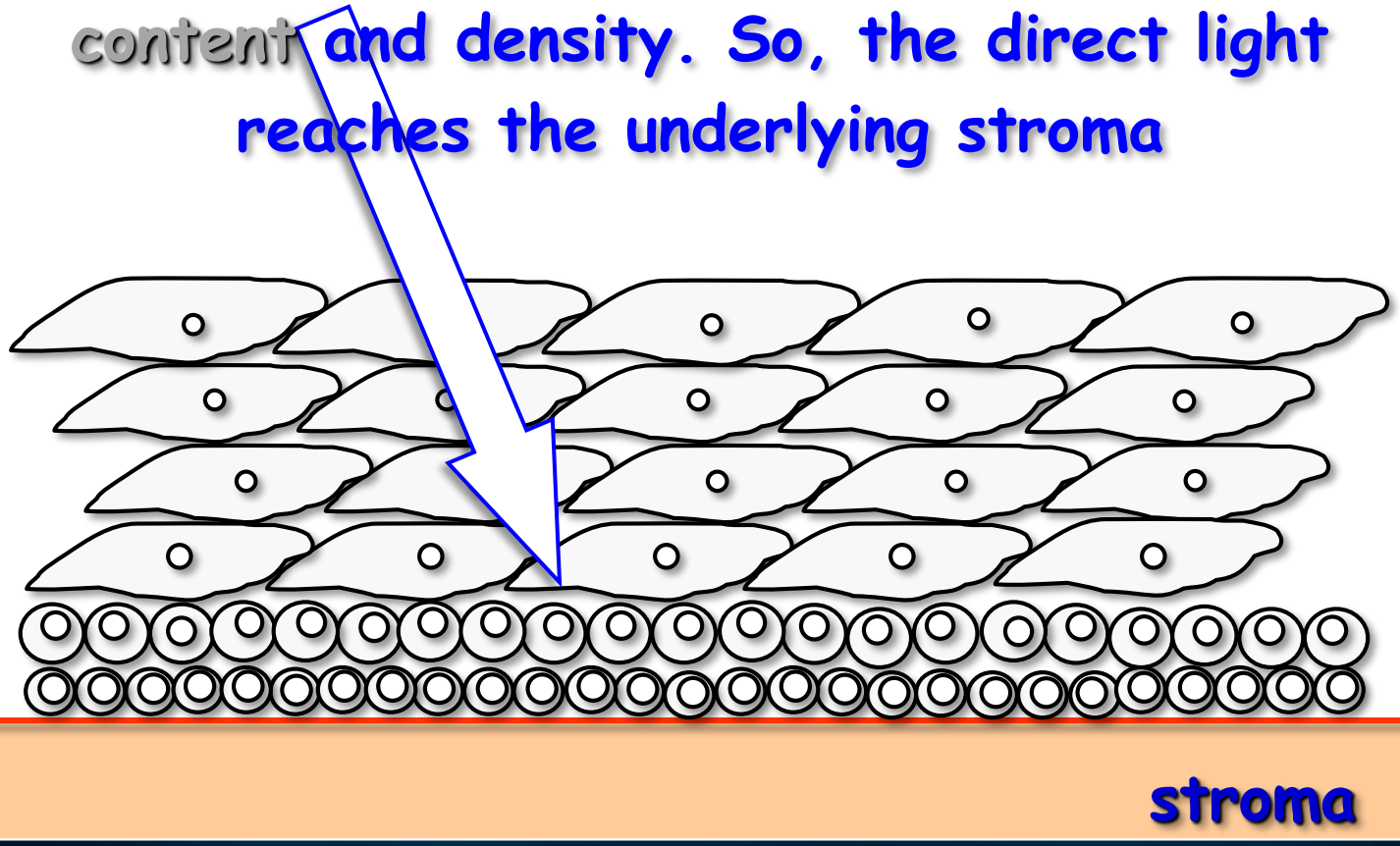
predominant nucleus

basal cell

basement membrane

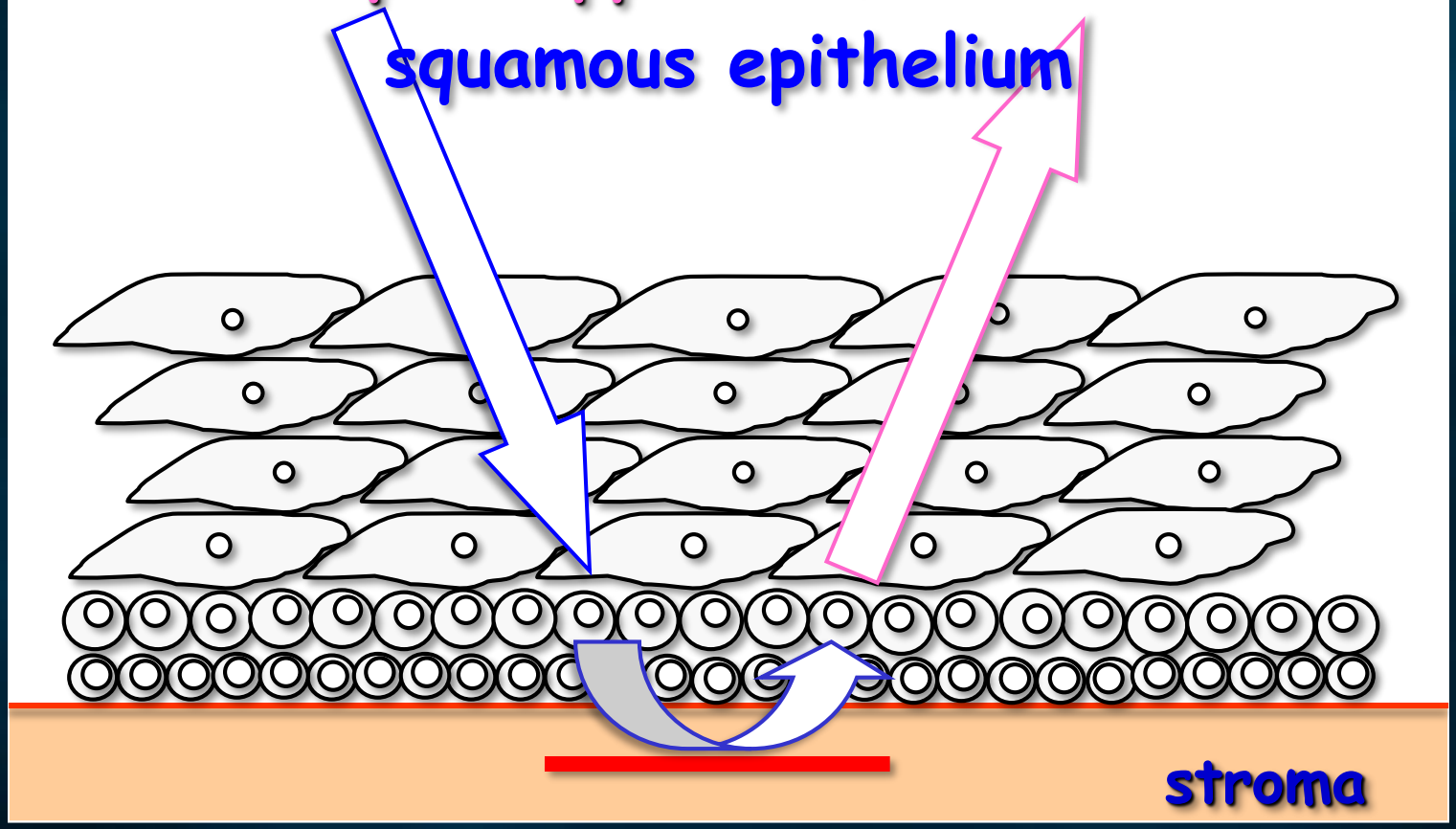
MATURE SQUAMOUS EPITHELIUM

The mature squamous epithelium acts as an effective filter due to its low nuclear content and density. So, the direct light reaches the underlying stroma



MATURE SQUAMOUS EPITHELIUM

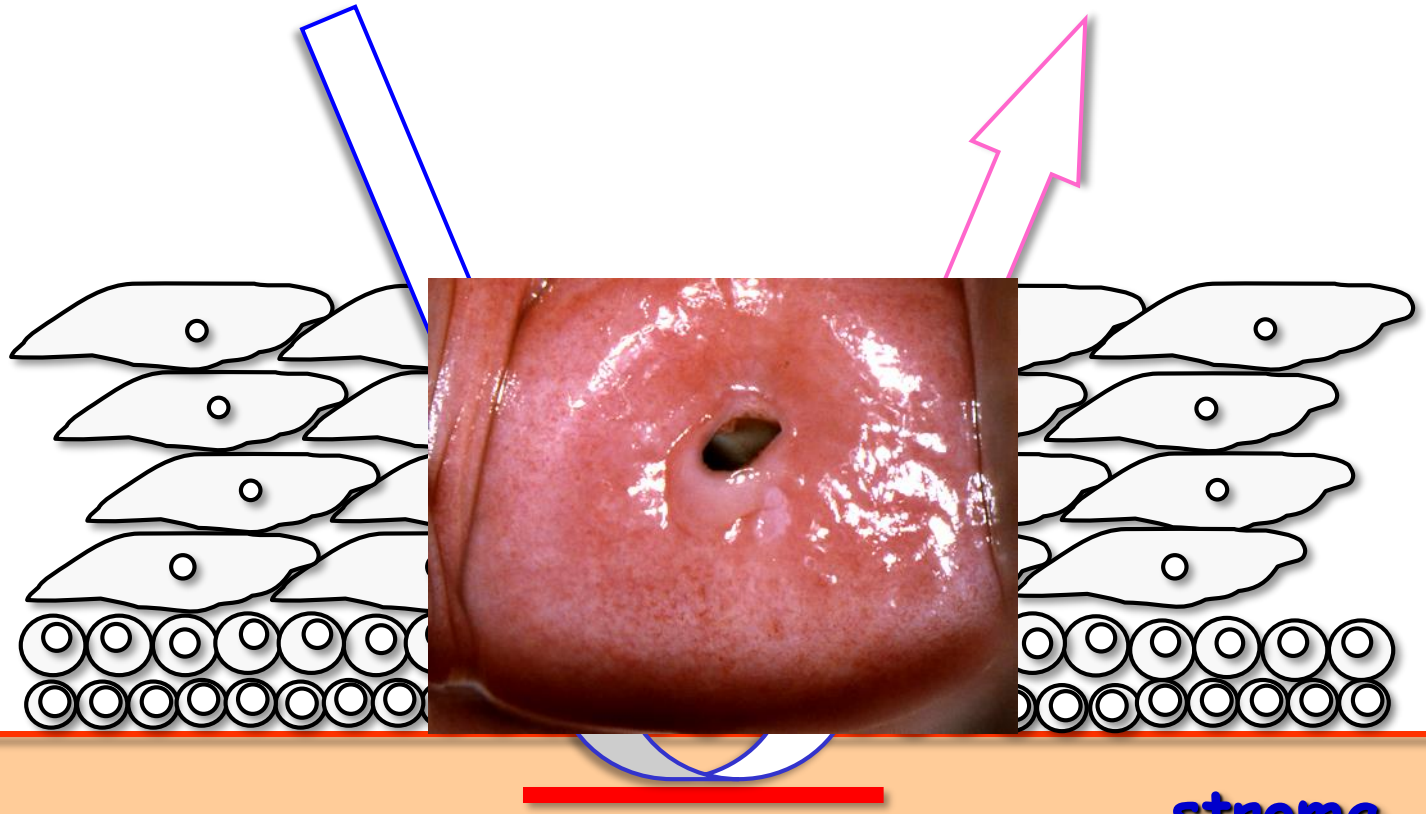
The reflected light will give a pink appearance to the squamous epithelium



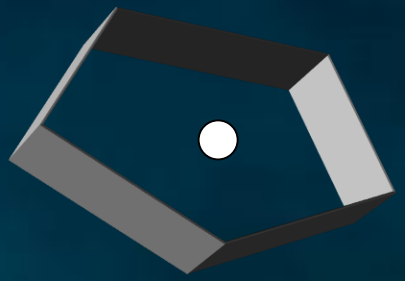
MATURE SQUAMOUS EPITHELIUM

DIRECT light passes through the entire EPITHELIUM

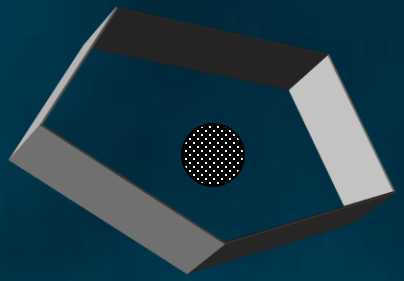
REFLECTED light from STROMA is TRANSLUCENT PINK



SQUAMOUS EPITHELIUM

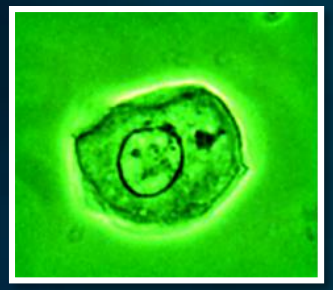


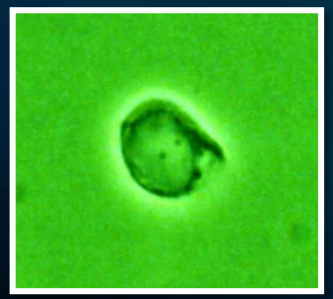
superficial cell

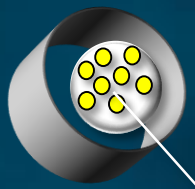


intermediate cell

large nuclei

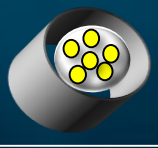






parabasal cell

proteins ⇨ acetowhiteness

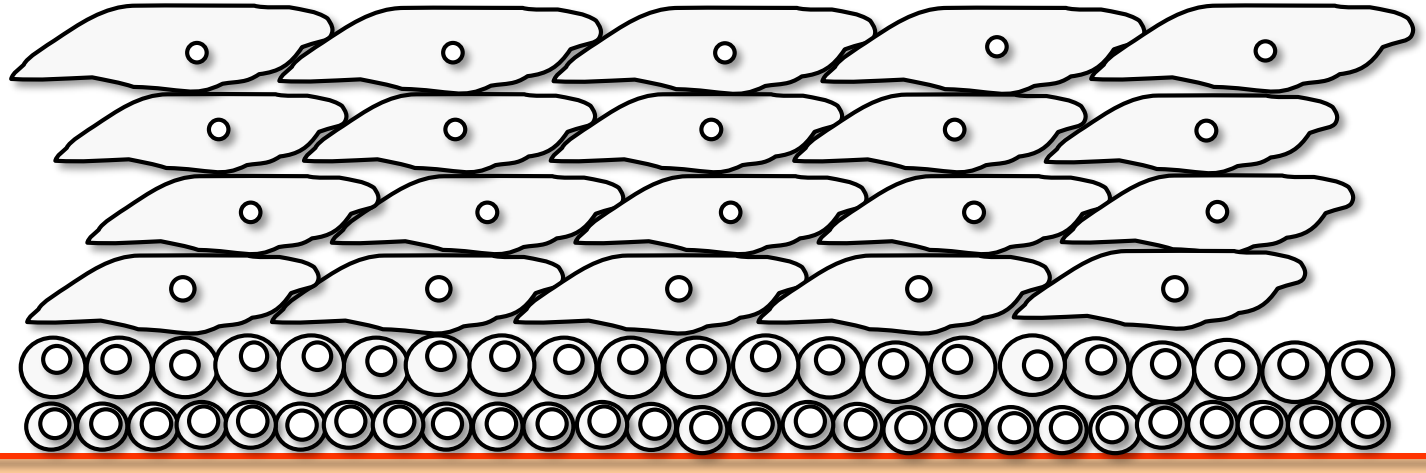


basal cell

basement membrane

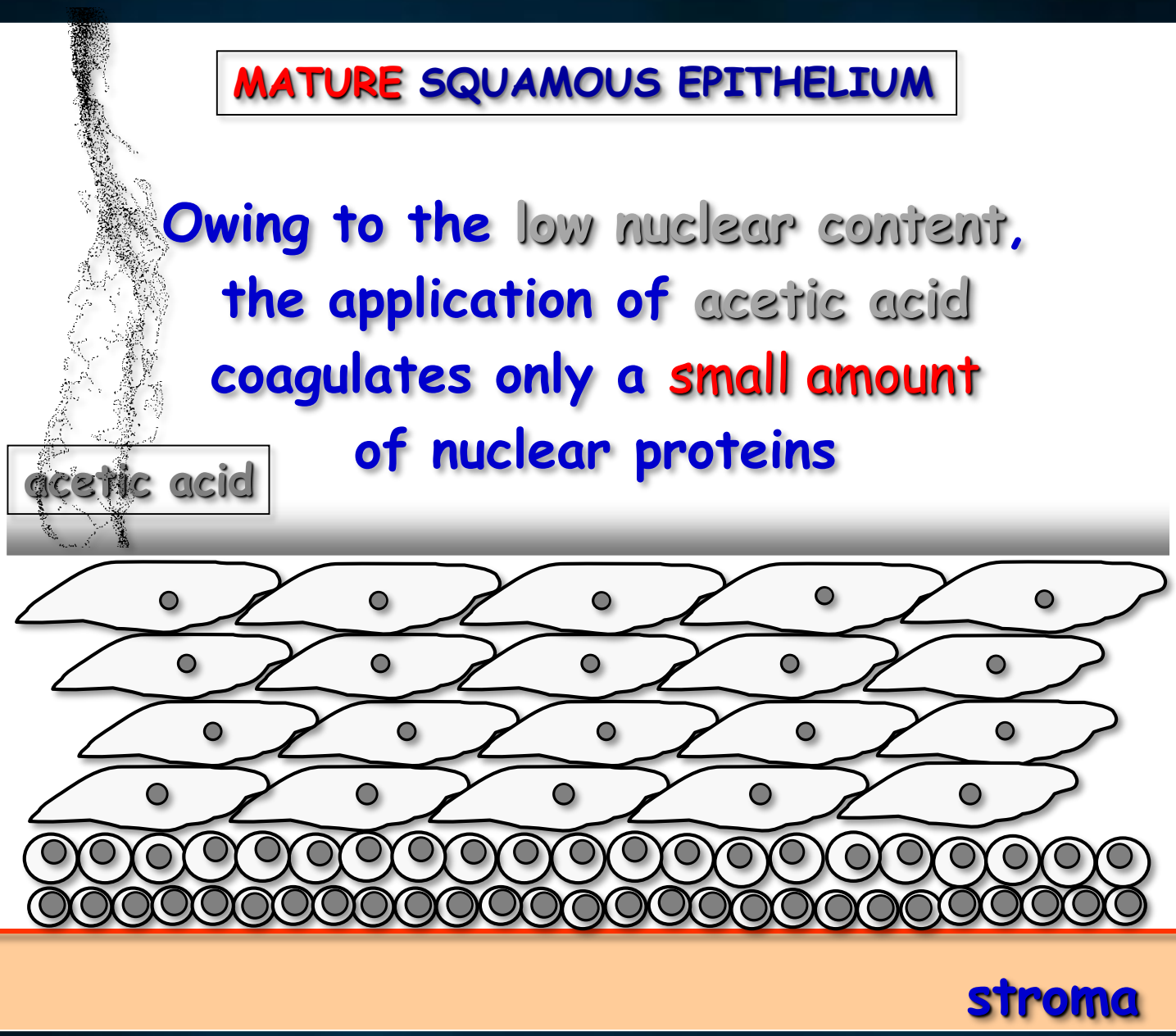
MATURE SQUAMOUS EPITHELIUM

Mature squamous epithelium is predominantly costituted by large squamous cell with small nuclei and so a low nuclear content



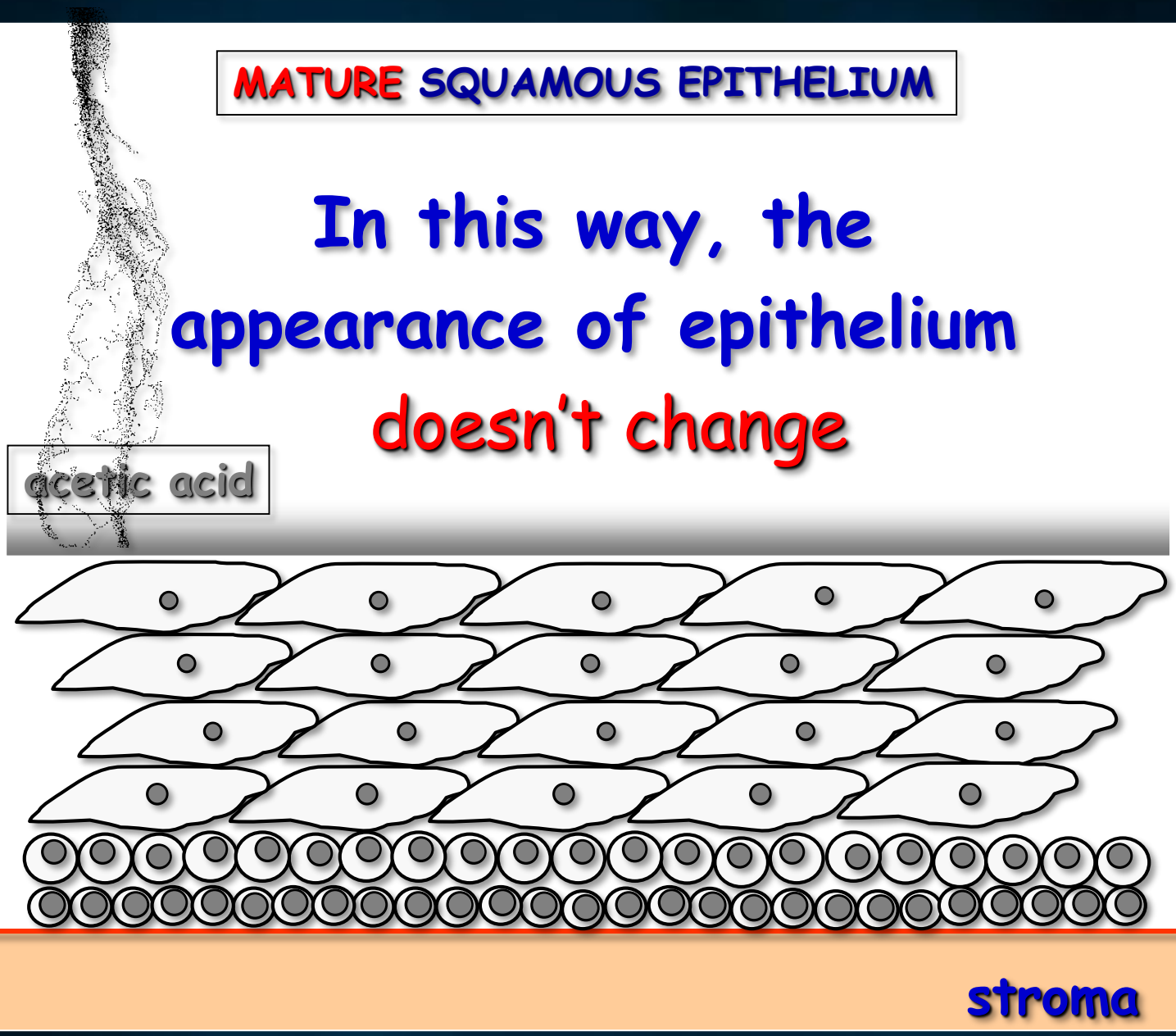
MATURE SQUAMOUS EPITHELIUM

Owing to the low nuclear content, the application of acetic acid coagulates only a small amount of nuclear proteins



MATURE SQUAMOUS EPITHELIUM

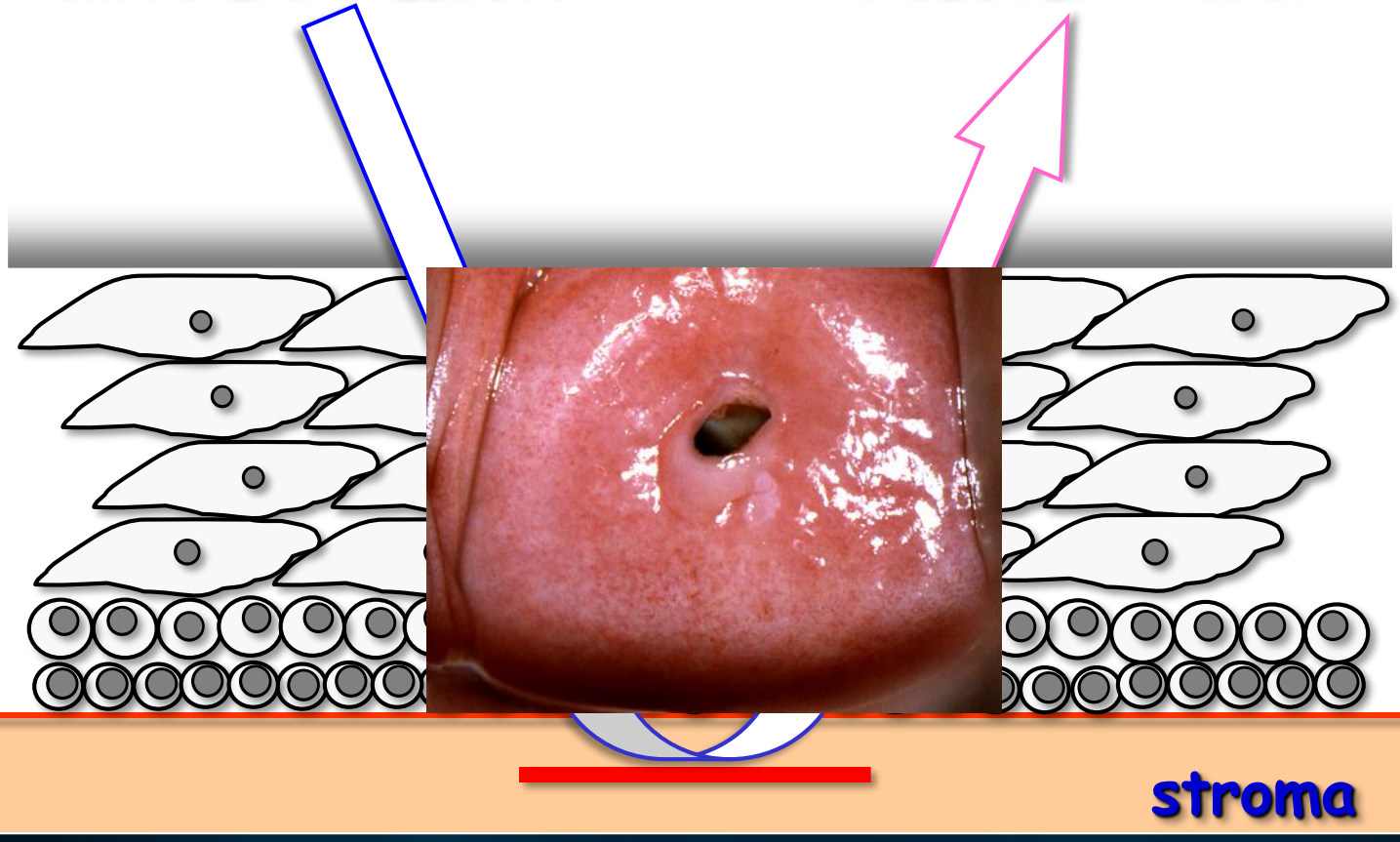
In this way, the appearance of epithelium doesn't change



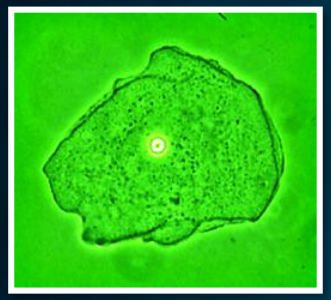
MATURE SQUAMOUS EPITHELIUM

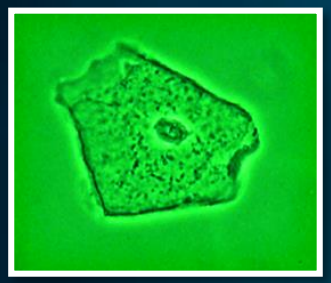
DIRECT light passes through the entire EPITHELIUM

REFLECTED light from STROMA is TRANSLUCENT PINK

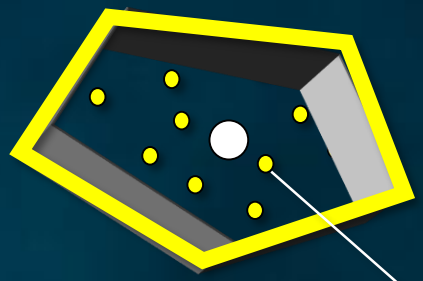


SQUAMOUS EPITHELIUM



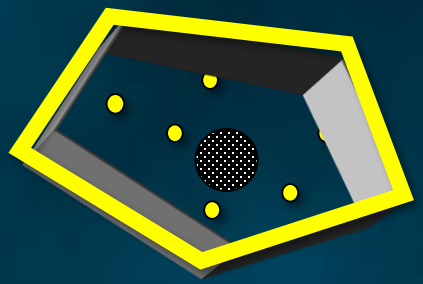


large cytoplasm



superficial cell

glycogen ⇨ capture of Lugol's jodine



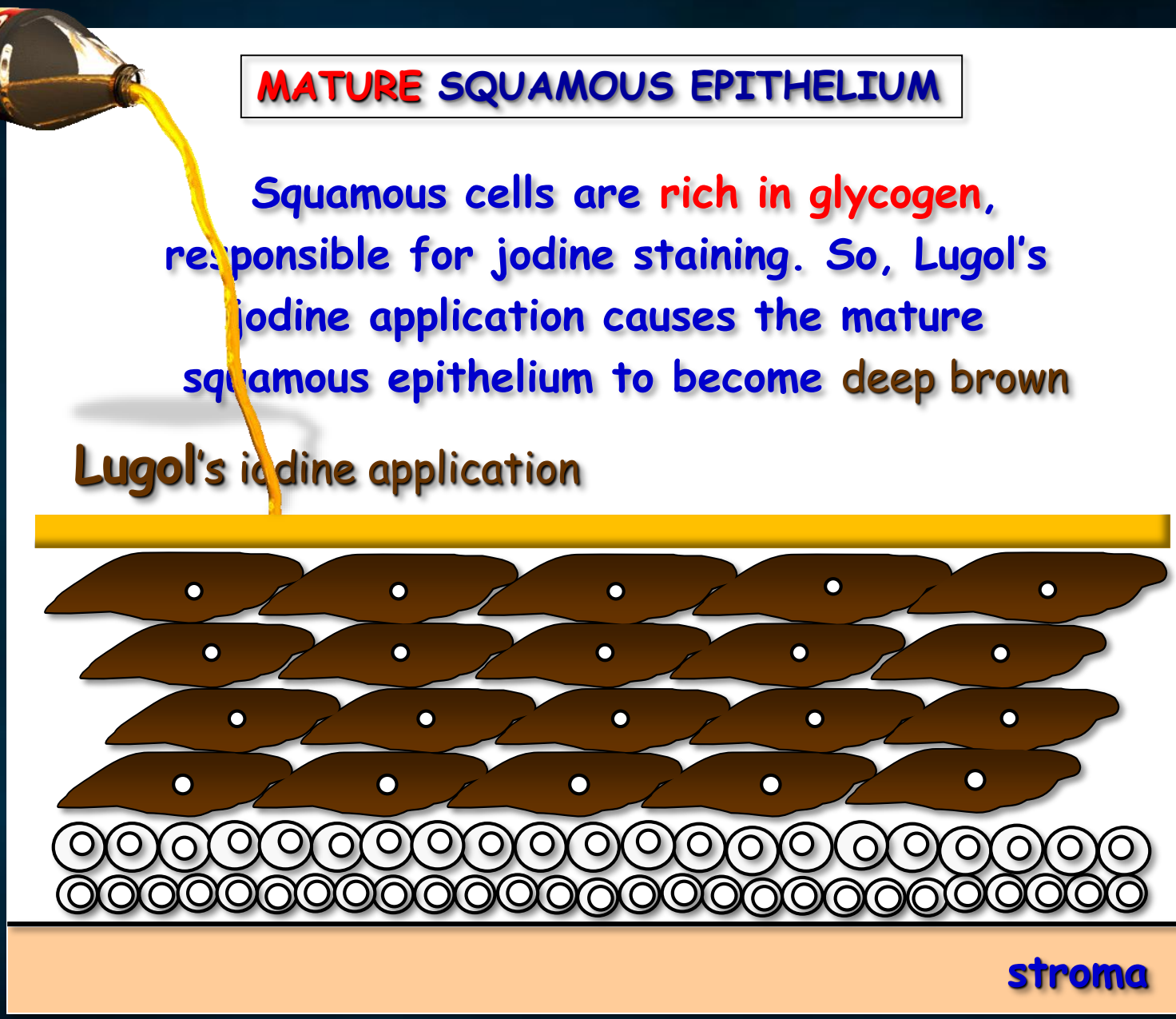
intermediate cell

parabasal cell

basal cell

MATURE SQUAMOUS EPITHELIUM

Squamous cells are rich in glycogen, responsible for jodine staining. So, Lugol's jodine application causes the mature squamous epithelium to become deep brown

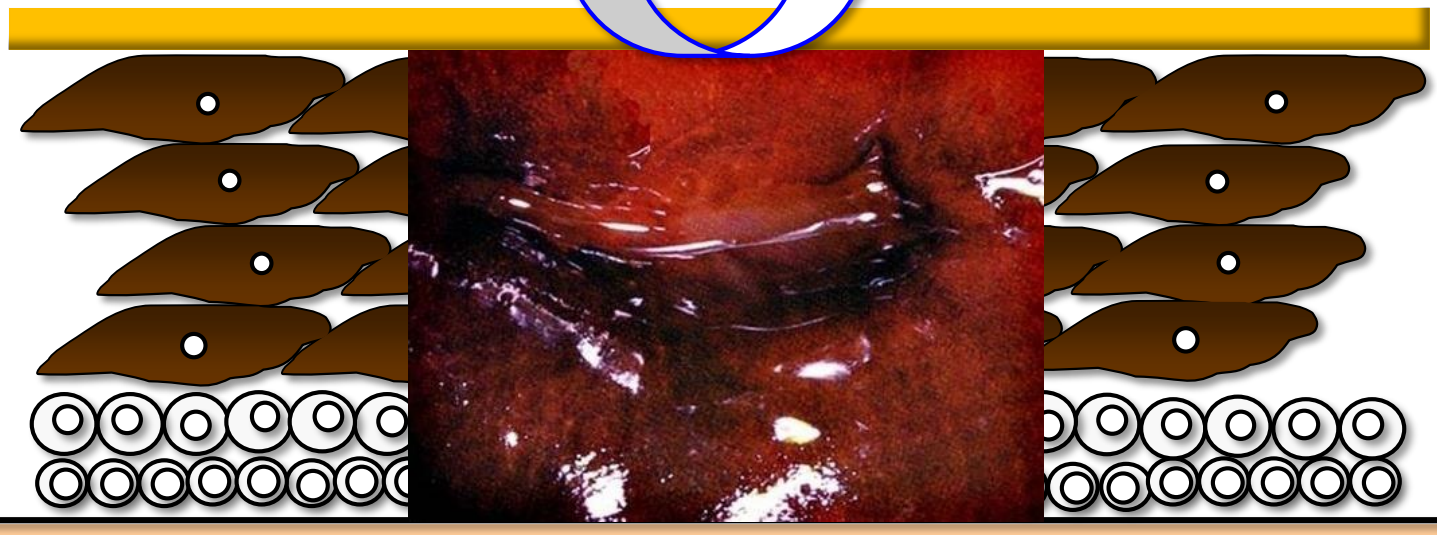


MATURE SQUAMOUS EPITHELIUM

DIRECT light cannot accross the epithelium

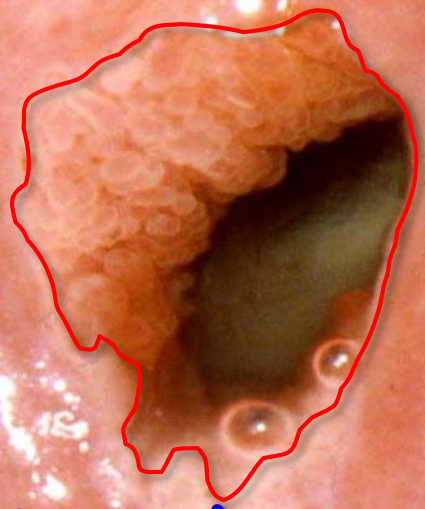
REFLECTED light from EPITHELIUM is DEEP BROWN

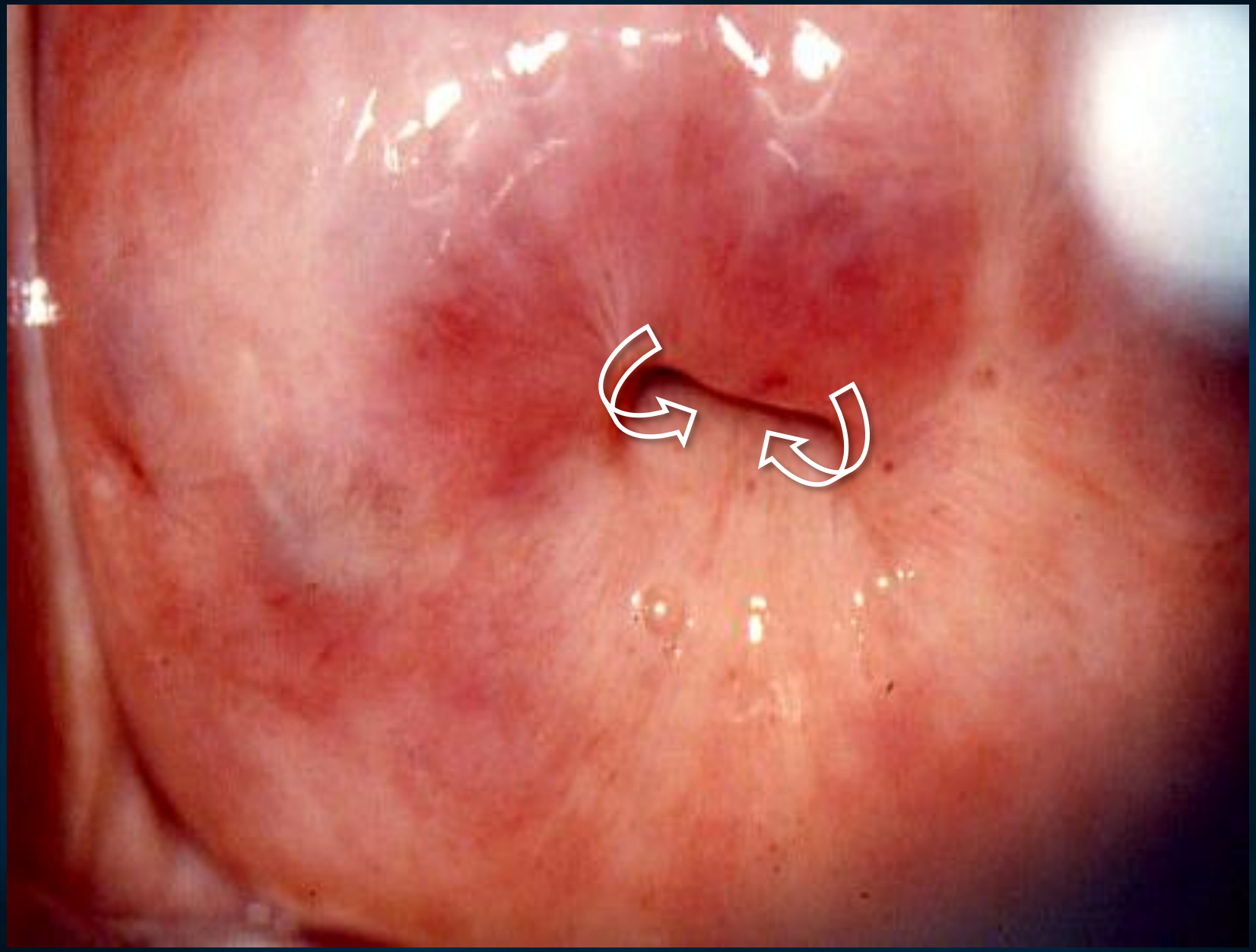
jodine POSITIVE area

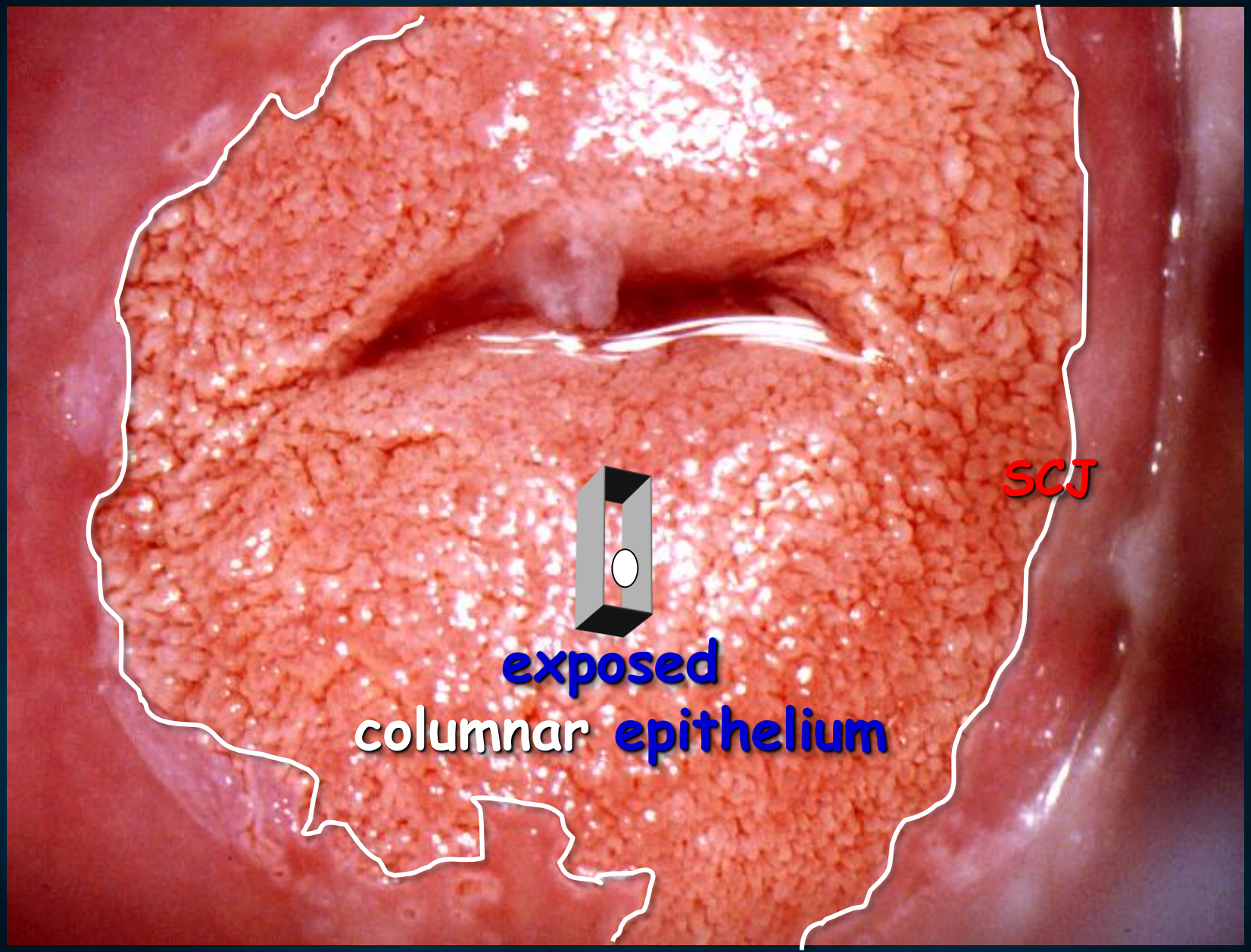


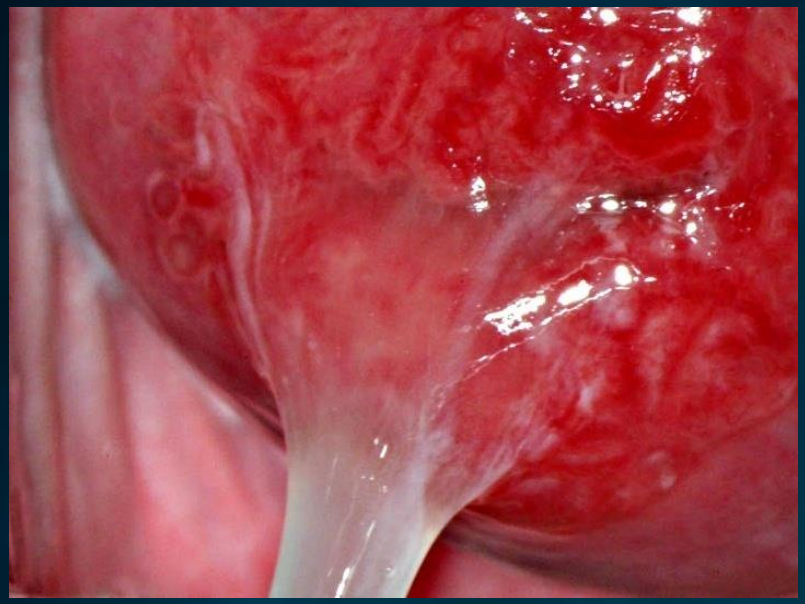
stroma

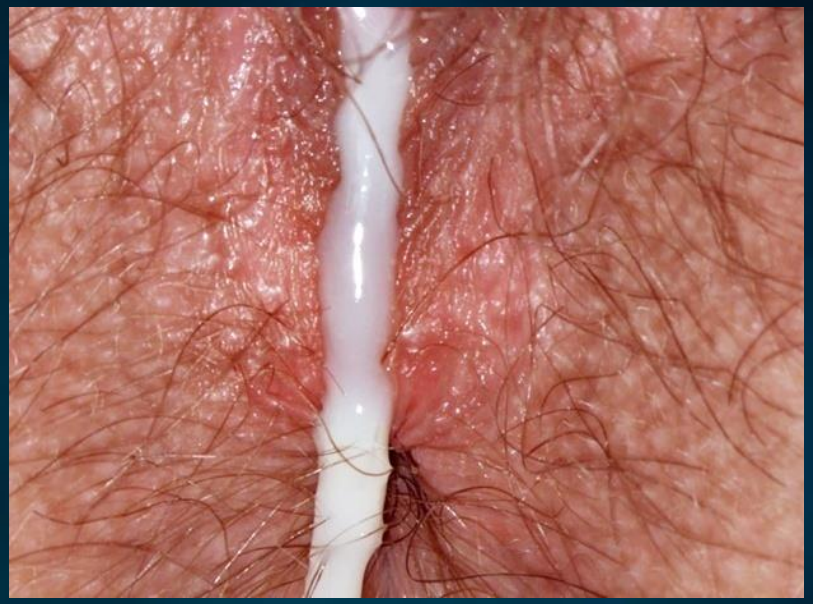
The SCJ is not static but moves in relation to the whole cervix, depending on the hormonal conditions



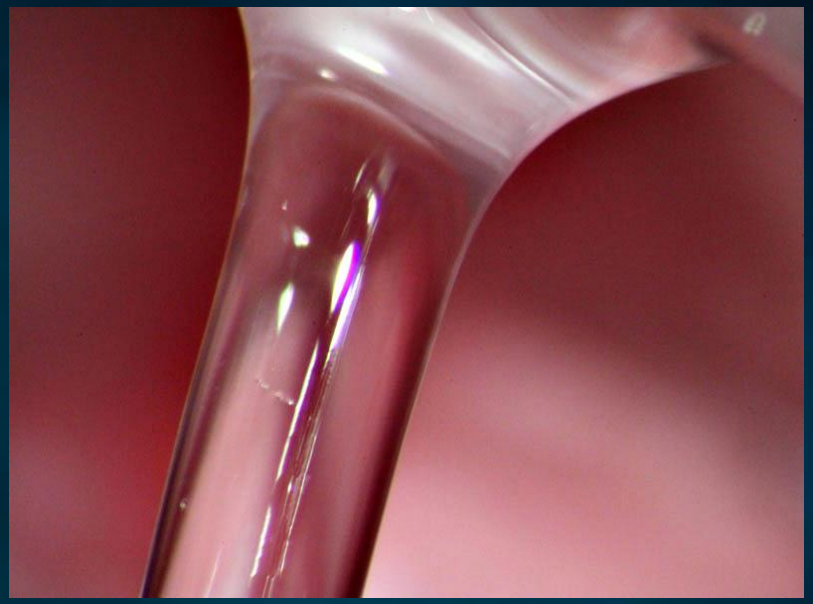



SCJ
exposed
columnar epithelium

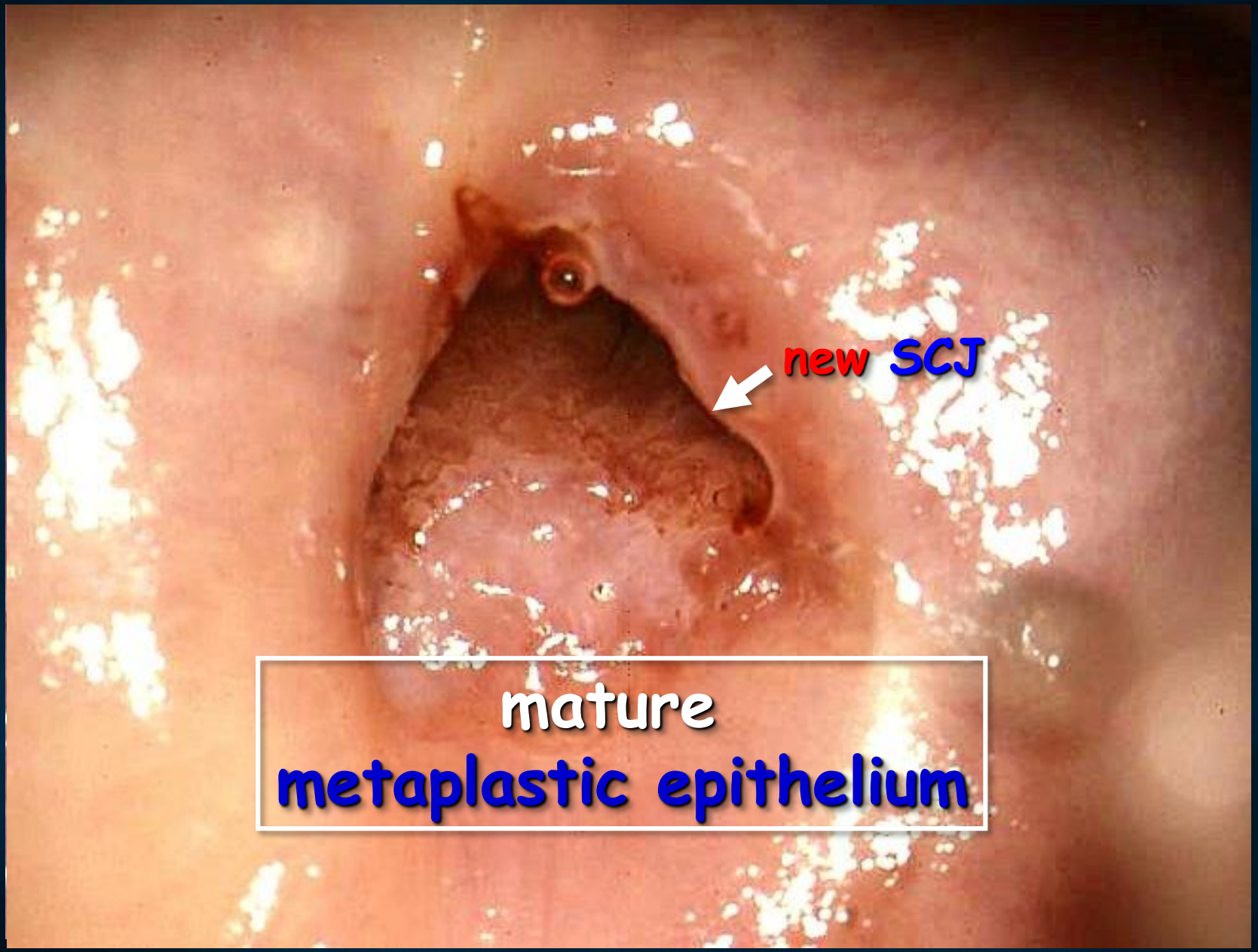


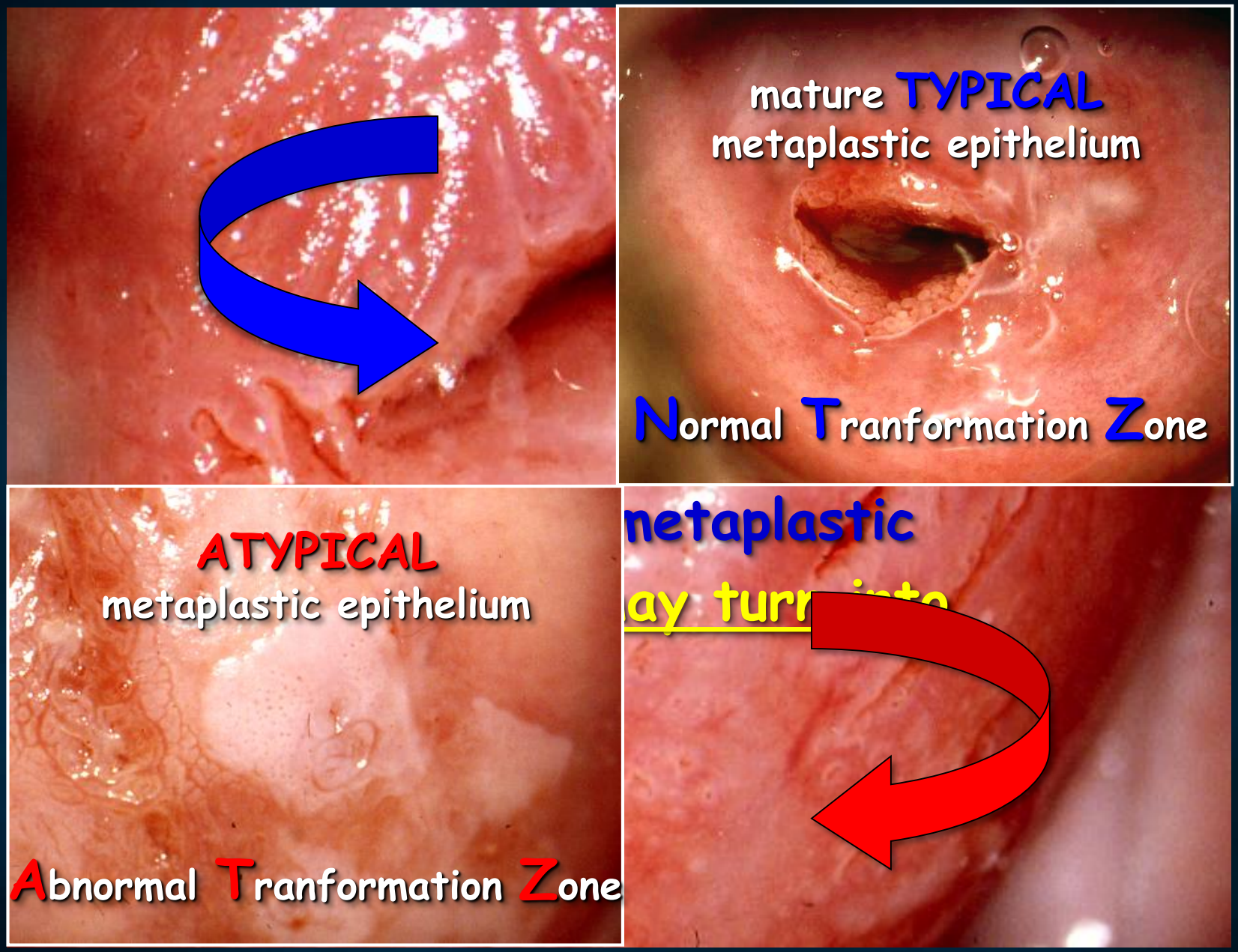


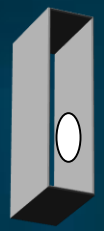
The persistent egg white or creamy cervical mucus from exposed epithelium

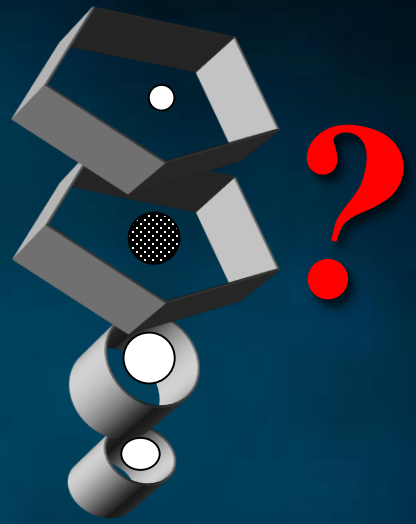


is different from watery cervical mucus visible only at the time of ovulation


new SCJ
mature
metaplastic epithelium

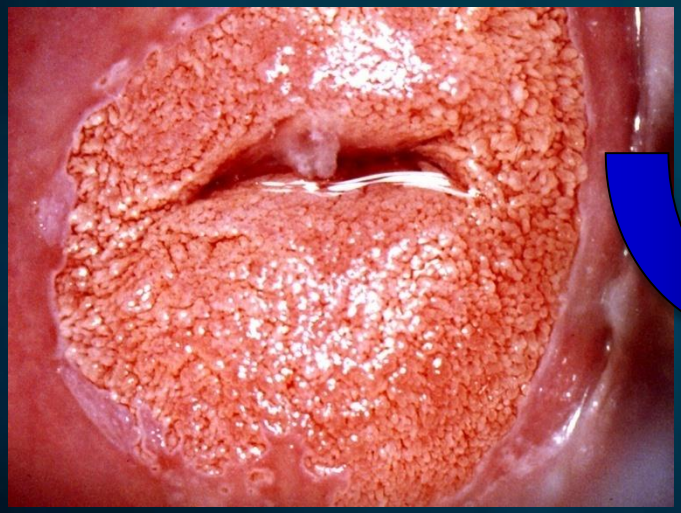

mature TYPICAL
metaplastic epithelium
Normal Tranformation Zone
ATYPICAL
metaplastic epithelium
Abnormal Tranformation Zone
netaplastic

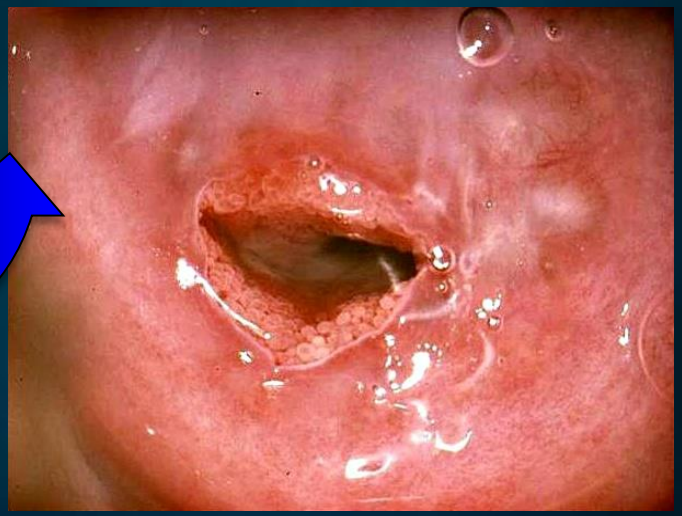


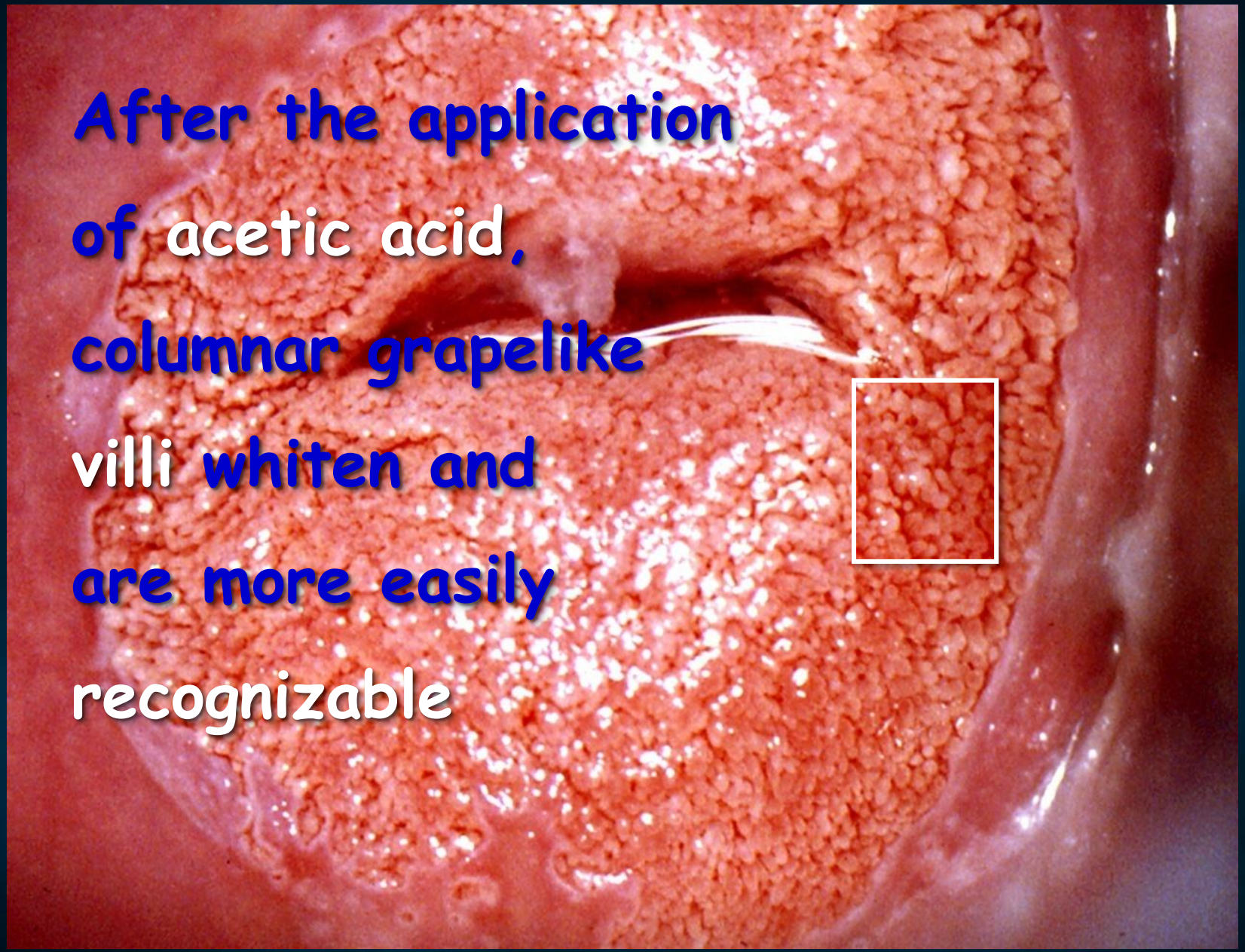


MONOlayered columnar ep

STRATIFIED squamous ep



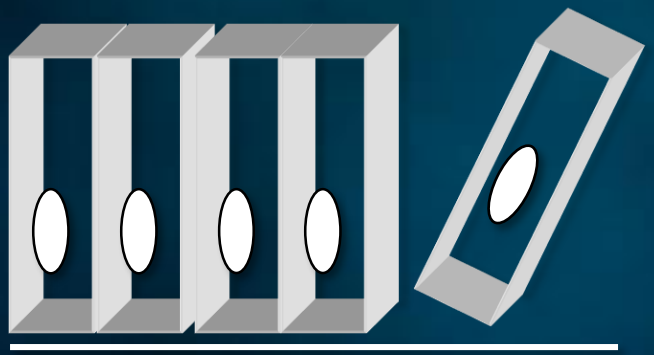


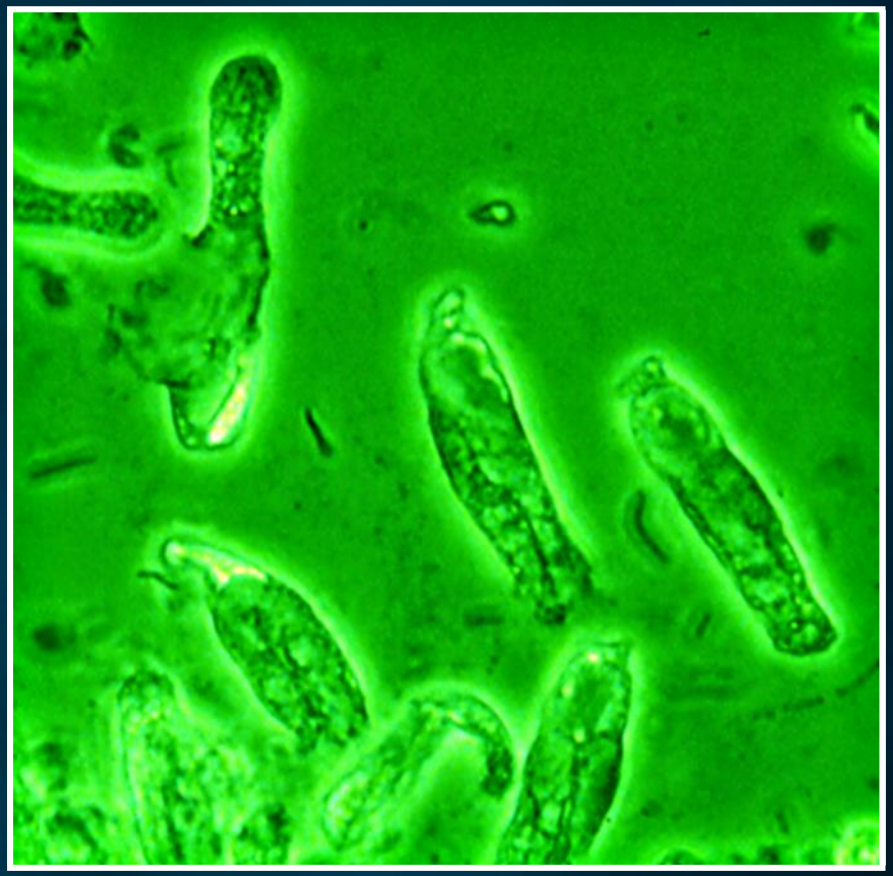

After the application
of acetic acid,
columnar grapelike
villi whiten and
are more easily
recognizable

Each **villus** contains one or more capillary loops with an overlying single layer of columnar cells

low vaginal pH

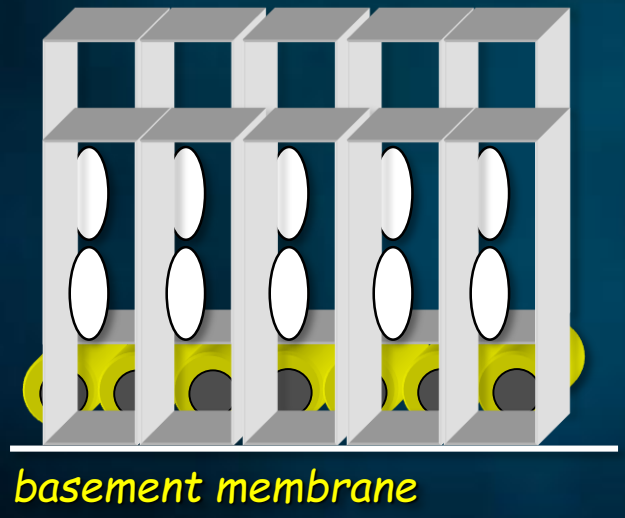
✓ causes the shedding of columnar cells



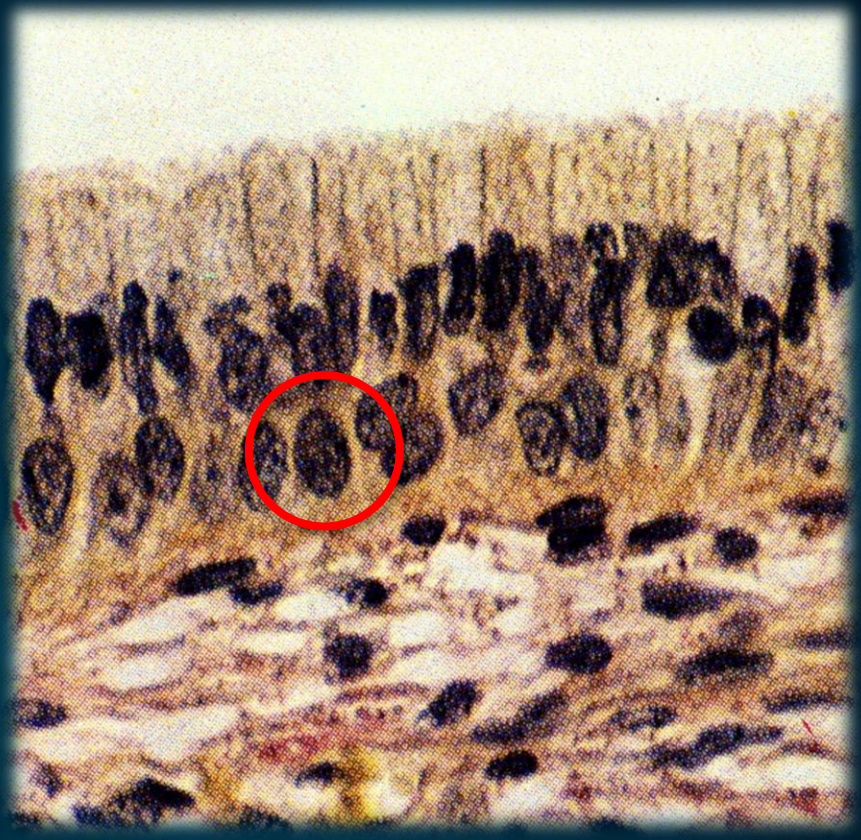


exposed shedding columnar cells (lateral view)

✓ squamous metaplasia is preceded by the appearance of **reserve** cells

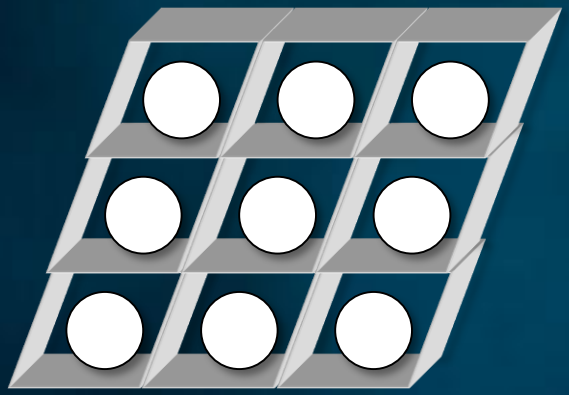


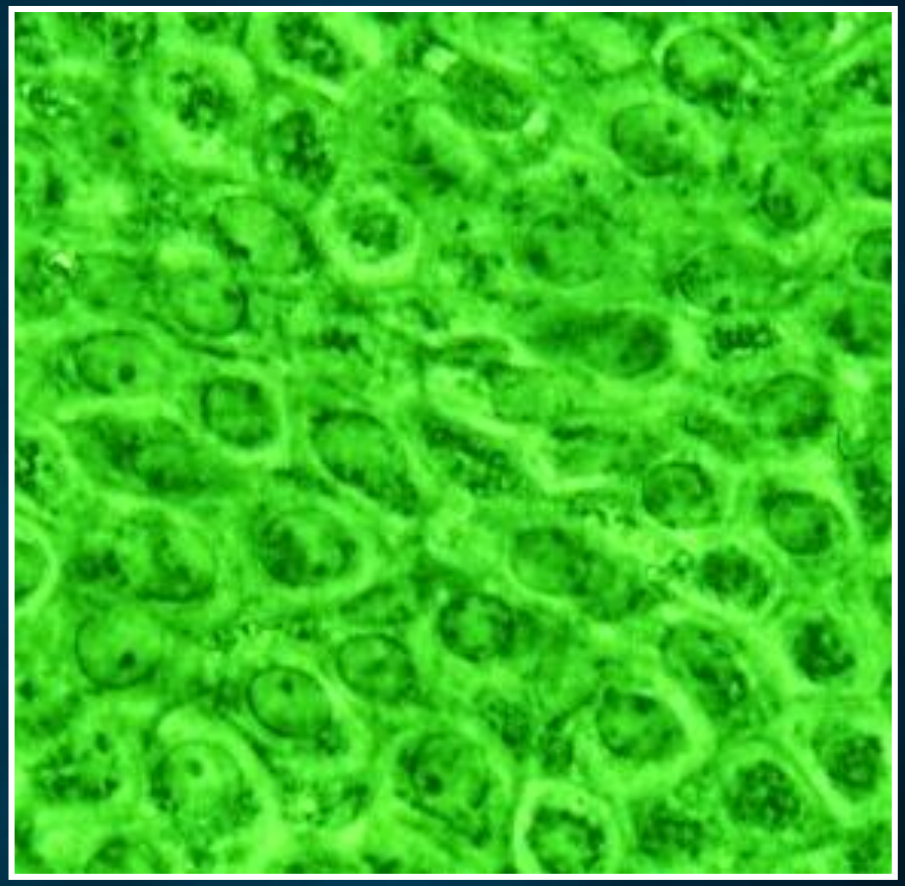
reserve cells



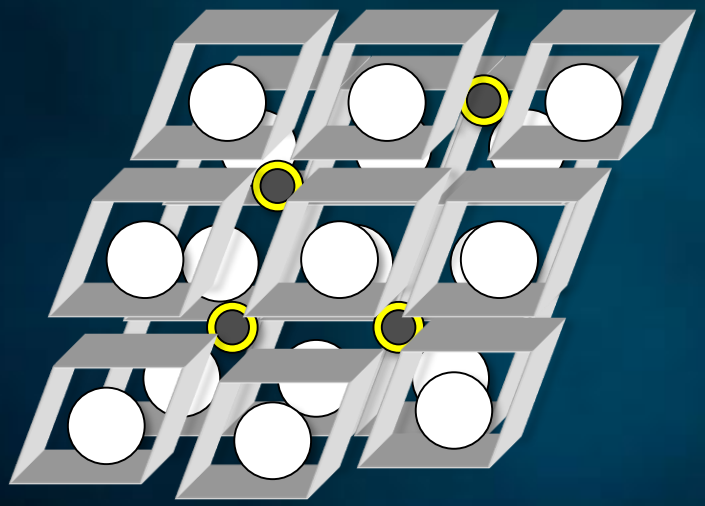
contain a dark nucleus and a thin cytoplasmic ring

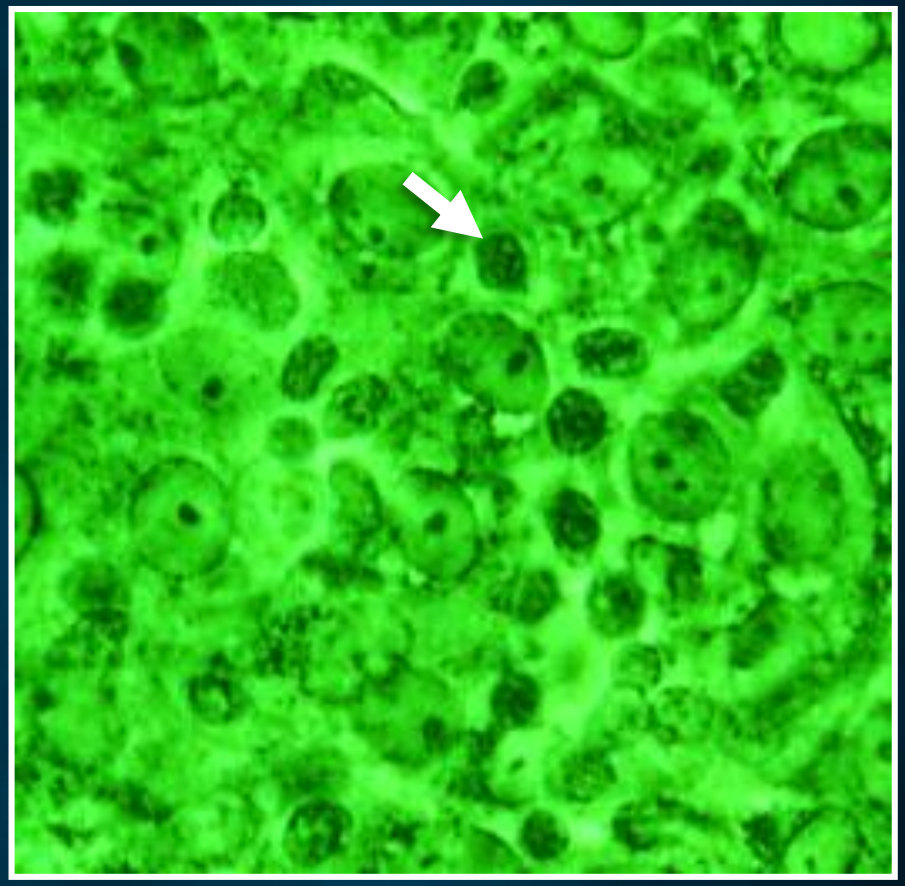
✓ exposed columnar cells, when seen end on, show the honeycomb pattern





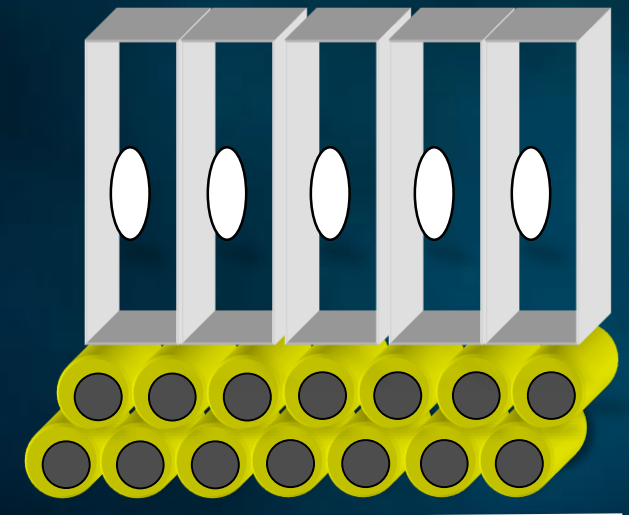
✓ At the beginning, few **reserve** cells are interspersed with **predominant** columnar cells





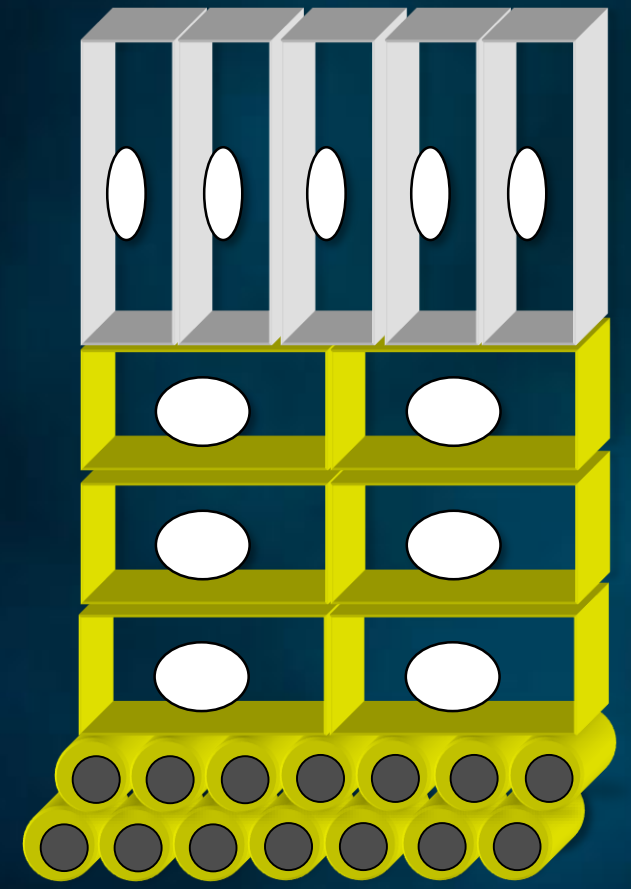
low vaginal pH

✓ proliferation of reserve cells



basement membrane

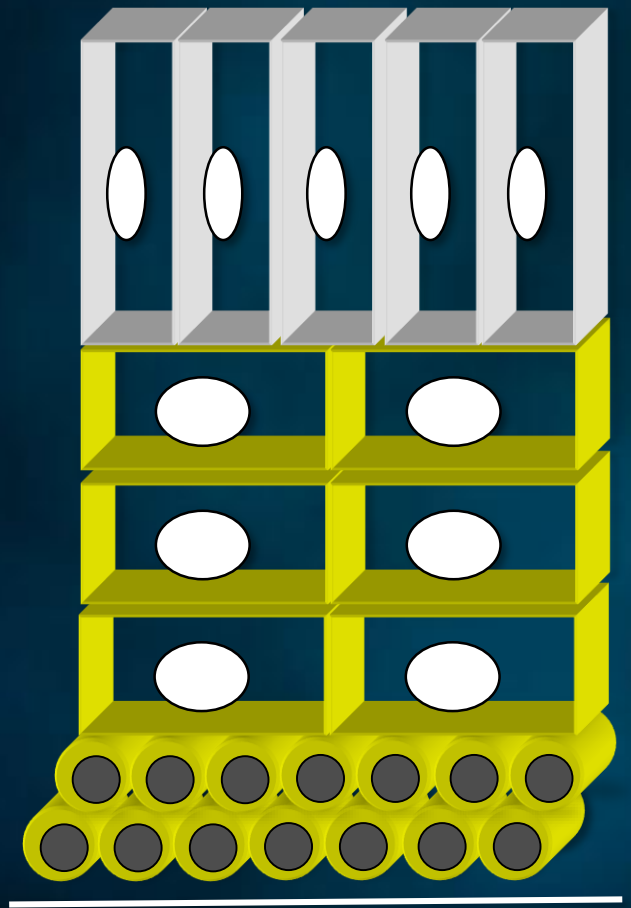
✓ proliferation of metaplastic cells



basement membrane

✓ immature metaplastic epithelium

✓ residual columnar cells are unsaddled



✓ immature metaplastic epithelium

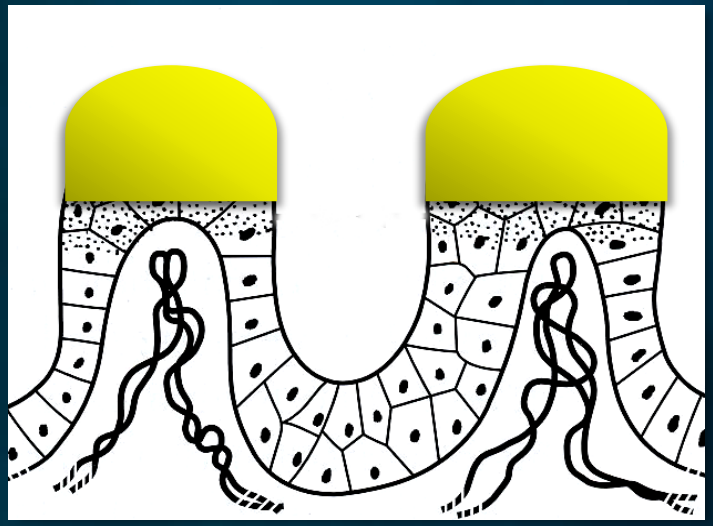
At the beginning,

the acetowhite

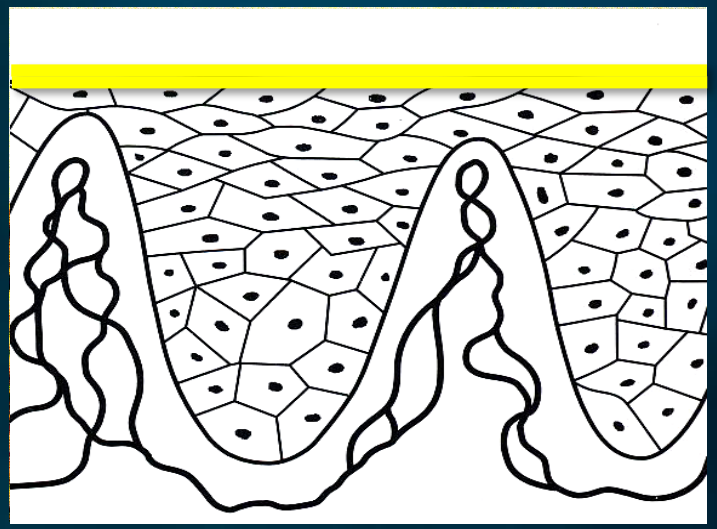
metaplastic

epithelium

caps the villus

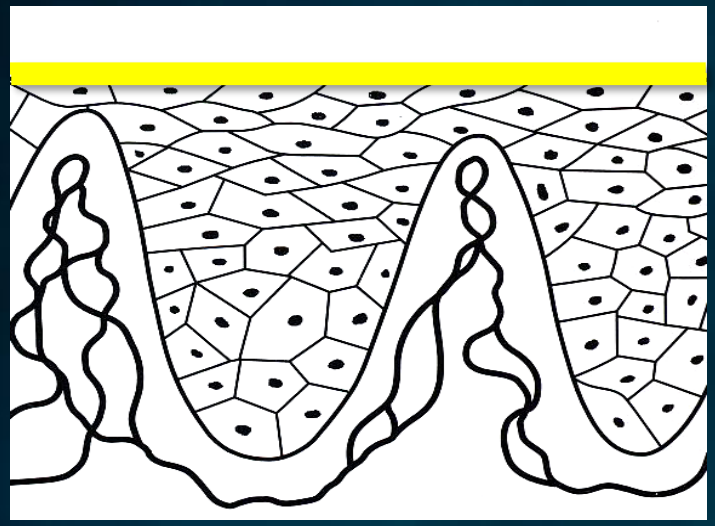


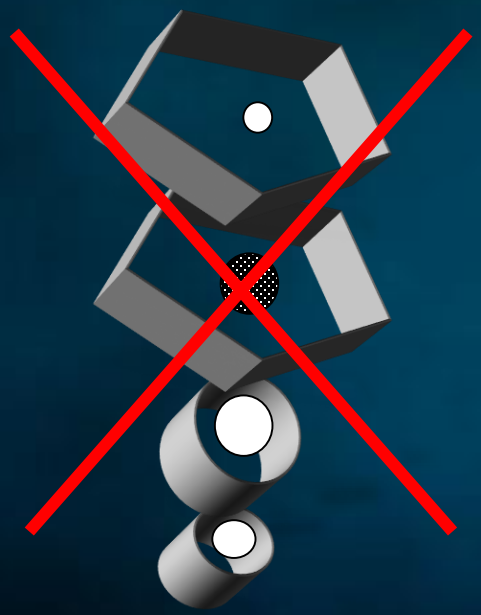
Later, it extends into the clefts of two adjacent villi, until a smooth surface is produced



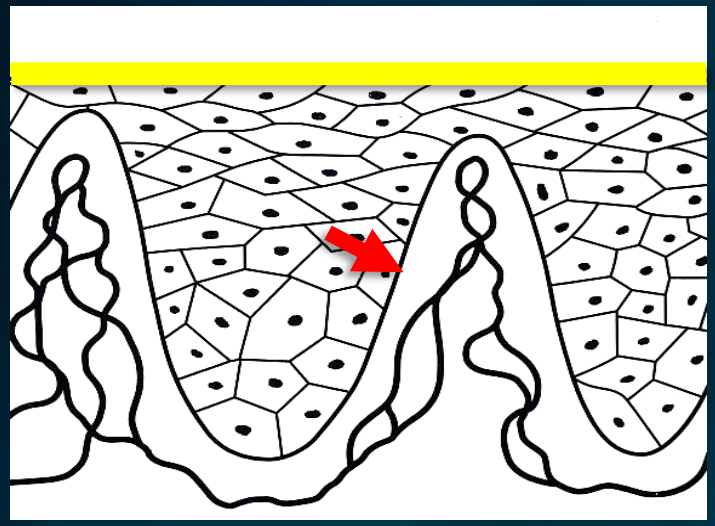
The acetowhite metaplastic epithelium over the villi may exceed in height the smooth surface, developing white punctation

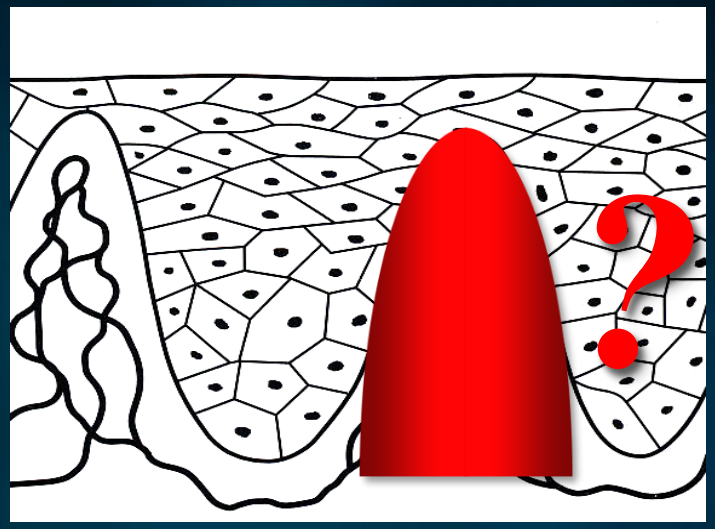
epithelium





This immature metaplastic epithelium is multilayered but not yet differentiatd

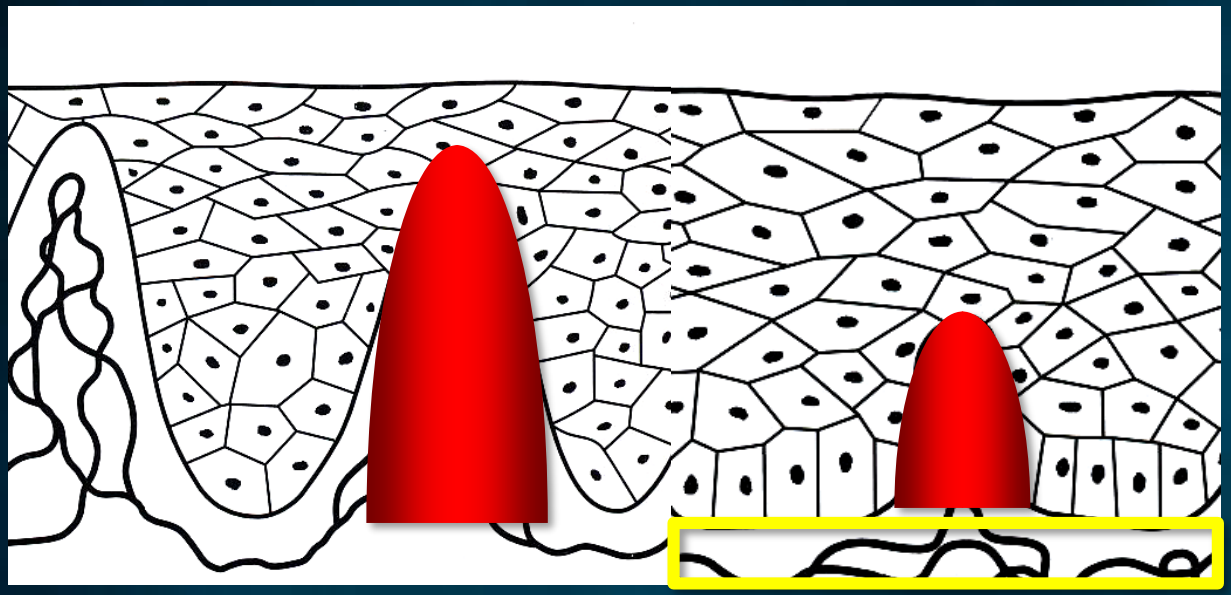




stromal papillae

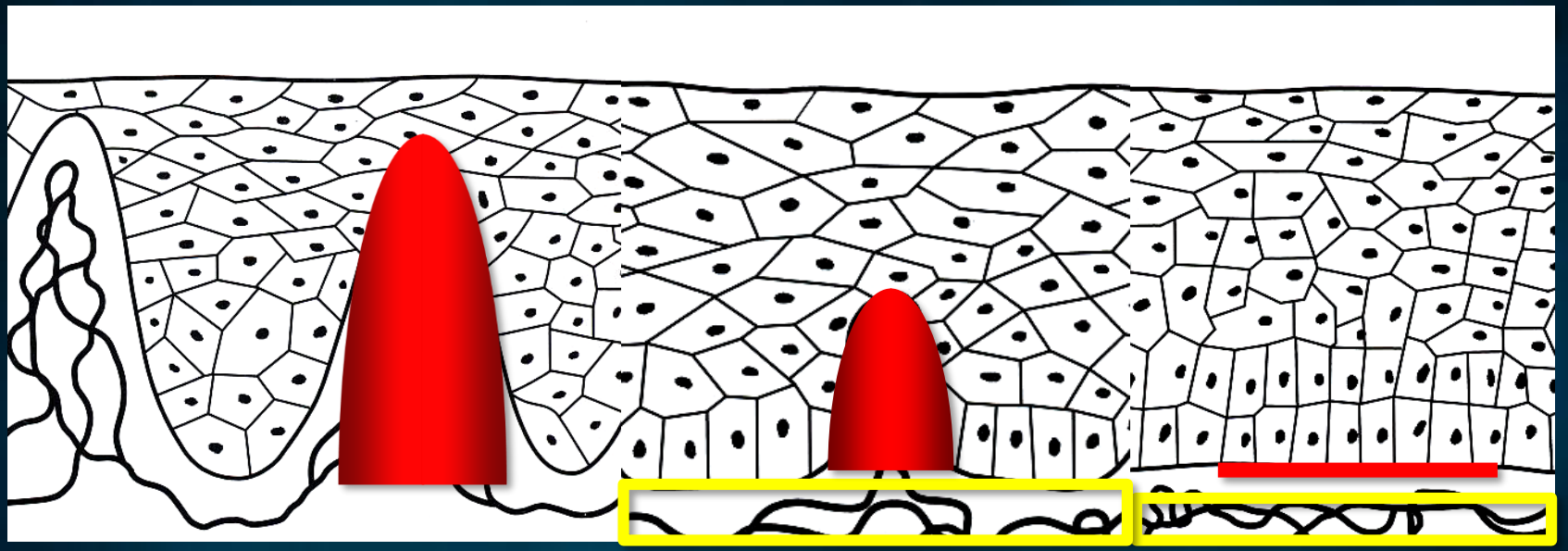
Which is the behaviour of stromal papillae?

TYPICAL metaplastic process



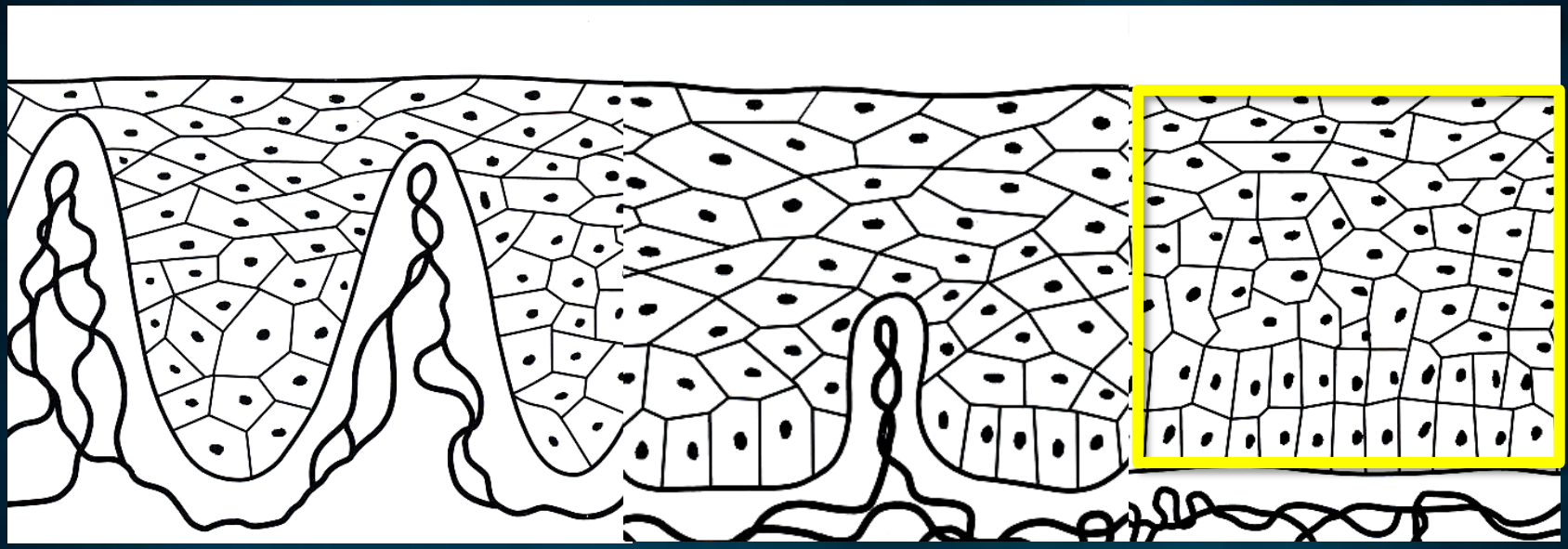
Individual stromal papillae become flatter and the capillary structures in the villi are compressed and reduced in height

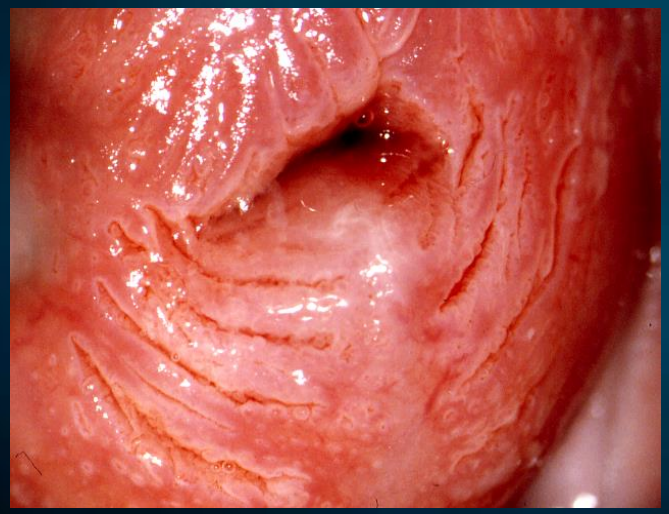
TYPICAL metaplastic process



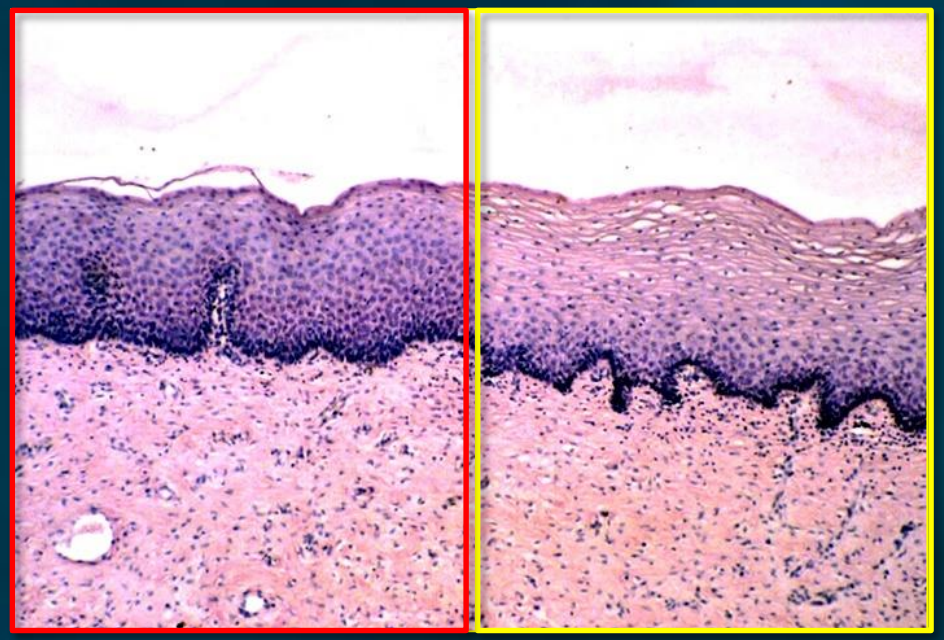
Ultimately, capillary structures form a network under the epithelium

TYPICAL metaplastic process





This immature metaplastic epithelium is multilayered, but not yet differentiated

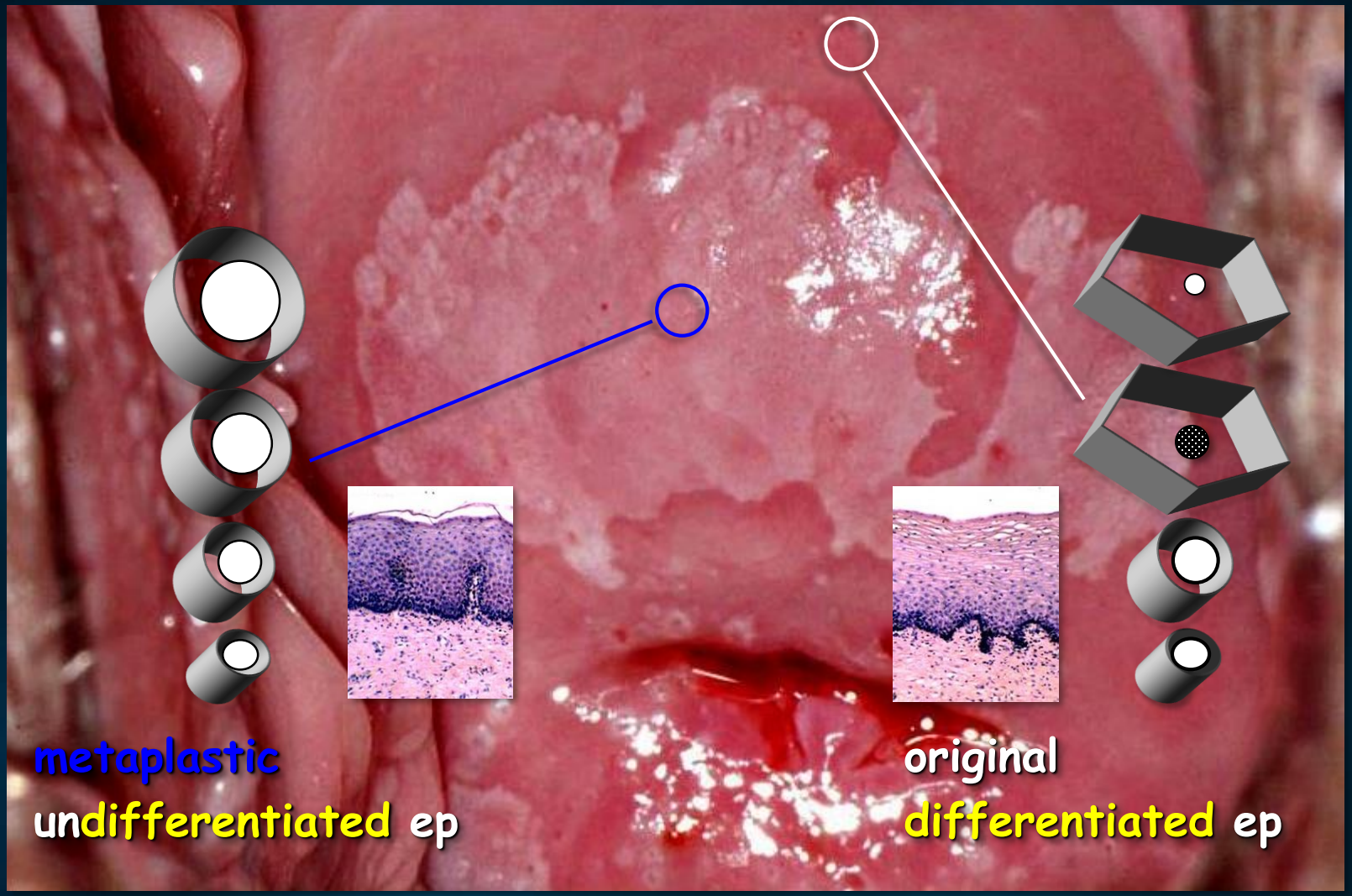


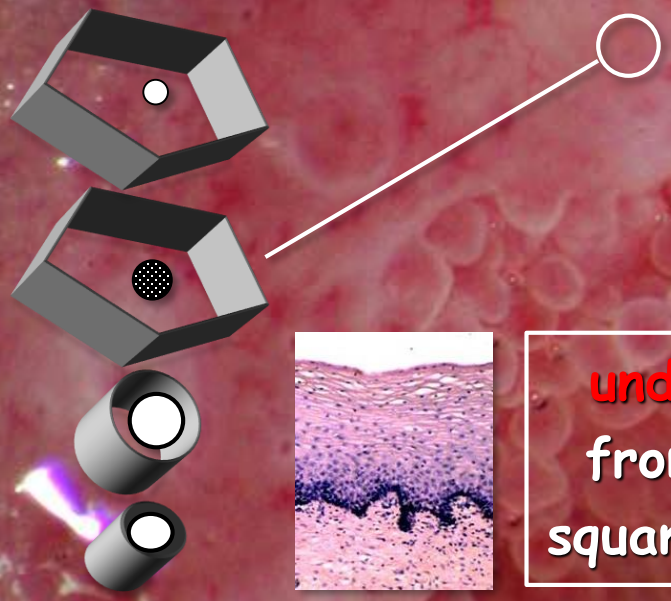
metaplastic

undifferentiated ep

squamous

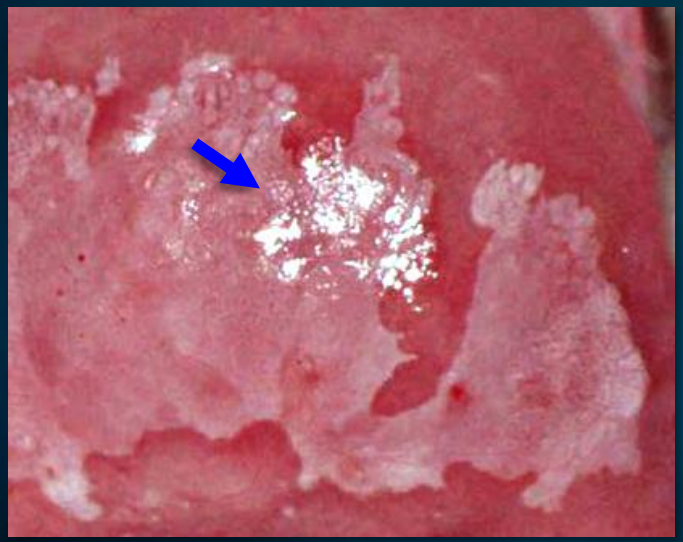
differentiated ep


metaplastic
undifferentiated ep
original
differentiated ep



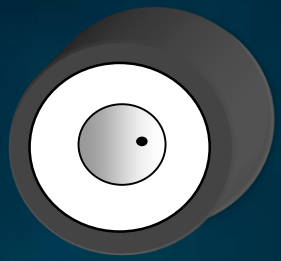
undistinguishable
from the original
squamous epithelium

mature metaplastic
differentiated ep

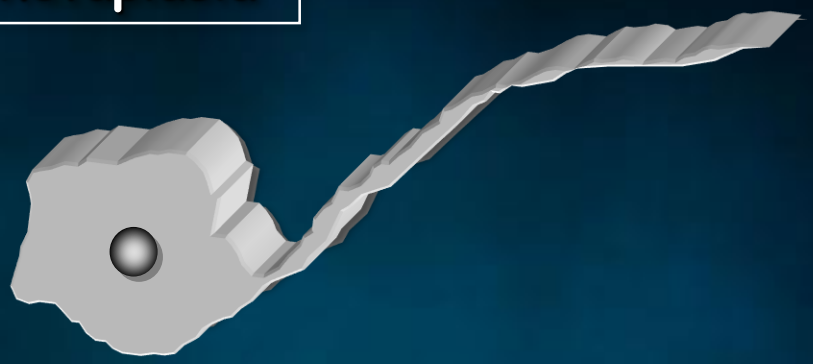


Which is the **composition** of this **undifferentiated** metaplastic epithelium?

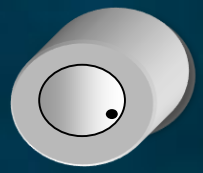
Squamous Metaplasia



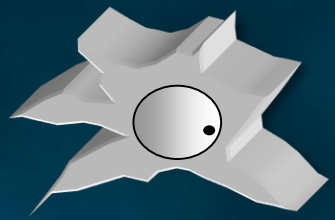
maturing metaplastic cell



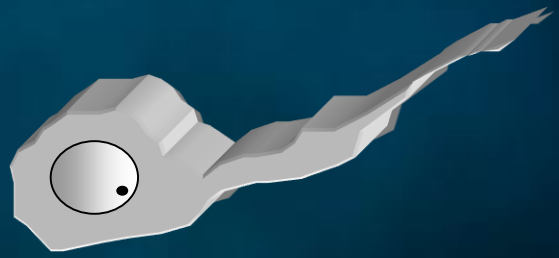
premature metaplastic cell



parabasal-like cell



spider cell



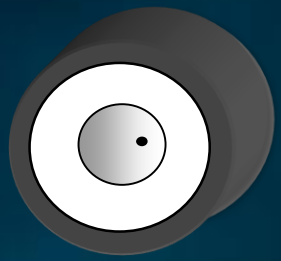
tadpole cell

immature metaplastic cells

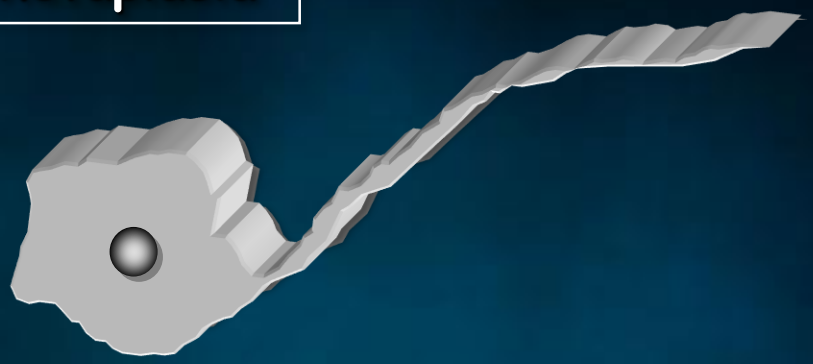
reserve cell

Miniello G. Integrated Colposcopy and Phase Contrast Microscopy, CIC Ed. 1998

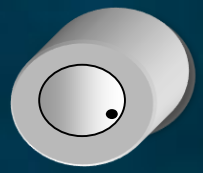
Squamous Metaplasia



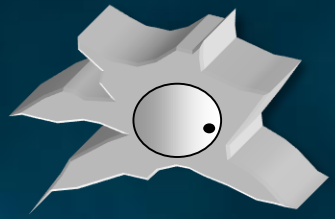
maturing metaplastic cell



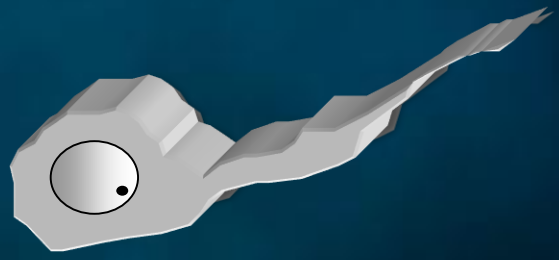
premature metaplastic cell



parabasal-like cell

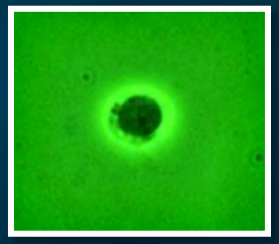


spider cell



tadpole cell

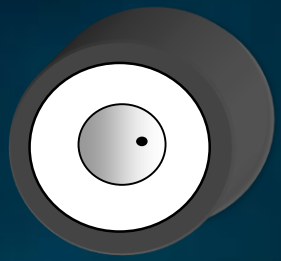
<u>immature</u> metaplastic cells



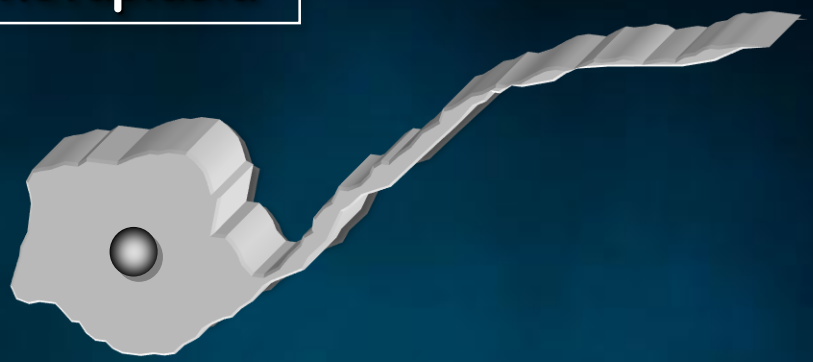
contains a dark nucleus and a thin cytoplasmic ring

reserve cell

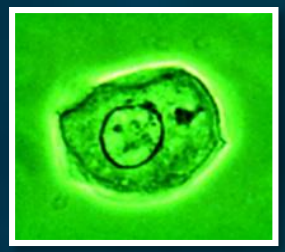
Squamous Metaplasia



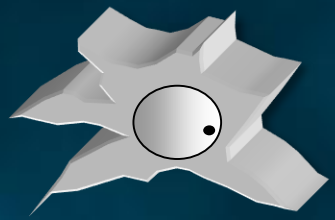
maturing metaplastic cell



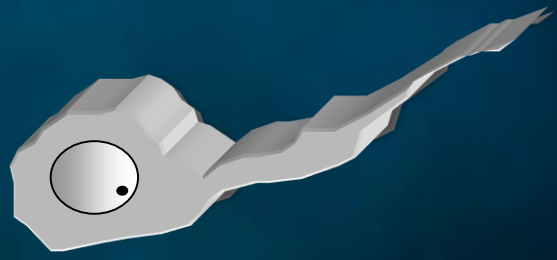
premature metaplastic cell



parabasal-like cell



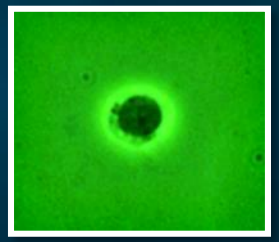
spider cell



tadpole cell

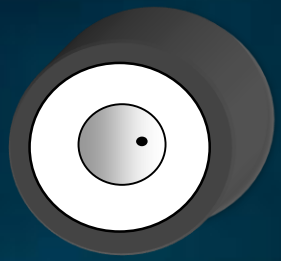
immature metaplastic cells

looks like a parabasal cell

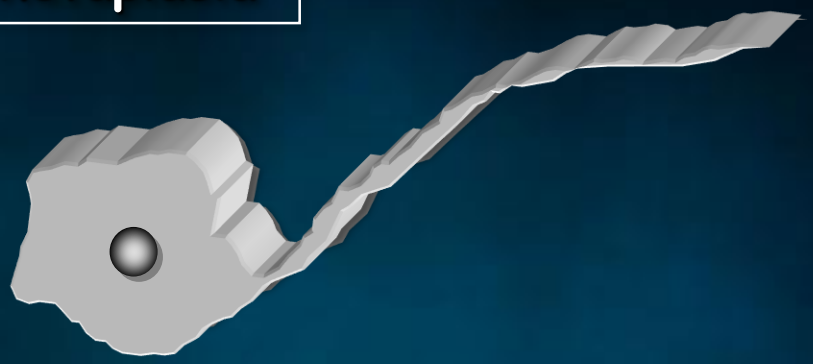


reserve cell

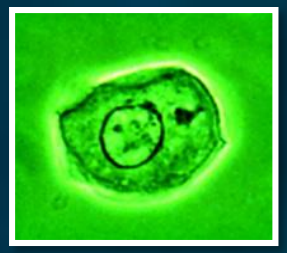
Squamous Metaplasia



maturing metaplastic cell

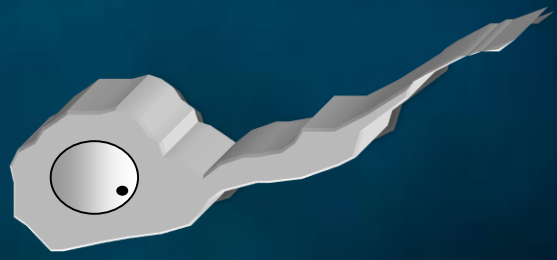


premature metaplastic cell



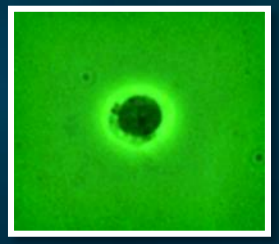
parabasal-like cell

spider cell



tadpole cell

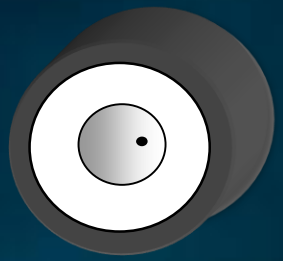
immature metaplastic cells



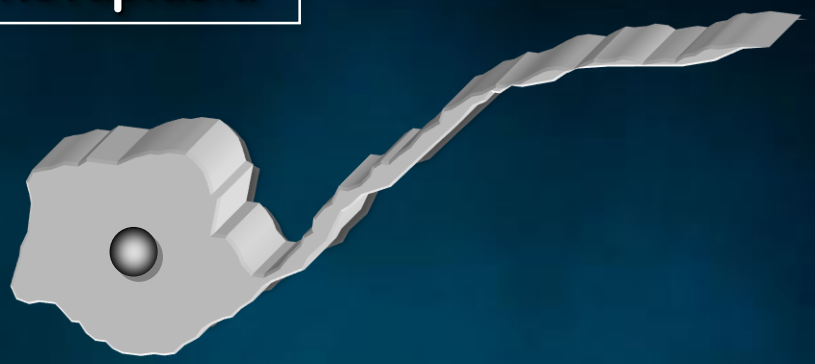
reserve cell

shows spider-like cytoplasmic processes

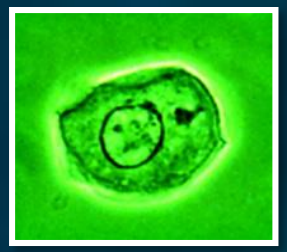
Squamous Metaplasia



maturing metaplastic cell



premature metaplastic cell

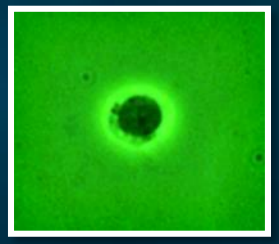


parabasal-like cell

spider cell

tadpole cell

immature metaplastic cells

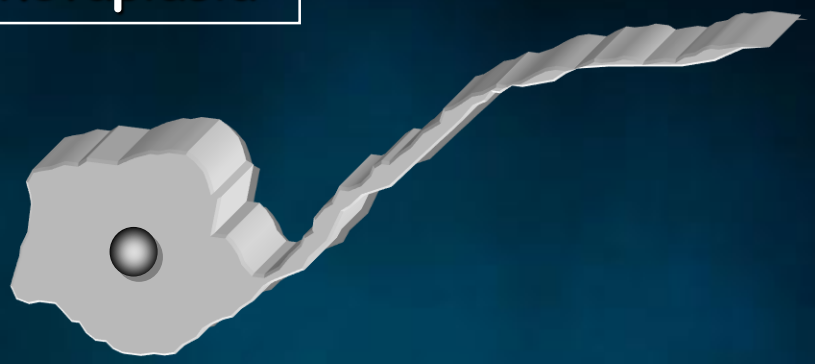


reserve cell

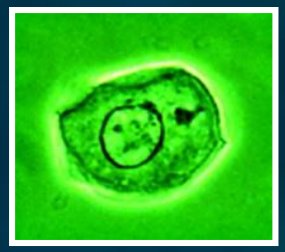
exhibits a long single cytoplasmic process

Squamous Metaplasia

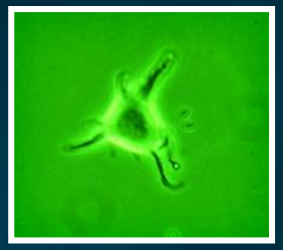
maturing metaplastic cell



premature metaplastic cell



parabasal-like cell

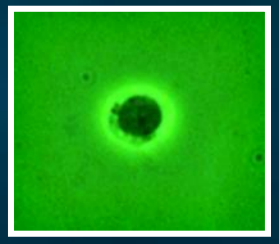


spider cell

tadpole cell

immature metaplastic cells

shows a sharp border between the dark viscous esoplasmic ring and the pale endoplasmic area

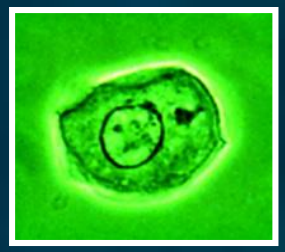


reserve cell

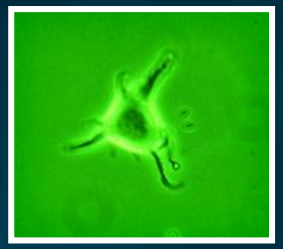
Squamous Metaplasia

maturing metaplastic cell

premature metaplastic cell



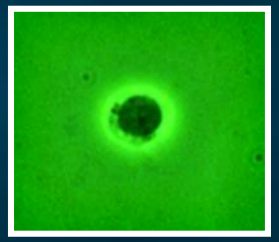
parabasal-like cell



spider cell

tadpole cell

immature metaplastic cells



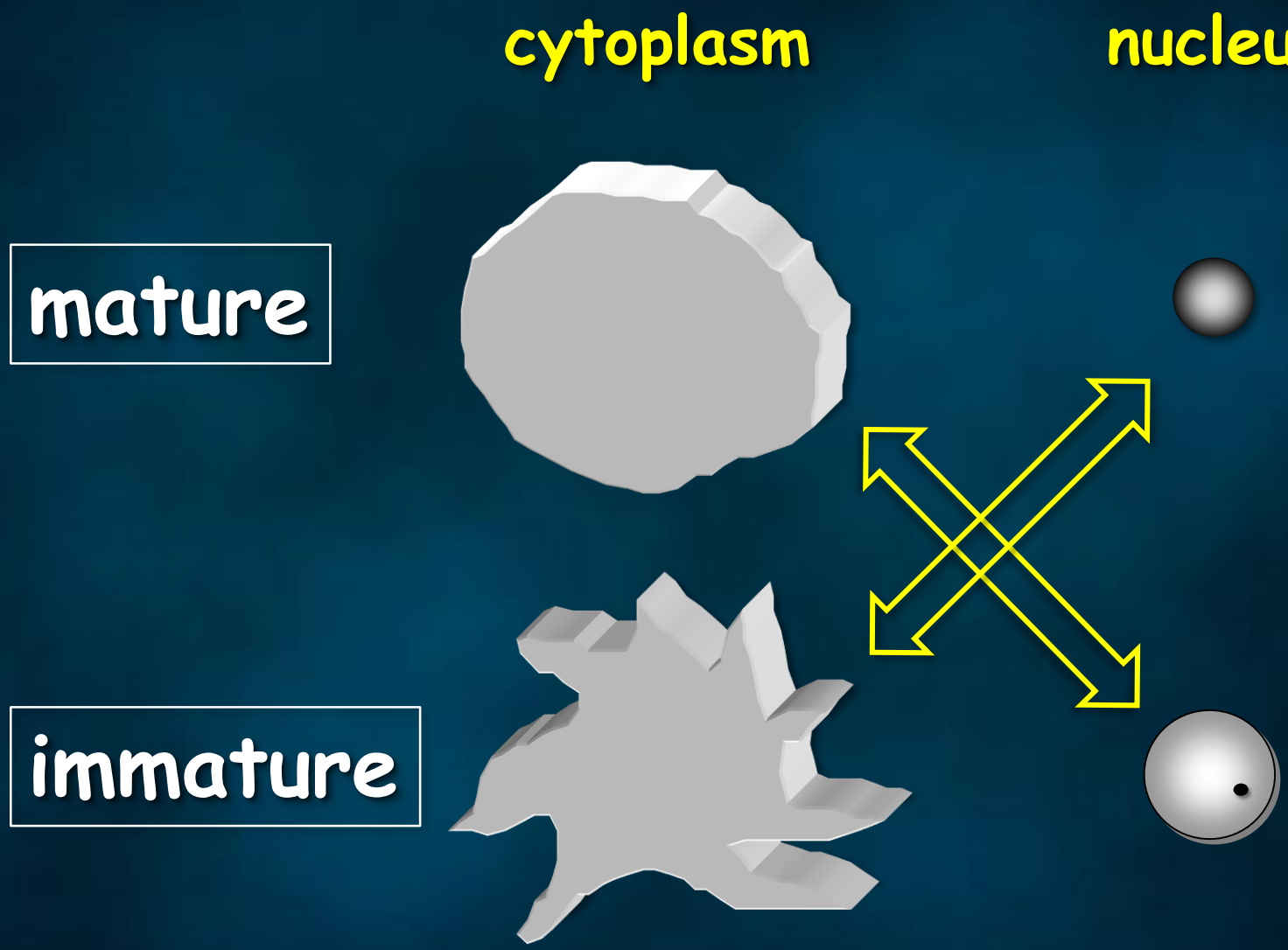
reserve cell

Squamous Metaplasia

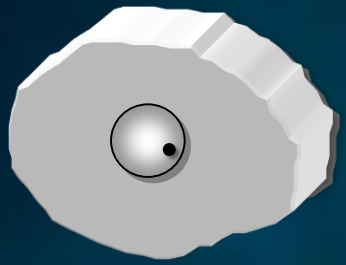
premature metaplastic cell

Contemporary presence of an **immature** and a **mature** element **either** in the nucleus or in the cytoplasm

PREMATURE metaplastic cells

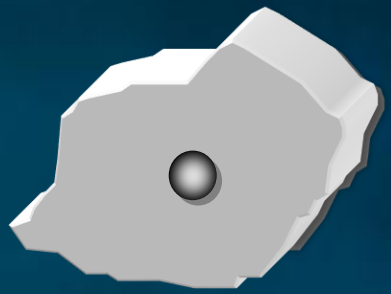


PREMATURE metaplastic cells

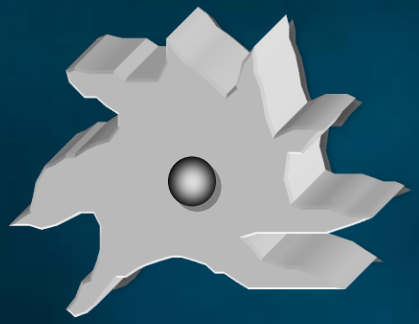


a) premature m.c. from immature parabasal-like c.

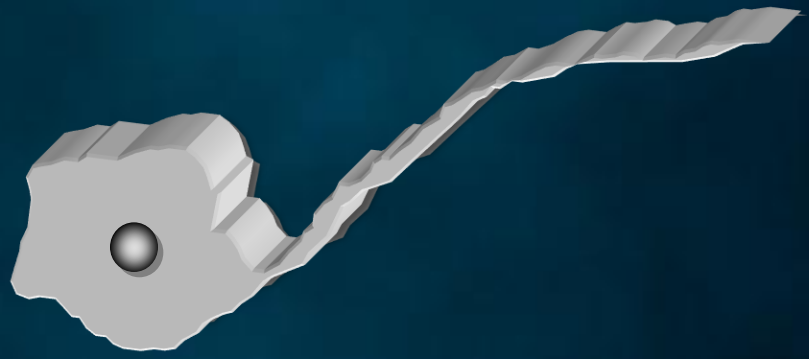
d) premature m.c. from maturing c.



mature metaplastic cell



b) premature m.c. from immature spider c.



c) premature m.c. from immature tadpole c.

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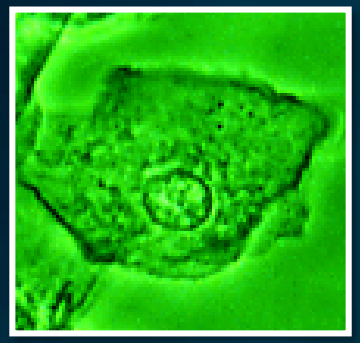
PREMATURE metaplastic cells



a) premature m.c. from immature parabasal-like c.

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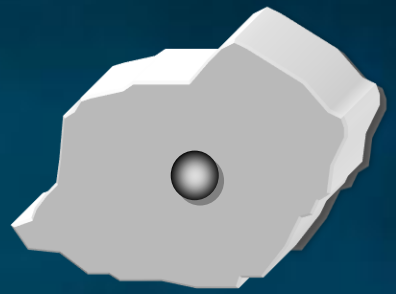
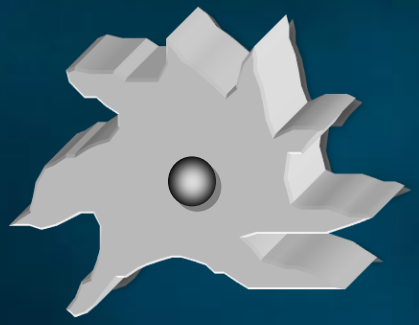


mature metaplastic cell



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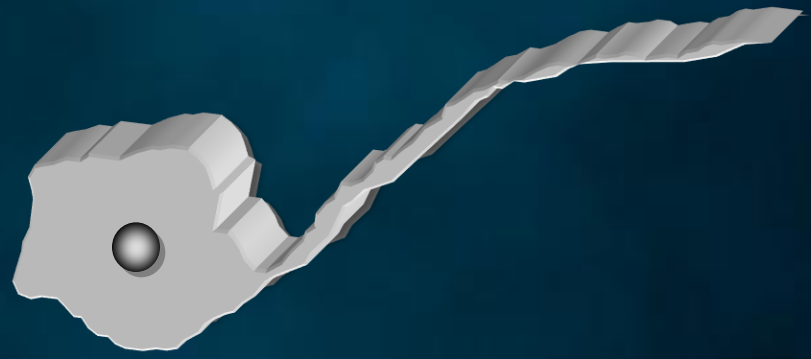

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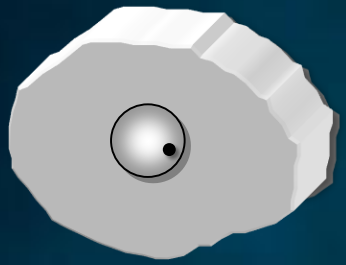
PREMATURE metaplastic cells



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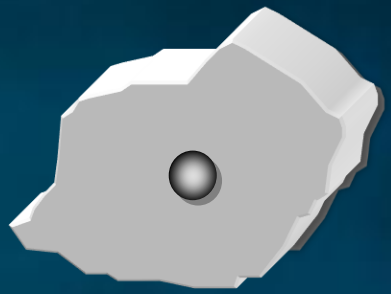
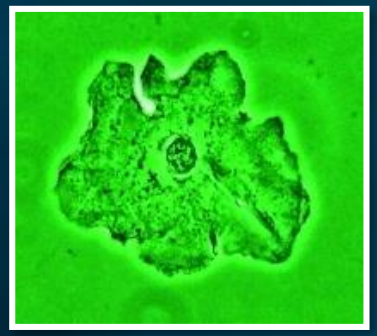


mature metaplastic cell



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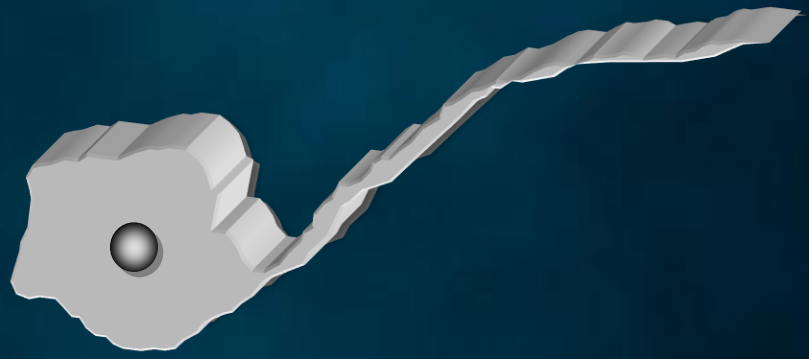

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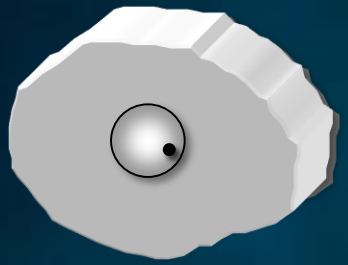
PREMATURE metaplastic cells



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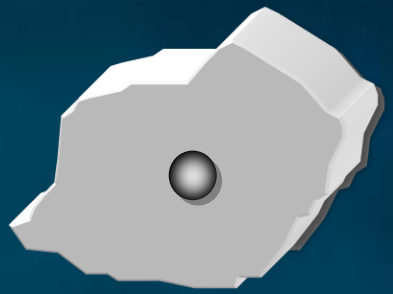
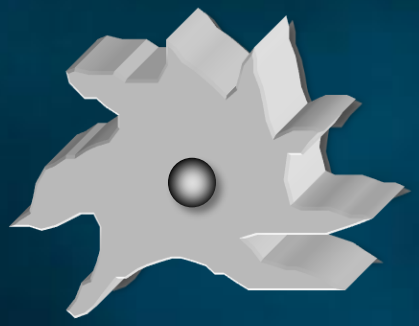


mature metaplastic cell



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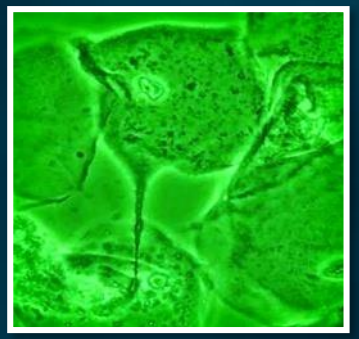

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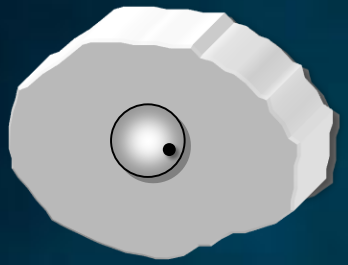
PREMATURE metaplastic cells



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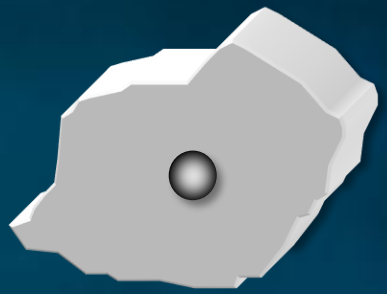
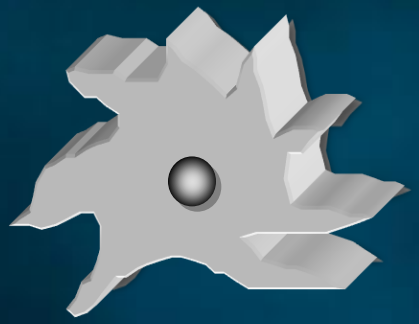


mature metaplastic cell



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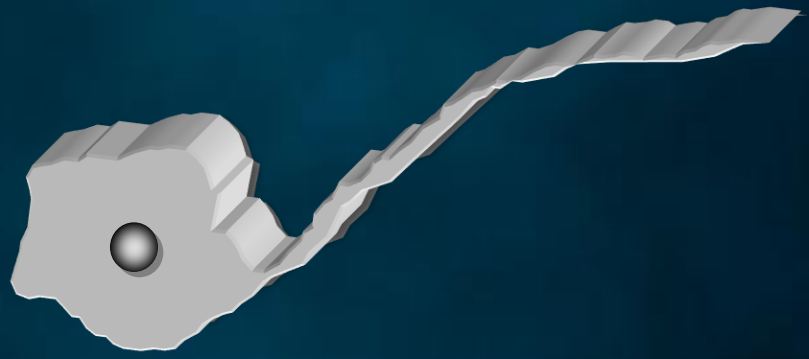

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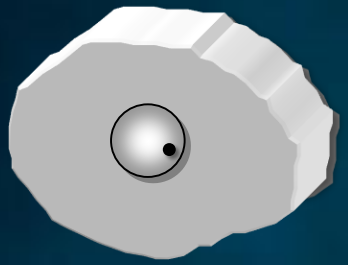
Miniello G. Integrated Colposcopy and Phase Contrast Microscopy, CIC Ed. 1998

PREMATURE metaplastic cells



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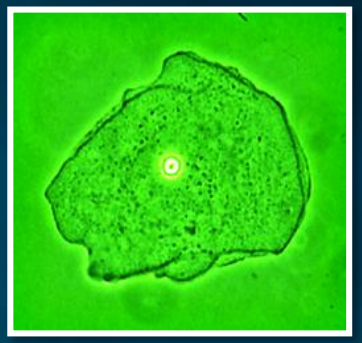
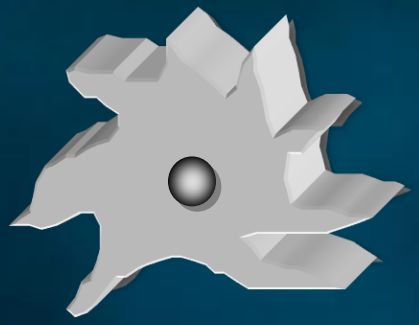


mature metaplastic cell



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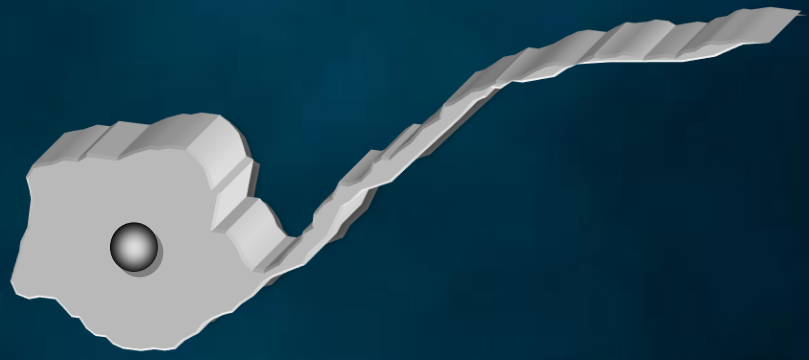

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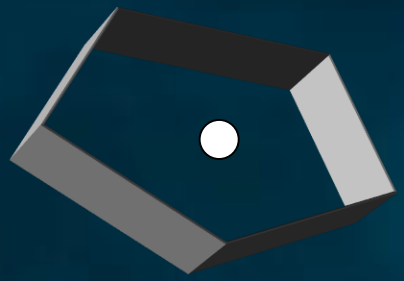
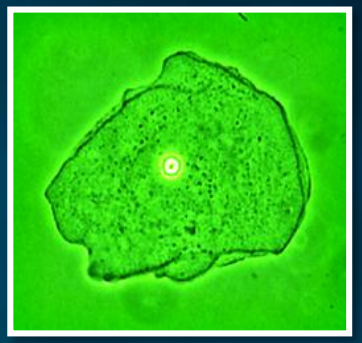
Miniello G. Integrated Colposcopy and Phase Contrast Microscopy, CIC Ed. 1998

Squamous Metaplasia



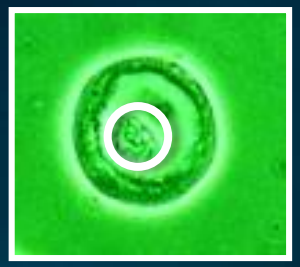


mature metaplastic cell

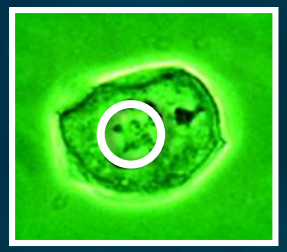
The **mature** metaplastic cell completes the metaplastic maturation.

It is practically undistinguishable from the ORIGINAL squamous cell

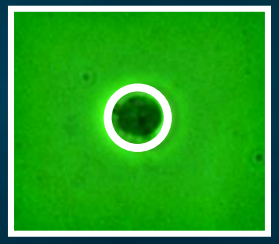
Squamous Metaplasia



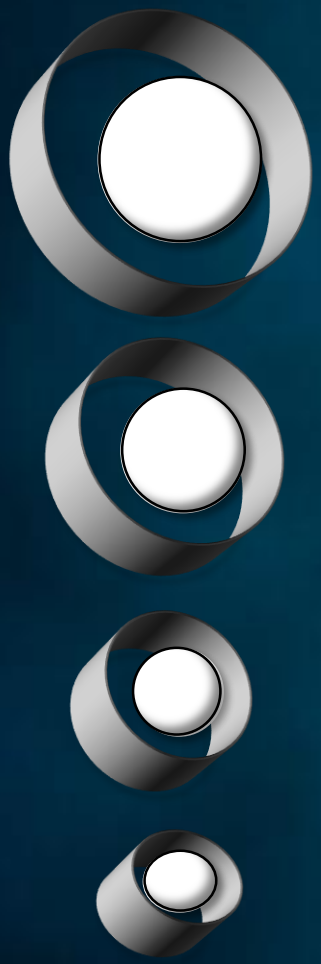
Most of metaplastic cells have



a significant nuclear content

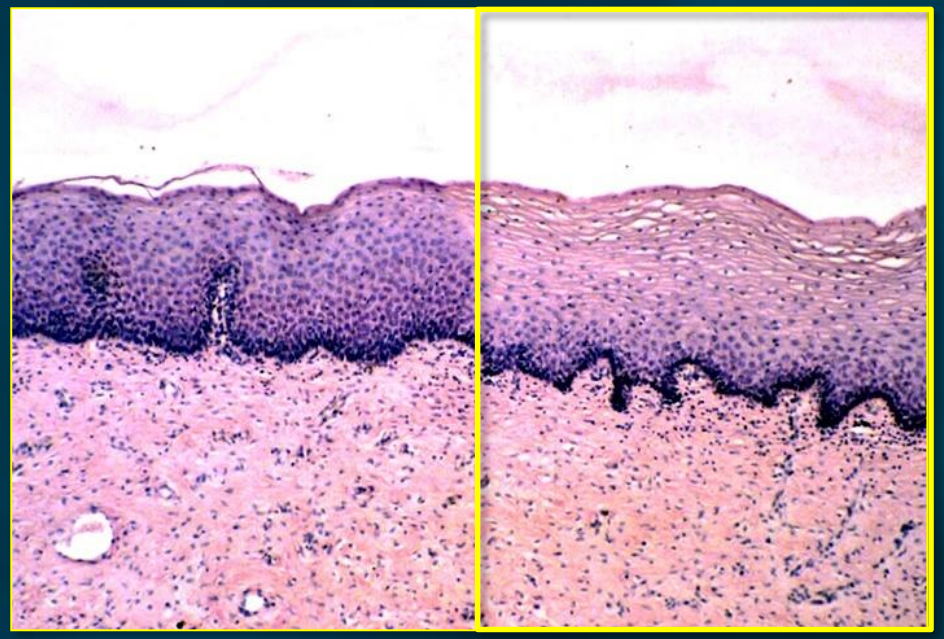


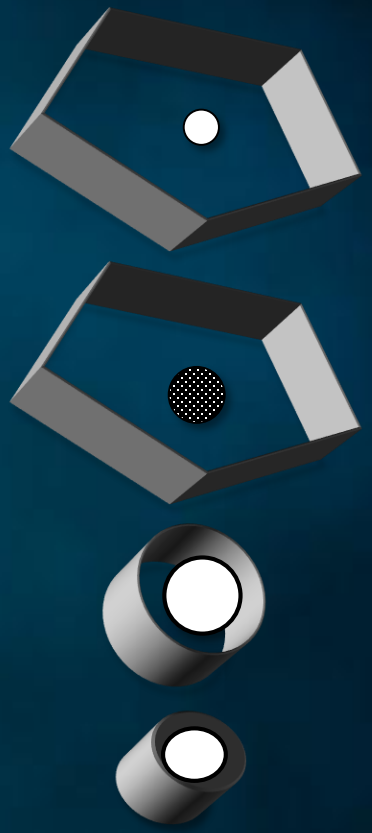
IMMATURE METAPLASTIC EPITHELIUM



Immature metaplastic epithelium contains a **great amount** of immature **nuclei**, rich in proteins

MATURE METAPLASTIC EPITHELIUM



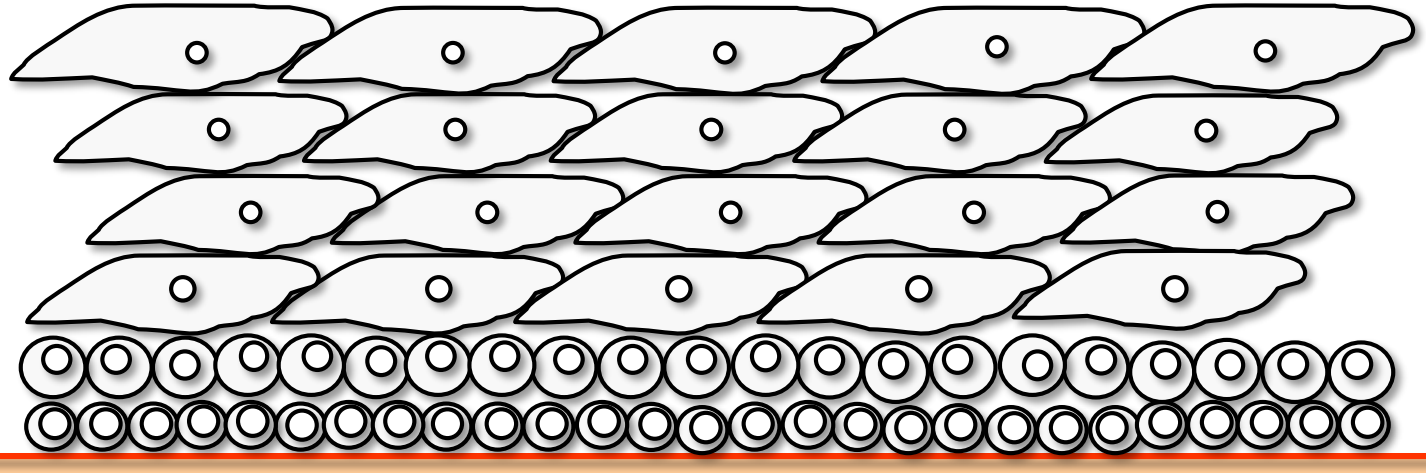


squamous

differentiated ep

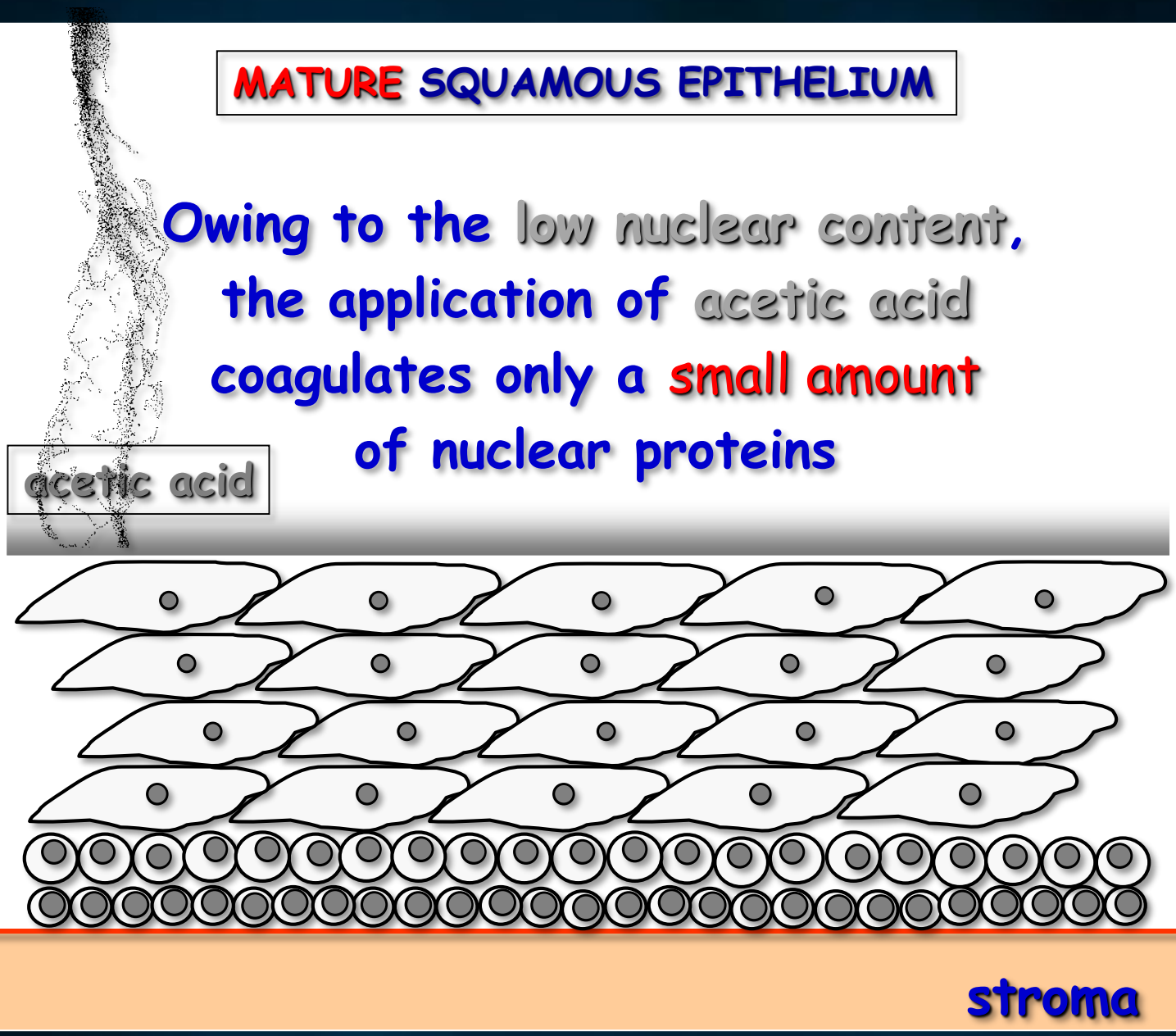
MATURE SQUAMOUS EPITHELIUM

Mature squamous epithelium is predominantly costituted by large squamous cell with small nuclei and so a low nuclear content

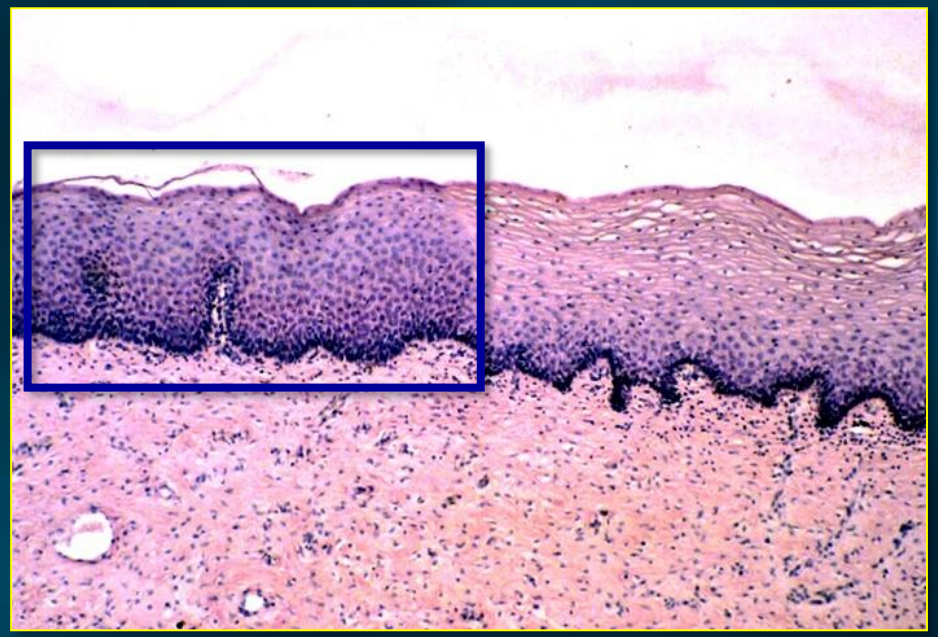


MATURE SQUAMOUS EPITHELIUM

Owing to the low nuclear content, the application of acetic acid coagulates only a small amount of nuclear proteins



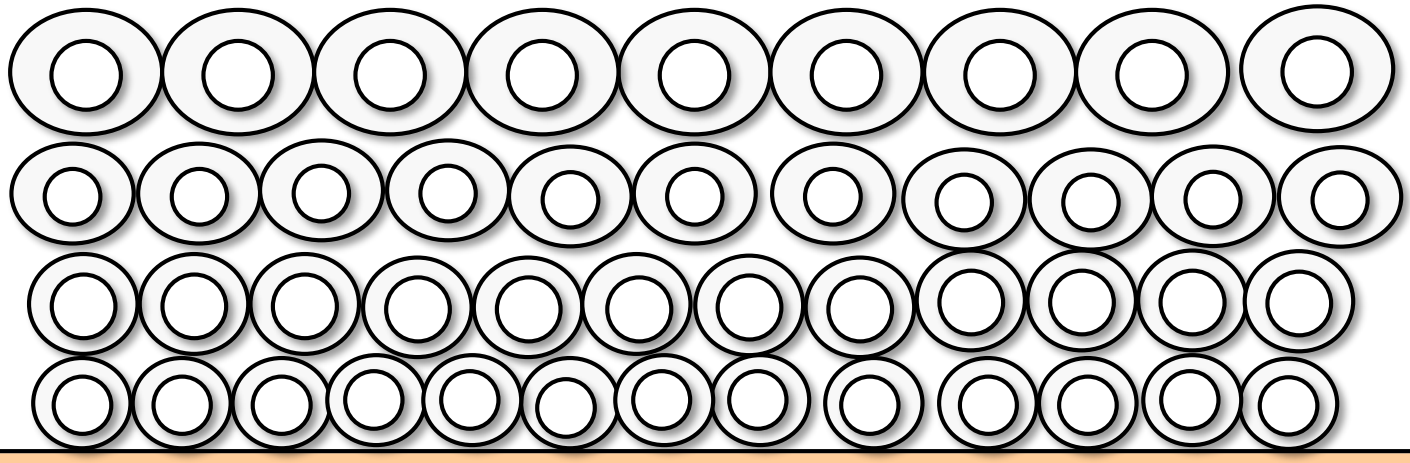
IMMATURE METAPLASTIC EPITHELIUM



high nuclear content

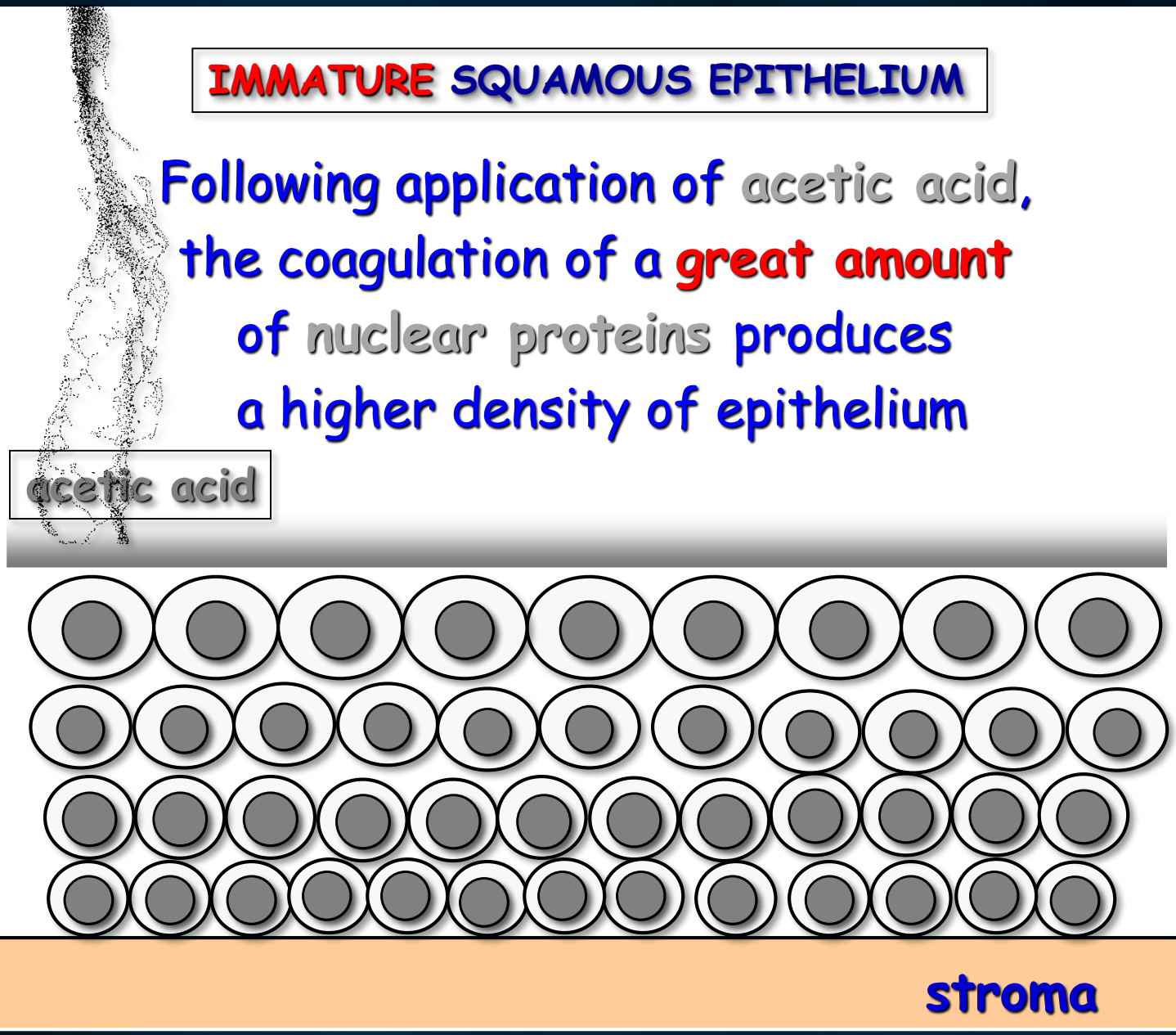
IMMATURE SQUAMOUS EPITHELIUM

The immature metaplastic epithelium differs from mature epithelium in that is more cellular with a higher nuclear content



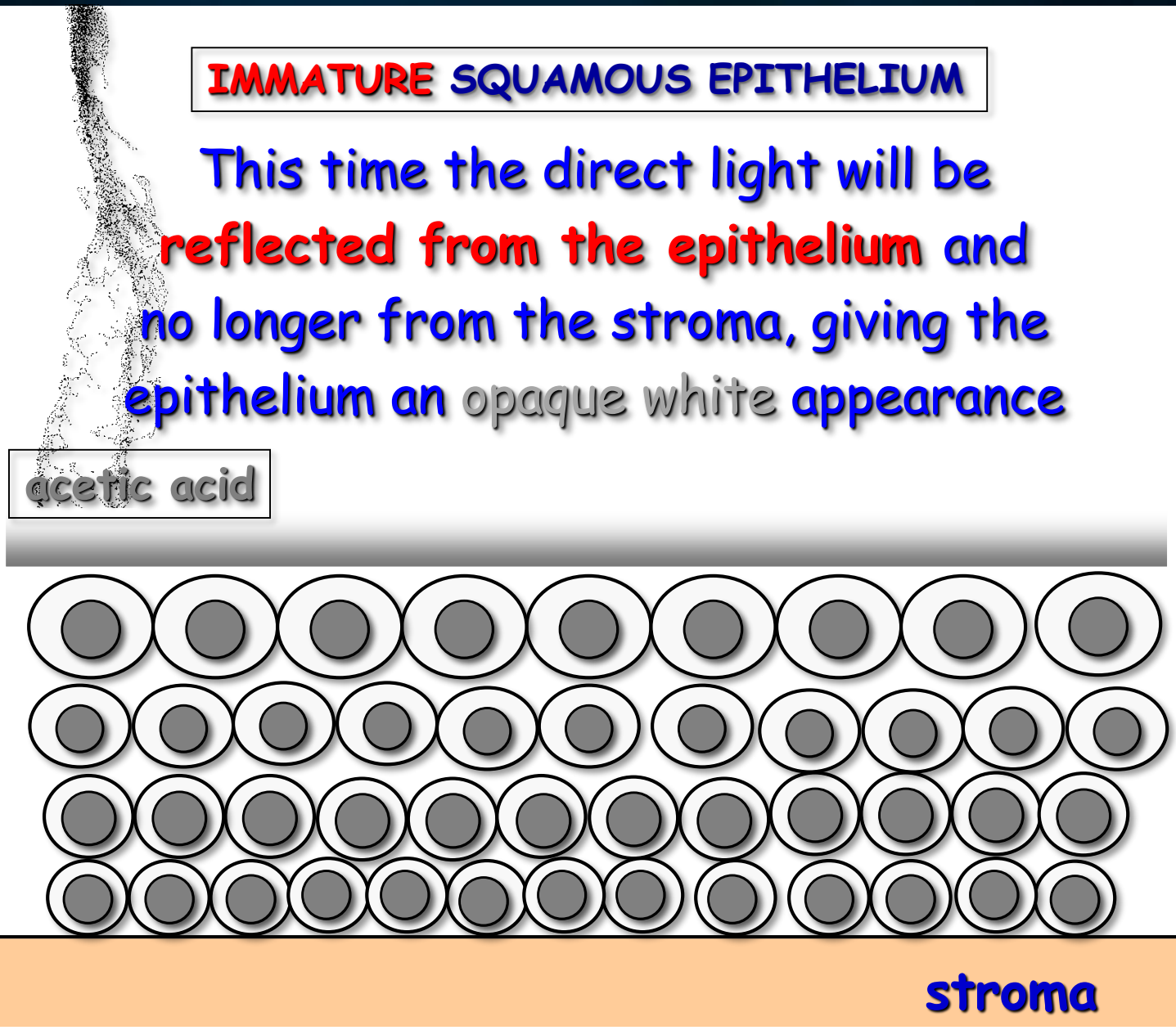
IMMATURE SQUAMOUS EPITHELIUM

Following application of acetic acid, the coagulation of a great amount of nuclear proteins produces a higher density of epithelium



IMMATURE SQUAMOUS EPITHELIUM

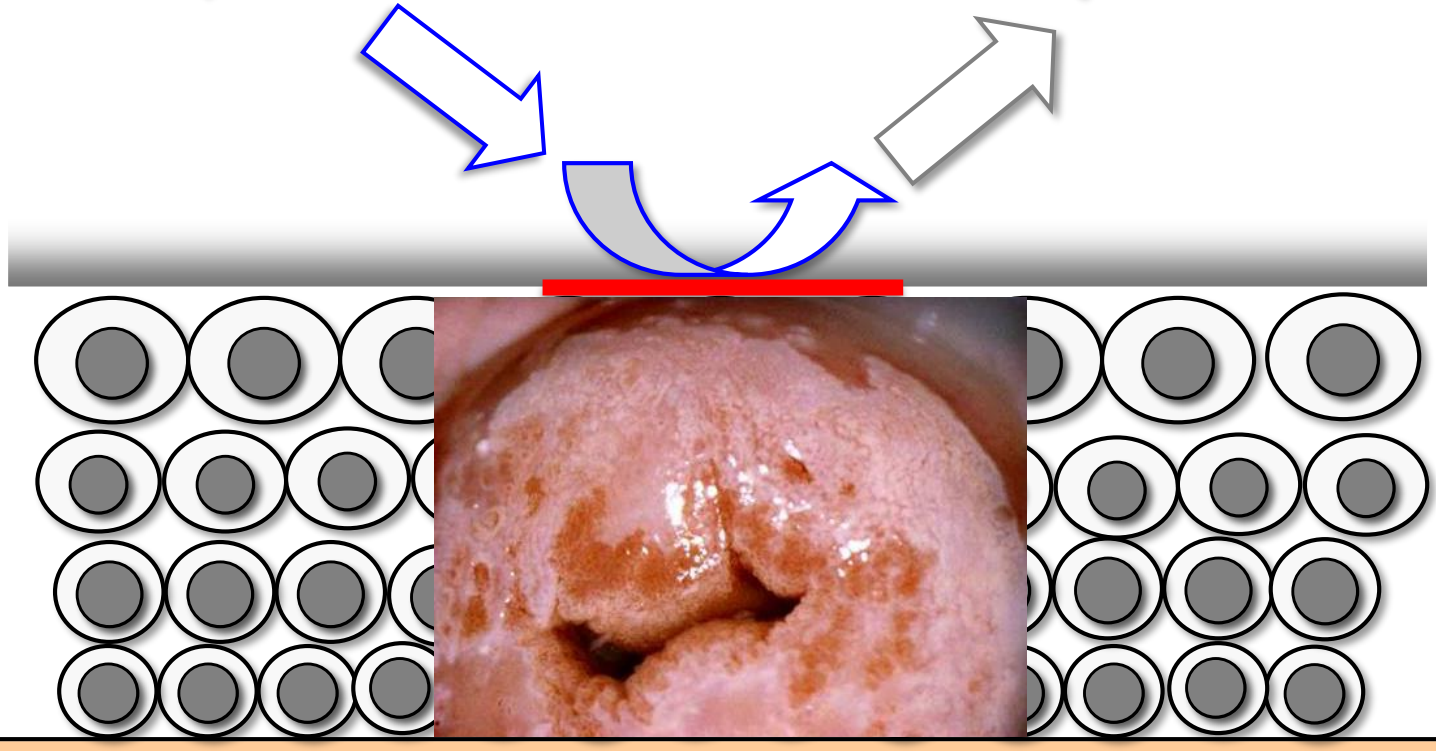
This time the direct light will be reflected from the epithelium and no longer from the stroma, giving the epithelium an opaque white appearance



IMMATURE SQUAMOUS EPITHELIUM

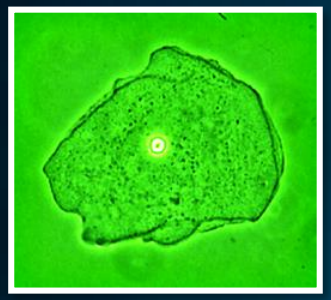
DIRECT light cannot accross the epithelium

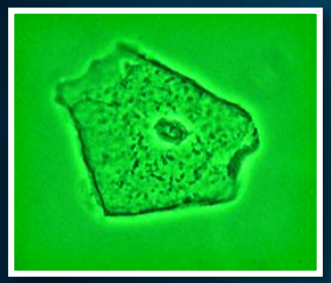
REFLECTED light from EPITHELIUM is OPAQUE WHITE



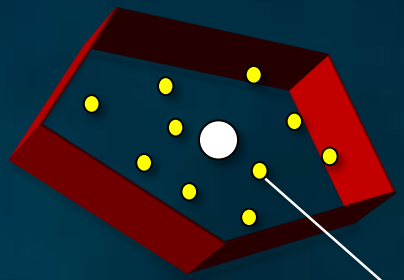
stroma

VAGINAL SQUAMOUS EPITHELIUM



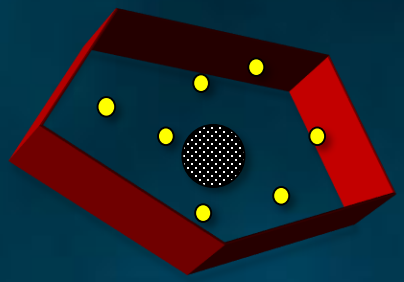


large cytoplasm



superficial cell

glycogen ⇨ jodine positivity



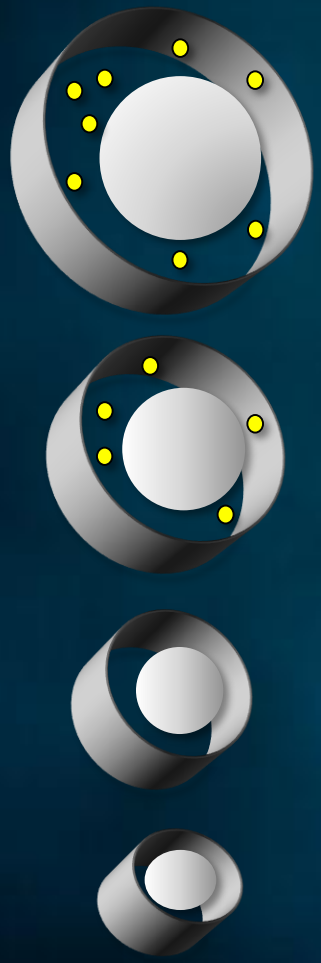
intermediate cell

parabasal cell

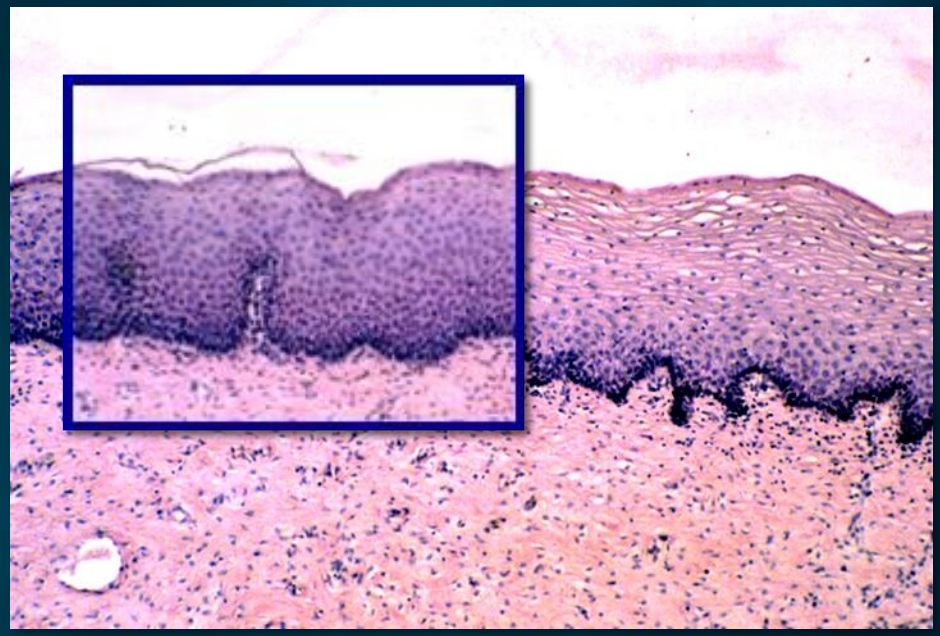
basal cell

IMMATURE SQUAMOUS EPITHELIUM

NO squamous cs



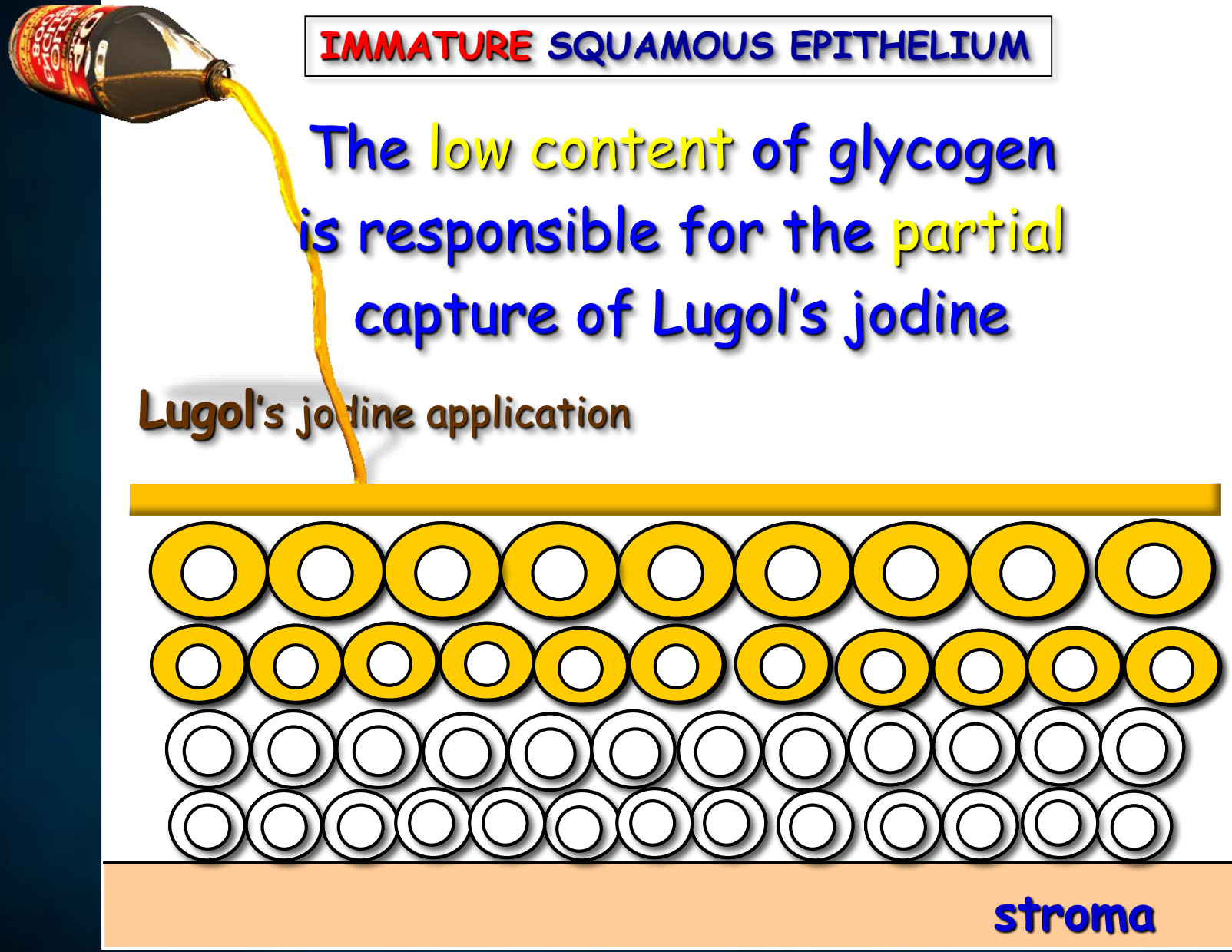
partial jodine staining



poor in glycogen

IMMATURE SQUAMOUS EPITHELIUM

The low content of glycogen is responsible for the partial capture of Lugol's jodine

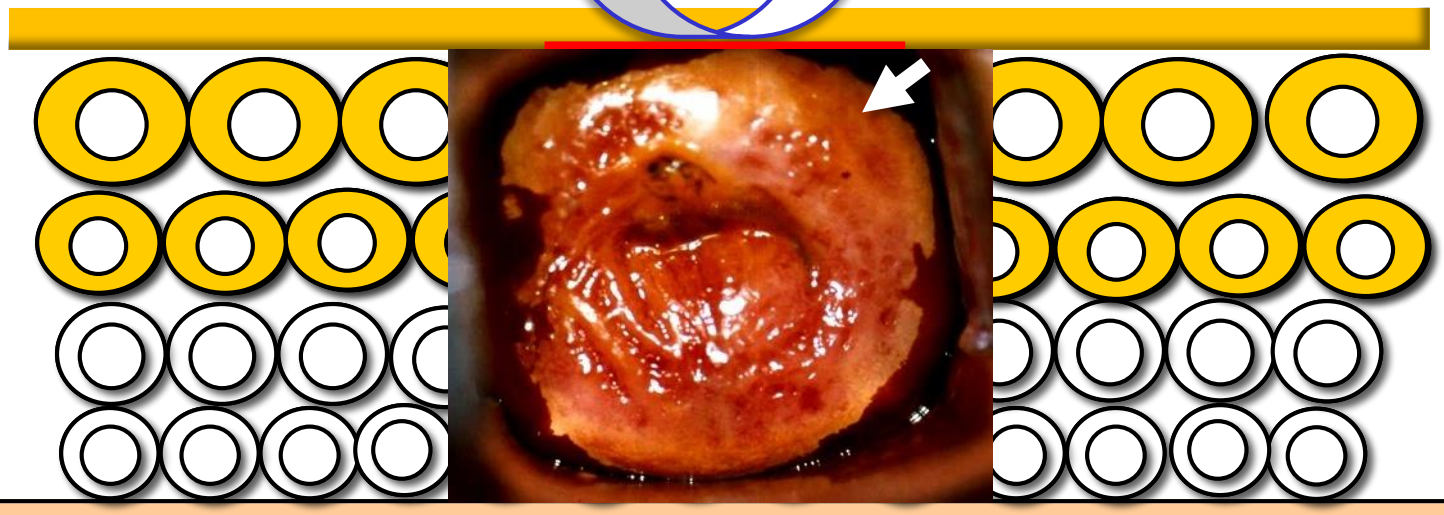


IMMATURE SQUAMOUS EPITHELIUM

DIRECT light cannot accross the epithelium

REFLECTED light from EPITHELIUM has a SPLECKLED appearance

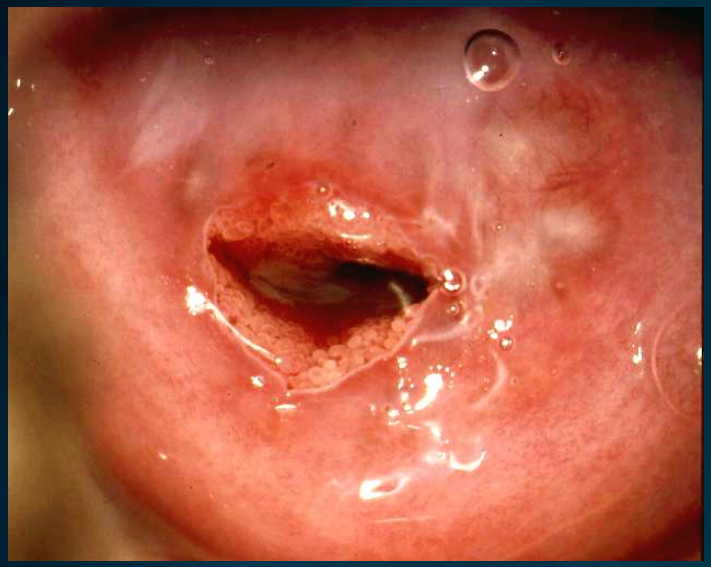
jodine PARTIAL POSITIVE area



stroma

The behavior of squamous metaplasia **holds the key** to the understanding of cervical **oncogenesis**

Coppleson & Reid, 1967



Mature

metaplasia is

a permanent change

During the development of squamous metaplasia, exposure to a mutagenic agent results in the production of an atypical epithelium

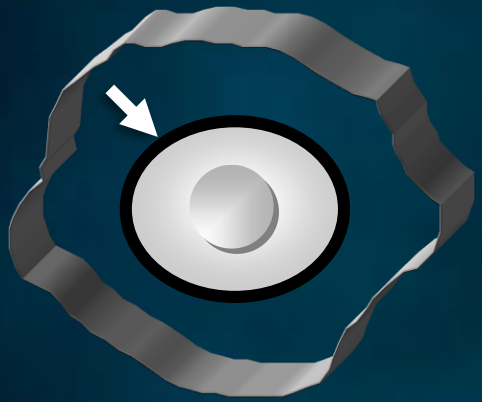
During the immature metaplastic change, epithelium may attain neoplastic potential and may become abnormal

HPV

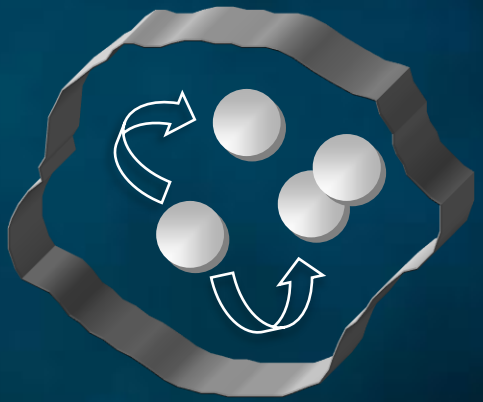
HPV is the major infectious aetiological agent associated with the development of pre-cancerous lesions of cervix

HPV cell changes

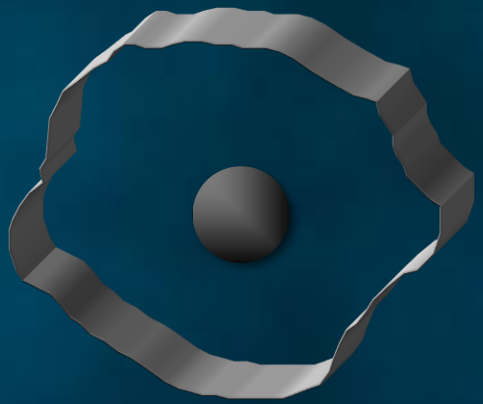
Pap smear



koilocyte



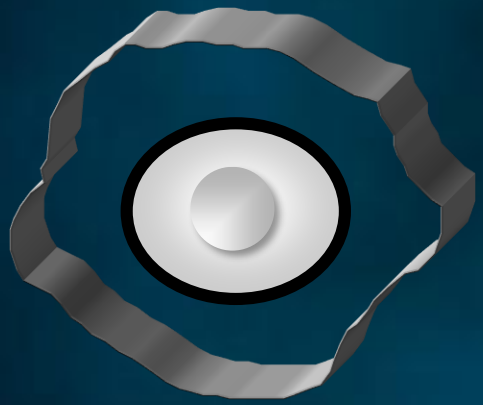
multinucleation



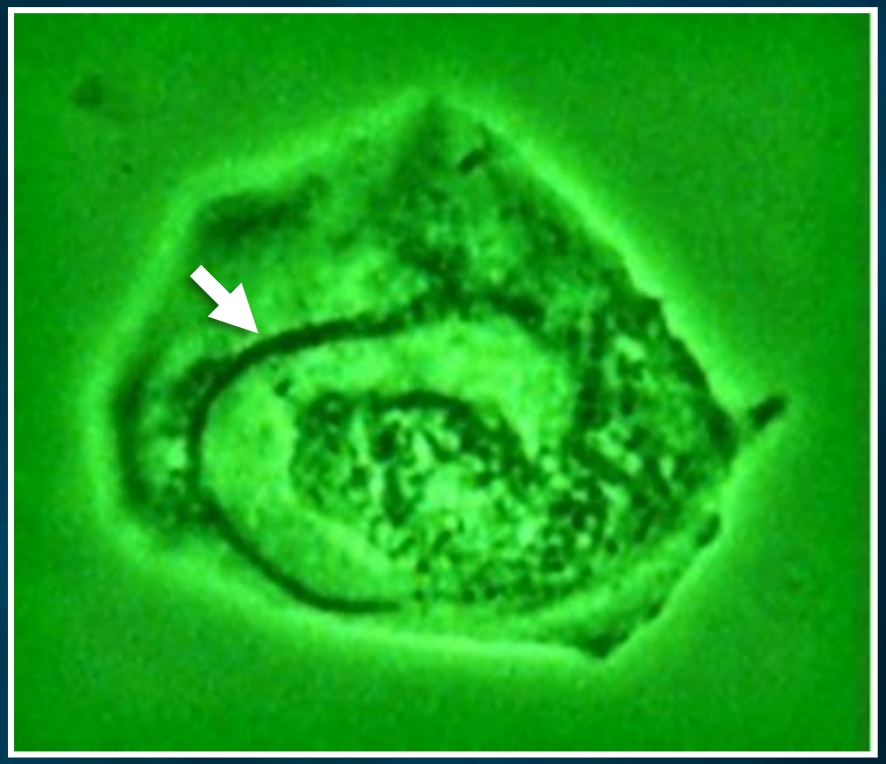
dark nucleus

Miniello G. Integrated Colposcopy and Phase Contrast Microscopy, 1998

WET mount



koilocyte



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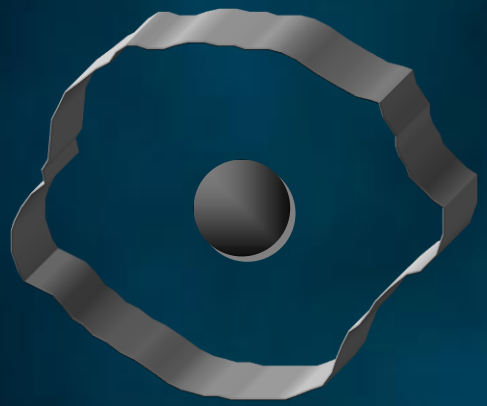
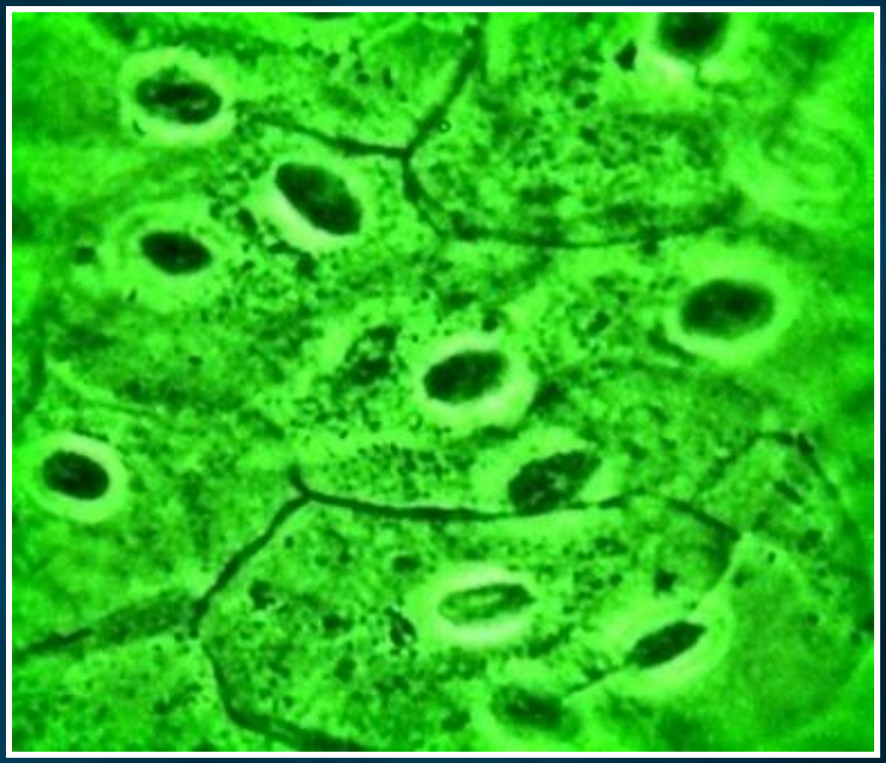
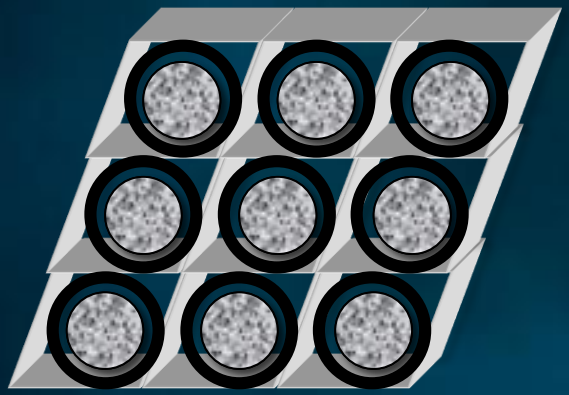


dark nuclei

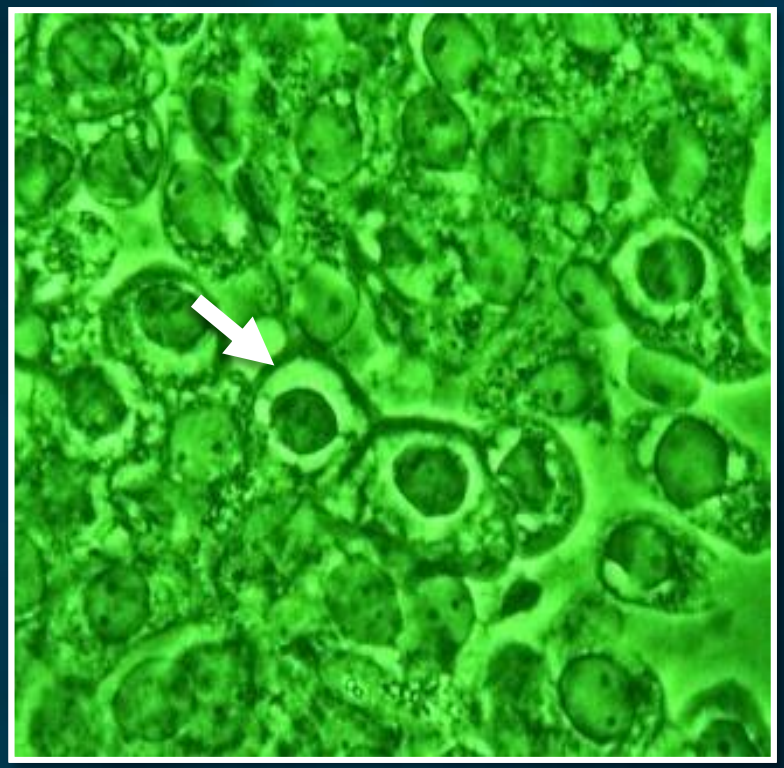


WET mount

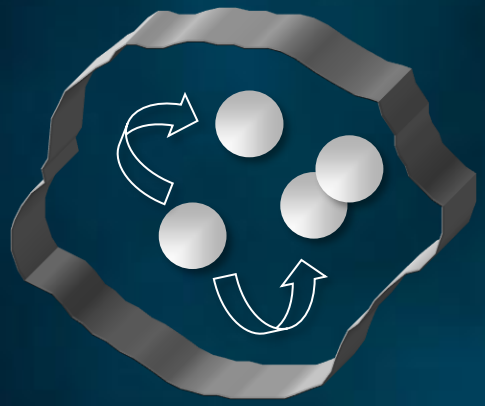


columnar cells
(seen end on)

koilocytes &
dark nuclei

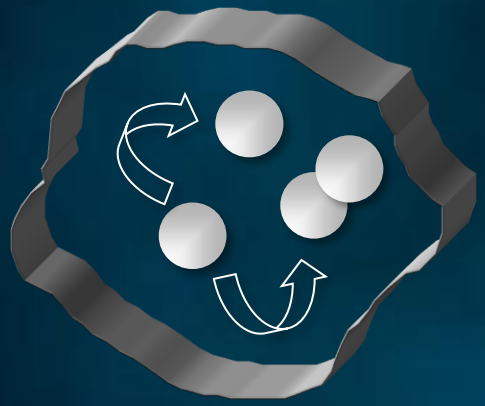


WET mount



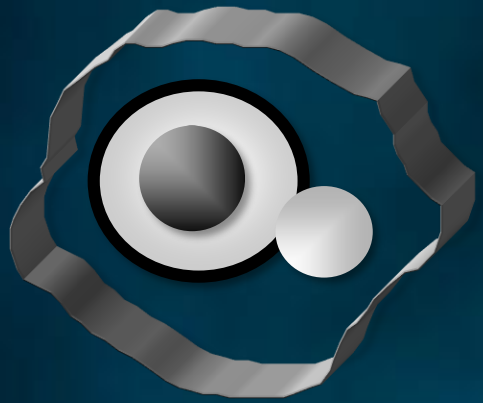
multinucleation

WET mount

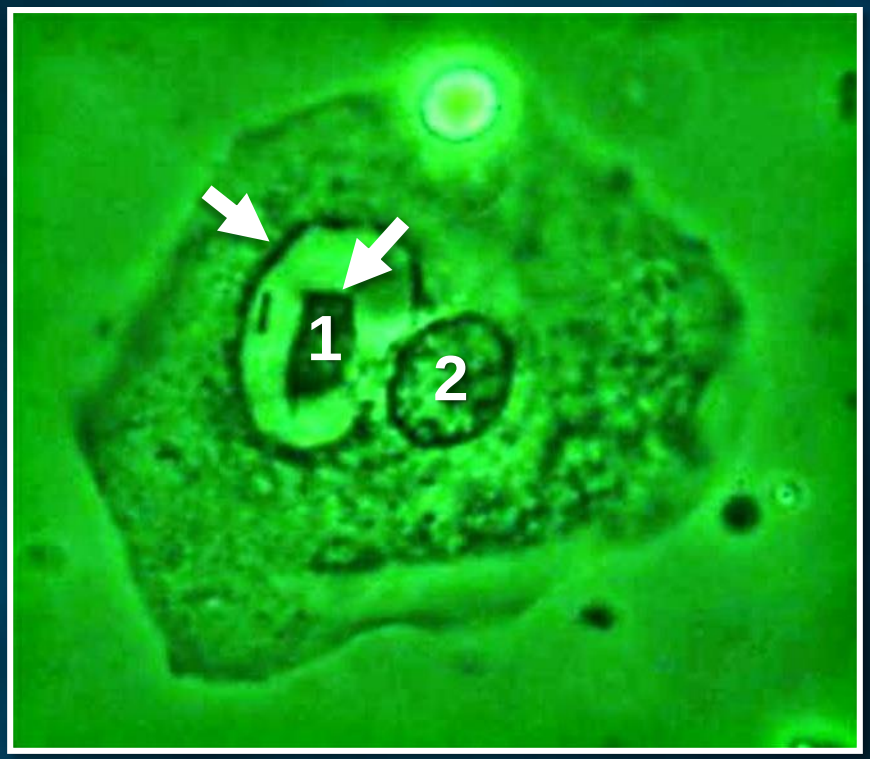


multinucleation

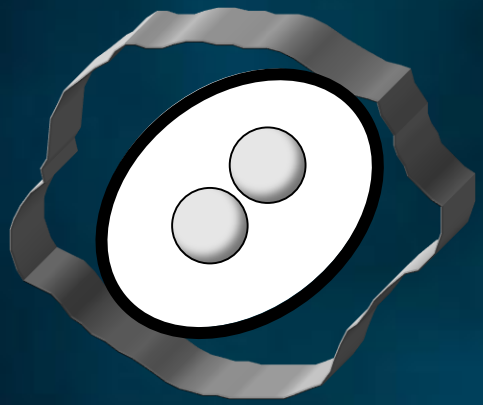
combined findings



Koilocyte
&
dark nucleus
&
binucleation

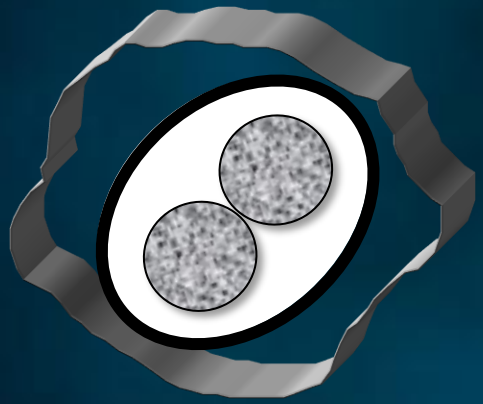


combined findings

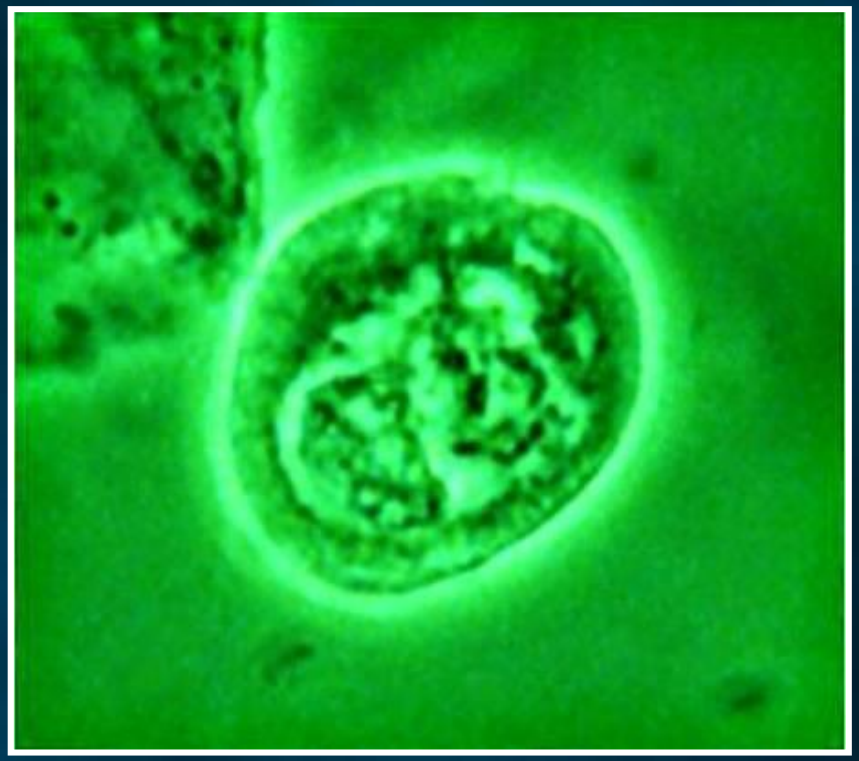


koilocite
&
binucleation

dyskaryotic cells

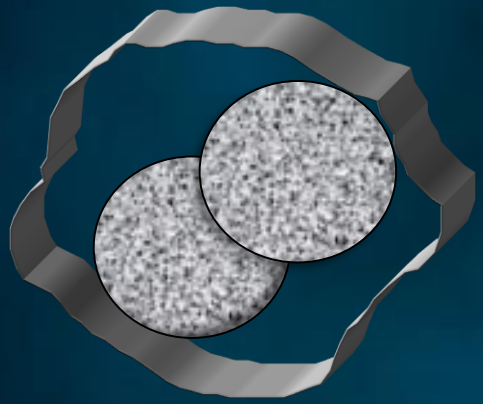


koilocyte
&
binucleation
with altered N/C R

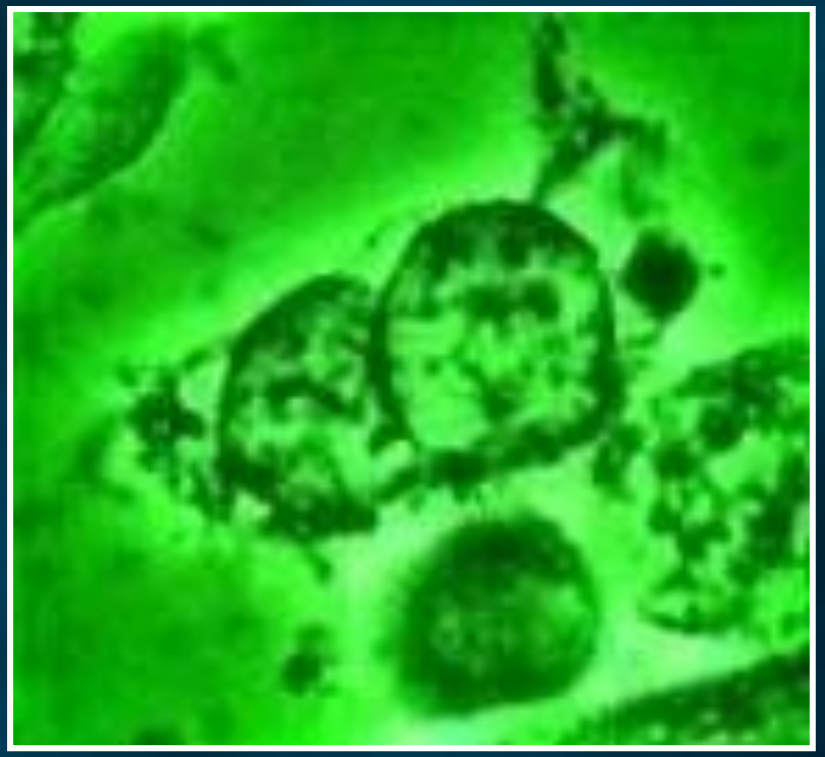


CIN 2

dyskaryotic cells



binucleation
&
inverted N/C R



CIN 3

HPV test

cytology

Which is the use of cytology if HPV test is available?

Positive

HPV test

indicates infection

NOT disease!

+HPV test

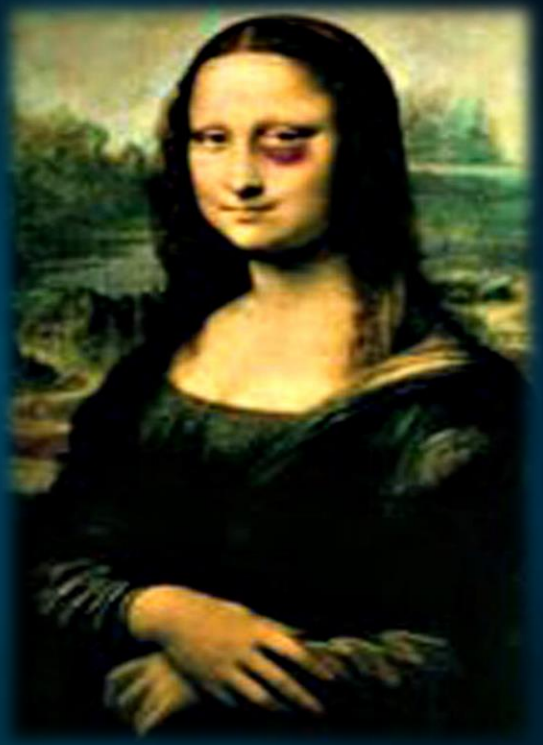
+cytology

LATENT infection

PRODUCTIVE infection (LSIL)

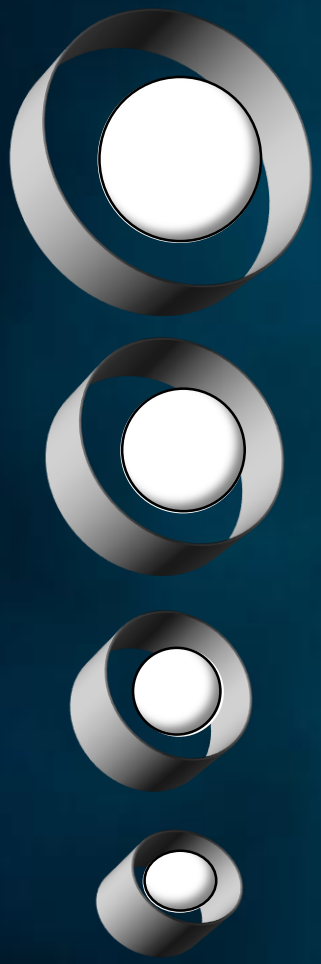
TRANSFORMING infection (HSIL)

Direct microscopy may represent the only warning signal during gynecological examination in patients not referred for Pap smear



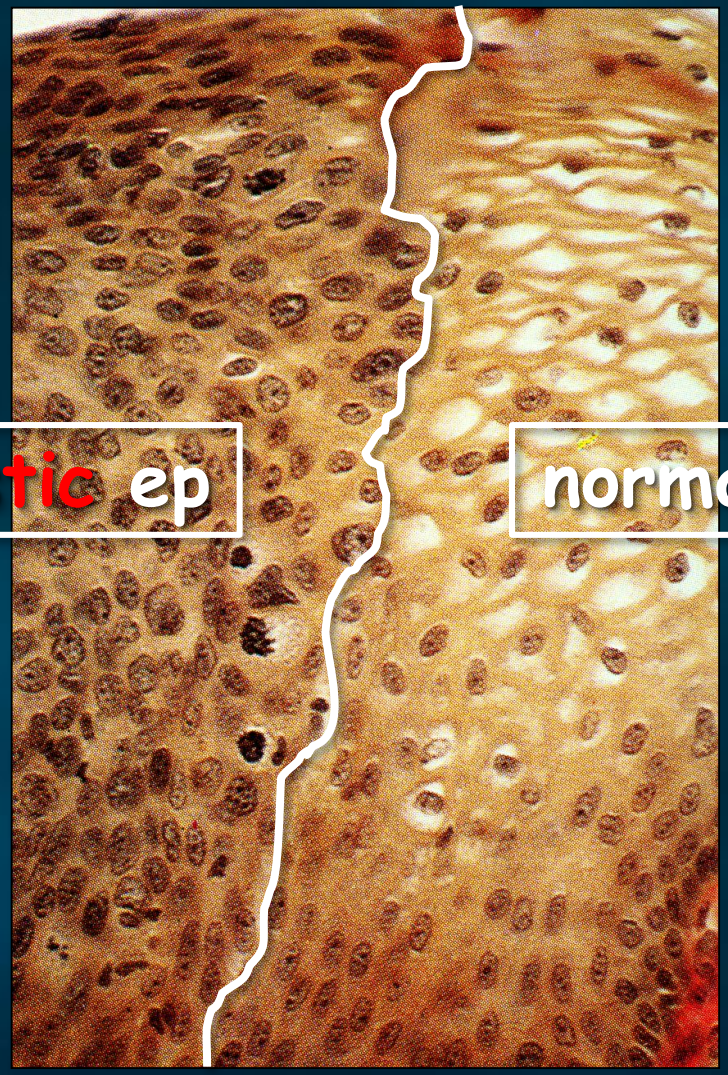
Saraya UB, Miniello G. Atlas of Cytology and Colposcopy. Jaypee Brs Pbs, 2009

HPV epithelium



Epithelium affected by HPV has a great content of nuclear proteins

DYSPLASTIC epithelium



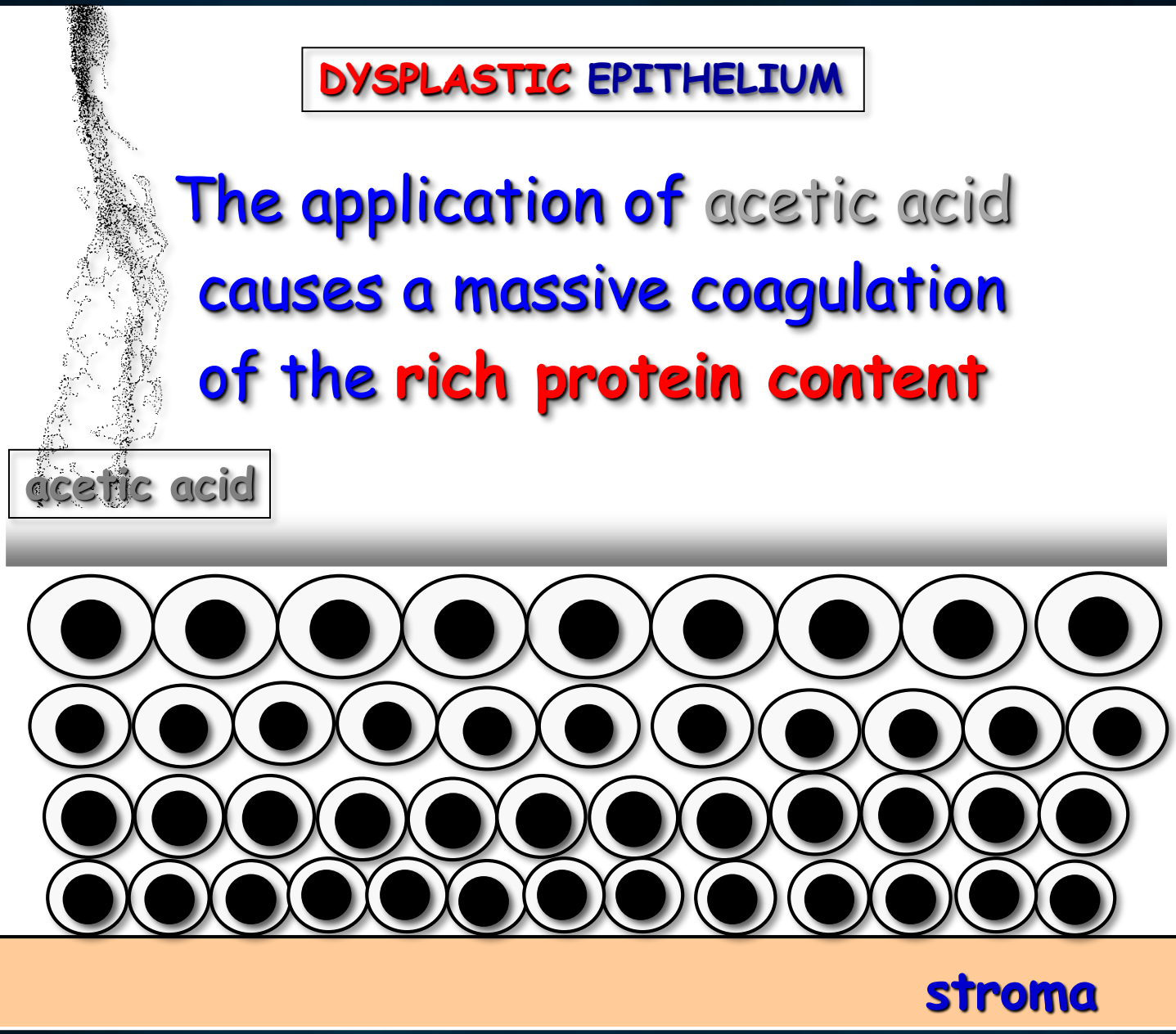
DYSPLASTIC epithelium

massive coagulation of proteins after a.a.application

very high nuclear content

DYSPLASTIC EPITHELIUM

The application of acetic acid causes a massive coagulation of the rich protein content



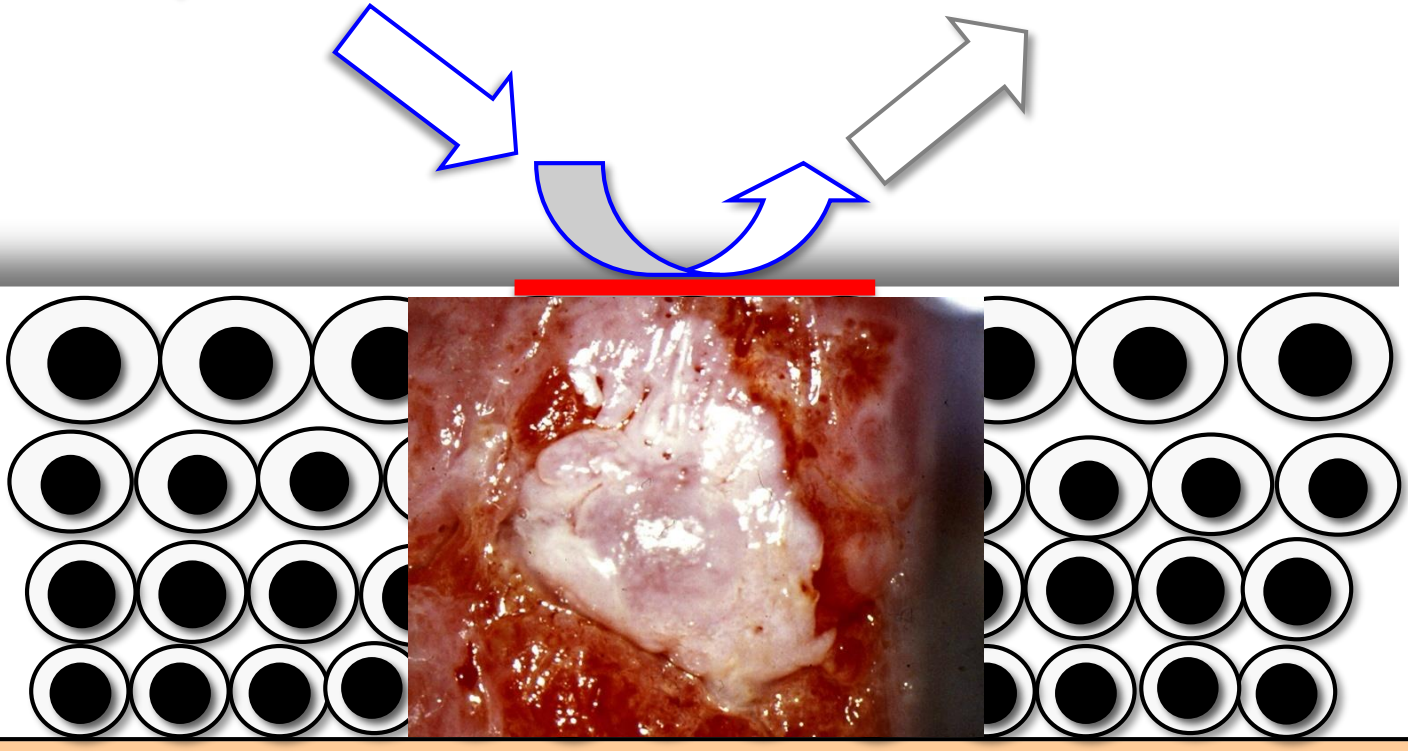
DYSPLASTIC EPITHELIUM

This time the direct light will be reflected from the epithelium and no longer from the stroma, giving the epithelium a snow white appearance

DYSPLASTIC EPITHELIUM

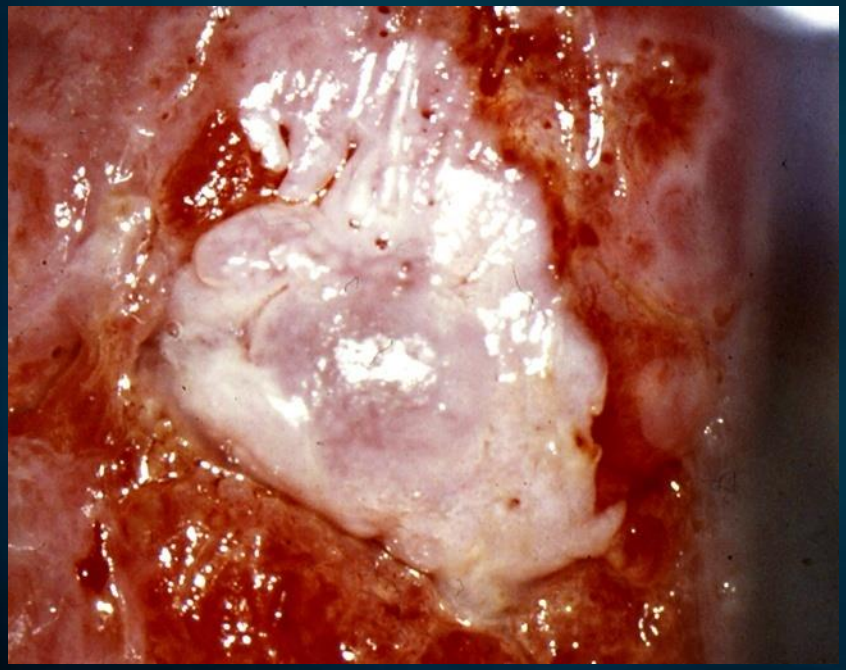
DIRECT light cannot accross the epithelium

REFLECTED light from EPITHELIUM is SNOW WHITE



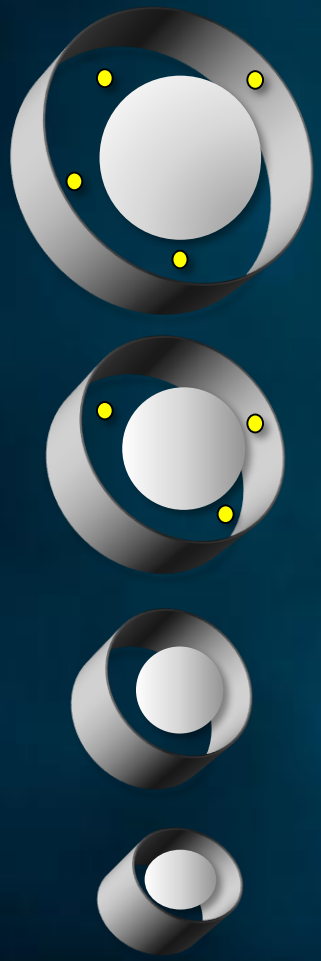
stroma

flat acetowhite epithelium: immature metaplasia

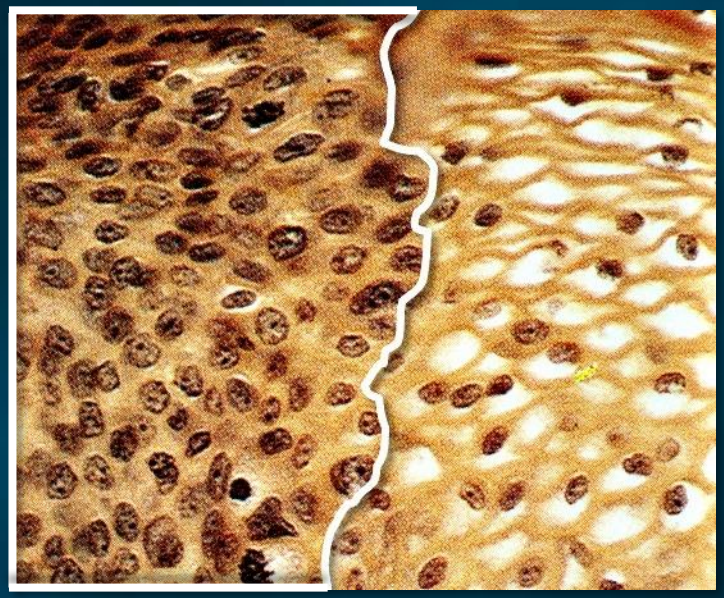


dense acetowhite epithelium: CIN 3

DYSPLASTIC epithelium



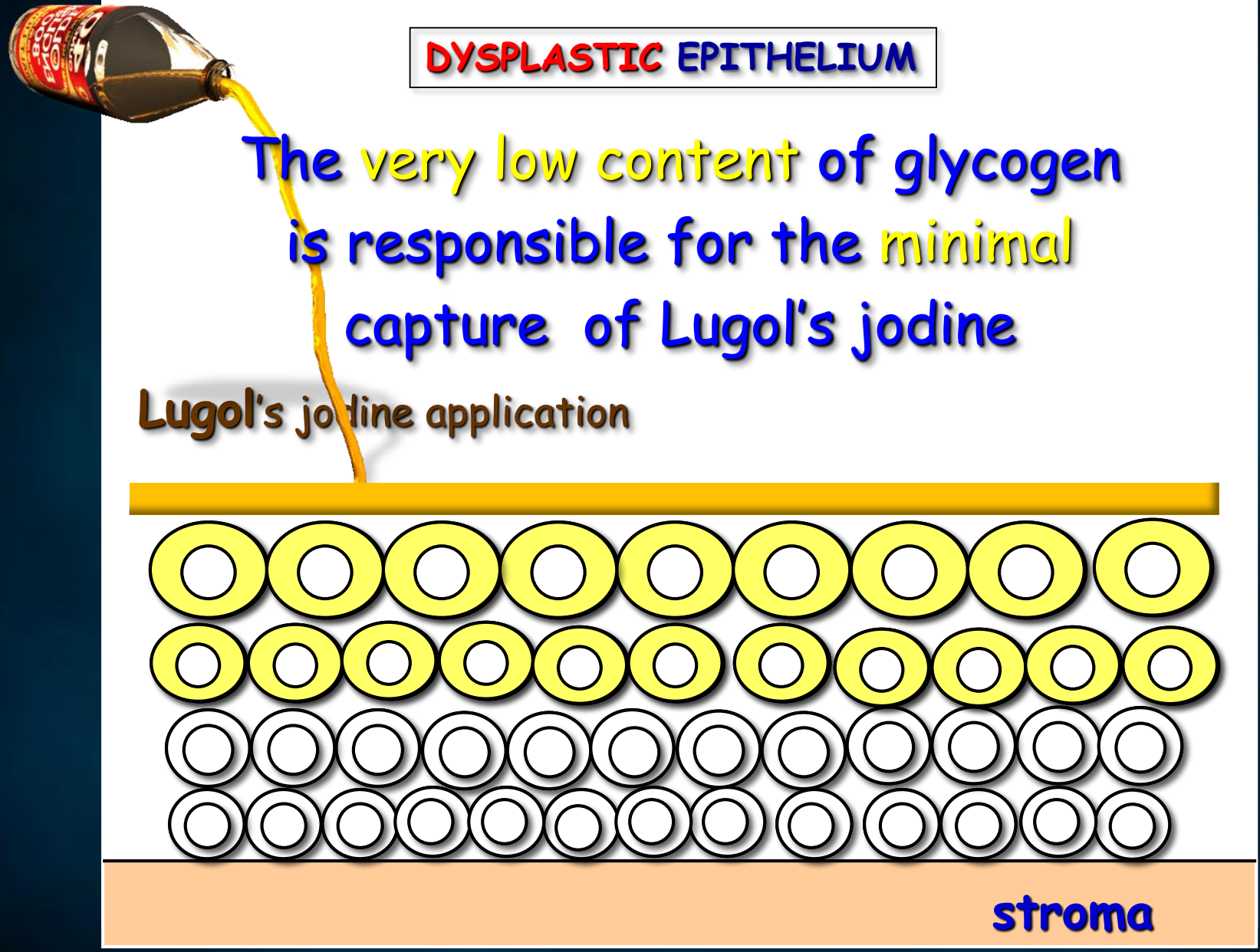
jodine negativity



almost devoid of glycogen

DYSPLASTIC EPITHELIUM

The very low content of glycogen is responsible for the minimal capture of Lugol's jodine

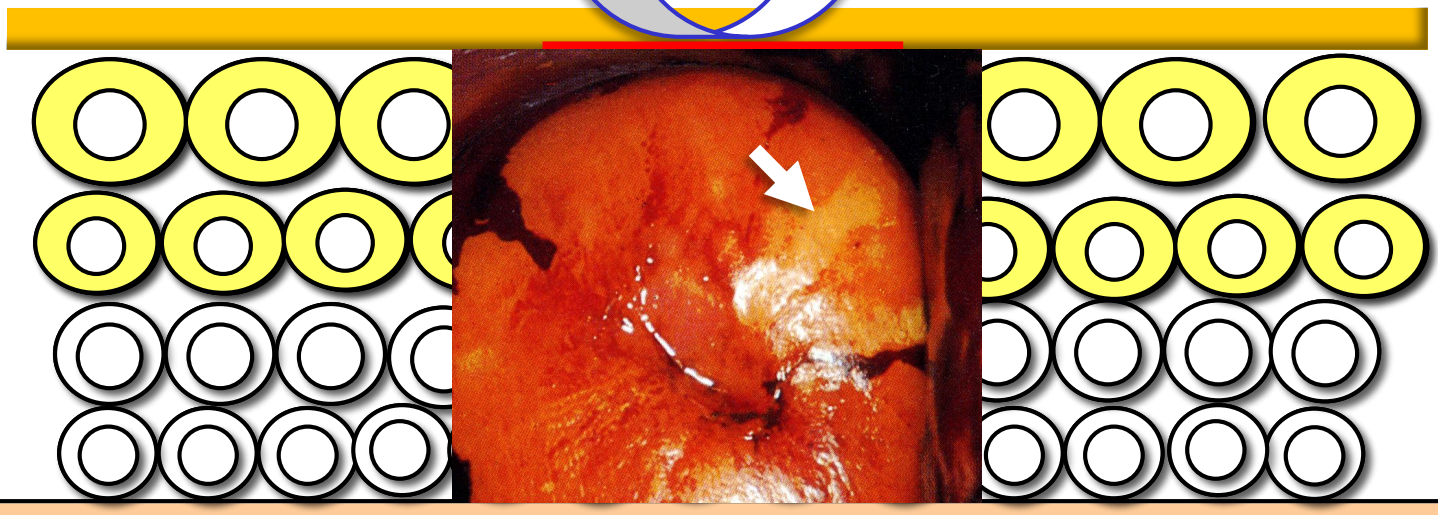


IMMATURE SQUAMOUS EPITHELIUM

DIRECT light cannot accross the epithelium

REFLECTED light from EPITHELIUM is YELLOW staining

JODINE NEGATIVE area

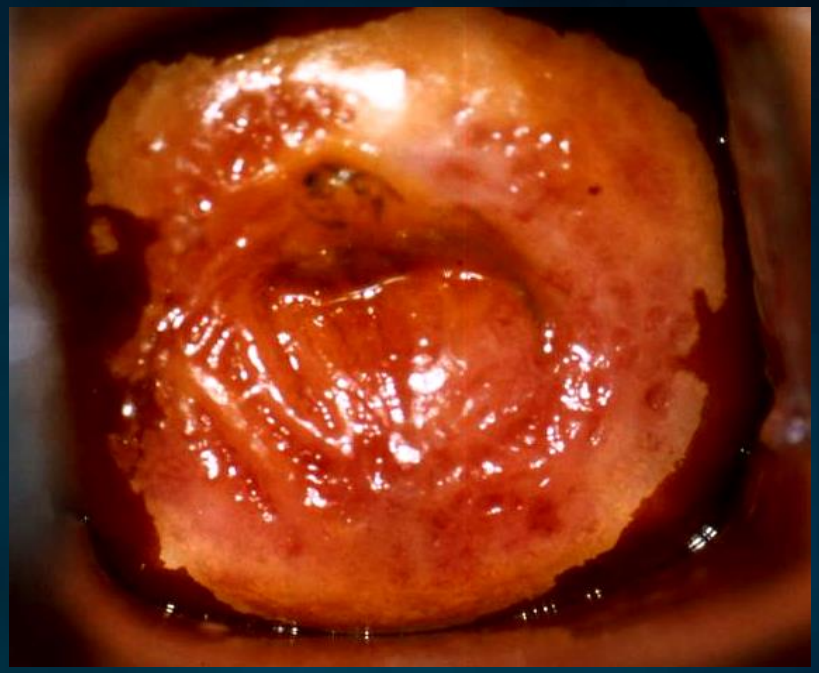


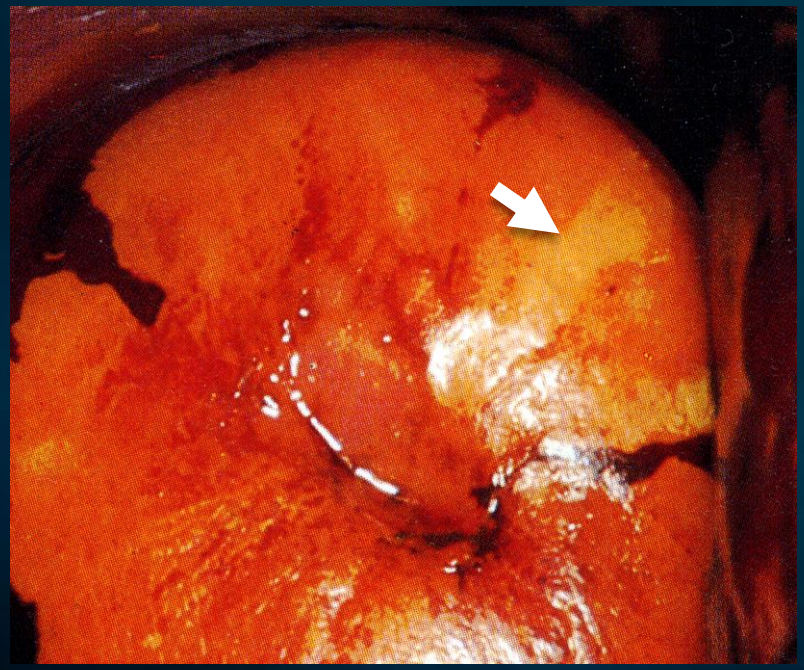
stroma

jodine

partial positivity:

immature metaplasia



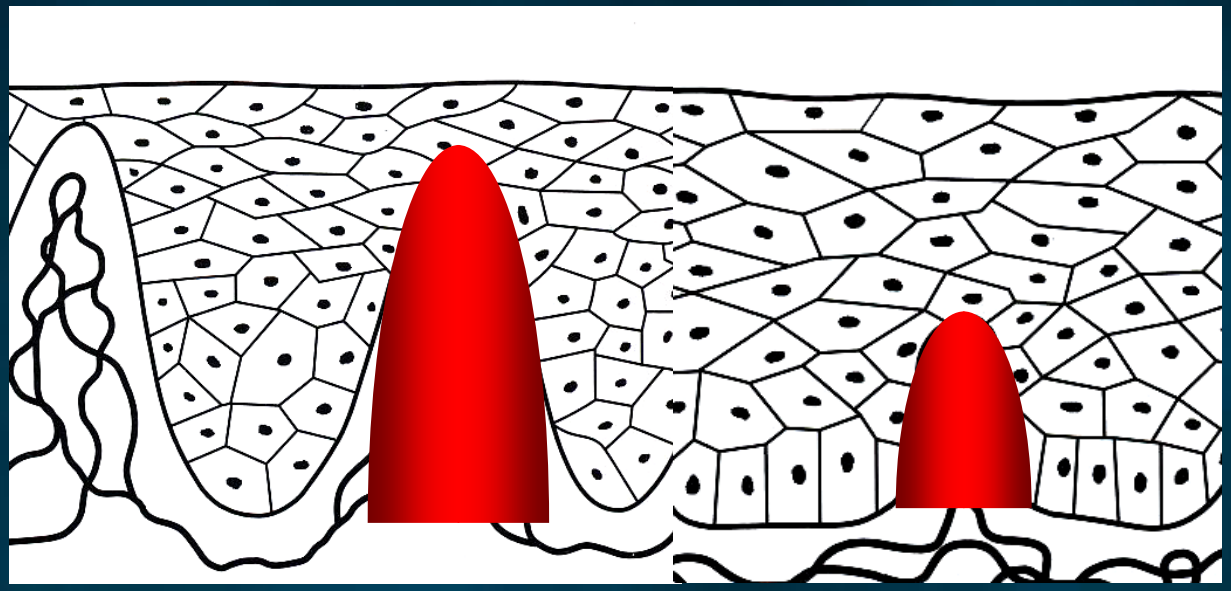


jodine

negativity:

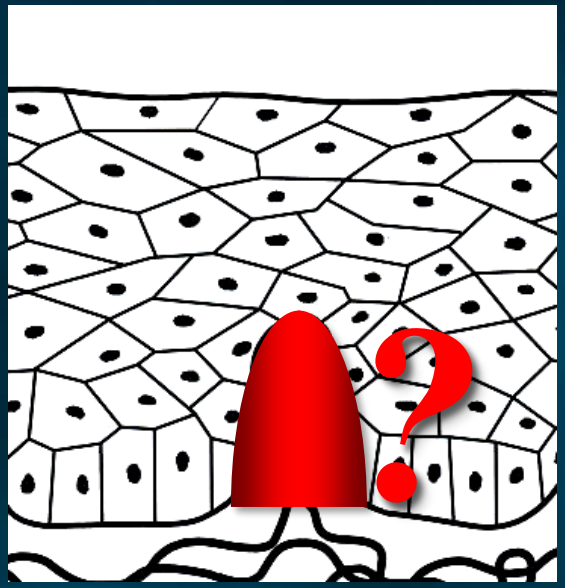
ISC

TYPICAL metaplastic process



Individual stromal papillae become flatter

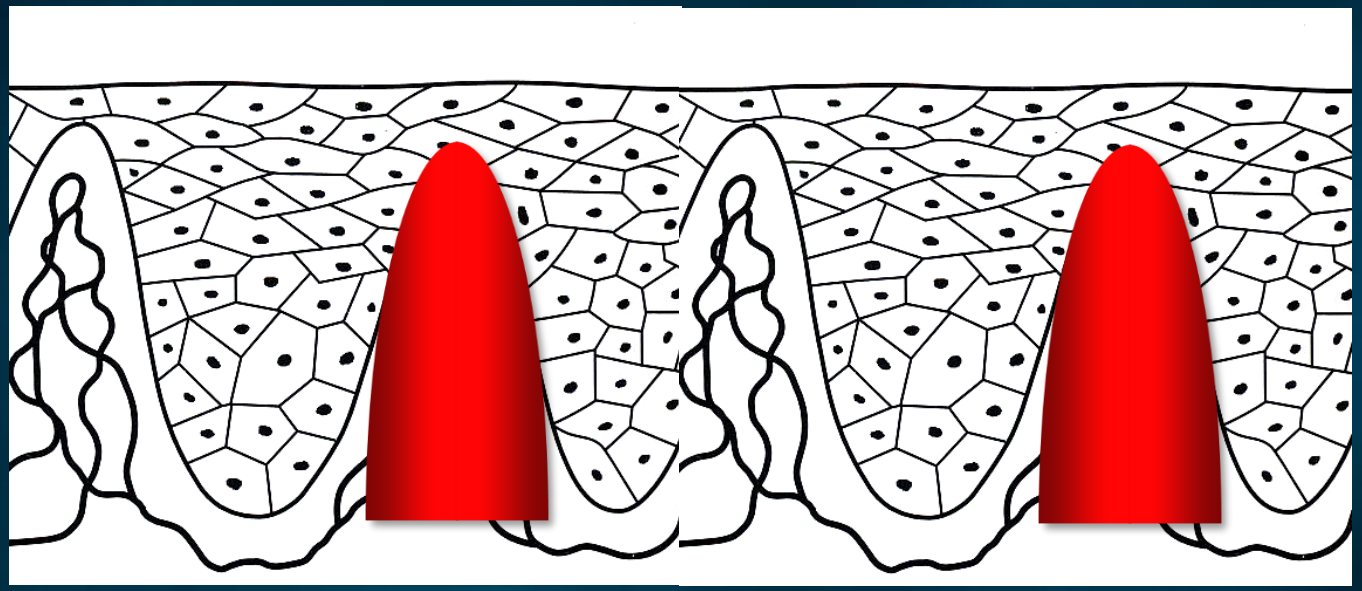
ATYPICAL metaplastic process



stromal papillae

Which is the behaviour of stromal papillae?

ATYPICAL metaplastic process

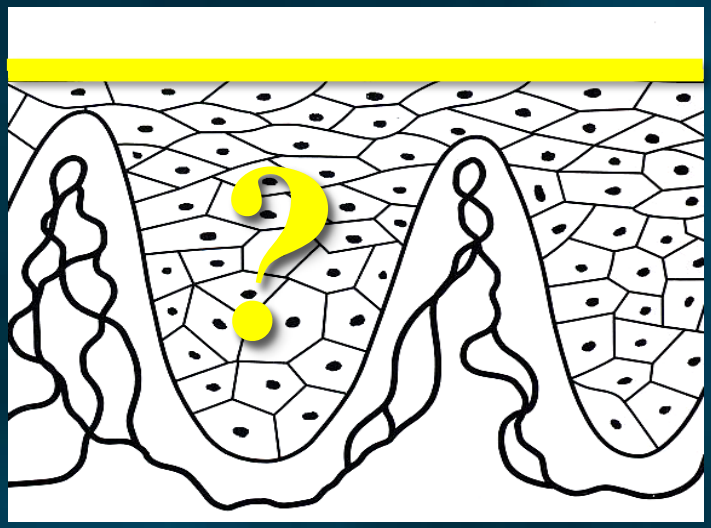


Individual stromal papillae

do not become flatter

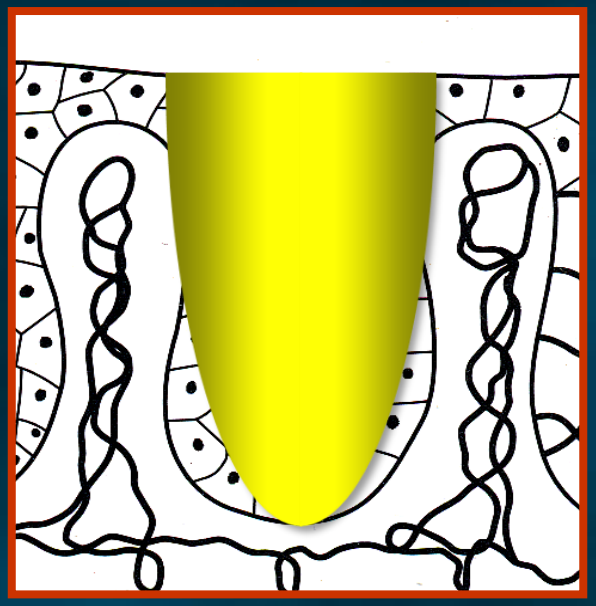
ATYPICAL metaplastic process

epithelium



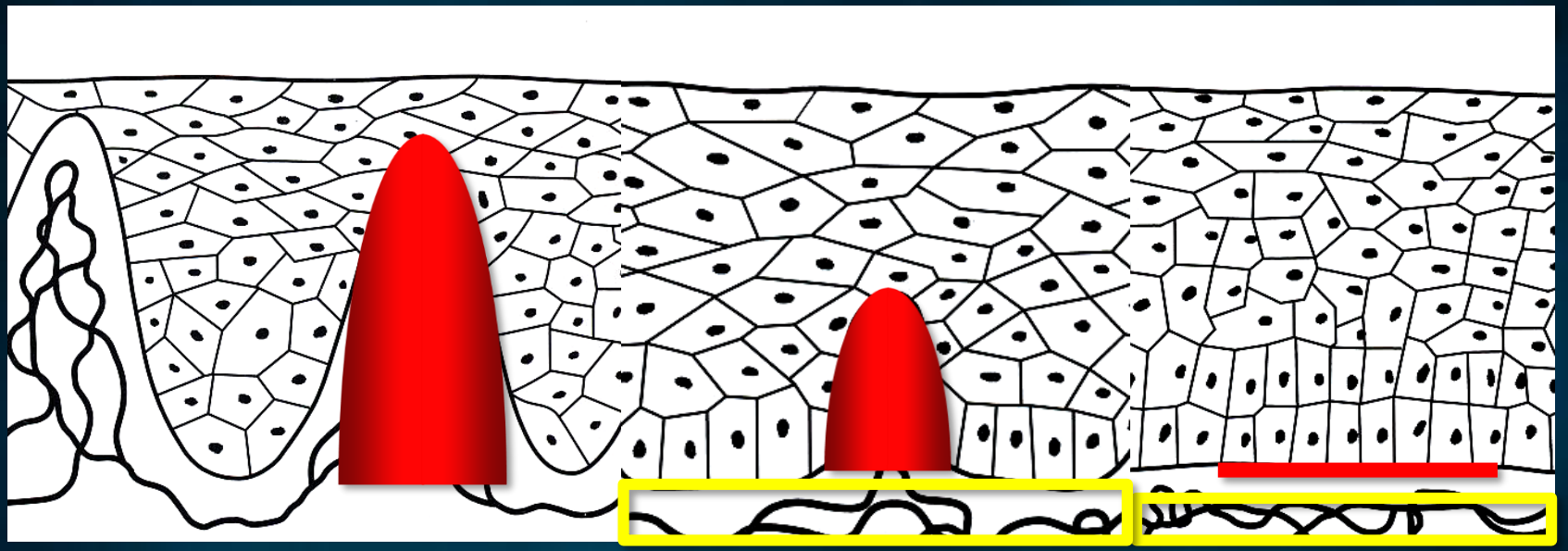
Which is the behaviour of epithelium?

ATYPICAL metaplastic process



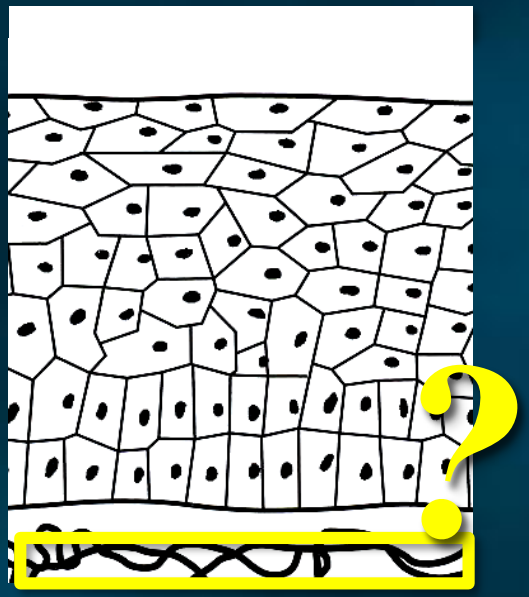
The metaplastic epithelium starts to growth in buds or blocks

TYPICAL metaplastic process



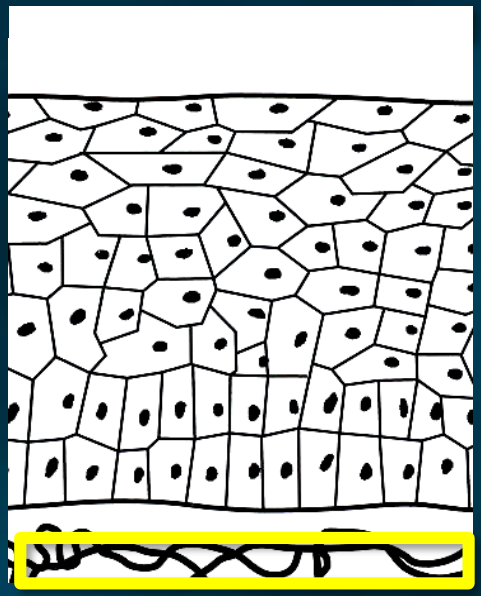
Ultimately, capillary structures form a network under the epithelium

ATYPICAL metaplastic process

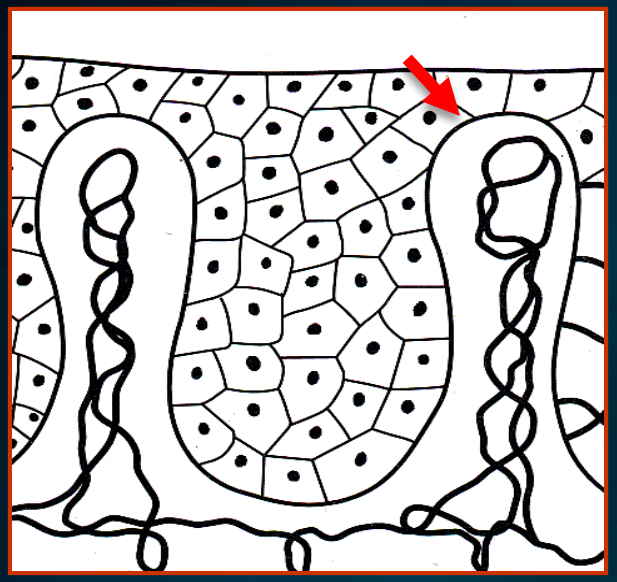


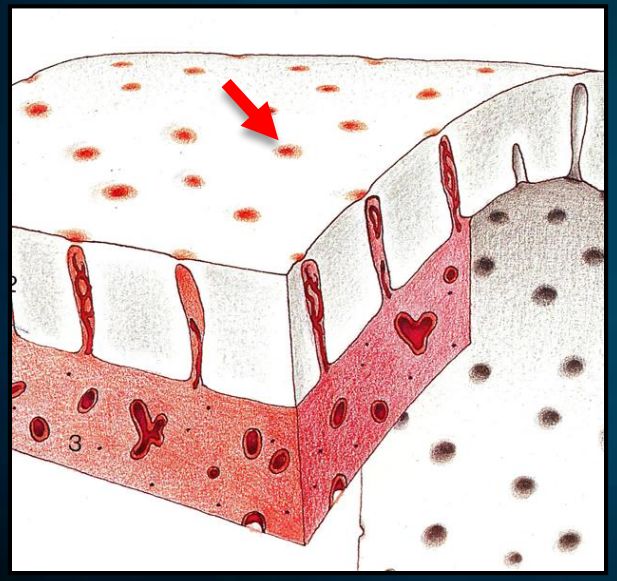
Which is the behaviour of capillary structures?

ATYPICAL metaplastic process



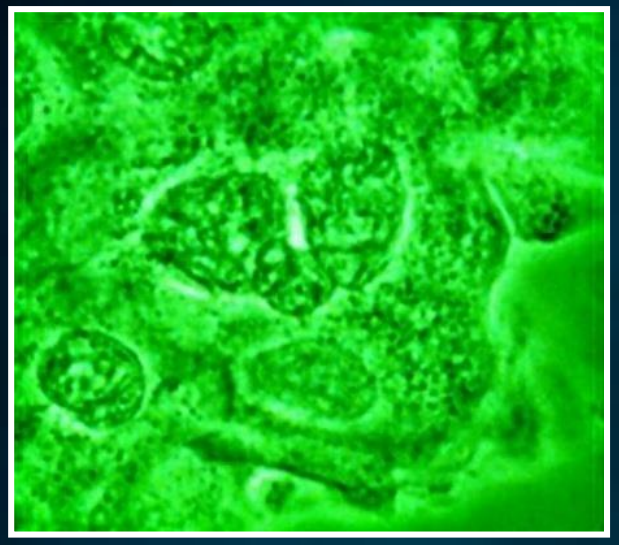
An abnormal angiogenesis takes place

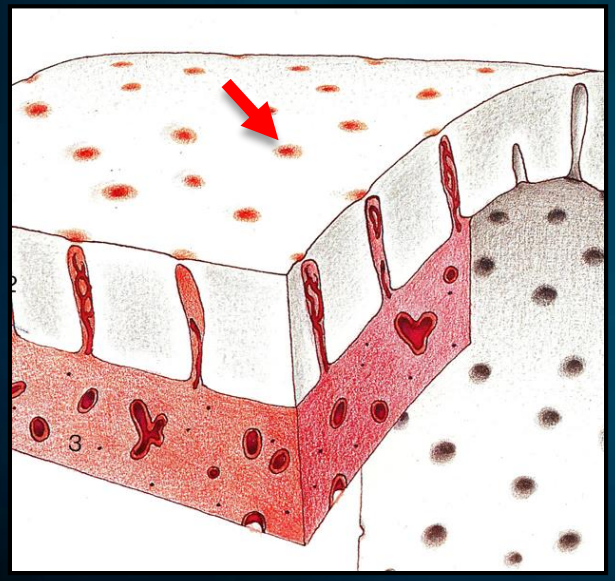




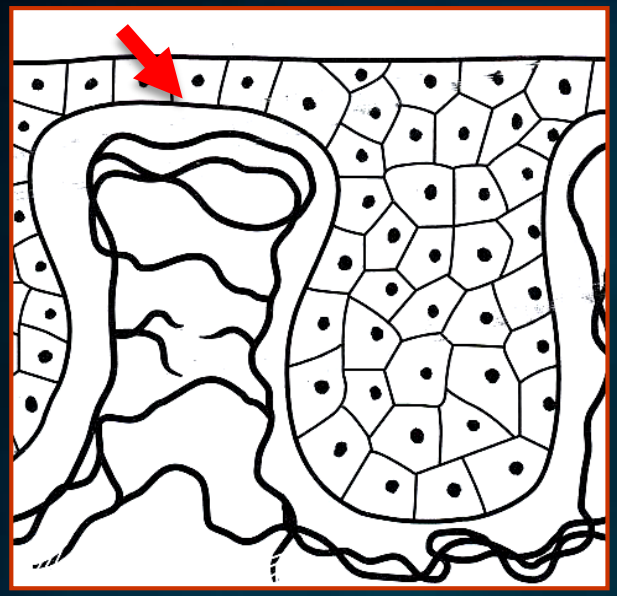
PUNCTATION

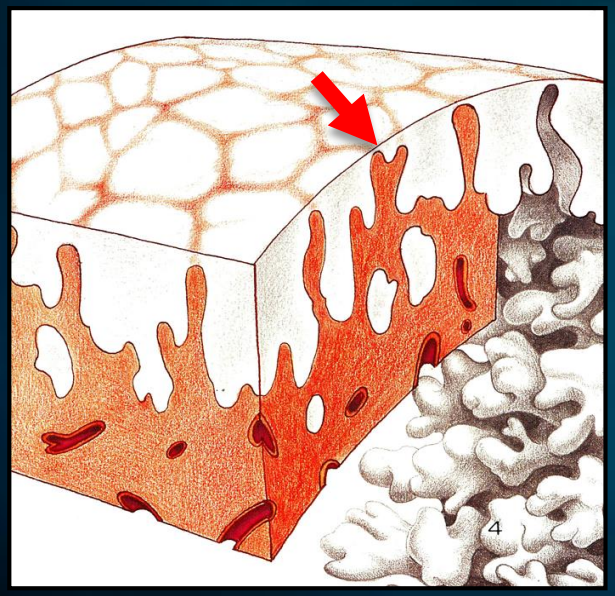
Vessels within these papillae may undergo **dilatation** and **proliferation** near the surface, and appear as **dots** on a white or opaque background





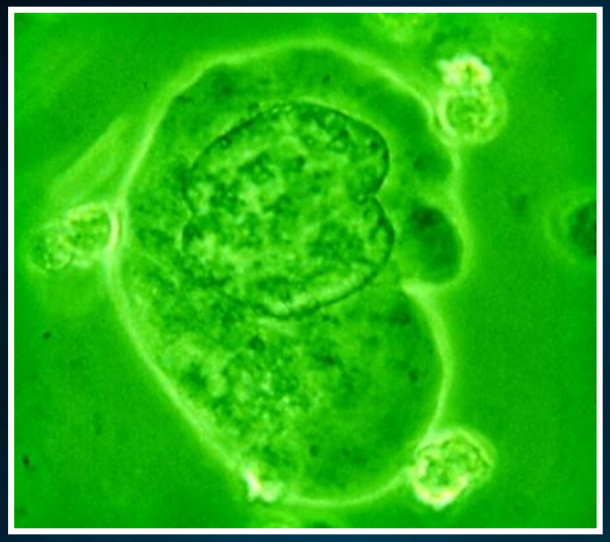
coarse punctation

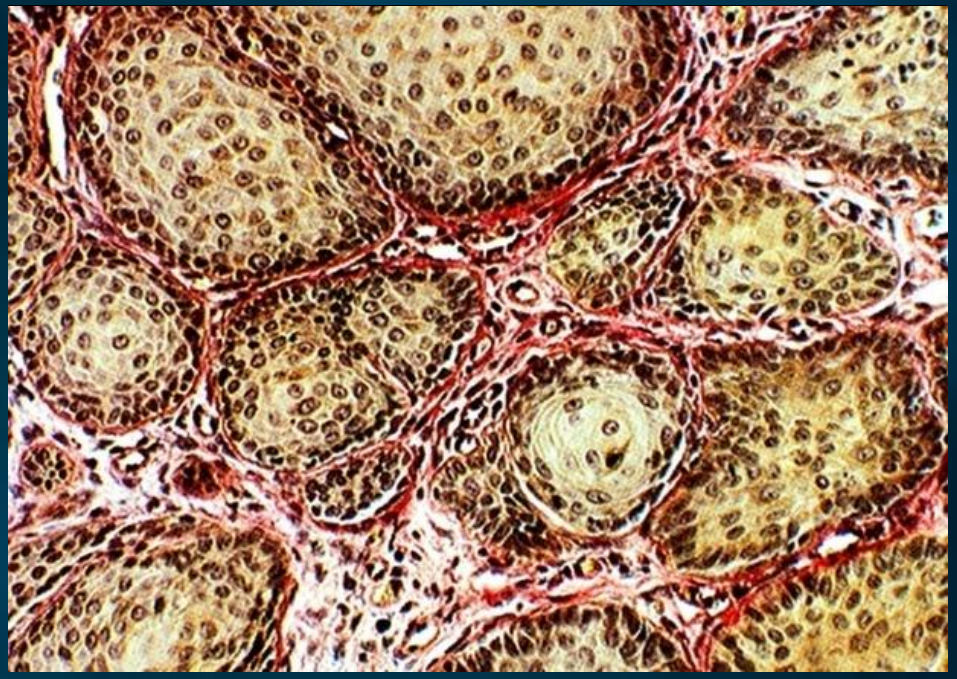


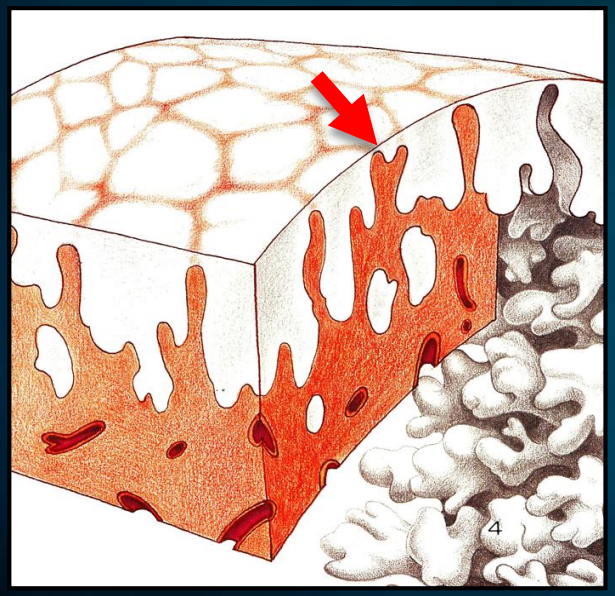


MOSAIC epithelium

Thickening of the stromal papillae is associated with an arborizing network of stromal ridges subdividing the surface epithelium into discrete fields



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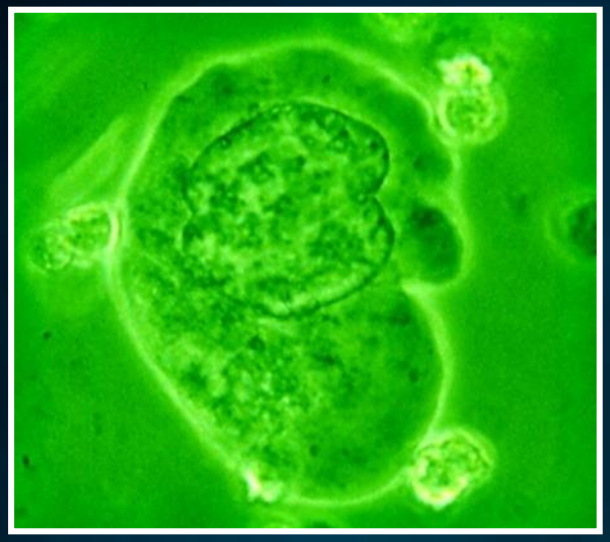
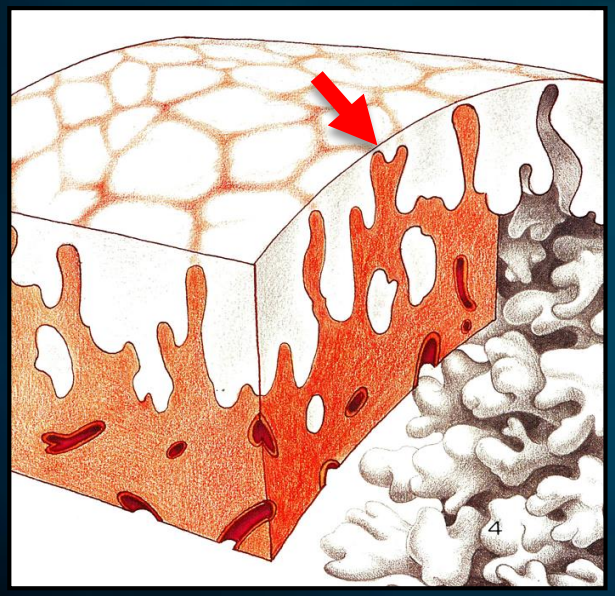
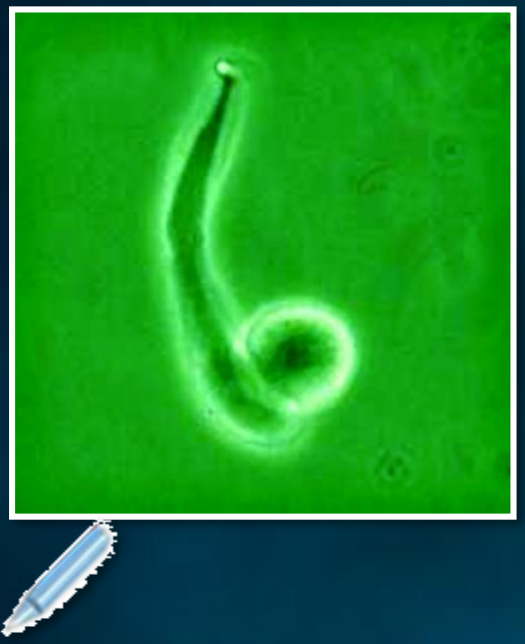




coarse **mosaic** epithelium

CRAZY METAPLASIA



golf metaplasia

sexy metaplasia