

HPV and pathogenesis of SIL

Behrooz Shokouhi, MD ACP

cancer of the cervix

- a burden of human suffering and mortality
 - is disproportionate to its size
- due to the susceptibility of the epithelium of the cervical transformation zone to infection by oncogenic HPV
- cervical screening programs
- Vaccination against HPV
- remains one of the most common cancers

HPV

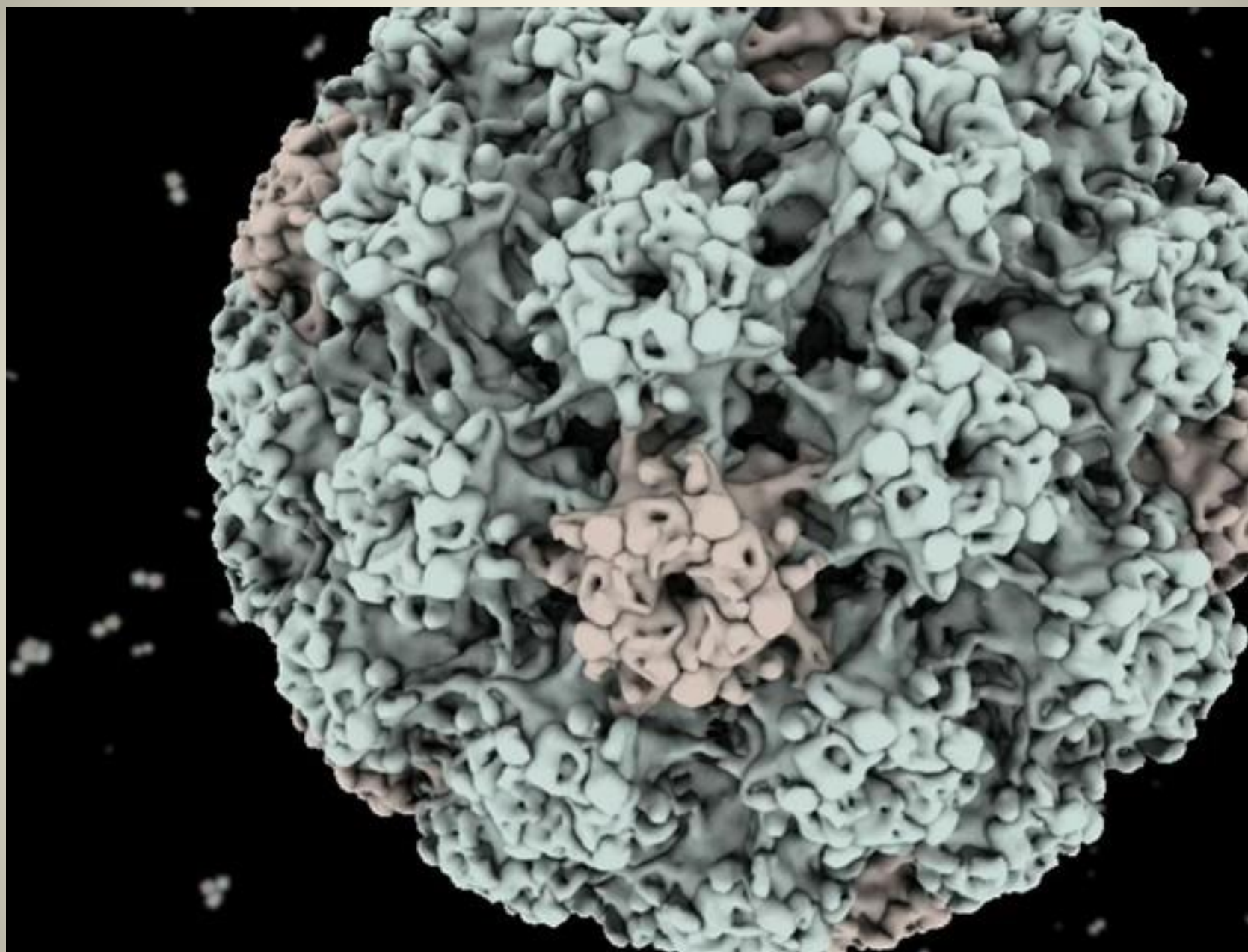
and

the Lower Female Genital Tract

a rapidly advancing field

The role of HPV in the pathogenesis

- of both condyloma and carcinoma
- **Relatively recently** was unsuspected
- **greater than 99% of cervical carcinomas** are associated with oncogenic HPV
- **the molecular mechanisms** of virus-mediated oncogenesis are understood in considerable detail



HPV, a DNA virus

- is classified on the viral genome into different genotypes
- HPV-2 is the most common cause of verruca vulgaris
- **the genital HPV genotypes**, transmitted by sexual contact
 - associated with condyloma, the low-risk HPV genotypes, 6 & 11
 - associated with cervical carcinoma, the high-risk genotypes (oncogenic), the risk varies, 16 & 18
 - possibly oncogenic, of uncertain oncogenic potential

Table 1 | **Papillomavirus types in genital lesions**

Type of genital lesion	HPV type	
	Less prevalent	More prevalent
Condylomata acuminata	42,44,51,53,83	6,11
Intraepithelial neoplasias	6,11,18,26,30,31,33,34,35,39,40,42,43,45,51,52,53,54,55,56,57,58,59,61,62,64,66,67,68,69,70,71,73,74,79,81,82,83,84	16
Cervical and other anogenital cancers	(6,11),18,31,33,35,39,45,51,52,54,56,58,59,66,68,69	16

Human papillomavirus (HPV) types in brackets indicate extremely rare prevalence.

The genital HPVs are epitheliotropic

- the high-risk HPV types, in particular, have a tropism for **the metaplastic squamous cells at the squamocolumnar junction** of cervix
- This has very important consequences for cytologic screening of cervix
- Also for **native squamous epithelium** of other sites, in contrast to most cervical cases

cytologic screening of cervix

- The **most precursor lesions and carcinomas** arise at SCJ
- is **amenable to sampling** with a brush or spatula
- if the lesions of HPV-associated neoplasia of the genital tract were **randomly distributed** within the squamous mucosa, screening would have failed
 - as it has in the oral cavity, pharynx, esophagus, larynx, skin, vulva, vagina and ectocervix

Potentially infectious virus particles

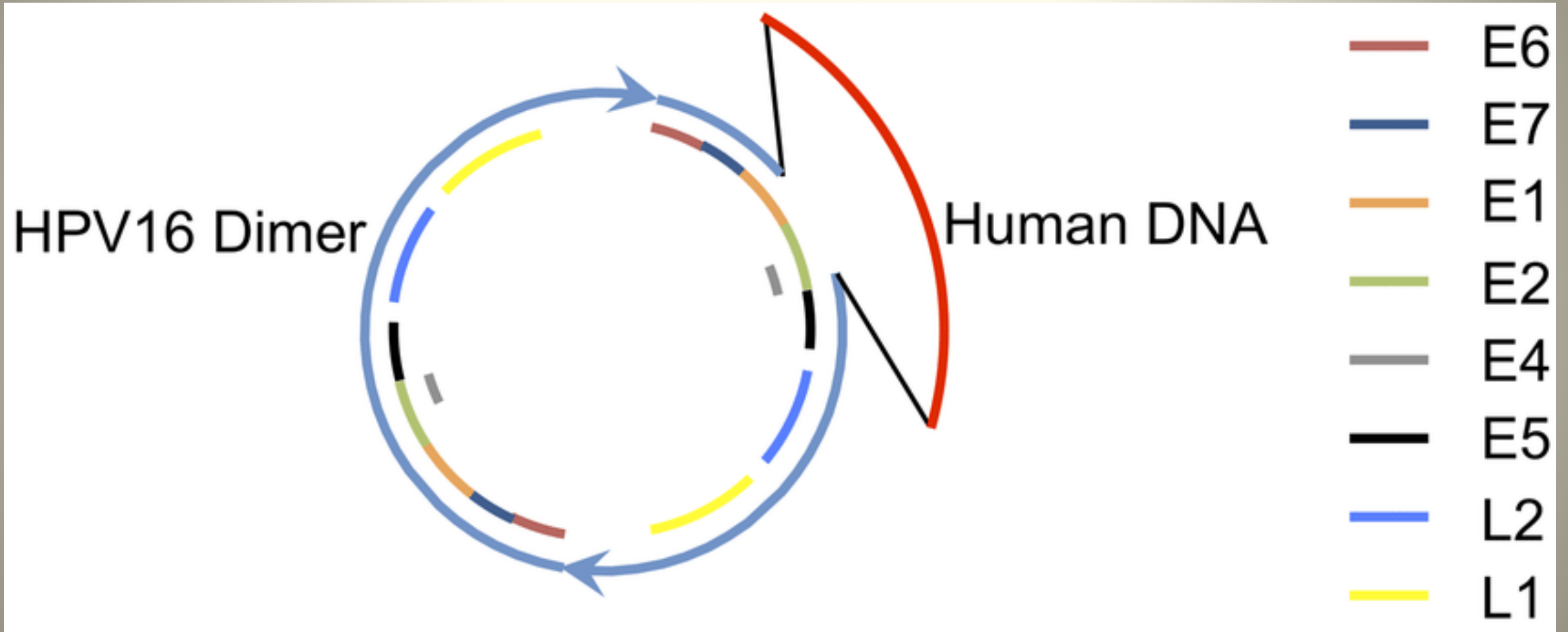
- must reach the **proliferating basal cells** for productive infection to take place
- **a micro-injury** to the squamous epithelium is required
- In the case of glandular epithelium
 - the stem cell compartment should be more accessible
 - infection of cervical glandular epithelial cells is less likely

silent infection
productive infection

silent infection

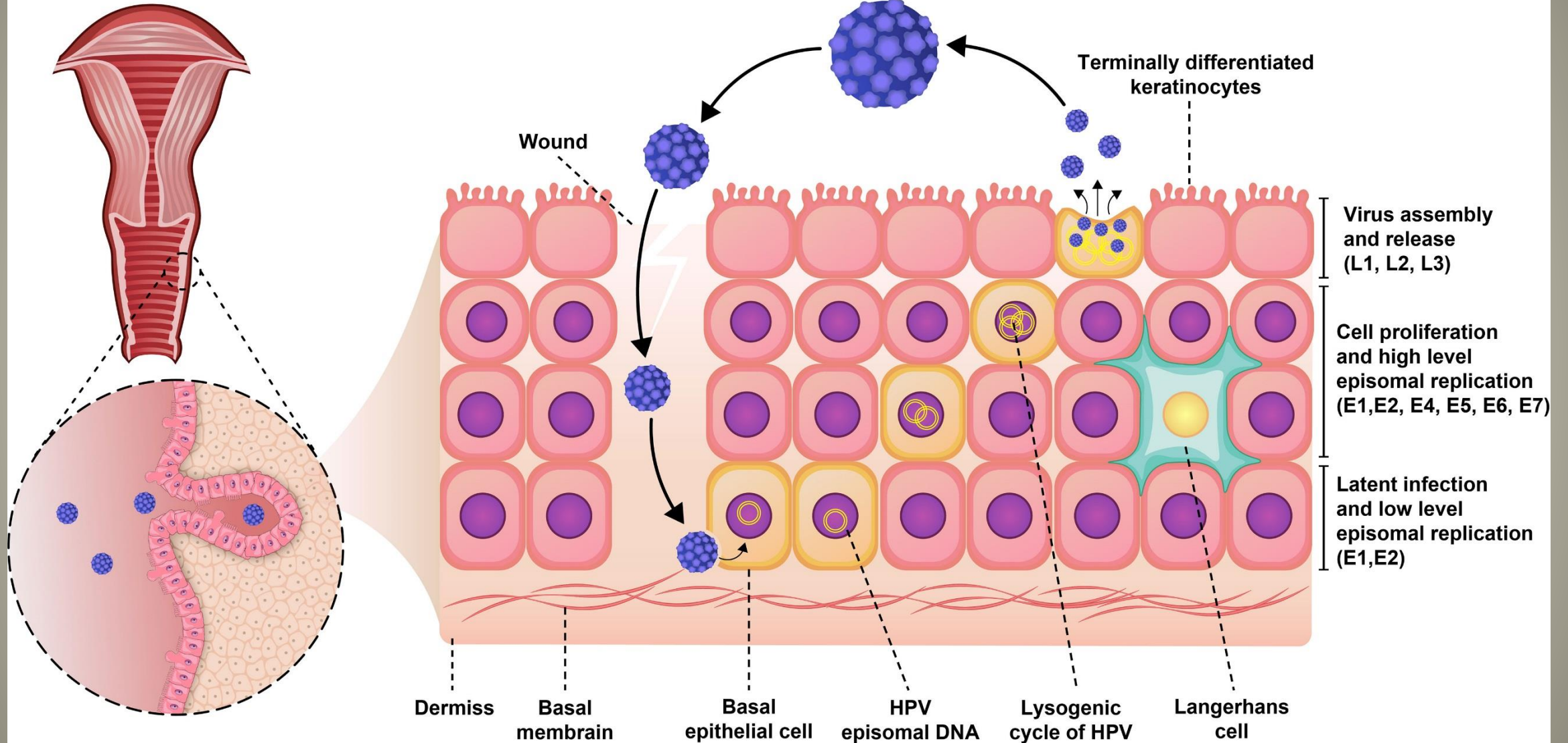
- Once the virus particles are taken up by the basal epithelial cells
- methylation of the viral genome
- **Episomic viral DNA remains in the cell**
- but is not transcribed or translated

the HPV Dimer-Human DNA Hybrid Episome



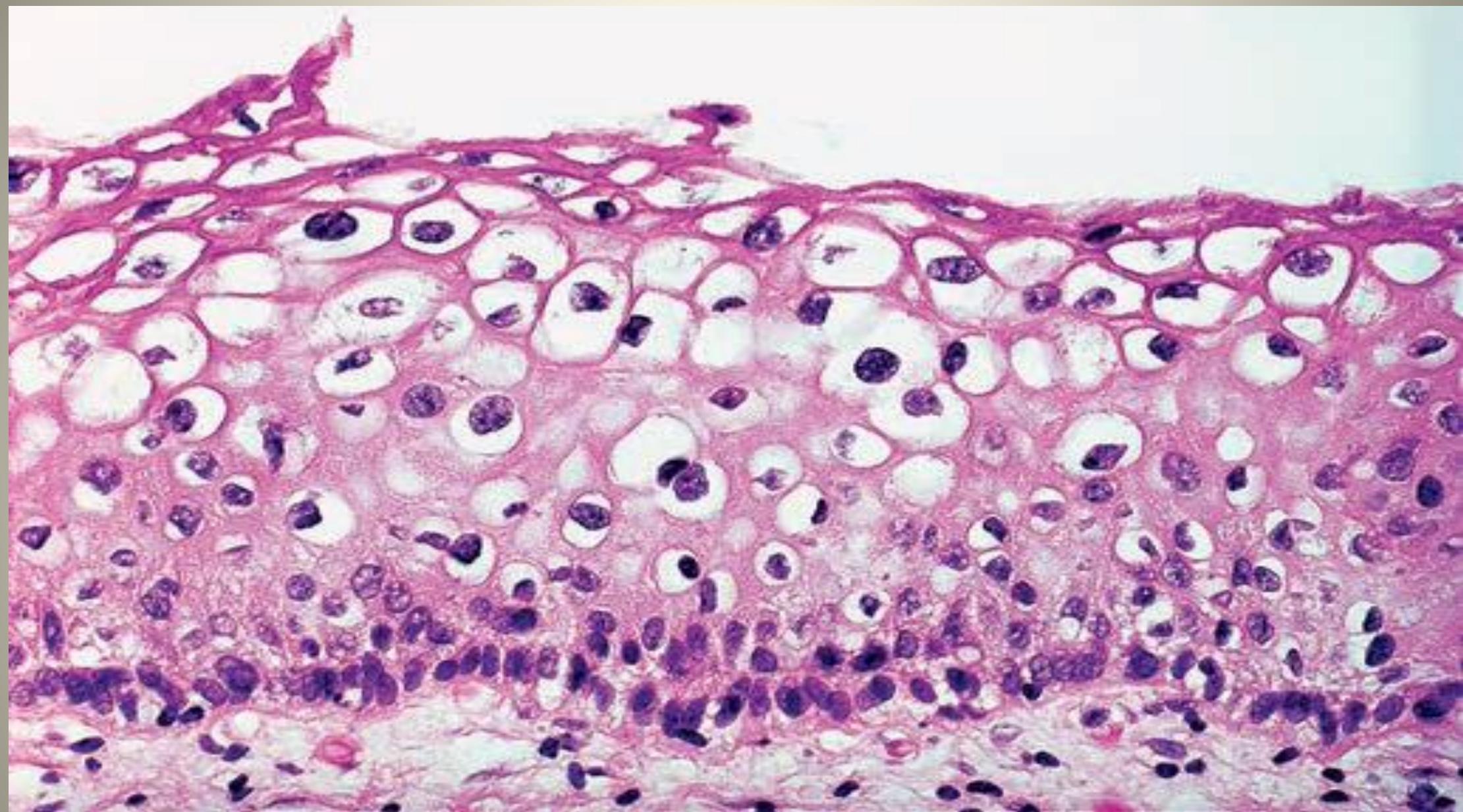
Cervix

HPV



productive infection may result

- may result in **orderly expression of viral genes**
- the host squamous cells mature
- assembly and release of infectious virus particles at the epithelial surface
- This is typically associated with **koilocytic change**
- a viral cytopathic effect: the E4 protein encoded by the viral genome causes disruption in the cytoplasmic keratin matrix



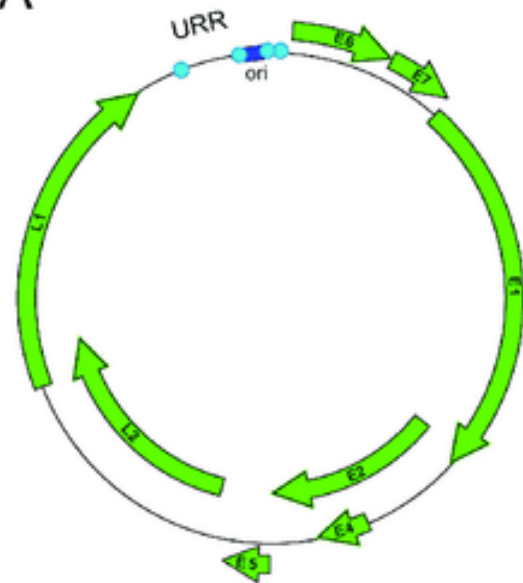
LSIL

- either a diploid or polyploidy nuclear DNA distribution
- orderly expression of the viral genome
- the squamous cells mature and move to the surface

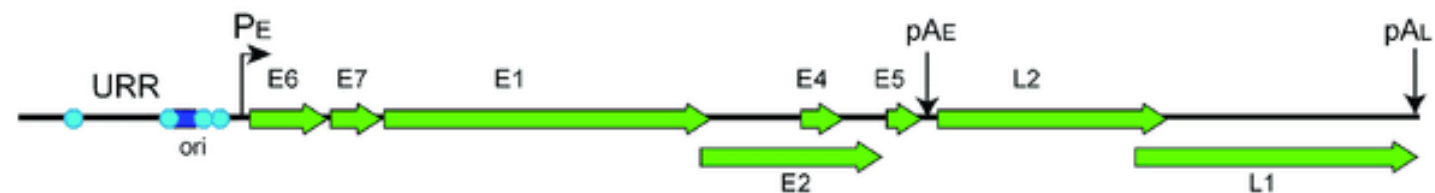
high-risk/oncogenic HPV infection

- deregulated expression of the viral genome
- The E6 and E7 proteins encoded by the genomes
- bind and inactivate the proteins encoded by the *TP53* and *RB* anti-oncogenes
- **unfettered proliferation of the host cell**
- decreased E4 expression and virion production
- decreased or absent koilocytic change

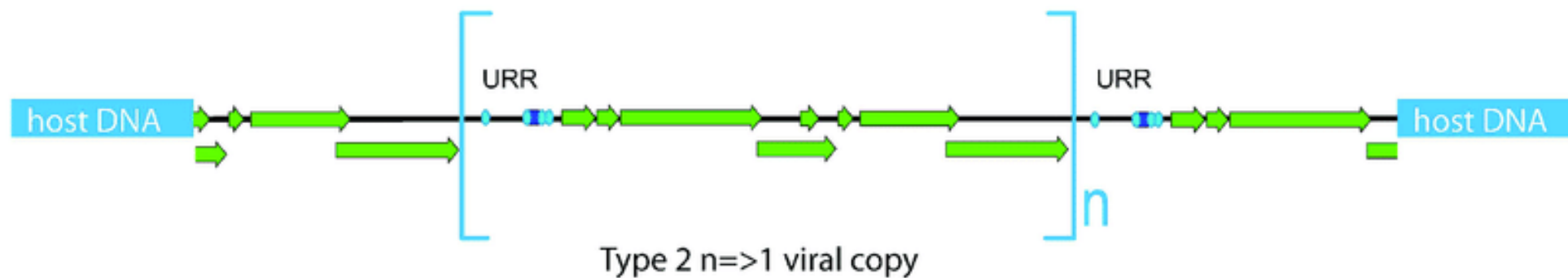
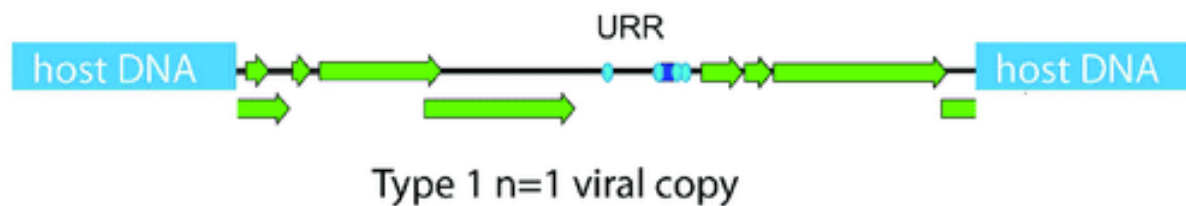
A



B

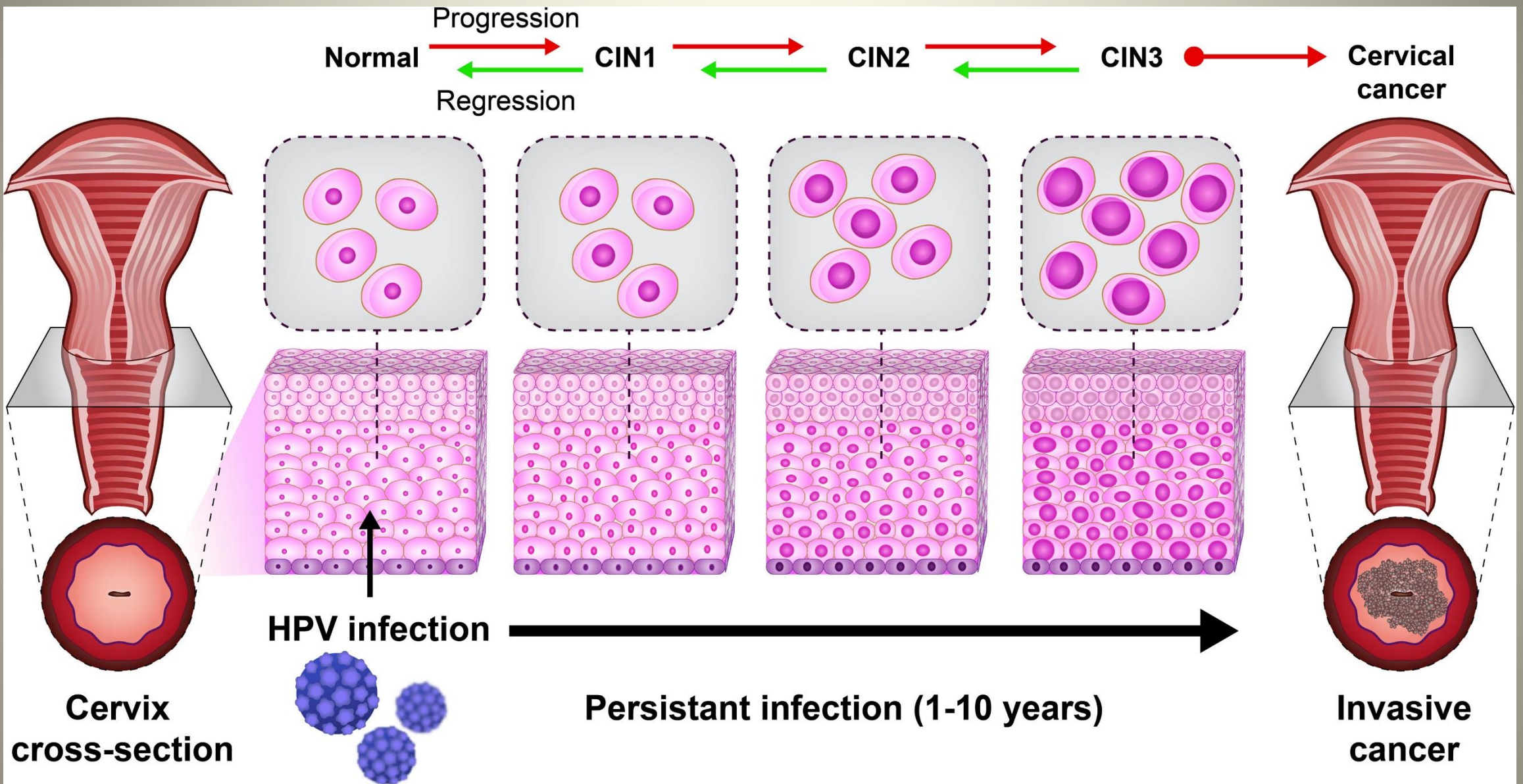


C



increased likelihood of:

- **integration** of the viral genome into the host genome
- acquisition of **other genetic abnormalities** in the host cell
- **malignant transformation**



**Not all viral infections
lead to transformation**

**most are cleared by the immune system of the
host**

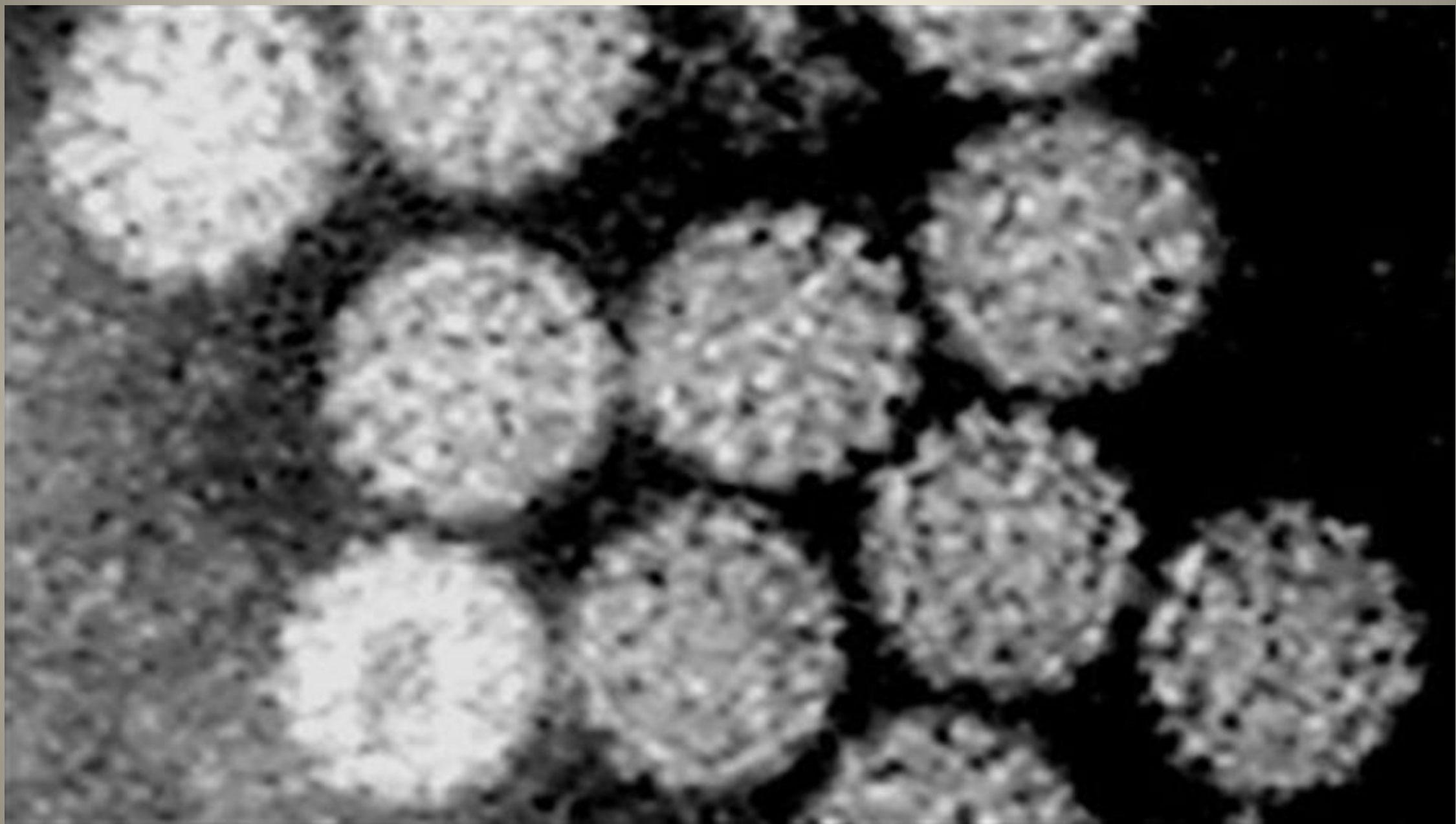
through cell-mediated immunity

productive infection due to

- **By low-risk HPV, 6 or 11**
 - LSIL/condyloma with viral cytopathic effects
- **By high-risk HPV, most commonly 16 or 18**
 - LSIL
 - progress to HSIL
 - invasive squamous cell carcinoma

HPV can be detected

- **electron microscopy:**
 - intranuclear crystalline occasionally filamentous inclusions
- specific identification: **nucleic acid hybridization**
 - with or without amplification
 - from DNA or RNA
 - either a liquid-based or *in situ* analysis



The p16 antioncogene

- in cells infected by high-risk HPV
- inactivation of the RB protein by the viral E7 protein
- **phosphorylated RB protein**
- **absence of the normal downregulation of p16 expression**
- **high-level expression of p16**
- **strong nuclear and cytoplasmic immunoreactivity**

Immunostaining for p16 (p16INK4a)

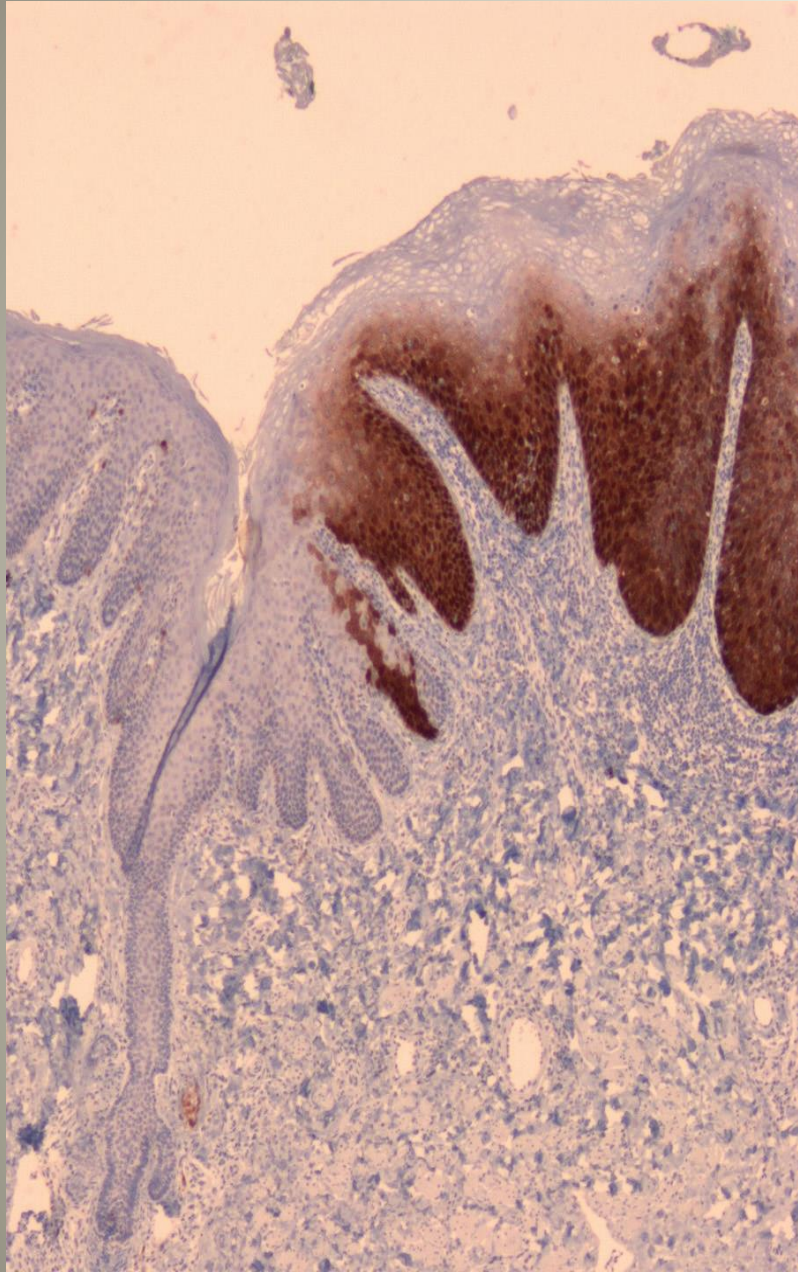
- a sensitive and specific surrogate for detection of HPV-associated versus HPV-independent vulvar squamous neoplasia
 - sensitivity of 100%
 - specificity of 98%–99%
- performed on intraepithelial lesions or early invasive carcinomas
 - p16 expression can be lost during tumor progression

Correct interpretation of p16 immunostaining

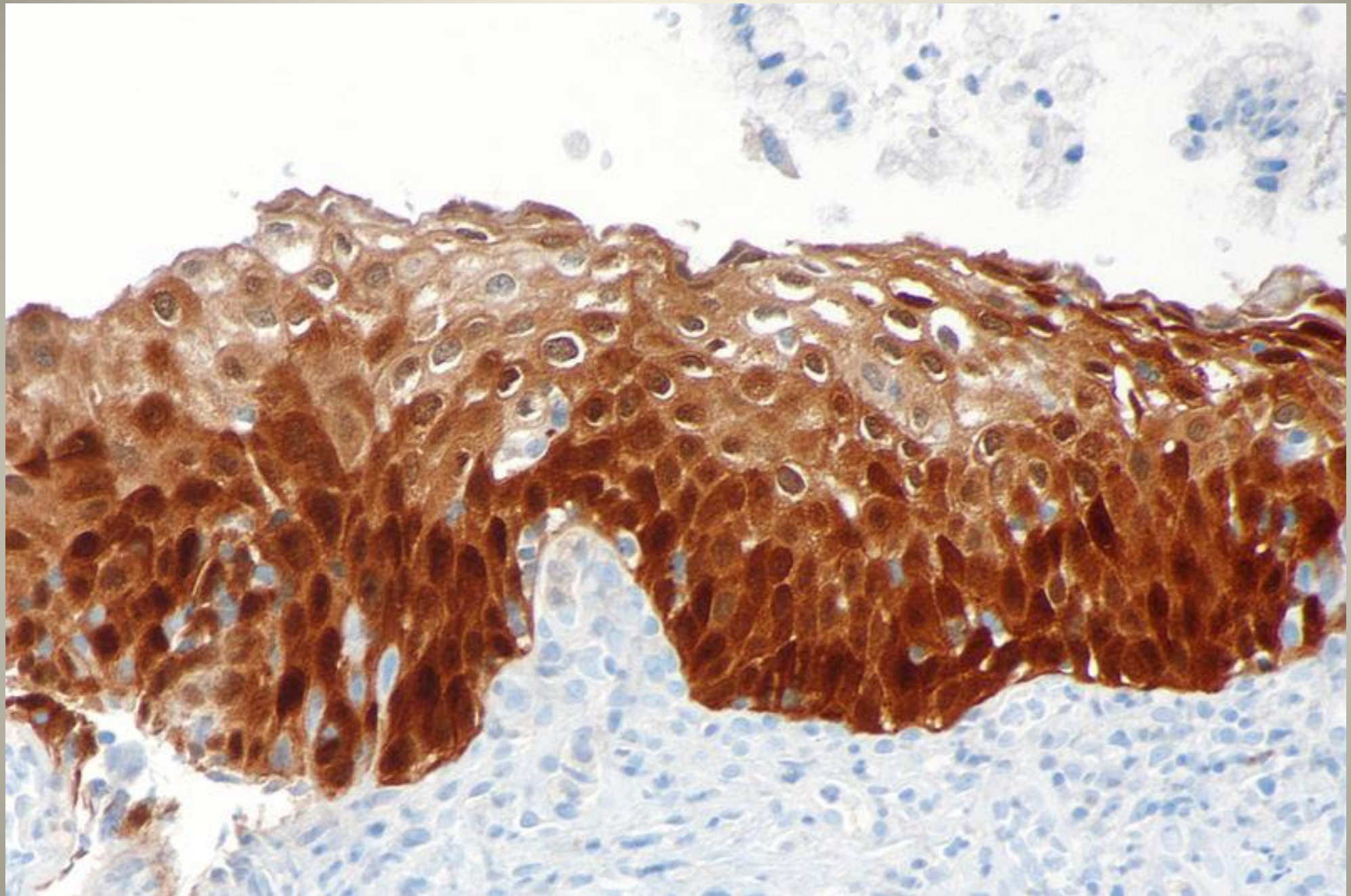
- the staining protocol **has been properly validated**
- appropriate **controls** run
- a number of antibody **clones** specific for p16
- it is incumbent on **each lab to optimize the staining** for the clone they have chosen
- a responsibility that is sometimes **neglected**

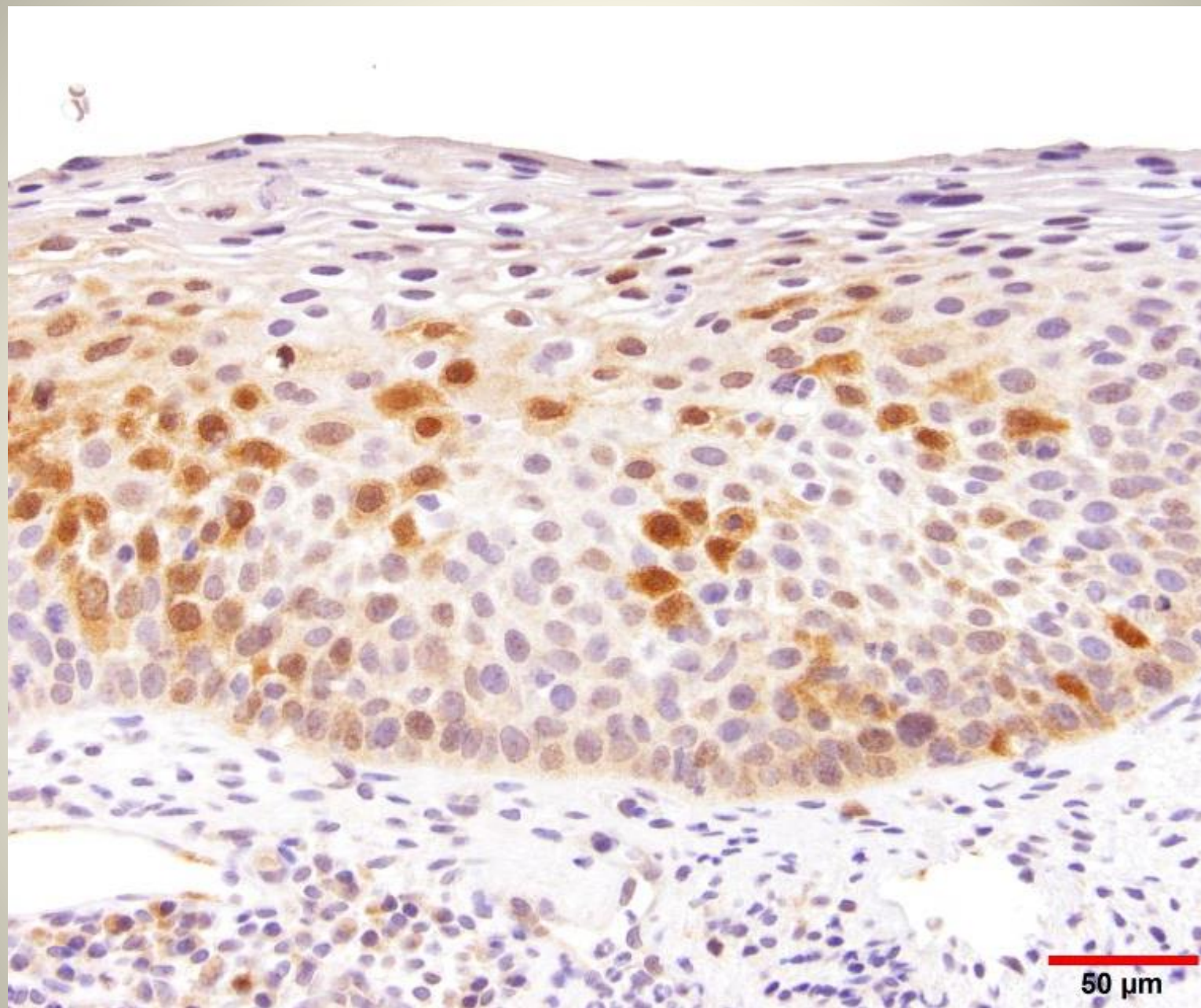
block positivity for p16

- indicative of high-risk HPV infection
- strong nuclear and cytoplasmic staining of every cell in the basal third of the epithelium
- typically extending into the middle and upper thirds



“Block” immunoreactivity in HSIL
a test for the presence of oncogenic HPV





p16 immunostaining		HSIL n (%)	LSIL n (%)
Percentage of positive cells (%)	0(<5%)	5 (41.7%)	11(57.9%)
	1(5-49%)	4(33.3%)	6(31.6%)
	2 (50-80%)	3 (25.0%)	2(10.5%)
Intensity of reaction	0 (No reaction)	1 (8.3%)	3 (15.8%)
	1(Weak)	3 (25.0%)	10 (52.6%)
	2 (Variable)	4 (33.3%)	4 (21.1%)
	3 (Strong)	4 (33.3%)	2 (10.5%)
Cellular reaction pattern	0 (No reaction)	1 (8.3%)	3 (15.8%)
	1 (Focal)	10 (83.3%)	16 (84.2%)
	2 (Diffuse)	1 (8.3%)	0 (0%)
p16 Negative (0–3)	0	1 (8.3%)	3 (15.8%)
	2	3 (25.0%)	7 (36.8%)
	3	1 (8.3%)	4 (21.1%)
Positive (4–8)	4	4(33.3%)	2 (10.5%)
	5	0 (0%)	2 (10.5%)
	6	2 (16.7%)	1(5.3%)
	7	1 (8.3%)	0 (0%)

Immunoreactivity for p16

- is not specific for HPV
 - other tumor types, unrelated to HPV, dysregulation of RB:
 - high-grade serous carcinoma of tubo-ovarian or endometrial origin
- can be lost through mutation, as cervical cancer progresses
 - rare in the HSIL or in situ adenocarcinoma

Combined staining for Ki-67 and p16

- ✓ a higher proliferative index
- ✓ The strong, diffuse, block positivity for p16

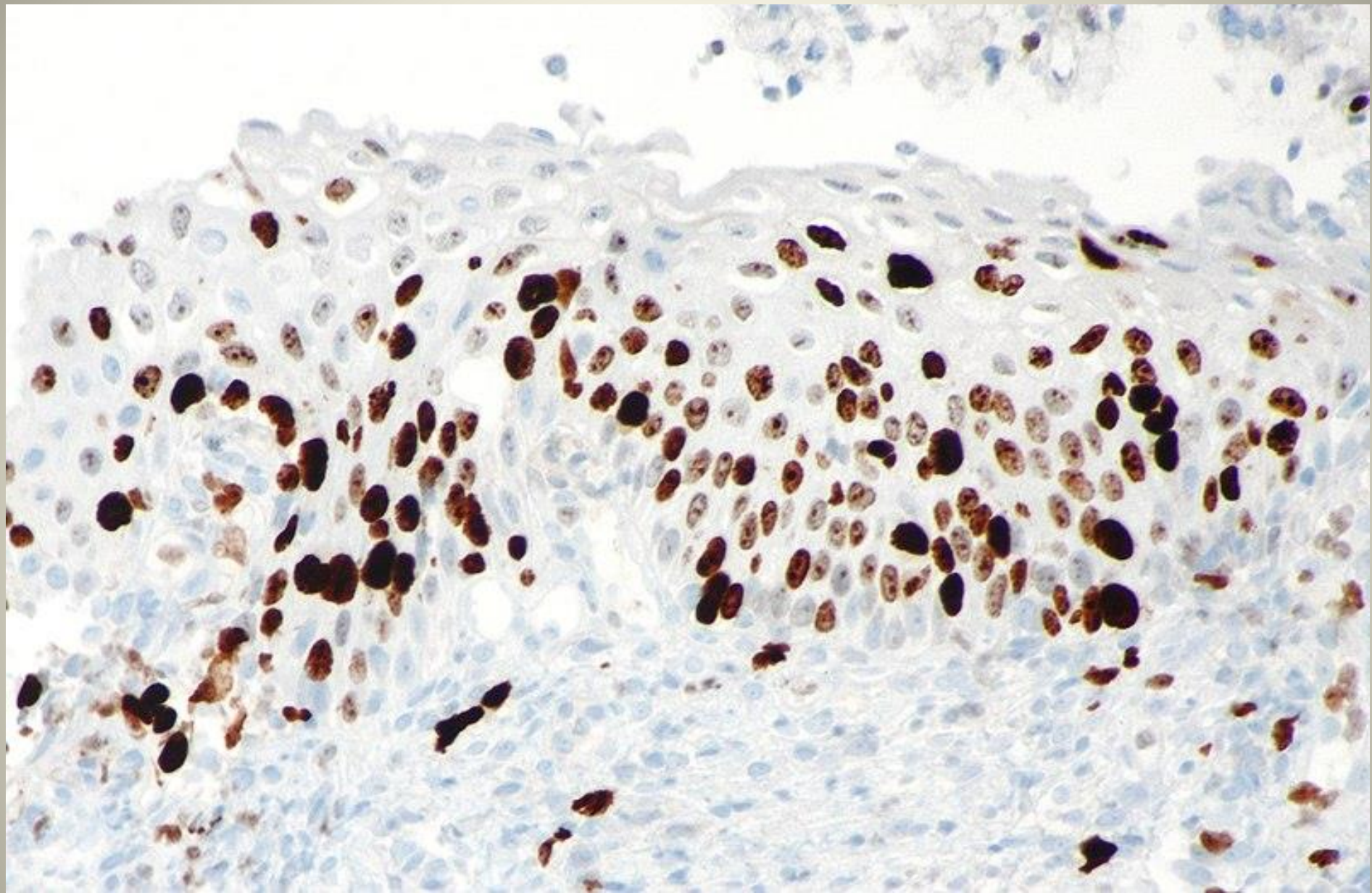


Table 3. Ki-67 grading in HSIL and LSIL

Ki67	HSIL n (%)	LSIL n (%)	Chronic Cx
0	0(0%)	0(0%)	16(80%)
1 (<5%)	6 (50.0%)	15 (78.9%)	4(20%)
2 (5-30%)	4 (33.3%)	4 (21.1%)	0(0%)
3 (>30%)	2 (16.7%)	0 (0%)	0(0%)

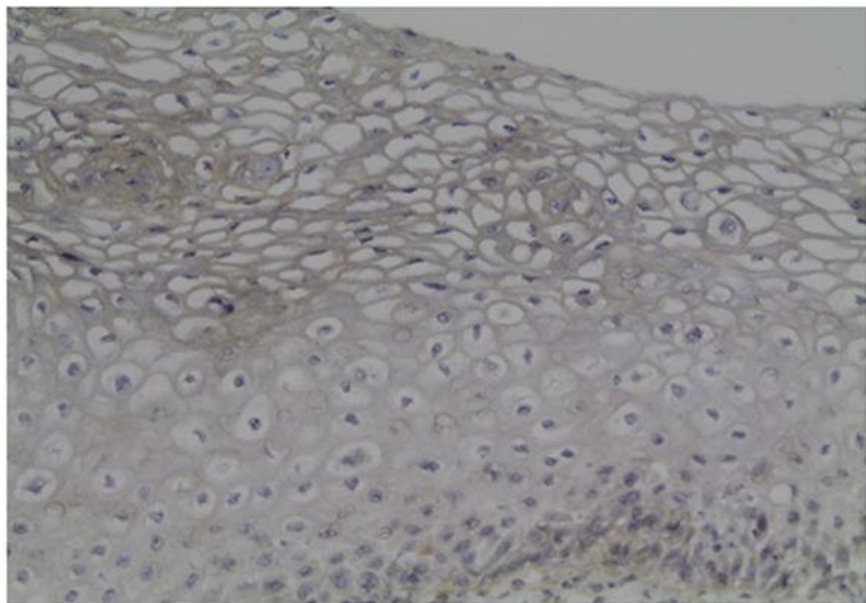
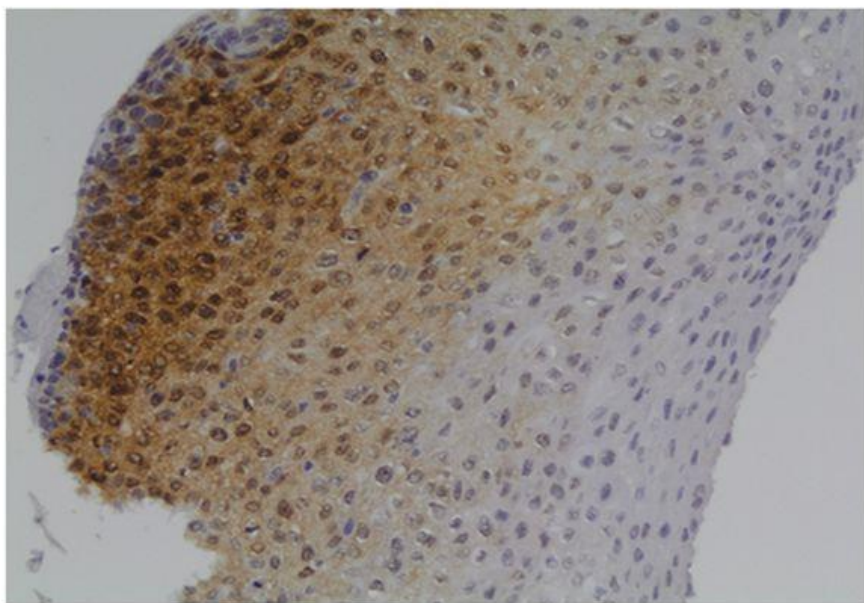
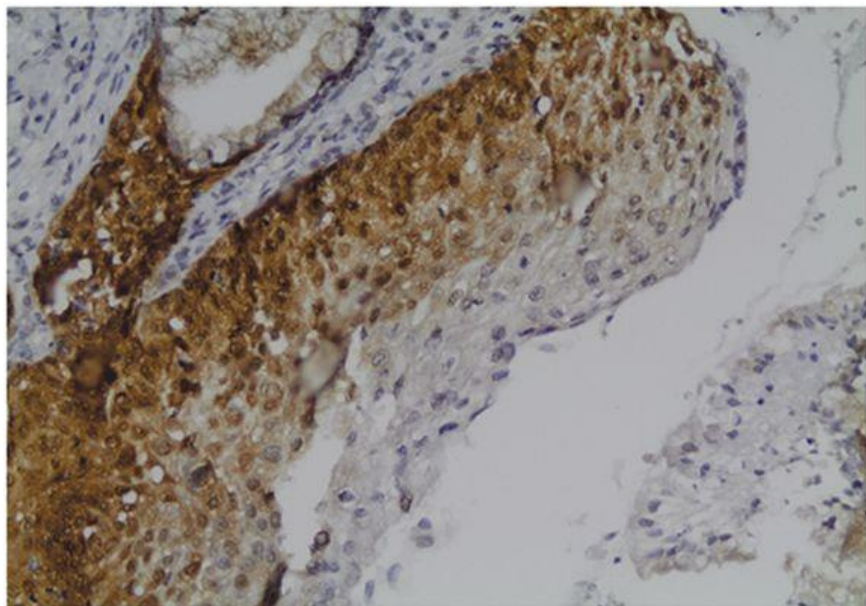
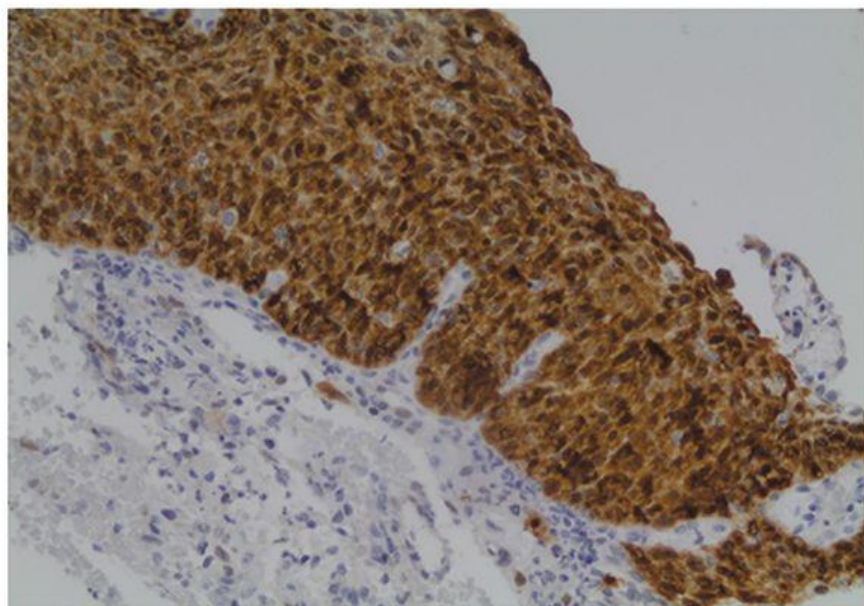
Risk factors for progression

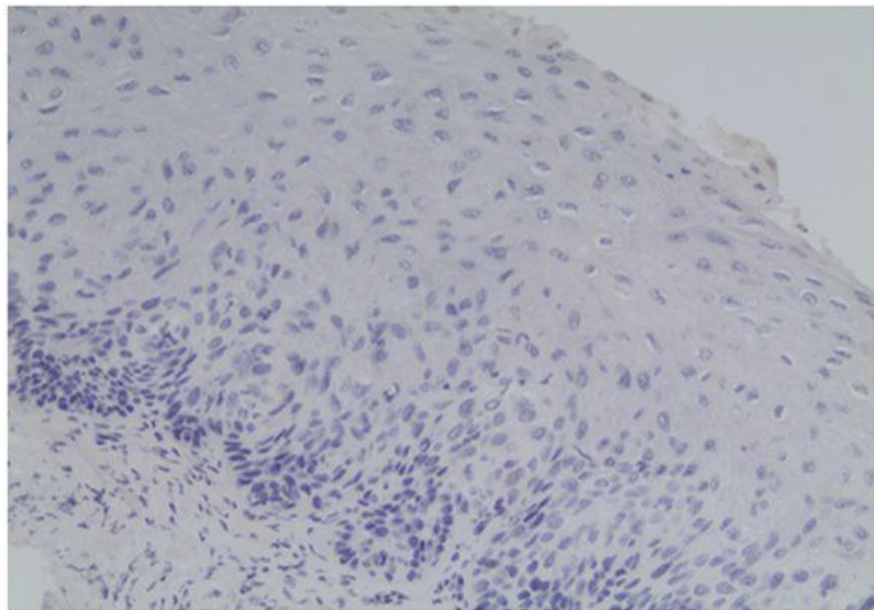
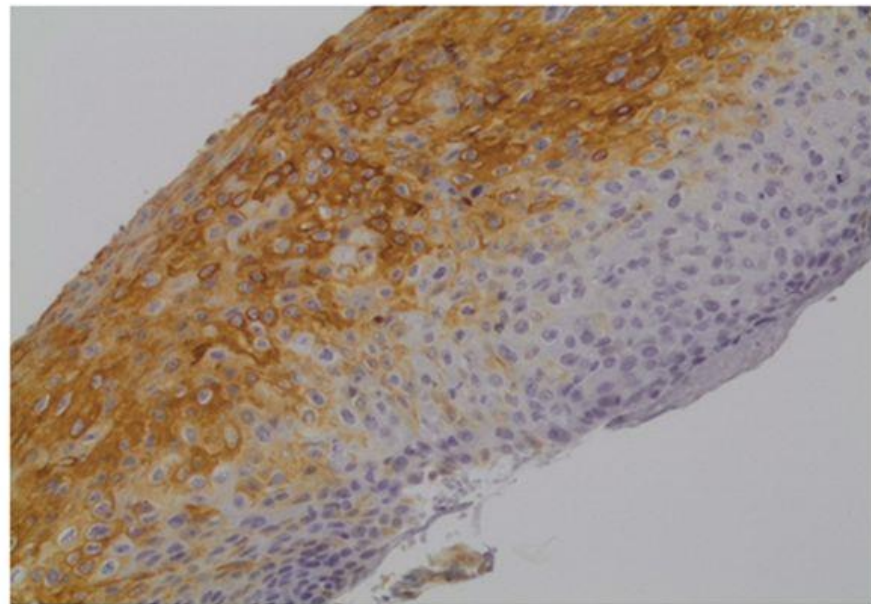
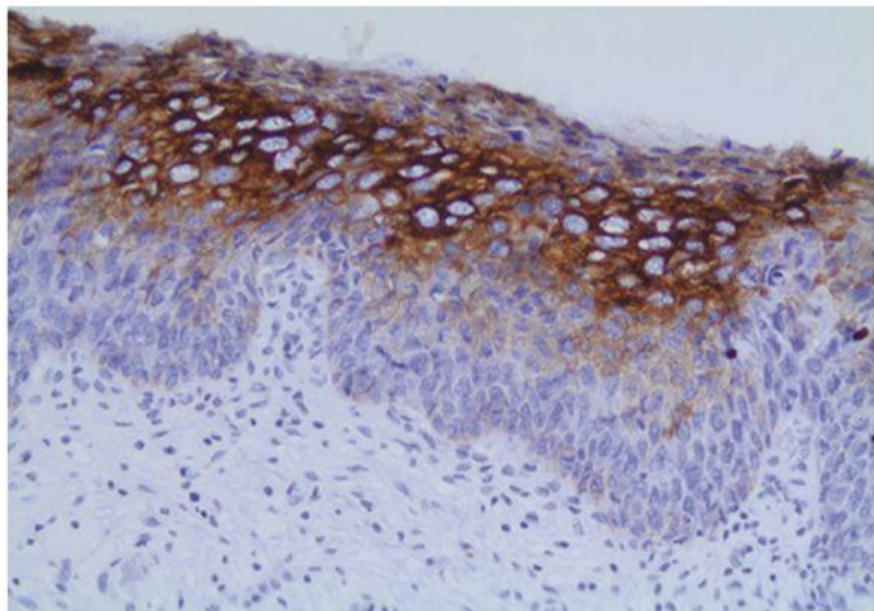
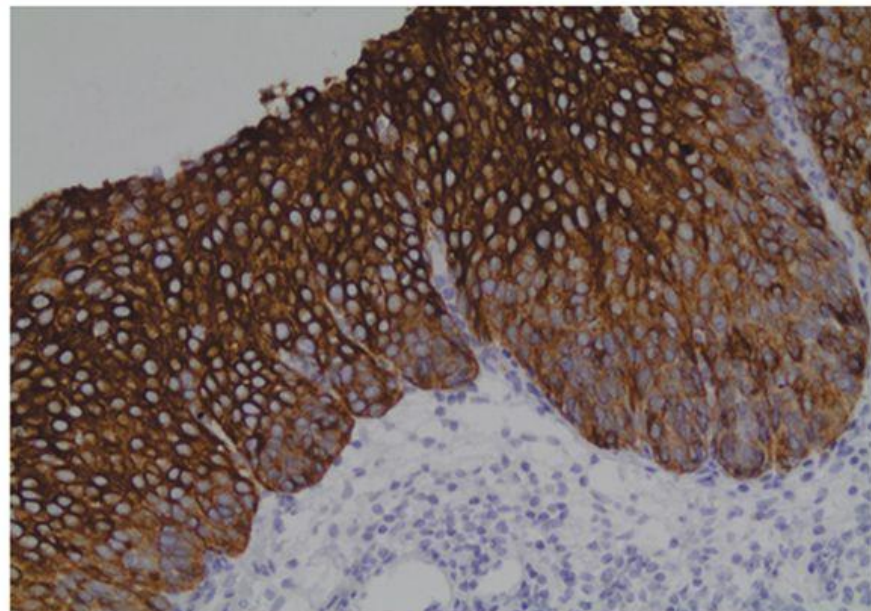
- **the presence of high-risk HPV**

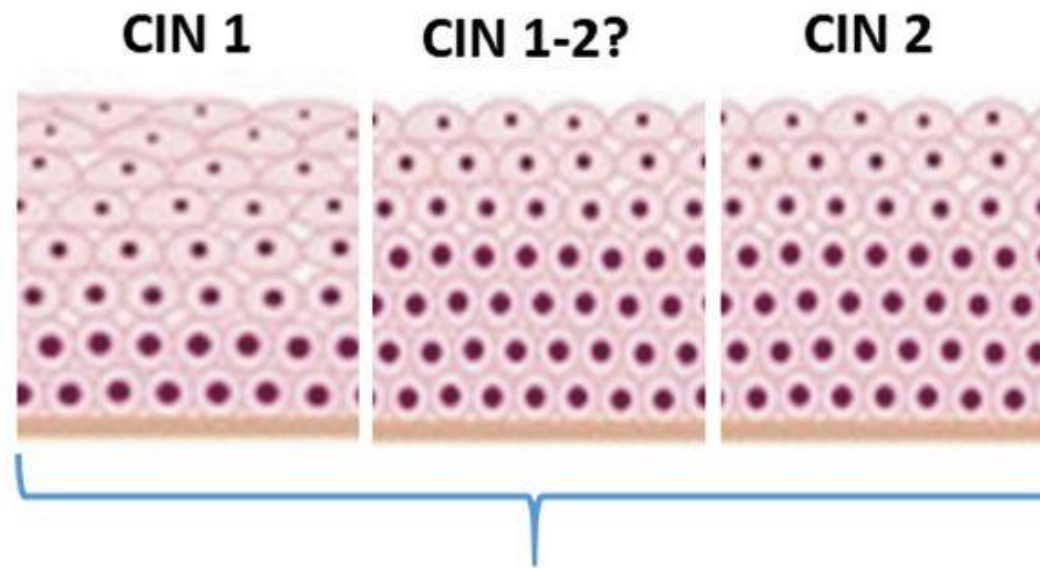
- ✓ high-risk HPV are present in most LSIL

- **Cytokeratin 7**

- ✓ a marker of metaplastic cells of the transformation zone
- ✓ a marker of LSIL that is more likely to progress
- ✓ LSIL/condyloma can arise on the ectocervix or elsewhere in the lower female genital tract: little risk of progression to HSIL
- ✓ further validation is required before it enters routine practice

A**B****C****D**

A**B****C****D**



**CDKN2A and CK7
immunoexpression**



CDKN2A- and CK7- : lower risk lesion (higher NPV)

CDKN2A+ and CK7+ : higher risk lesion

Other tests

- ✓ In addition to p16 immunostaining:
- ✓ can be valuable in establishing HPV status
- ✓ for cases where the clinical, histomorphologic, and p16 immunostaining data **are not concordant**

Other tests

- **PCR for HPV DNA**
 - viral genotyping
- **The Hybrid Capture HPV test**
- **In situ hybridization for HPV**
- **viral E6/E7 oncoprotein mRNA**

PCR for HPV DNA

- allows for **viral genotyping**
- is highly sensitive
- lacks specificity
- may be present as a bystander if there is no transcription of the viral oncogenes

presence of HPV DNA may reflect

- (1) virus particles on the surface of the epithelium secondary to **recent exposure**, without infection
- (2) productive infection that **will be cleared completely** by the host
- (3) a **latent** infection
- (4) **oncogenic** HPV DNA that is integrated into the host genome

identification of the specific genotype of HPV

- is of import
- but **does not mean** premalignant change or malignancy
- Especially in the young, HPV **may be cleared** by the host

The Hybrid Capture HPV test

- a signal-amplified hybridization microplate-based array
- detect **multiple HPV genotypes**
- a **liquid based** nucleic acid detection technique
- more sensitivity than ISH techniques

In situ hybridization for HPV

- is highly specific
- is more expensive than immunostaining
- has a longer turnaround time

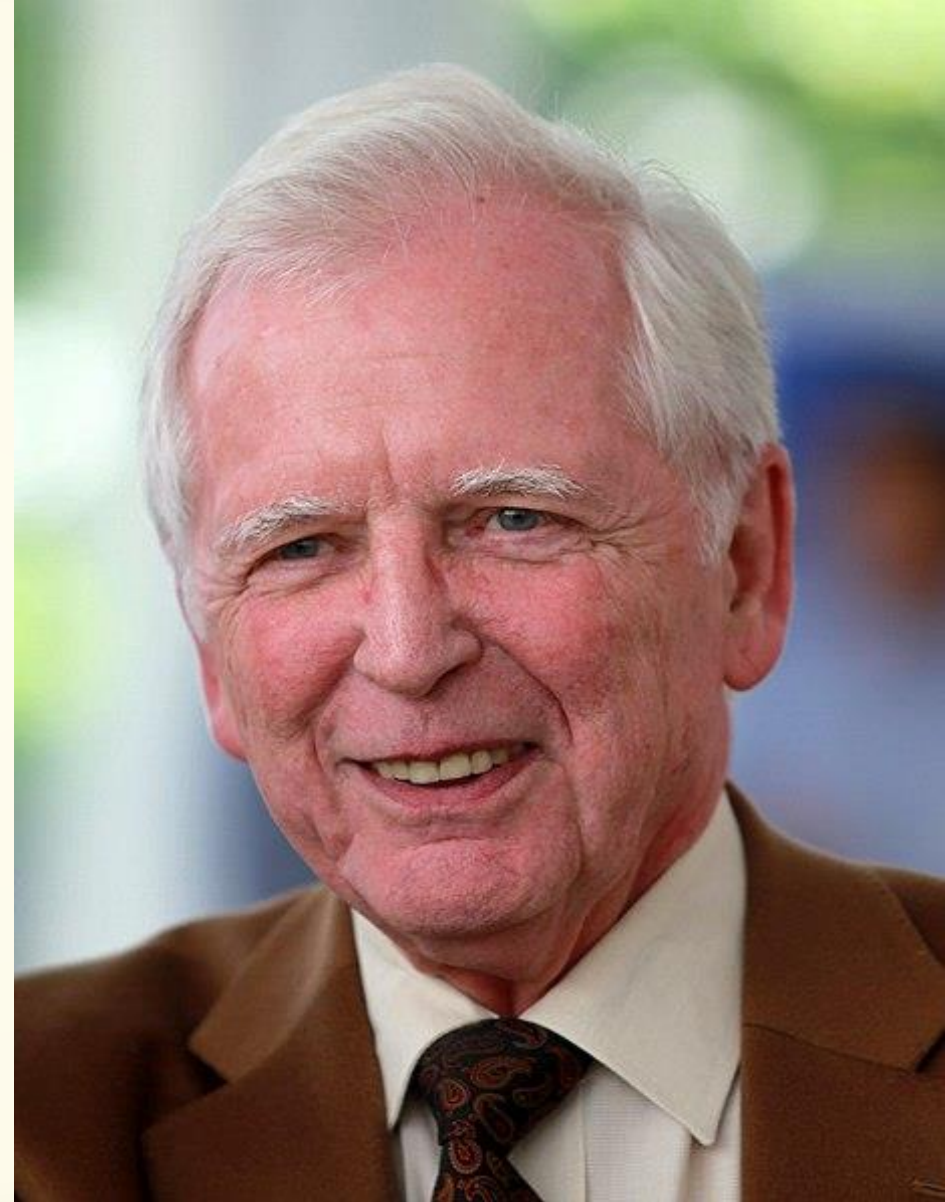
Detection of mRNA of HPV oncogene E6/E7

- Expression of the oncoprotein mRNA
- the virus genome is being transcribed
- **a better marker of HPV**
- establish an etiologic role: a causative role in oncogenesis
- is currently **not widely available** in clinical laboratories

- **Harald zur Hausen**

- هارالد تسور هاوزن

- deservedly won the **Nobel prize in 2008** for his work establishing the link between HPV and cervical cancer



role of HPV in cervical cancer

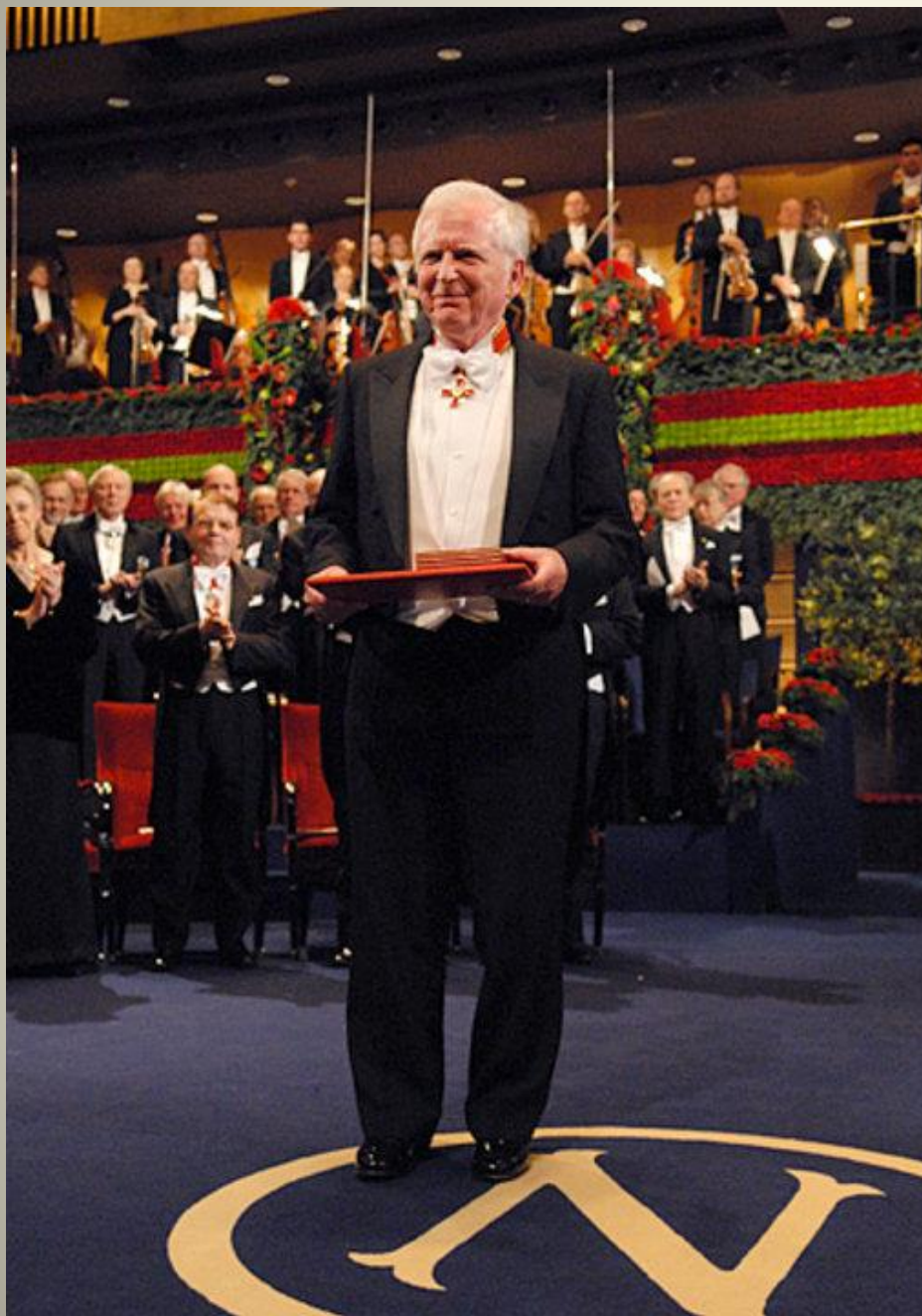
- researchers started to postulate and analyse a **possible role** of HPV in cervical cancer, 1974
- the appearance of **Koilocytes** in cervical smears indicates the presence of a papillomavirus infection, 1976
- The demonstration of **heterogeneity** within the papillomavirus family
- **HPV16 and HPV18** were cloned in 1983 and 1984

role of HPV in cervical cancer

- expression of specific viral genes (such as **E6 and E7**) was shown in cervical cancer biopsies, 1985
- viral ring molecule was shown for **integrated** genome copies
- the **immortalization** property of viral DNA, 1987
- **viral oncogene expression** for the maintenance of the malignant phenotype, 1992
- **E6-p53** and **E7-pRB** interactions, 1994

1994-2008

- a more detailed knowledge of the natural history of HPV infection
- epidemiological studies have also been performed
- **high-risk HPV** as the primary risk factor
- **persisting** HPV infections were the most significant risk factor



HPV pathogenesis

The papillomavirus life cycle

- differs from all other virus families
- the availability of epidermis or mucosal epithelium that are **still able to proliferate** (basal cells)
- **microlesions of skin or mucosa**

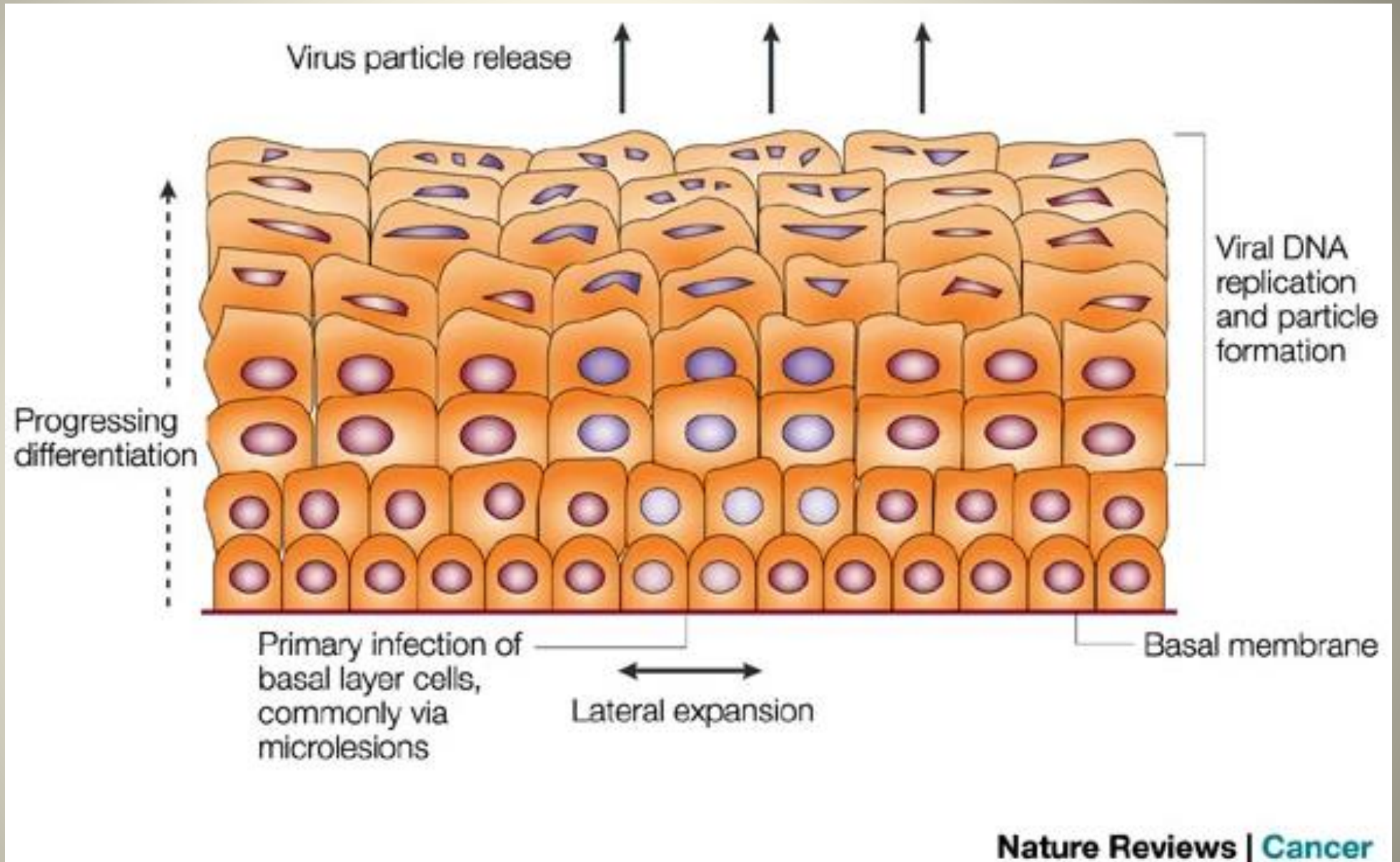
The papillomavirus life cycle

- viral gene expression is largely suppressed
- But limited expression of specific '**early**' **viral genes** (E5, E6 and E7) **results in enhanced proliferation** and their lateral expansion
- The infected cell divides
- **the population spreads laterally**
- **Some migrate into the upper layers**

the upper differentiating cells

- **'late' viral gene** expression is initiated
- the circular viral genome is then **replicated**
- **structural** capsid proteins are formed
- Viral particle formation ensues: complete viral particles are **assembled**
- **Particles are released at the surface** and might then infect additional tissues

HPV life cycle



HPV genome

- 6800-8000 base pairs
- eight open reading frames – E6, E7, E1, E2, E4, E5, L2 and L1 – coding for 'early' (E) or 'late' (L) functions
- Three genes possess **proliferation-stimulating activity**

✓ E5

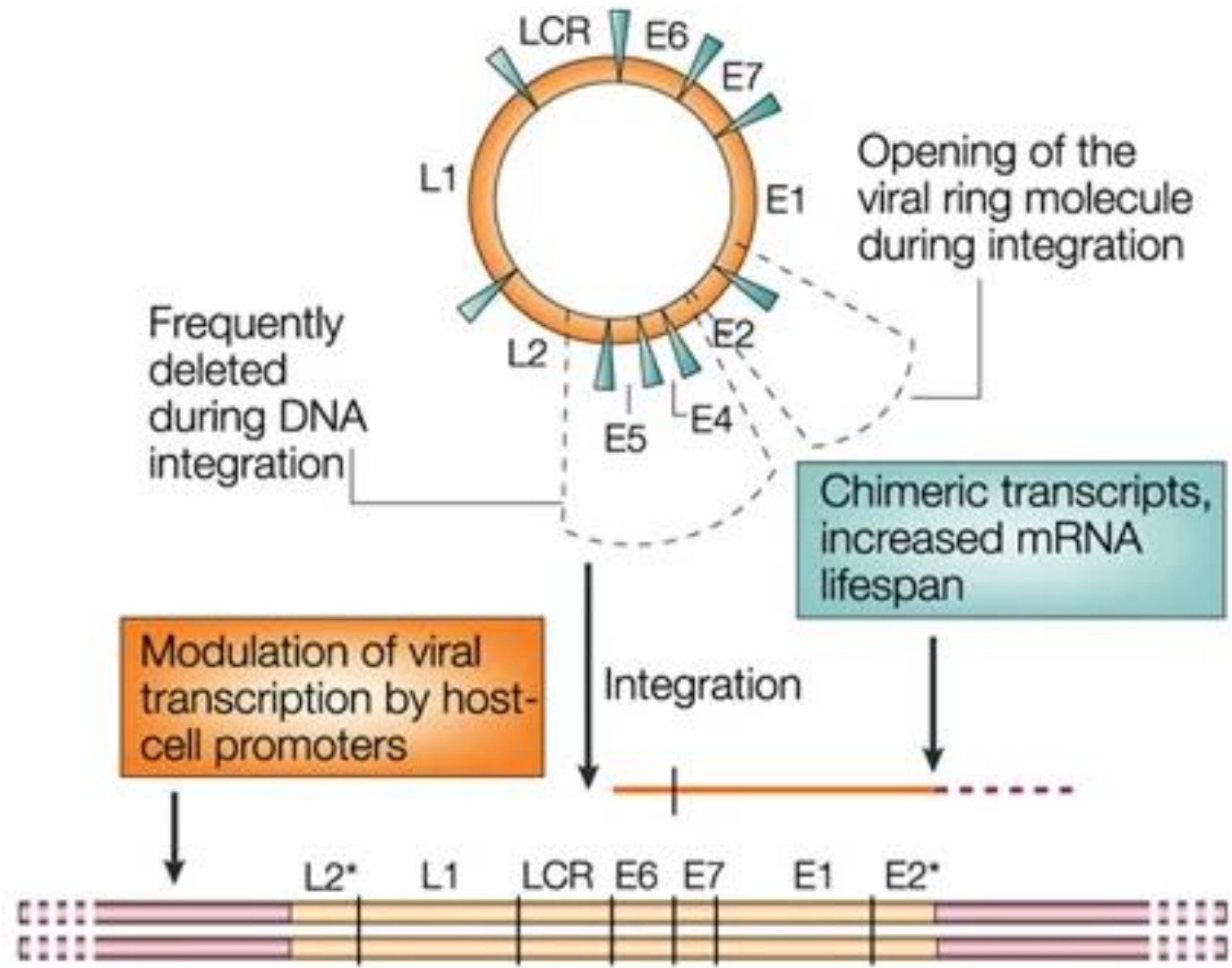
✓ E6

✓ E7

E5 is important in the early course of infection

- **stimulates cell growth** by forming a complex with the EGFR, PDGF- β R and the CSF-1R
- **prevent apoptosis** following DNA damage
- as HPV-infected lesions progress to cervical cancer, the episomal viral DNA frequently becomes integrated into host-cell DNA, and a substantial part of the genome, (including the E5 gene) is deleted
- **E5 is not obligatory** in late events of carcinogenesis

The circular HPV DNA and its integration



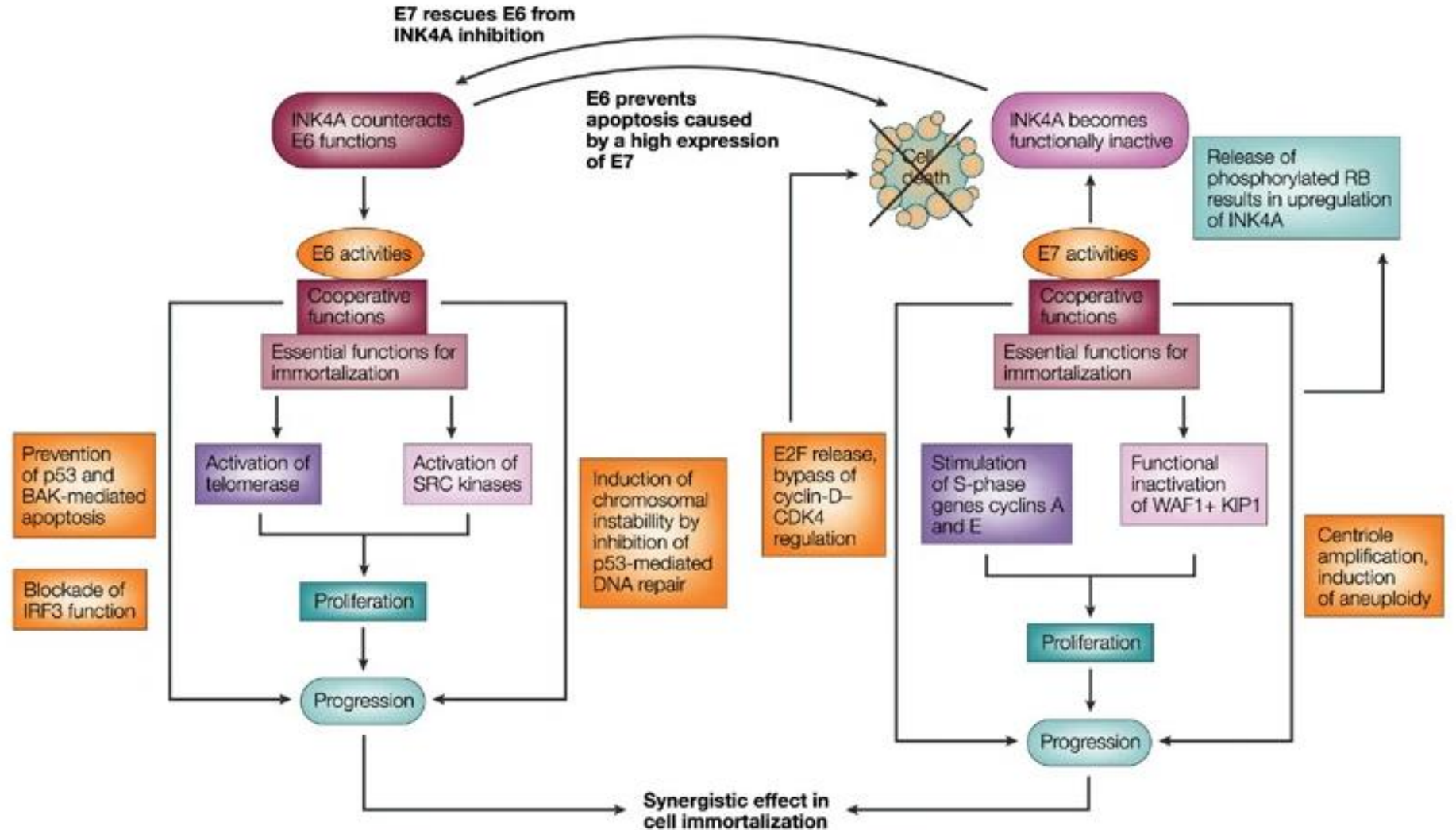
Integration of viral molecule into host-cell DNA

- The ring molecule is opened
 - Part of E2 and L2 and whole genes E4, E5 are deleted
- Viral transcripts uniformly span the **E6 and E7** region
- are often linked to **flanking cellular sequences**
 - transcription is enhanced by flanking host-cell promoters

E6 and E7 genes (their proteins)

- A more significant role for **malignant transformation**
- are **consistently expressed** in malignant tissue
 - inhibiting expression blocks the malignant phenotype
- They are **independently able to immortalize** various human cell types in tissue culture
- **efficiency is increased** when they are expressed **together**

Functions of the E6 and E7, and their actions for cell immortalization



functions for E6 and E7

- E6 interacts with p53
- E7 interacts with RB
- **block the activity of these tumor suppressors**

✓ **Immortalization**

E6 protein

✓ deregulated cellular growth and genomic instability

- both of which are characteristics of immortalized cells
- complex with **p53**
- resulting in the ubiquitination & **degradation** of p53
- **Loss of p53**

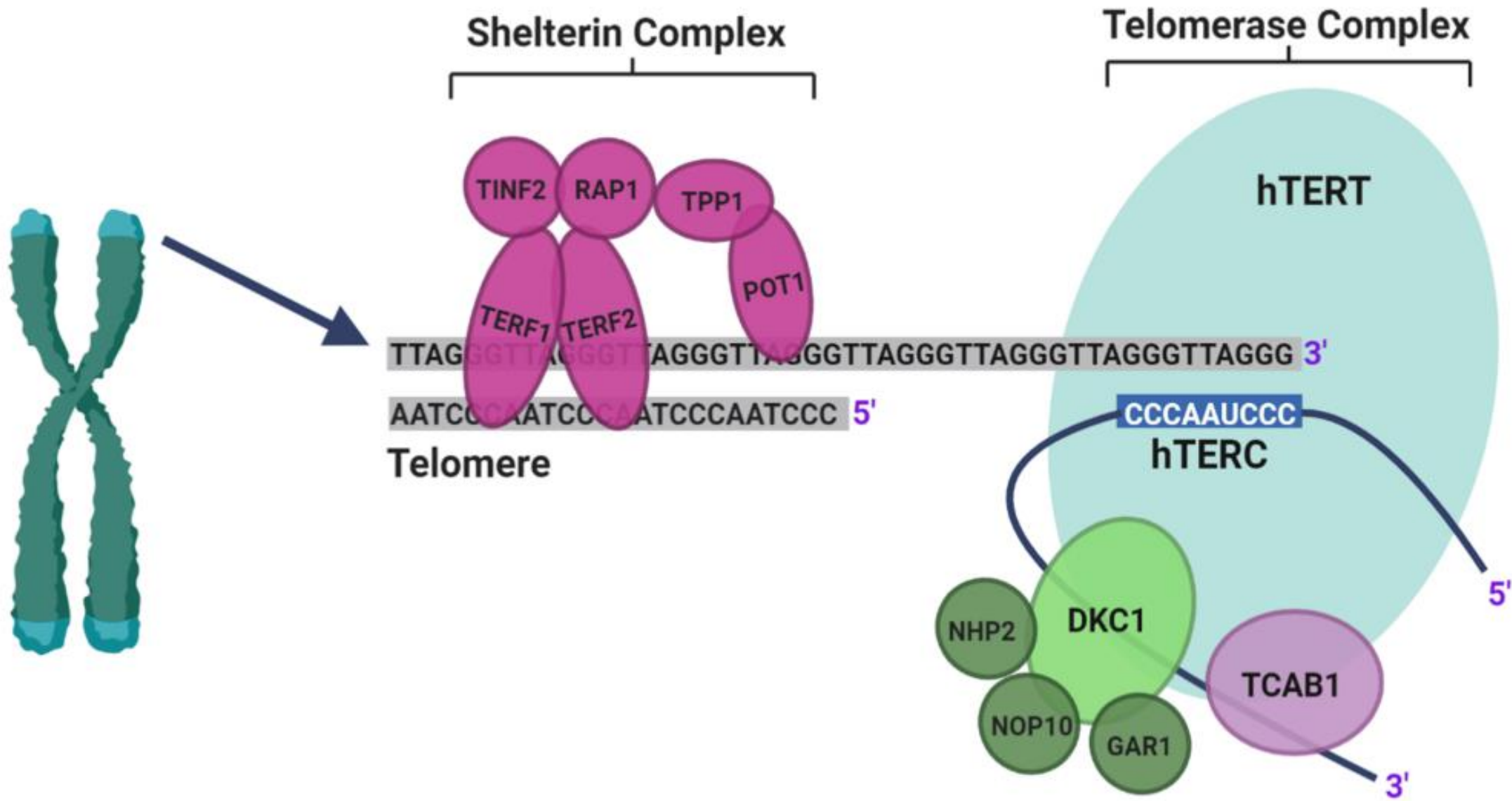
E6 protein

- ✓ increased **chromosomal instability**
- Due to resistance to apoptosis
 - interacts with **p53**
 - interacts with pro-apoptotic protein **BAK**

E6 protein

✓ growth stimulation

- the activation of **telomerase**
- inhibition of degradation of **activated SRC-family**
kinases

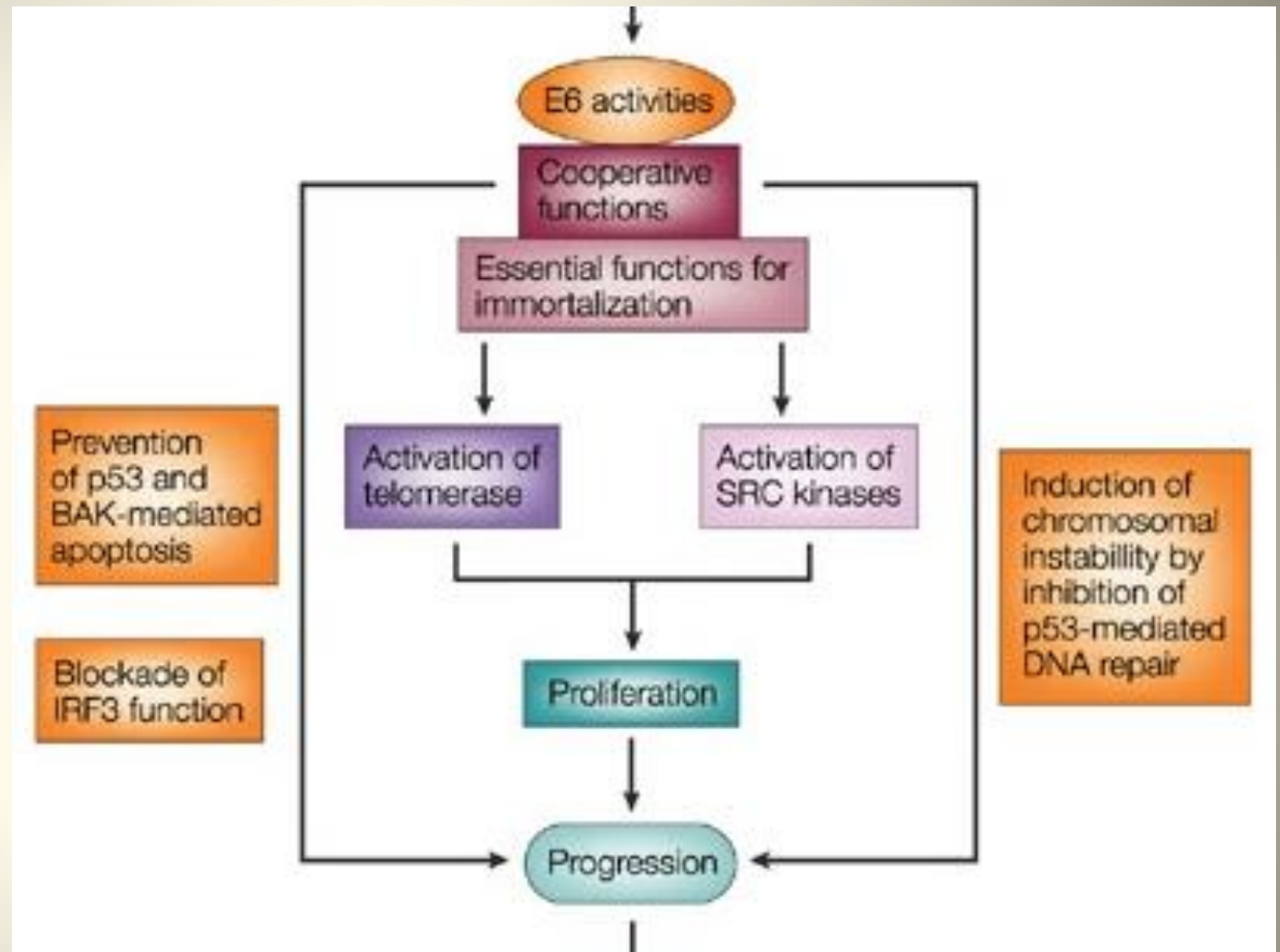


E6 protein

✓ **disrupts antiviral response**

- binding to **IRF-3** (interferon regulatory factor-3)
- the **inhibition** of its transcriptional activity
- significantly dampens the induction of **IFN β**

Functions of the E6



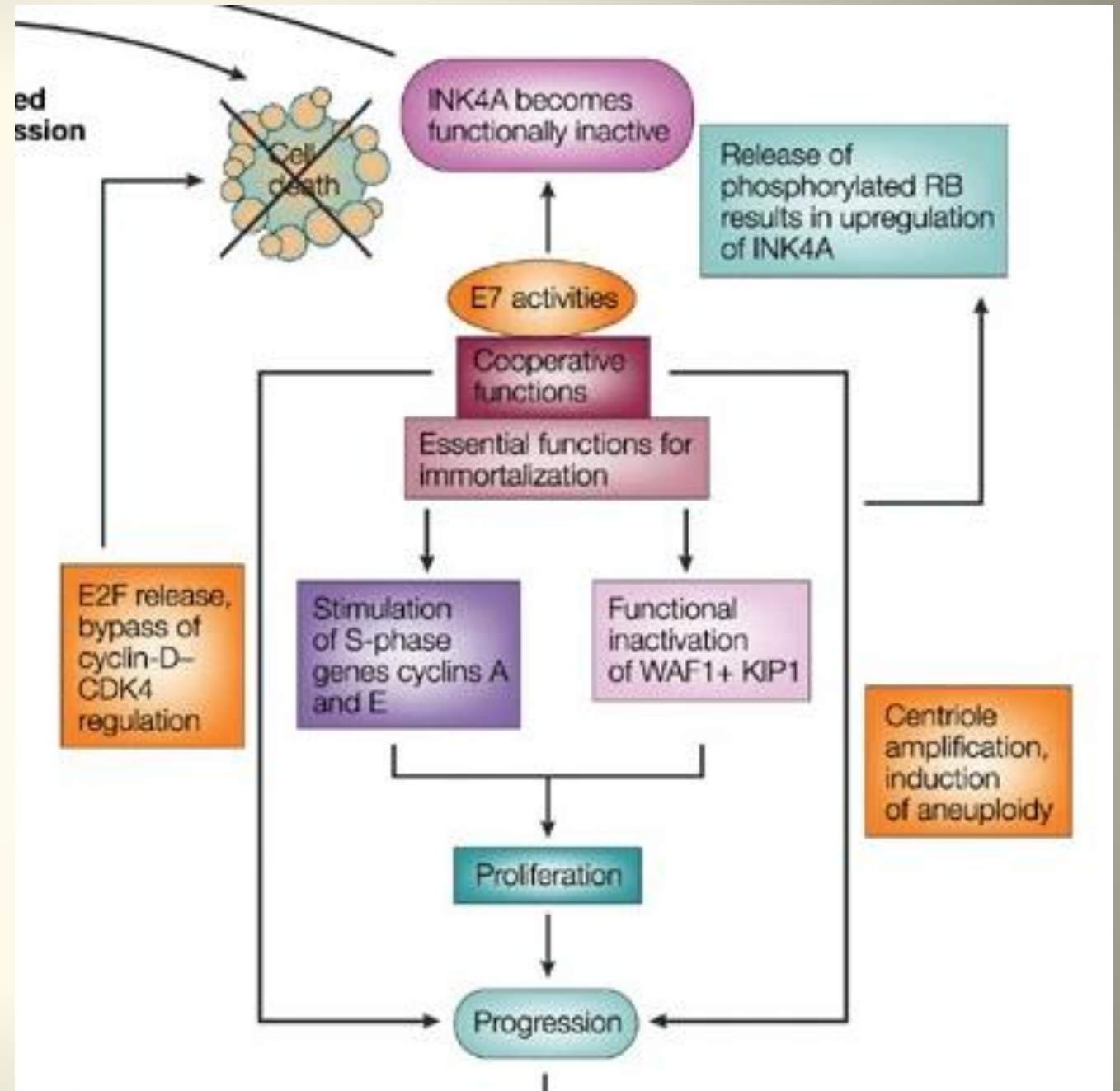
E7 protein

- interacts with and **degrades RB**
- releases the transcription factor E2F
 - might lead to apoptosis
 - upregulates cyclin-dependent kinase inhibitor INK4A
- **also inactivates INK4A (p16)**
- The INK4A (p16) counteract functions of **E6** protein

E7 protein

- stimulate **cyclins A** and **E** (s phase genes)
- inactivate the cyclin-dependent kinase inhibitors **WAF1** (CIP1 and p21) and **KIP1** (p27)
- inducing **centriole amplification**
 - induces **aneuploidy**
 - contributes to tumorigenesis

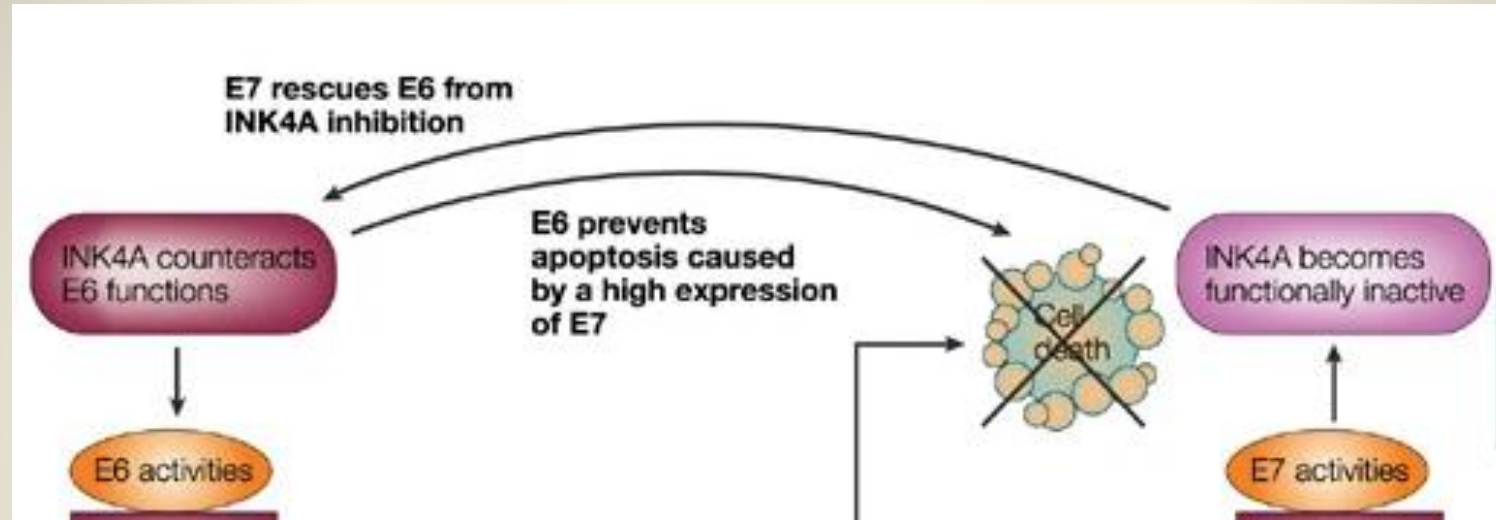
Functions of the E7



E6 and E7 **synergism**

- E6 prevents E7-induced apoptosis that is induced by E2F
 - By p53 and BAK
- E7 rescues E6 from inhibition by INK4A
 - inactivates INK4A E7
 - directly activating cyclins A and E
- ✓ their joint function results in a marked increase in **immortalization & transformation**

E6 and E7 synergism



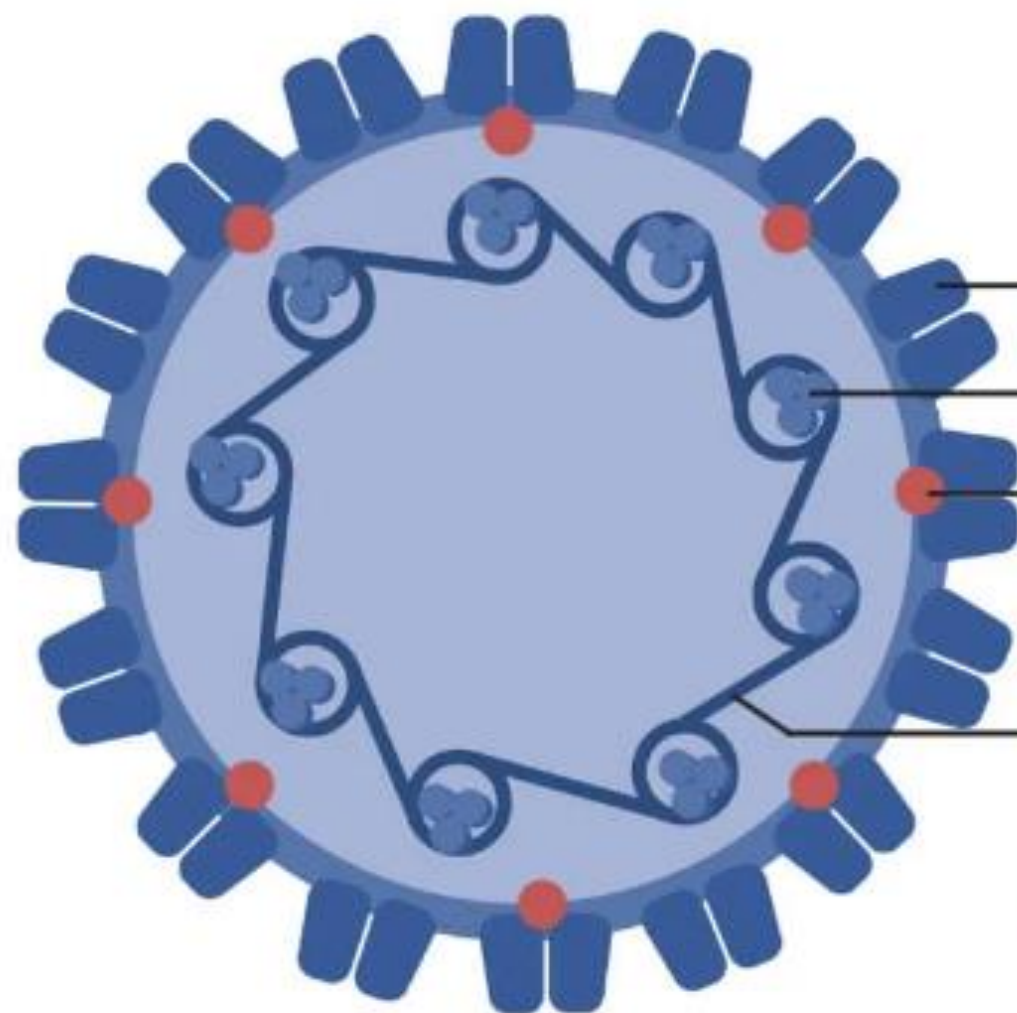
Prevention
of p53 and
BAK-mediated
apoptosis

E2F release,
bypass of
cyclin-D-
CDK4
regulation

two HPV early proteins

- structural proteins L1 and L2 are important for **vaccine development**

	Cervarix	Gardasil, Silgard	Gardasil-9
Valency	2-Valent	4-Valent	9-Valent
Types	HPV16/18	HPV6/11/16/18	HPV6/11/16/18/31/33/45/52/58
Adjuvant	ASO4 (0.5 mg aluminum hydroxide and 50 µg 3-O-desacyl-4"-monophosphoryl lipid A (MPL))	0.225 mg aluminum hydroxyphosphate sulfate	0.5 mg aluminum hydroxyphosphate sulfate
Expression system	Baculovirus-insect cell	Yeast	Yeast



Capsid Protein (L1)

Histone

Capsid Protein (L2)

Genomic DNA

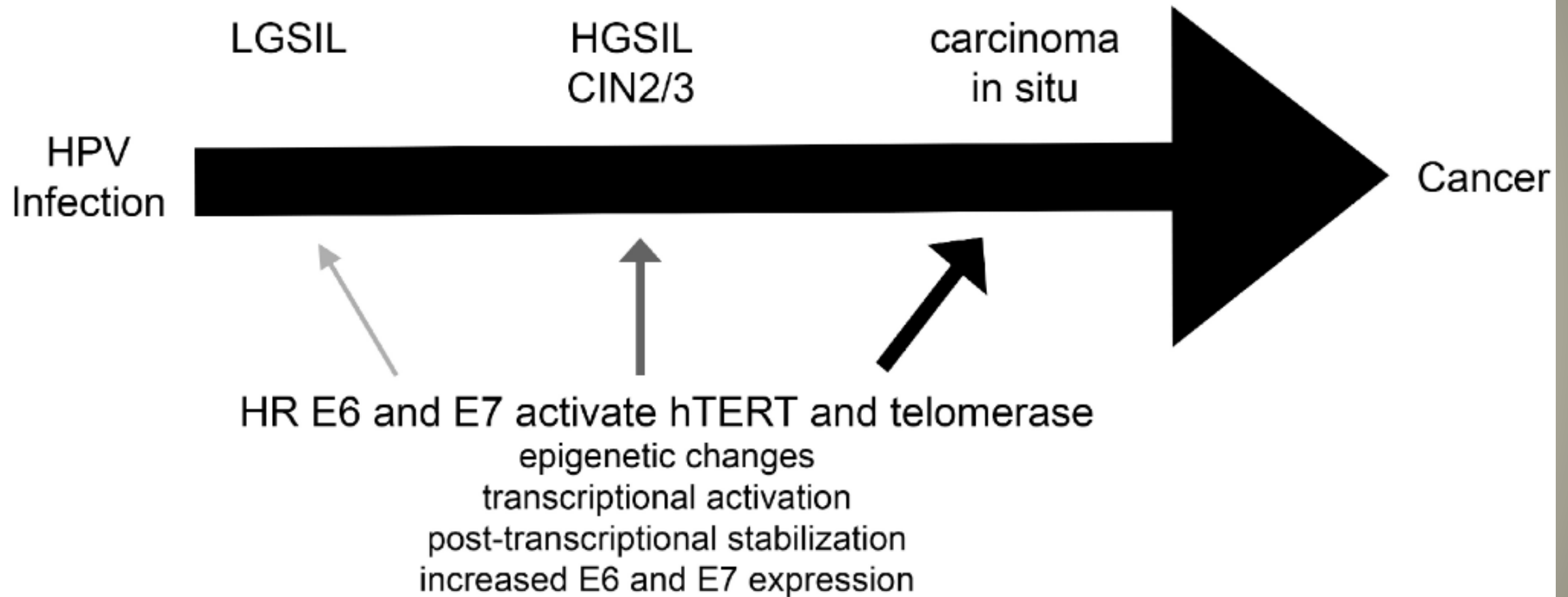
Human Papillomavirus (HPV)

High- and low-risk HPV infections

- 'high-risk' types
 - are found preferentially in cervical and other anogenital cancers
 - 'low-risk' types
 - found primarily in genital warts and non-malignant lesions
- ✓ **only the E6 and E7 genes of high-risk types were able to immortalize human cells**

High-risk HPV types

- are widespread within **all human populations**
- Infection is commonly **transmitted** by sexual contact
- results initially in inconspicuous **squamous intraepithelial lesions (SIL)** in women
- **Most of these lesions are cleared** 6–12 months after appearance, probably due to immunological intervention

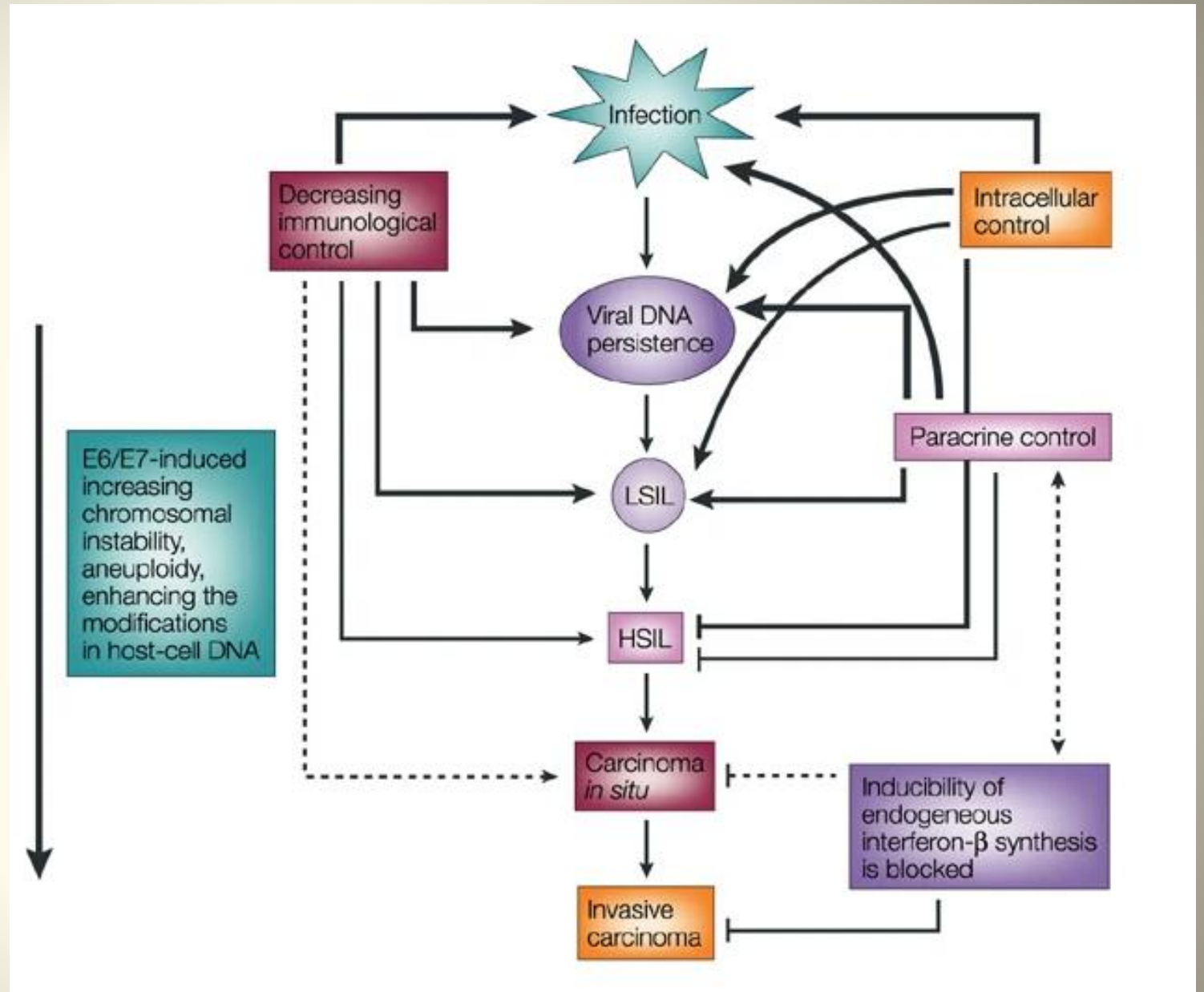


A small percentage

- Persists
- progresses to:
 - **high-grade SIL**
 - **carcinoma *in situ***
 - **Squamous cell carcinoma**
 - **adenocarcinoma**

HPV-induced progression:

failing control mechanisms



Host control of HPV infection

- an intracellular control
 - by cyclin-dependent kinase inhibitors
- a paracrine signaling cascade
 - by macrophages and cytokines
 - tumor necrosis factor- α
 - loss of synthesis of interferon- β
- a decreasing immunological control

Host immune response factors

- ✓ **Genes in the HLA region** of chromosome 6
 - increased susceptibility to the transforming properties of high-risk HPV
- ✓ a detectable Humoral and Cellular immune response against HPV antigens during the course of **regression**
- ✓ The **escape** from immunological control is one important step in the progression of HPV-linked tumors

Impaired immune function

- increased incidence and prolonged persistence of SIL in **immunosuppressed** women
 - ✓ a 5- to 10-fold increased risk
- immunosuppressant therapy in organ transplantation recipients
- HIV infection

High-risk HPV infections
progress to cervical cancer

in only a small percentage
after a long latency period

Factors that affect HPV malignancy

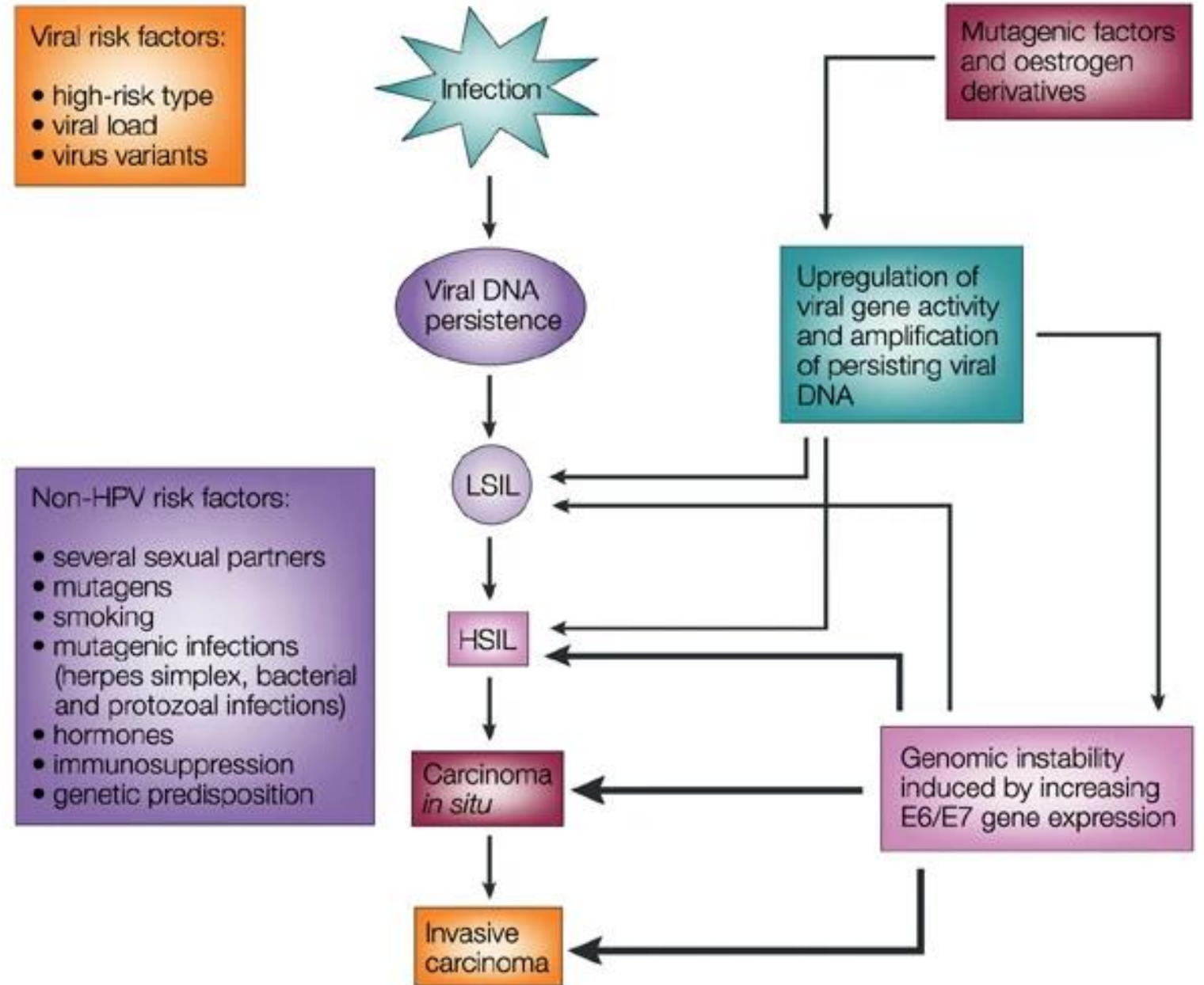
- modifications of cellular genes that influence antigen presentation
- signaling cascades that are engaged in viral oncogene transcription or viral oncoprotein function
- upregulating viral oncogene transcription
- modifying the viral promoter region
- amplifying the persisting viral genomes

HPV and non-HPV factors

that contribute to HPV-induced malignant progression

- **Hormones** (estrogen) activate the HPV promoter and facilitate immortalization of HPV-infected cells
- **Mutagenic agents** amplify persisting HPV DNA
- A rising level of **E6 and E7 oncogene expression**, results in increasing genomic instability and facilitates progression towards invasive growth

HPV and non-HPV factors that contribute to HPV-induced malignant progression



we now see the circle closing

- **primary HPV screening** to detect premalignant lesions
- **HPV immunization** to prevent such lesions increasingly being adopted

It is possible to envision

a world where the
burden of disease due to HPV is
dramatically reduced

SCC and Its Precursors

Squamous Intraepithelial Lesions/
Cervical Intraepithelial Neoplasia

SIL/CIN

- SIL terminology has gained **wide acceptance**, but there are still **holdouts** for the CIN terminology
- we will adopt the practice of providing **a two-part diagnosis**, with SIL first and the equivalent CIN in parenthesis thereafter
- LSIL (CIN1)
- HSIL (CIN2 and CIN3)

CIN2 and CIN3

- the distinction is arbitrary
- not clinically relevant
- Subtle differences in natural history have been reported
- **HSIL (CIN2/3)** for all high-grade lesions

LSIL (CIN1)

- is inclusive of **condyloma** in the LAST criteria
- The former practice of attempting to determine whether there is or is not dysplasia within condyloma **has mercifully been brought to an end.**
- **condyloma ± CIN1 ???**

Condyloma acuminatum

- one or several soft elevated masses of variable size
- is a venereal disease
- in vulva, vagina, cervix, bladder and penis
- is caused by HPV, usually type 6 (low-risk HPV infection)
- should be diagnosed as (VIN1, VaIN, PeIN)
- ✓ we do not recommend adopting LSIL, while we are able to endorse LSIL (CIN1) for cervical condyloma



Large
condyloma
of vulva

condyloma acuminatum

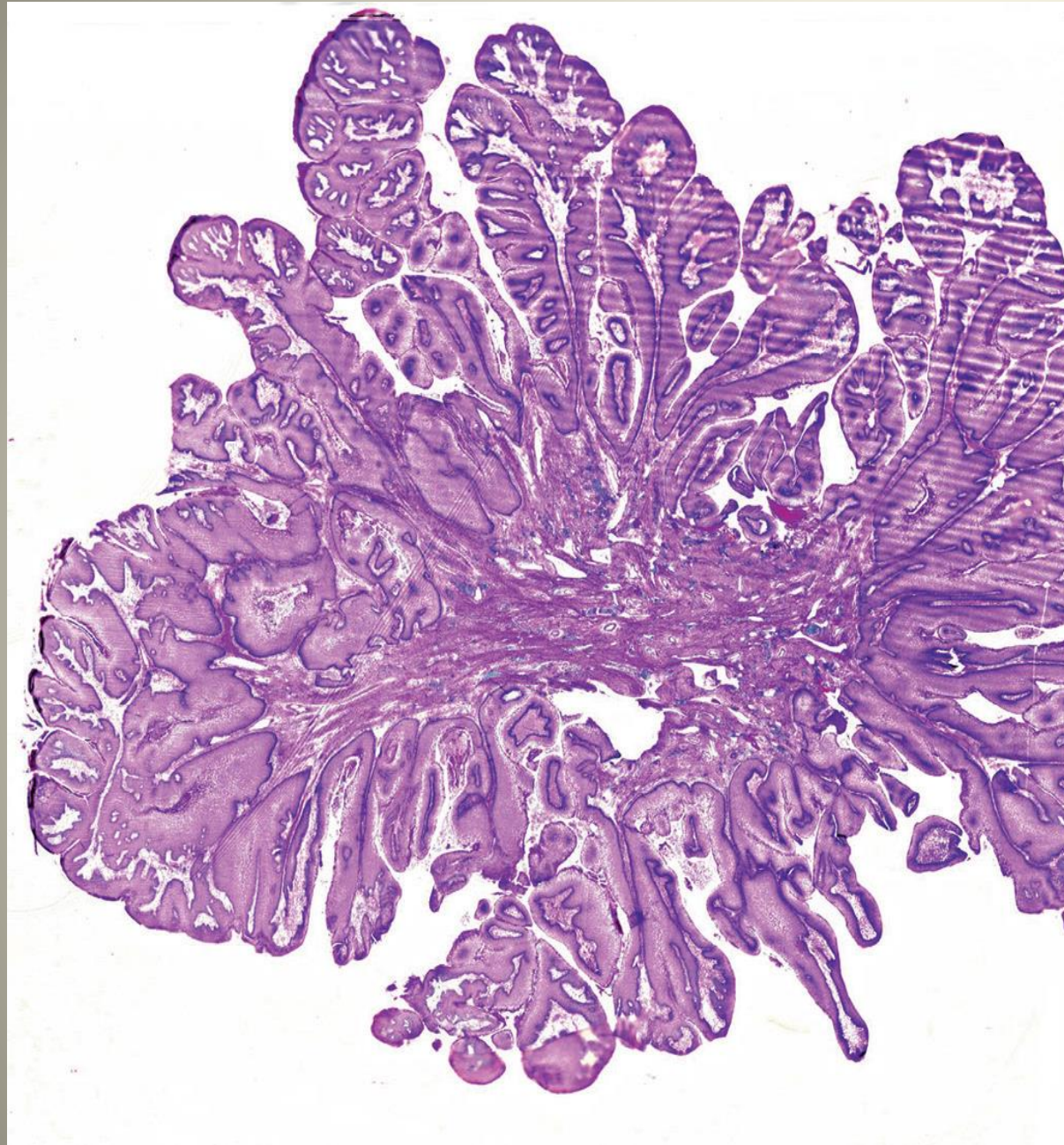
- **Exophytic** versus flat: grossly as a polypoid lesion
- considerably less common than the latter in cervix
- An **undulating** appearance of the epithelium on low-power
- **papillomatosis, acanthosis**
- expanded or hyperplastic parabasal cell layer

Microscopically

- **orderly maturation**; a smooth transition to intermediate and superficial cells
- **mitotic activity** confined to the lower third of the epithelium (but few or no abnormal mitoses)
- a variable degree of lymphocytic **inflammation** in the stroma

Condyloma acuminatum

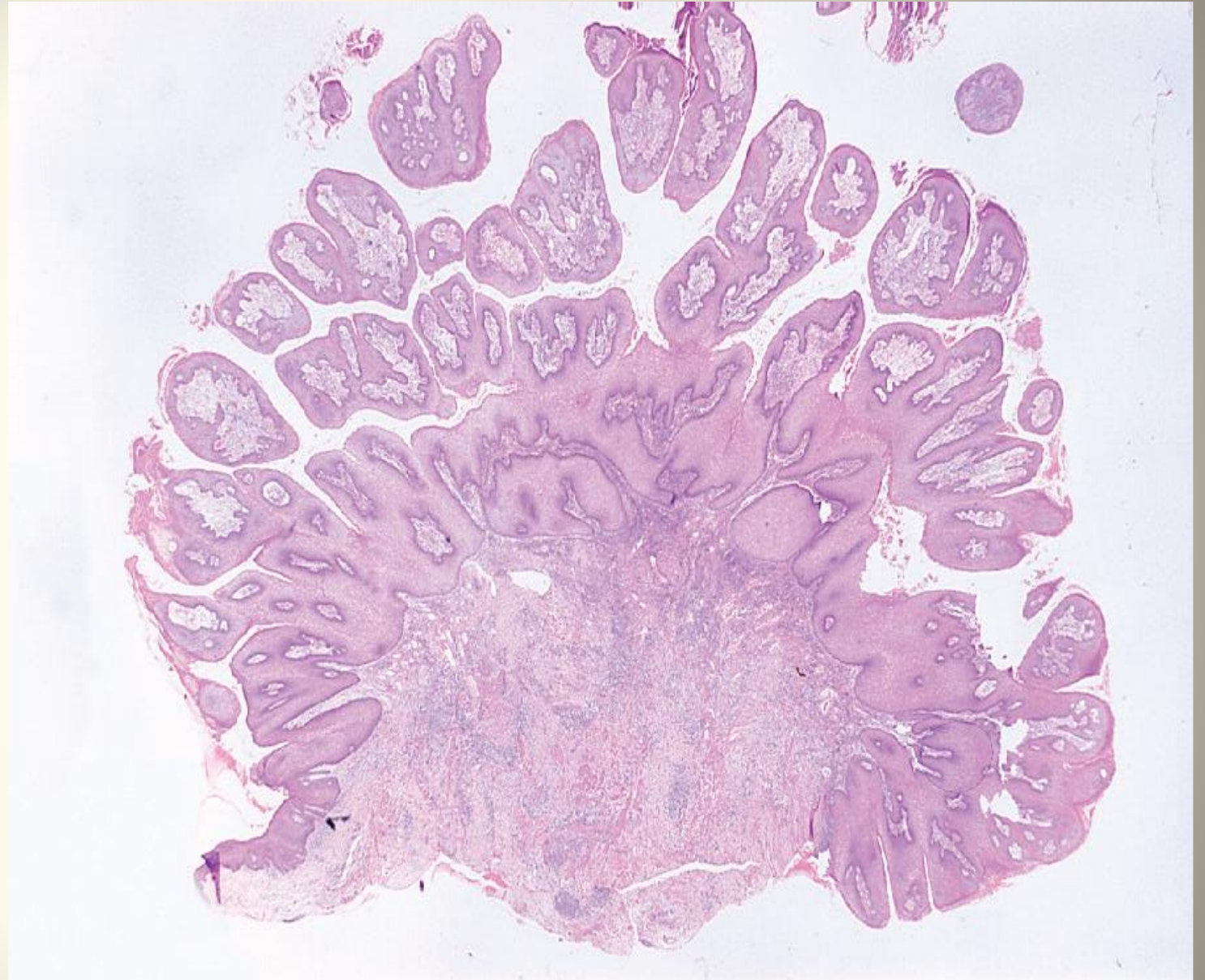
- A **mild degree of** basal or parabasal **atypia** is common
- if **more severe**, it should be evaluated and graded as for the flat SIL (is there HSIL [CIN2/3] present?)
- is associated with HPV-6 or HPV-11 in 70%–90% of the cases
- occasionally other types—such as HPV-16: high-grade cytologic atypia may be found

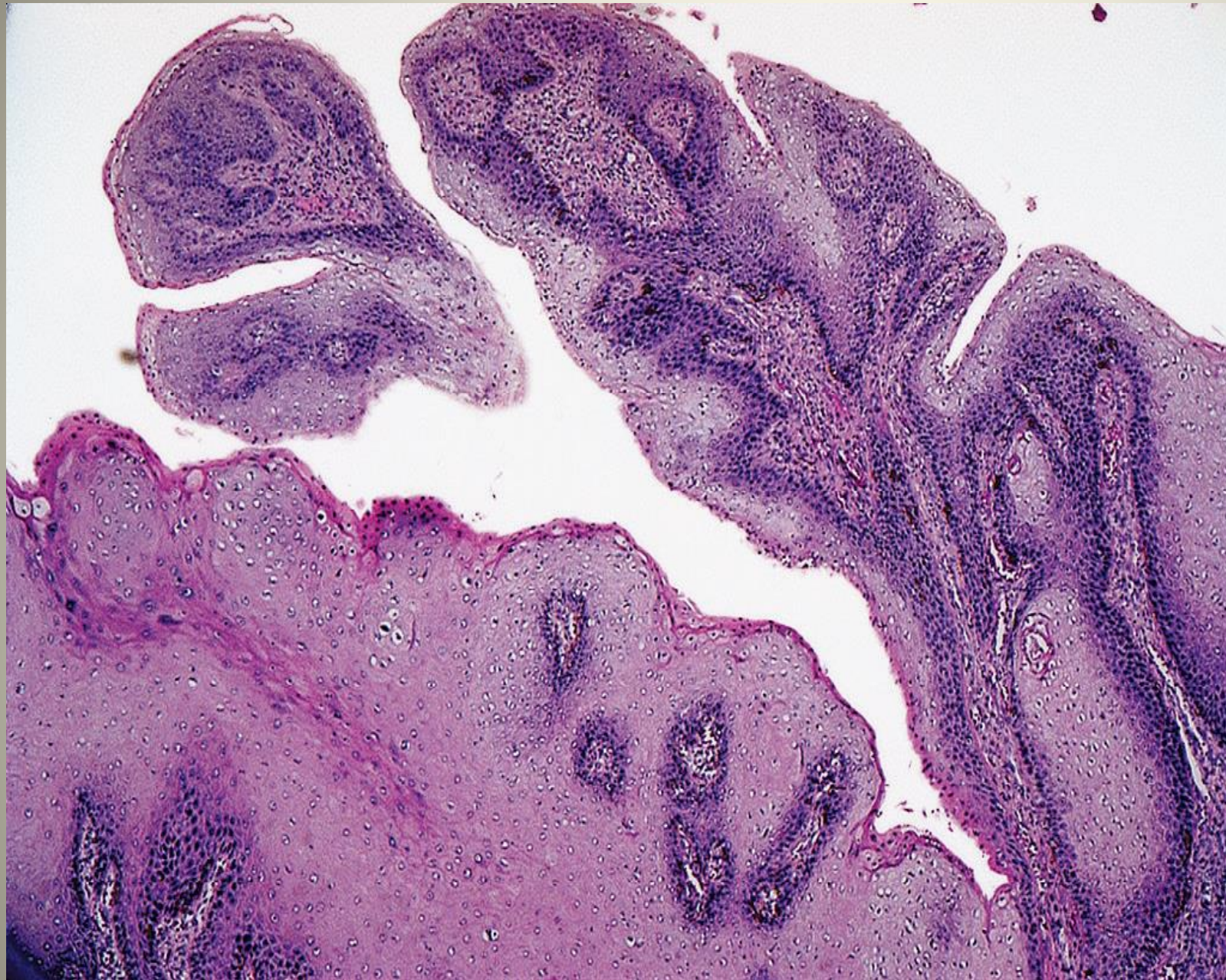


condyloma
acuminatum

Condyloma Acuminatum

Complex papillary pattern
composed of well-
differentiated squamous
epithelium





Papillomatous
shape of
vulvar
condyloma



Some condylomas
have a low-power
appearance
simulating
seborrheic
keratosis

The other form: **flat condyloma**

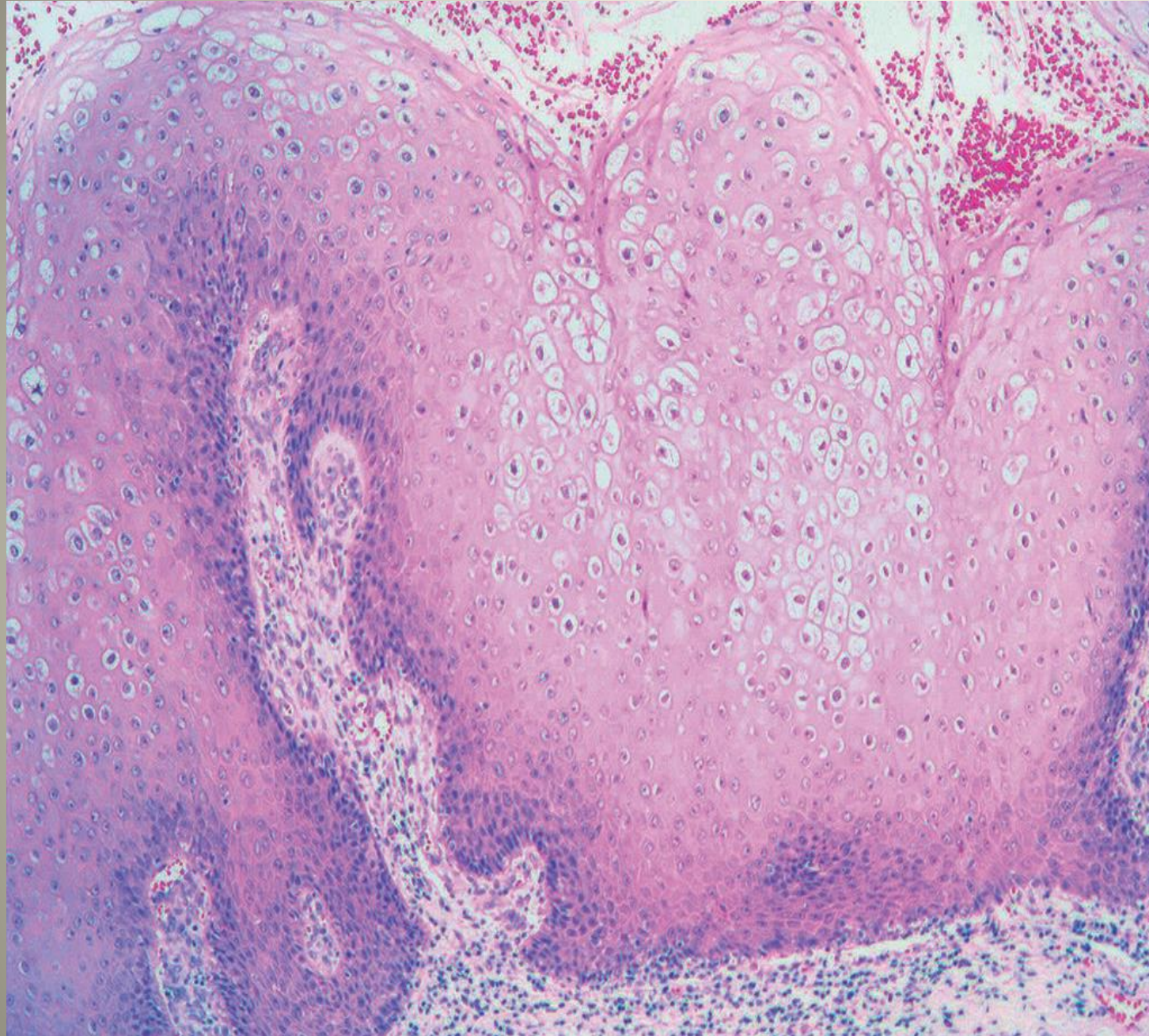
- **is more commonly encountered in cervix** than condyloma acuminatum
- The cytologic features are similar in both forms
- **the classic lesion of LSIL (CIN1)**
- It is typically not recognizable grossly

increased proliferative activity

- **mitoses** may be numerous, but are all typical
- with the **Ki-67 stain**
 - in contrast to fibroepithelial polyp and squamous papilloma
- The DNA content
 - Diploid
 - Polyploid (tetraploidy and octaploidy)

LSIL (CIN1)

- **Koilocytic viral cytopathic effect** is the pathognomonic
- it is **doubtful** whether LSIL (CIN1) can be diagnosed in the **absence of koilocytic change**
- koilocytic change (HPV effect) with or without dysplasia should not be distinguished

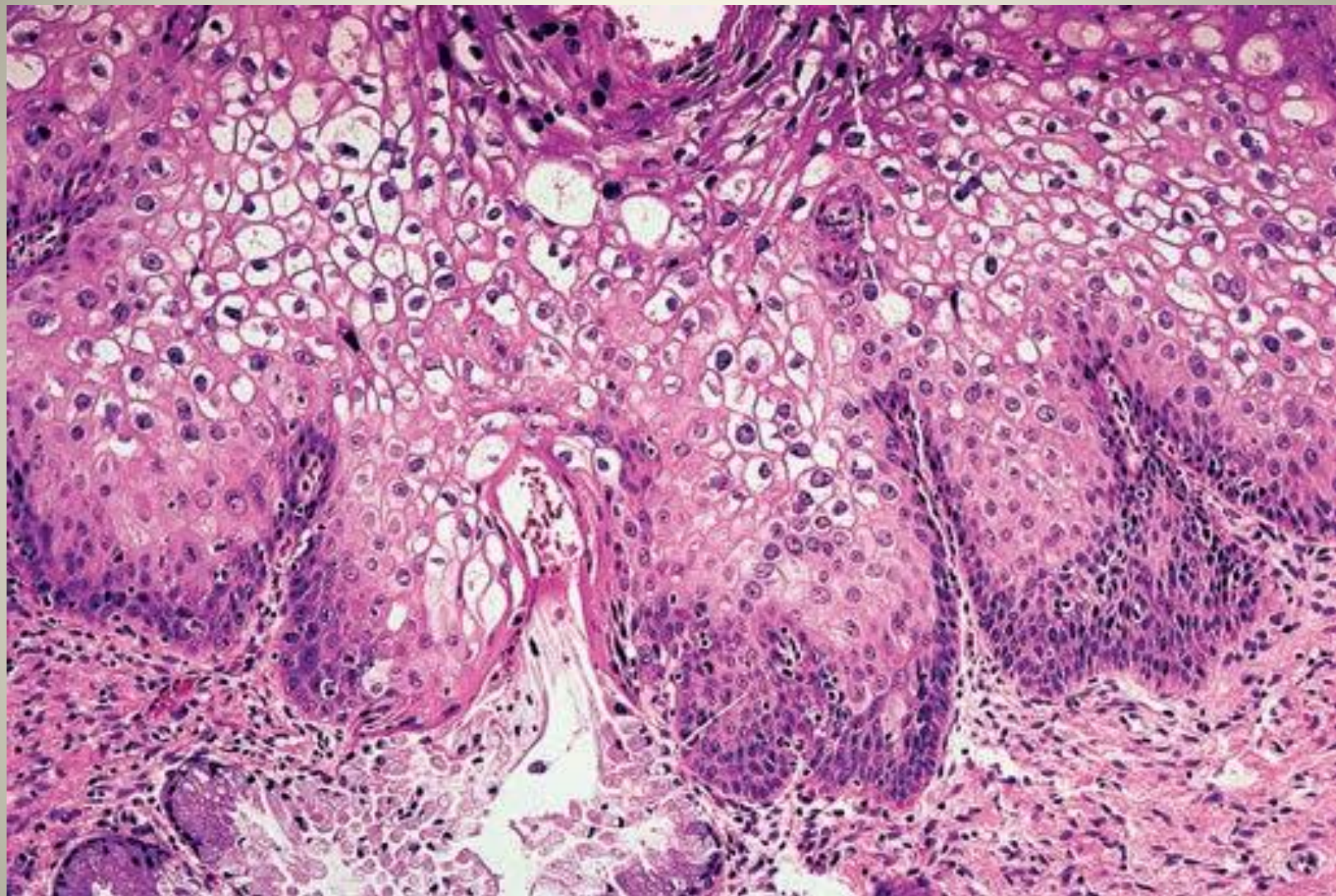


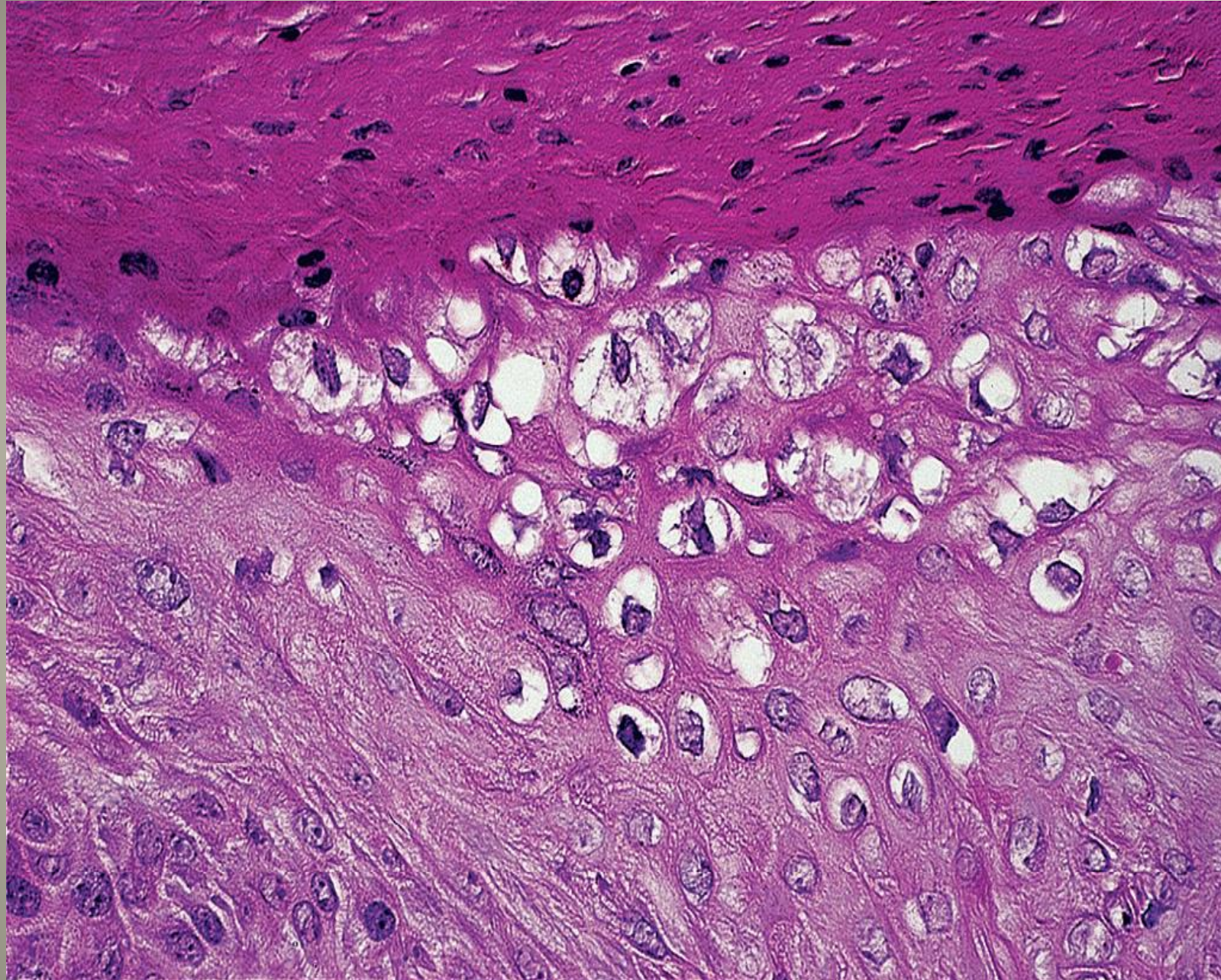
Virus induced
cytopathic
changes

Koilocytosis of the malpighian epithelium

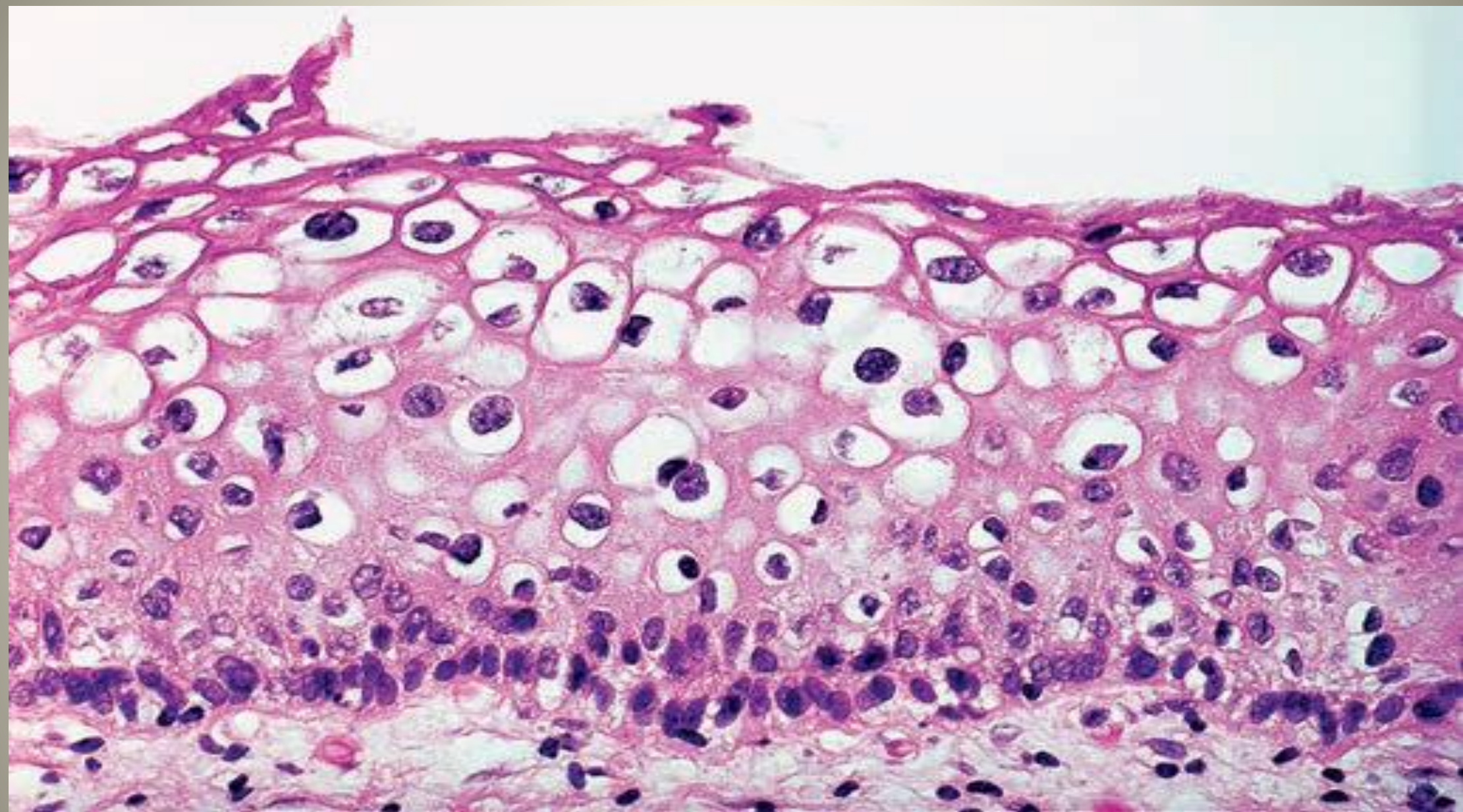
- a superficial or intermediate mature cell
- a sharply outlined perinuclear clear vacuolation
- an enlarged nucleus with an wrinkling or undulating nuclear membrane (prune-like or nuclear “**raisins**”)
- a rope-like chromatin pattern
- dense- and irregular-staining peripheral cytoplasm

- Binucleation and multinucleation
- **orderly maturation**; a smooth transition to koilocytotic intermediate and superficial cells
- Koilocytosis is not as florid as condylomas of the **cervix** in other areas





Prominent
koilocytotic
changes



LSIL

- dysplasia of the lower third of the epithelium
- the distinction between “dysplasia” and reactive expansion of the parabasal layer is **highly subjective.**

the old chestnut

should be relegated to the bin reserved for
medical trivia of historical interest only

- mild, moderate and severe cervical dysplasia (CIN1-3)
- dysplasia in the lower third, lower two thirds, and full thickness of the squamous epithelium

this is still repeated to **trainees** and has no underlying mechanistic basis

Bethesda classification

- **reflects the biology** of in situ squamous neoplasia of the cervix,
- especially as it relates to HPV
- a bipartite LSIL/HSIL system
- The proliferation rate of LSIL (CIN1) is higher than that of inflamed or metaplastic cervical squamous epithelium.

The natural history of LSIL

- most will **clear** spontaneously
- relatively few will **progress** to HSIL (CIN2/3)

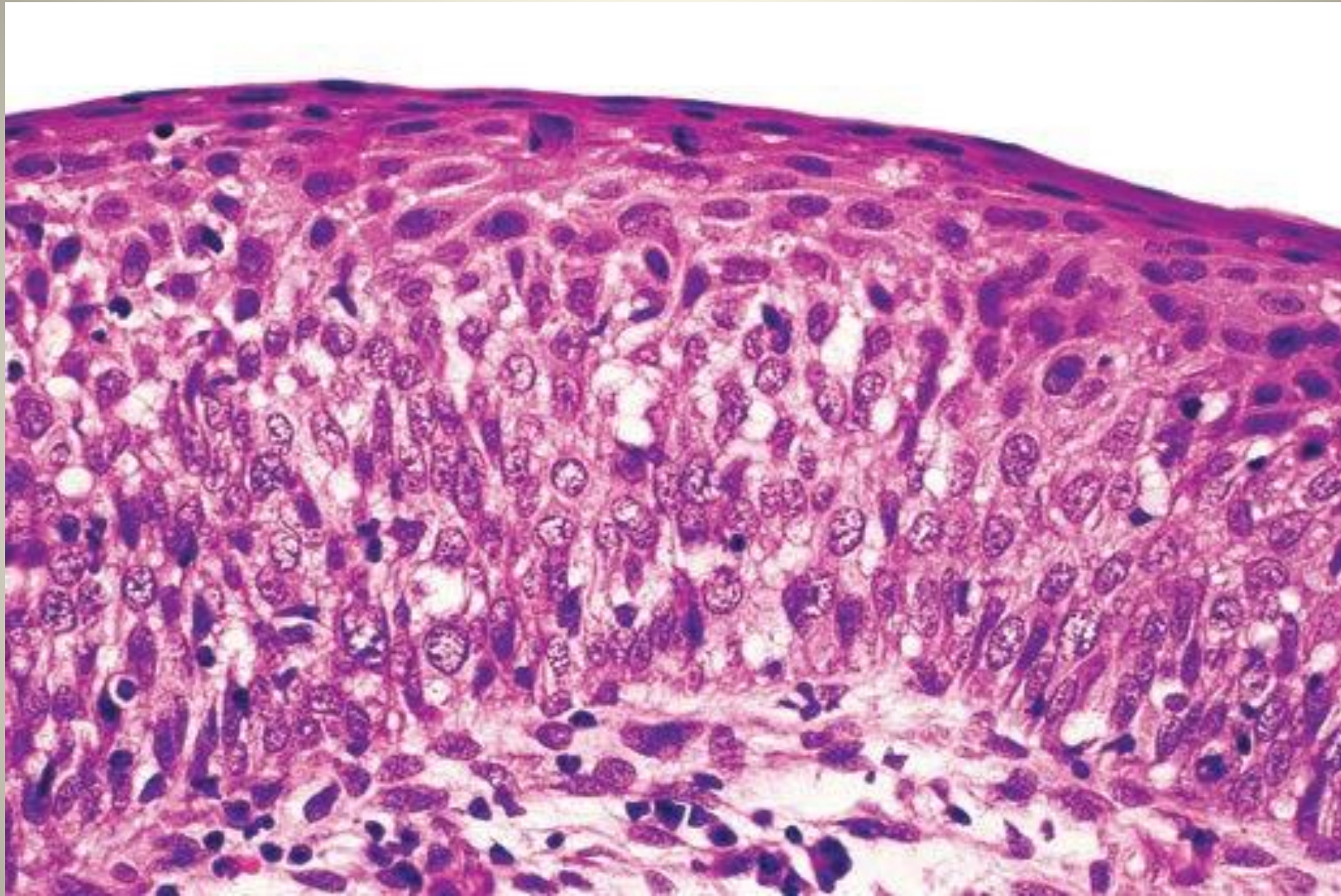
HSIL (CIN2/3)

- is best appreciated colposcopically
- may be seen **macroscopically**, when extensive



Mioscopically

- **high N:C ratio** in all layers of the epithelium
- Most importantly by **striking nuclear atypia**
 - nuclear pleomorphism, enlargement, and hyperchromasia
- Prominent **mitotic activity**, with atypical mitoses
 - in the upper layers of the epithelium

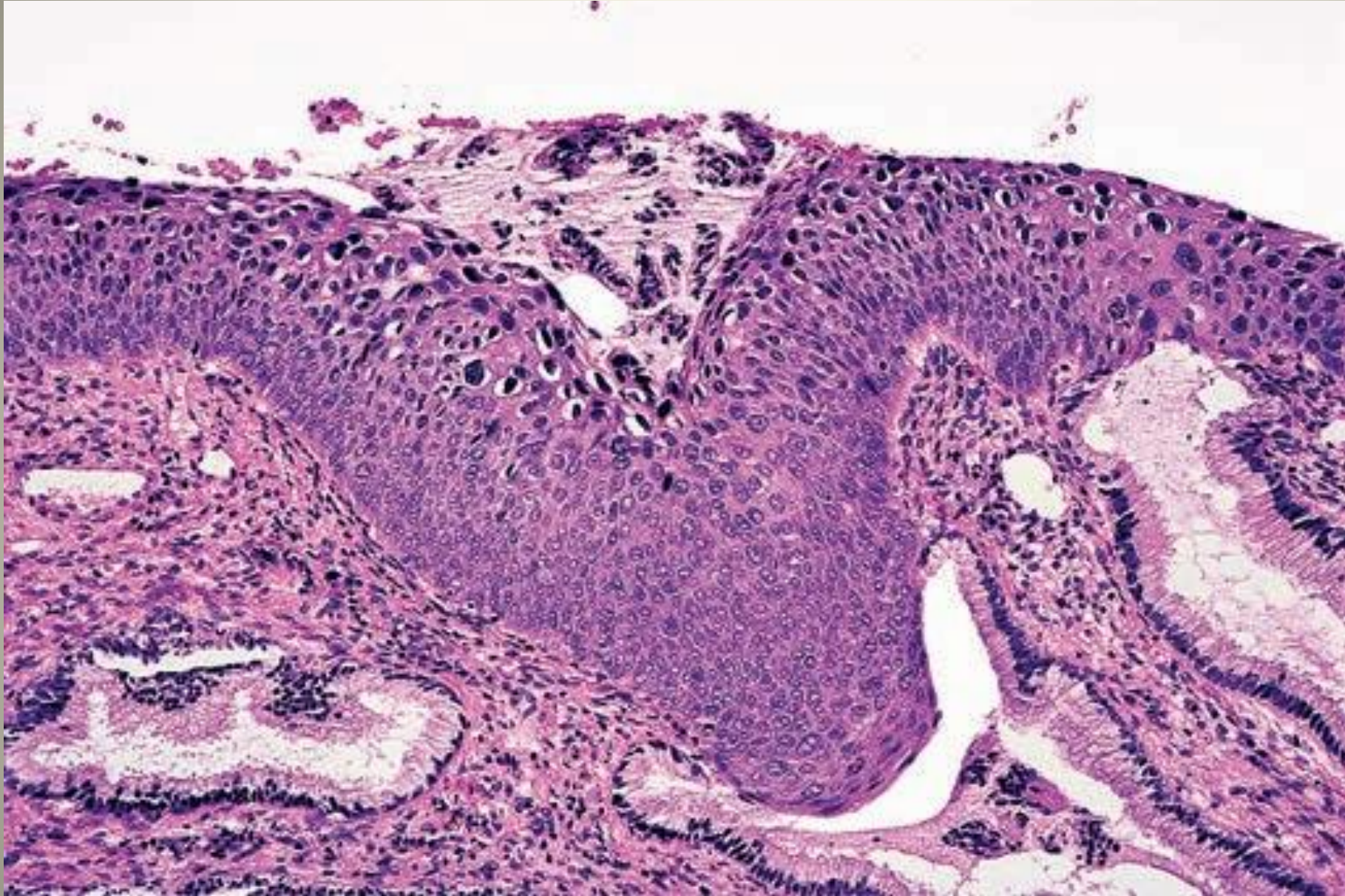


the differential diagnosis between LSIL and HSIL

- is made primarily based on H&E
- Only in selected borderline cases:
 - ✓ **p16 immunostaining strong and diffuse block positivity**
 - ✓ **Ki-67 stain:** increased proliferative activity

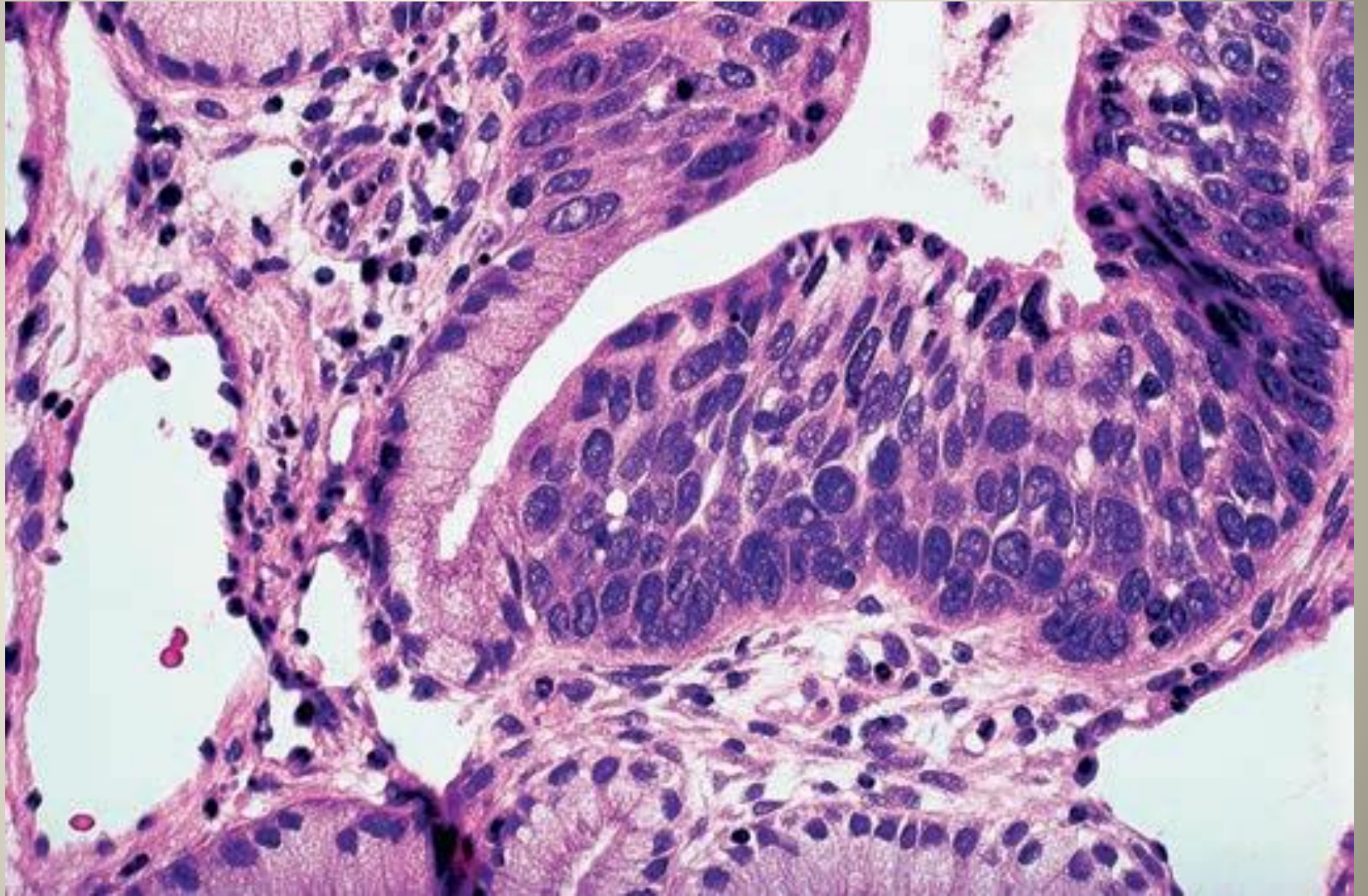
these have to be taken into account

- the surface
- Margins
- the possible depth of involvement
- extension into endocervical glands



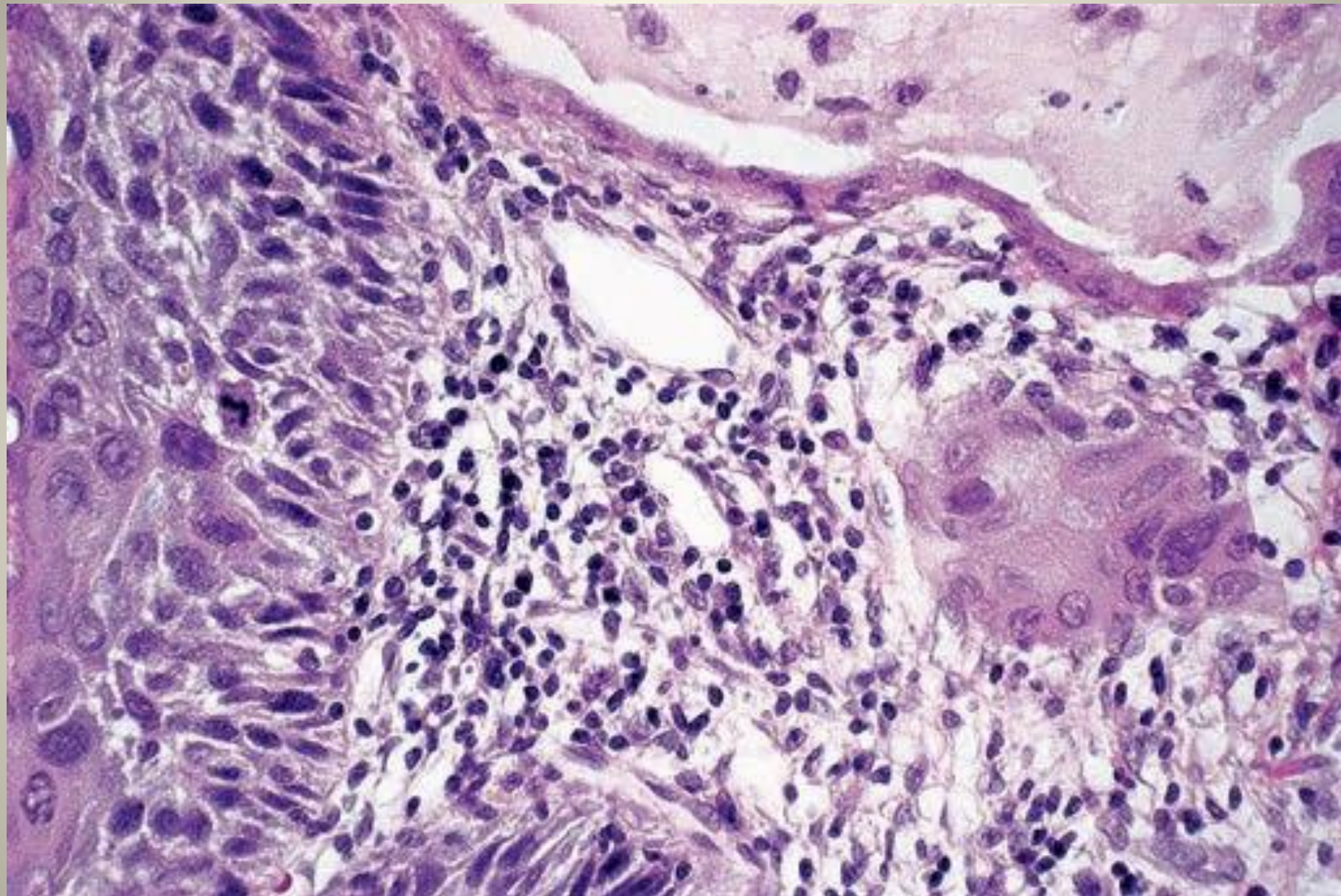
Extensive
involvement
by HSIL
(CIN2/3) of
surface
epithelium
and glands
of
endocervix

Partial
replacement
of
endocervical
glandular
epithelium
by
HSIL
(CIN2/3)



the presence or absence of
invasive carcinoma

- **Thorough cervical **sampling****
- **the proper **sectioning** of tissue**
- continuing abnormal **cytology** after initial treatment of HSIL (CIN2/3) were found to be 25 times more likely to develop invasive carcinomas than women with normal follow-up cytology



VIN2/3

- abnormal mitoses and nuclear pleomorphism, enlargement, and hyperchromasia **in the basal and parabasal cell layers**
- “block positivity” on p16 immunostaining,
 - at least the basal third of the epithelium
 - usually extending into the upper half
- The increased proliferative activity with the Ki-67 stain
- The DNA content is aneuploid pattern in most cases
- **a significant number of HPV-independent VIN**

VaIN2/3

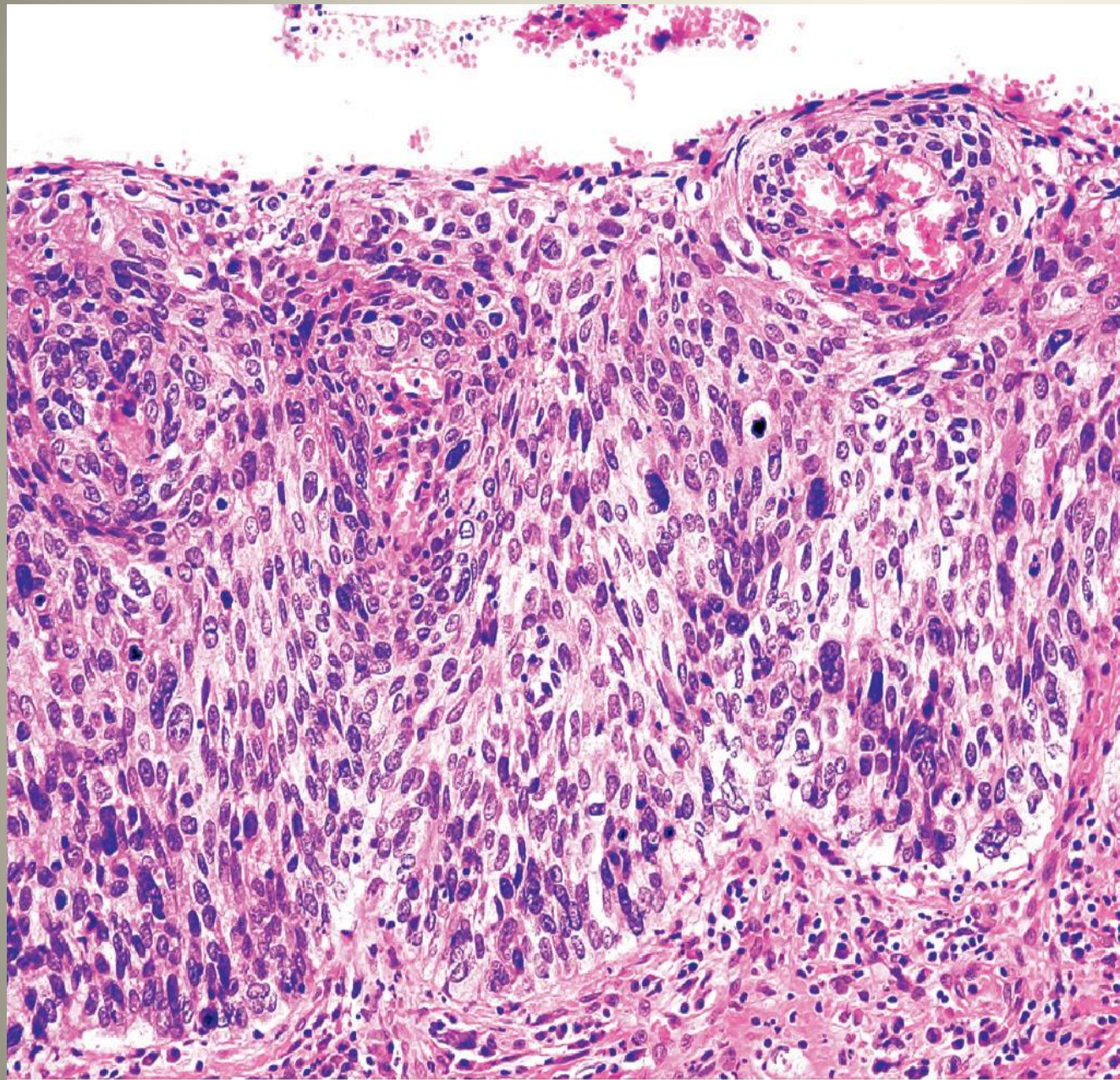
- The upper third of the vagina is the most common site, the vaginal and cervical lesions may be **confluent**
- arise from **native** squamous epithelium, in contrast to most cervical cases, which originate from *metaplastic* epithelium
- is **multifocal** in about half of cases
- very frequently associated with **concomitant, subsequent, or prior** (in situ or invasive) neoplasms elsewhere in the lower genital tract, especially the cervix

Penile Intraepithelial Neoplasia (PeIN)

- Human Papilloma Virus Related PeIN
 - **Basaloid (undifferentiated) PeIN**
 - **Warty (Bowenoid) PeIN**
 - **Warty-basaloid PeIN**, shows an admixture
- HPV-unrelated PeIN
 - **Differentiated PeIN** has been associated with lichen sclerosus or other chronic inflammatory conditions

Basaloid (undifferentiated) PeIN

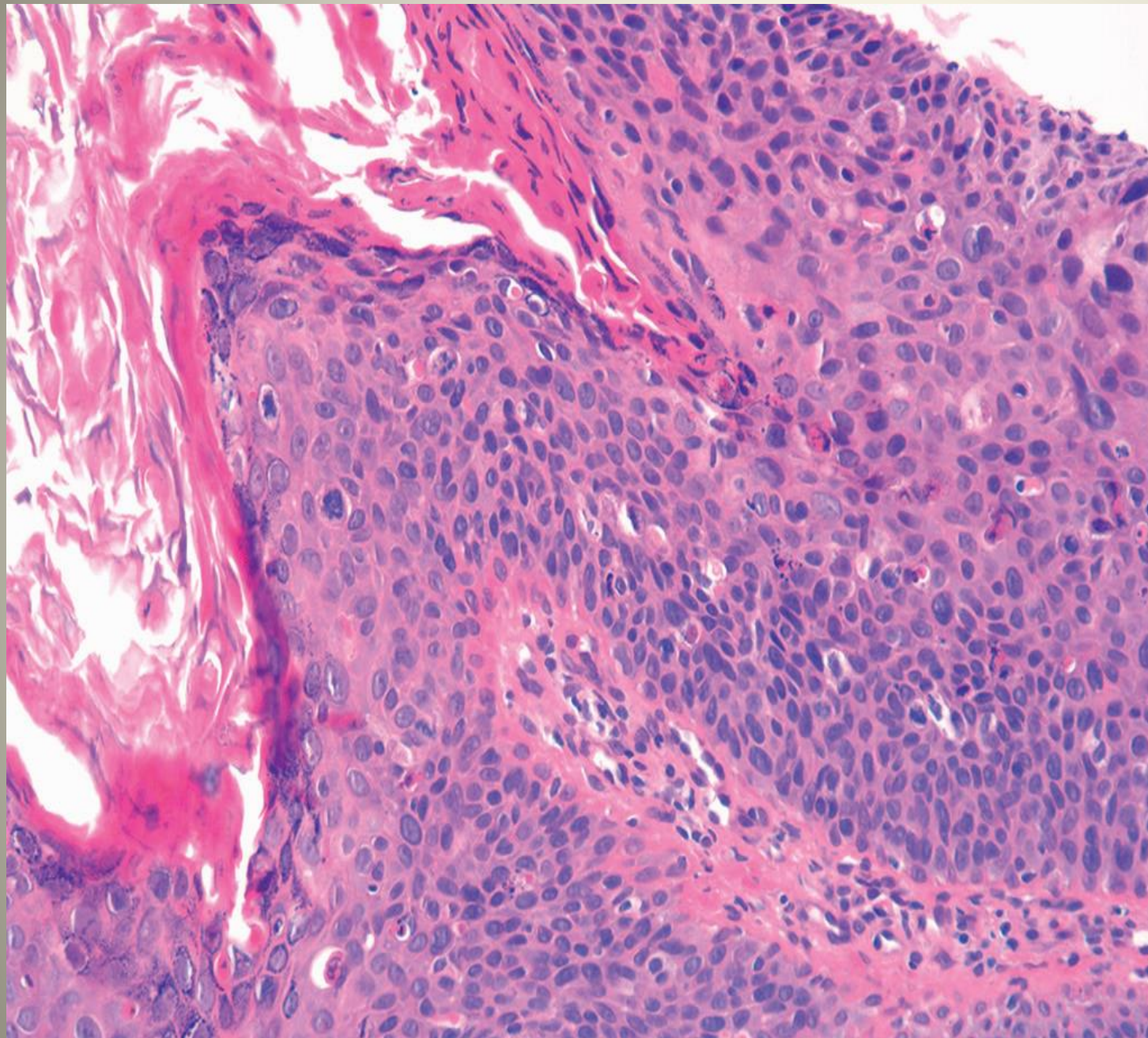
- typically involves the glans penis in young men
- **similar to HSIL of the cervix** with full-thickness involvement by small monotonous immature cells with high nuclearto-cytoplasmic ratio
- Mitotic activity and apoptotic bodies may be frequent, but squamous maturation is not characteristic
- show diffuse staining for p16
- a common association with HPV type 16



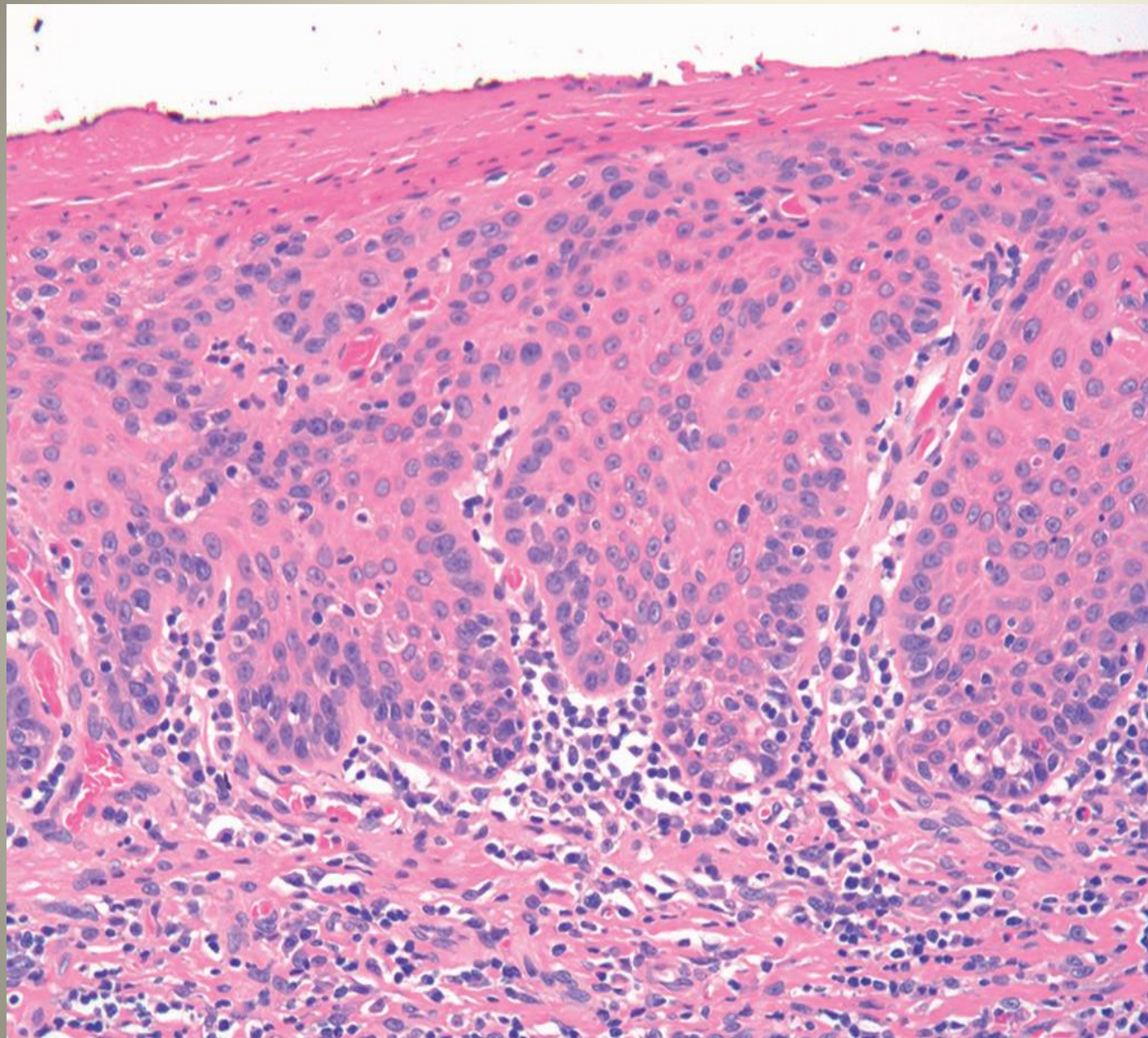
Basaloid PeIN

Warty (Bowenoid) PeIN

- has more complex architecture than basaloid PeIN
- frequent squamous maturation, a papillomatous surface and more abundant surface keratin, a contrasting point with basaloid PeIN
- more nuclear pleomorphism, and well-developed koilocytotic atypia
- expresses strong p16
- the associated HPV type is more variable



Warty-
basaloid PeIN



Differentiated
PeIN