Genital system-1

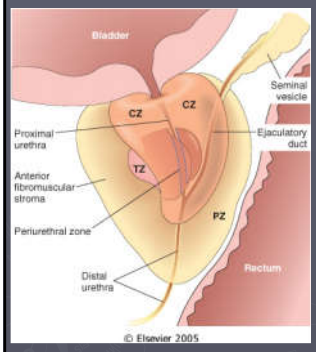
Benign prostatic hyperplasia (BPH)

Prostatic adenocarcinoma (PA)

Koilocytosis

Praeinvasive carcinoma of uterine cervix

Invasive cervical squamous cell carcinoma

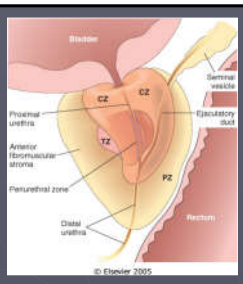


Adult prostate

The normal prostate contains several distinct regions, including a:
- central zone (CZ)- 20%,

- transitional zone (TZ)- 5%,

- peripheral zone (PZ)- 75%



Most carcinomas arise from the peripheral glands of the organ and may be palpable during digital examination of the rectum.
Nodular hyperplasia, in contrast, arises from more centrally situated glands and is more likely to produce urinary obstruction early in its course than is carcinoma.

Benign prostatic hyperplasia
syn. Nodular hyperplasia of the prostate

Prostatic hyperplasia is characterized by proliferation of both stromal an epithelial elements, with resultant enlargement of the gland and, in some cases, urinary obstruction

NH is an **extremely common** abnormality of the prostate.

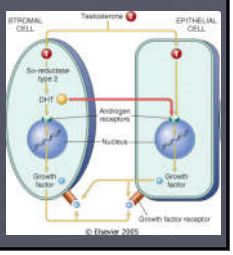
It is present in a significant number of men over 45-50, and its frequency rises progressively with age, reaching 90% men by the eighth decade of life

Benign prostatic hyperplasia

Etiology: androgens play a central role in development of BPH.

Dihydrotestosterone (DHT), an androgen derived from testosterone through the action of **5α-reductase**, and its metabolite, **3α-androstanediol**, seem to be major hormonal stimuli for stromal and glandular proliferation in men with nodular hyperplasia.
DHT binds to nuclear androgen receptors and, in turn, stimulates synthesis of DNA, RNA, growth factors, and other cytoplasmic proteins, leading to **hyperplasia**.

Experimental work has also identified age-related **increases in estrogen levels** that may increase the expression of DHT receptors on prostatic parenchymal cells, thereby functioning in the pathogenesis of nodular hyperplasia



Simplified scheme of the pathogenesis of prostatic hyperplasia.

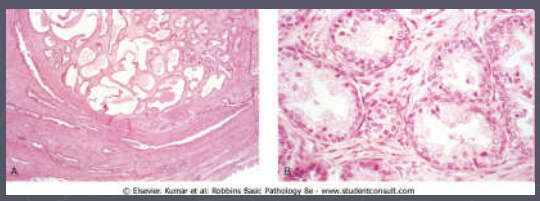
Benign prostatic hyperplasia

- **Ma:** nodular enlargement, nodules vary in color and consistency. This nodularity may be present throughout the prostate, but it is **usually most pronounced in the inner (central and transitional) region.** The nodules may have a solid appearance or may contain cystic spaces

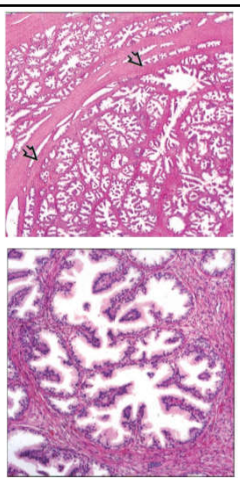
Nodular prostatic hyperplasia. A, Well-defined nodules of BPH compress the urethra into a slitlike lumen. B, A microscopic view of a whole mount of the prostate shows nodules of hyperplastic glands on both sides of the urethra.

Benign prostatic hyperplasia

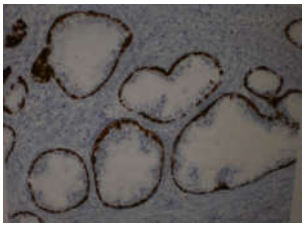
- **Mi:** glandular proliferation and dilatation, fibrous and muscular proliferation of the stroma. Glands are lined by **two layers** of epithelium (inner columnar and outer cuboidal or flattened) based on the basement membrane. Foci of squamous mataplasia. Small areas of infarction.



Nodular hyperplasia. **A,** Low-power photomicrograph demonstrates a well-demarcated nodule at the top of the field, populated by hyperplastic glands. **B,** Higher power photomicrograph demonstrates the morphology of the hyperplastic glands, with the characteristic dual cell population: the inner columnar secretory cells, and the outer flattened basal cell layer.



BPH



CKHMW

Benign prostatic hyperplasia

Clinical symptoms

Clinical manifestations of prostatic hyperplasia occur in **only about 10% of men with the disease.**

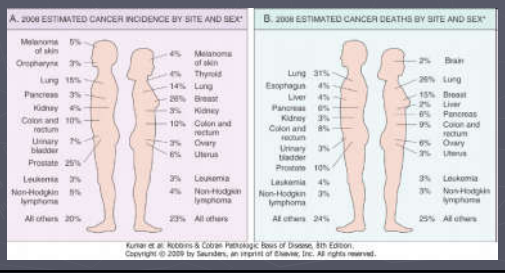
Because nodular hyperplasia preferentially involves the inner portions of the prostate, its most common manifestations are those of **lower urinary tract obstruction.** These include:
- difficulty in starting the stream of urine (hesitancy) and
- intermittent interruption of the urinary stream while voiding.

Some men may develop **complete urinary obstruction**, with resultant painful distention of the bladder and, if neglected, **hydronephrosis**. Symptoms of obstruction are frequently accompanied by urinary urgency, frequency, and nocturia, all indicative of bladder irritation.

The combination of residual urine in the bladder and chronic obstruction increases the risk of **urinary tract infections**.

Prostatic adenocarcinoma

- The most common cancer in males, the second most common cause of cancer-related deaths in men older than 50 years of age (US)
- It is predominantly a disease of older males, with a peak incidence between the ages of 65 and 75 years. Latent cancers of the prostate are even more common than those that are clinically apparent, with an overall frequency of **more than 50% in men older than 80 years of age**.



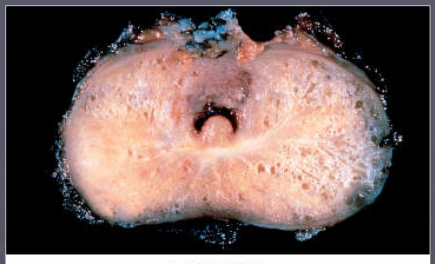
Prostate cancer- PATHOGENESIS

Clinical and experimental observations suggest that in the pathogenesis and progression of prostate cancer have roles:

- **Androgens.** Cancer of the prostate does not develop in males who are castrated before puberty
- **Heredity.** There is an increased risk among first-degree relatives of patients with prostate cancer.
- **Race.** Prostate cancer is uncommon in Asians and its incidence is highest among African-Americans and in Scandinavian countries.
- **Environment.**
- **Acquired genetic aberrations.** The most common gene rearrangements in PC create fusion genes consisting of the androgen-regulated promoter of the TMPRSS2 gene and the coding sequence of ETS family transcription factors. TMPRSS2-ETS fusion genes are found in approximately 40% to 60% of prostate cancers in Caucasian populations, and they occur relatively early in tumorigenesis.

Prostatic adenocarcinoma

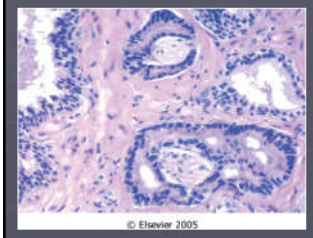
Peripheral zone of the gland in a posterior location (70-80% of PA)



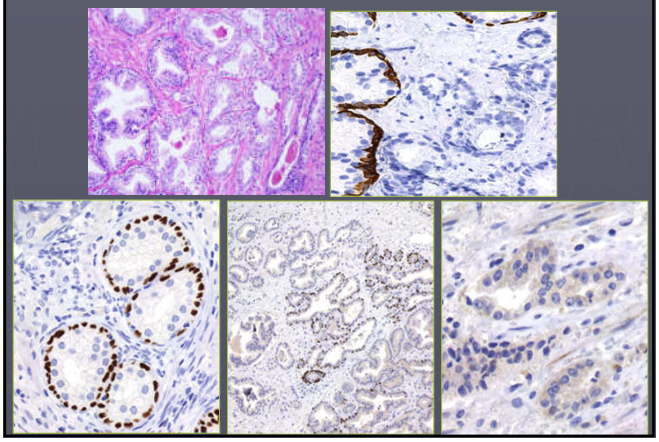
Adenocarcinoma of the prostate. Carcinomatous tissue is seen on the posterior aspect (lower left). Note the solid whiter tissue of cancer in contrast to the spongy appearance of the benign peripheral zone on the contralateral side.

Prostatic adenocarcinoma

- **Adenocarcinoma.** Irregular glands are **small** with a **single layer** of cuboidal cells with **conspicuous nucleoli**. The neoplastic glands have **„back to back"** appearence with scanty stroma. Invasion of the capsule with its lymphatic and vascular channels. Invasion of perineural spaces.



Prostatic adenocarcinoma vs normal/BPH glands



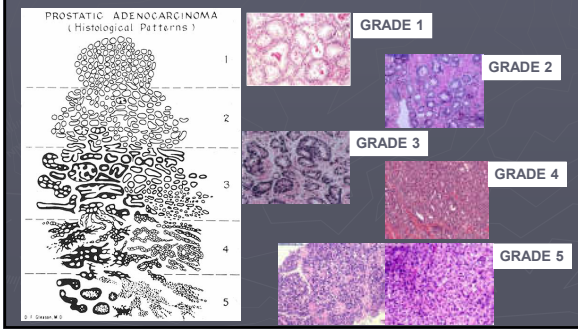
Prostatic adenocarcinoma is graded by the Gleason system

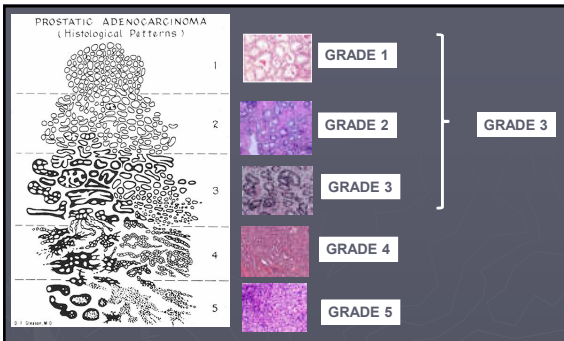
Donald F. Gleason 20.11.1920 – 28.12.2008

Gleason D.F.: Classification of prostatic carcinomas. Cancer Chemother Rep. 1966;50:125
Gleason D.F. et al..: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J. Urol 1974;111:58

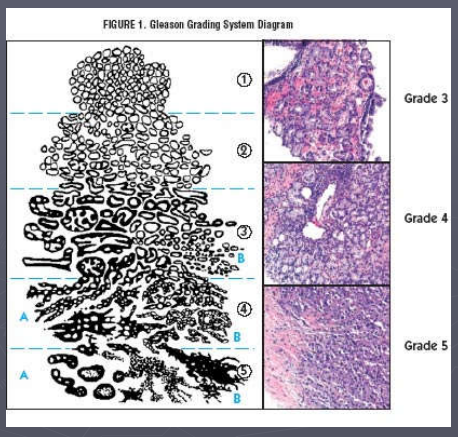
Prostatic adenocarcinoma- Gleason grading (GG) and Gleason score (GS)

- **PA is graded by the Gleason system**. According to this system, prostate cancers are stratified into five grades on the basis of glandular patterns of differentiation. **Grade 1 (GG1)** represents the most well-differentiated tumors and **grade 5 (GG5)** tumors show no glandular differentiation.

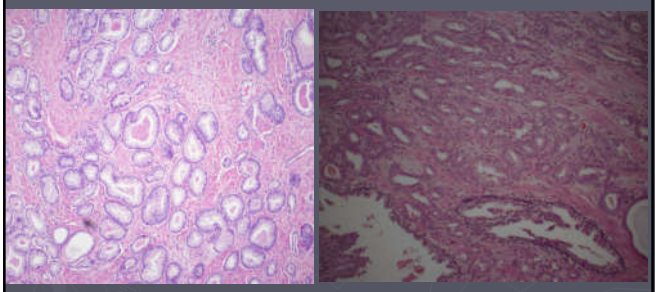




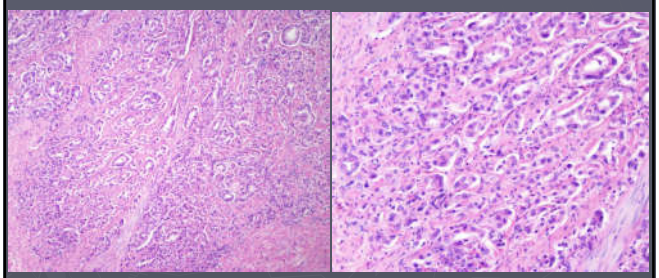
The current system of Gleason grading differs significantly from the original; for example grades 1 and 2 are no longer assigned (NOW: grade 1, grade 2 and grade 3 = grade 3)



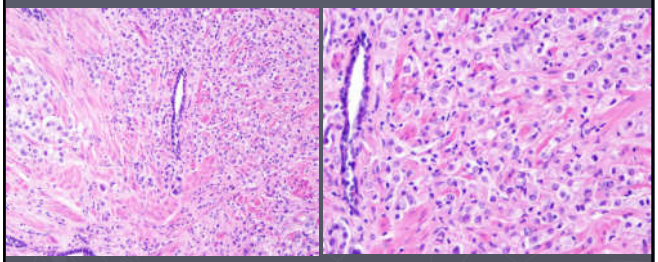
Gleason grade 3 (GG3)



Gleason grade 4 (GG4)



Gleason grade 5 (GG5)



Prostatic adenocarcinoma-
Gleason grading (GG) and Gleason score (GS)

Since most tumors contain more than one pattern, a **primary grade** is assigned to the dominant pattern (first number) and a **secondary grade** to the next most frequent pattern (second number). The two numerical grades are then added to obtain a combined Gleason score (GS).
If a tumour has only one histological pattern, then the primary and secondary patterns are assigned the same number (eg 3+3)

The Gleason Score ranges from 6 to 10

Prostatic adenocarcinoma-
Gleason grading (GG) and Gleason score (GS)

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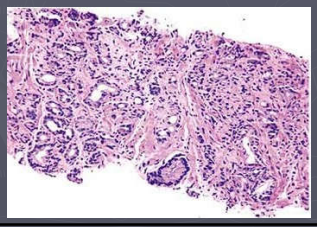
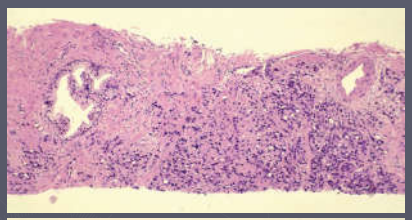
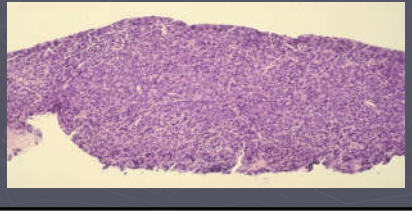


GS 7 (3+4)

Prostatic adenocarcinoma-
Gleason grading and Gleason score



GS9 (5+4)



GS10 (5+5)

A new set of grade groups (ISUP groups):

Grade group 1 – GS 3+3= 6 (only individual discrete well-formed glands)

Grade group 2 – GS 3+4=7 (predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands)

Grade group 3 – GS 4+3=7 (predominantly poorly formed/fused/ cribriform glands with lesser component of well-formed glands)

Grade group 4 – GS 4+4=8; 3+5=8; 5+3=8

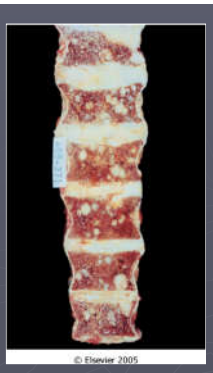
Grade group 5 – GS 9-10 (lack gland formation)

Grading of prostate cancer by the Gleason system correlates with pathologic stage and prognosis

Prostatic adenocarcinoma

The biochemical markers:
- Prostate specific antigen PSA
- Prostatic acid phosphatase

Spread:
- Local invasion
- Through the bloodstream and lymph (bones, particulary axial sceleton, widely to the viscera)



Metastatic osteoblastic prostatic carcinoma within vertebral bodies.

Neoplasia of the Cervix

- Most tumors are of **epithelial origin** and are caused by **oncogenic HPV** (it has tropism for the immature cells of the transformation zone)
- The peak age incidence of precancerous lesions is about 30 years, whereas that of invasive carcinoma is about 45 years.

IMPORTANT RISK FACTORS are directly related to HPV exposure and include :

- early age at first intercourse
- multiple sexual partners
- a male partner with multiple previous sexual partners
- persistent infection by "high-risk" papillomaviruses (e.g. HPV 16, 18, 45, 31)

Carcinoma of the uterine cervix

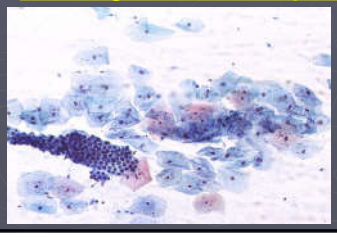
- Cervical carcinoma was once the most frequent form of cancer in women around the world.
- Since the introduction of the **Papanicolaou (Pap) smear** 50 years ago, the incidence of cervical cancer has decreased. Currantly, it ranks 14th in frequency for all cancers affecting U.S. women

George Papanicolaou was a Greek physician and anatomist in the US (1883-1962). Papanicolaou is the discoverer of "Pap Smear" or "Papanicolaou Smear"

Carcinoma of the uterine cervix

- Between 1955 and 1992, the rate of cervical cancer deaths in the U.S. declined by nearly 70%. It continued declining more gradually to 2003 before stabilizing
- The overall decline is mainly attributed to the use of the Pap test. This screening method is able to find changes in the cervix before cancer has a chance to develop

The Pap smear remains the most successful cancer screening test ever developed.



Cervical Intraepithelial Neoplasia (CIN)

✓ Nearly all invasive cervical squamous cell carcinomas arise from precursor epithelial changes referred to as **CIN**

✓ Cytologic examination can detect CIN long before any abnormality can be seen grossly.
The follow-up of such women has revealed that precancerous epithelial changes may precede of an overt cancer by many years, or even decades.

Classifications Systems
for Precursor Squamous Cervical Lesions

On the basis of histology, precancerous changes are graded as follows:

DYSPLASIA	mild	moderate	severe	carcinoma in situ
CIN	CIN I	CIN II	CIN III	
SIL	LG-SIL	HG-SIL		

SIL – Squamous Intraepithelial Lesion

Natural History of CINs/SILs

CIN usually starts as low-grade dysplasia (CIN I) and progresses to moderate (CIN II) and then severe dysplasia (CIN III)

However, progression from a lower grade to a higher grade is not inevitable.

Although studies vary, with **CIN I** the likelihood of **regression** is 50% to 60%, that of **persistence** is 30%, and that of **progression** to CIN III, is 10-20%. With progression, only 1% to 5% become invasive.

With **CIN III** the likelihood of regression is only 33% and of progression (to invasive carcinoma) 10% (in various studies).

Lesion	Regress	Persist	Progress
LSIL (CIN I)	60%	30%	10% (to HSIL)
HSIL (CIN II, III)	30%	60%	10% (to carcinoma)*

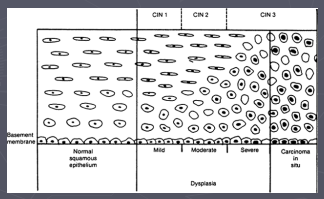
*** Progression within 10 years**

It is evident that the higher the grade of CIN, the greater the likelihood of progression, but it should be noted that in many cases even the higher grade lesions do not progress to cancer

Dysplasia of squamous epithelium
Intraepithelial squamous cell neoplasia

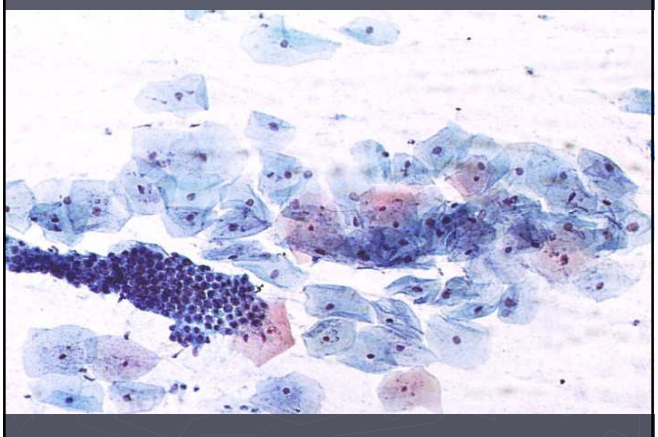
Definition:

Loss in the uniformity of the individual cells (cellular atypia) and a loss in their architectural orientation (architectural anarchy)



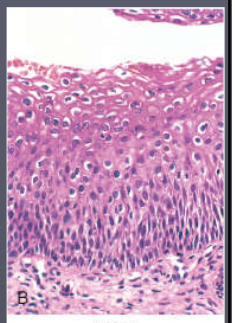
CELLULAR ATYPIA:

- **Pleomorphism**- cell size and shape
- **Abnormal nuclear morphology**.
  - **Hyperchromasia** -characteristically the nuclei contain an abundance of DNA and are extremely dark staining
  - **Hypernucleosis** (↑ N/C)- nuclear enlargement
  - **Heteronucleosis** -the nuclear shape is very variable,
  - **Marginalization of chromatin** - the chromatin is often coarsely clumped and distributed along the nuclear membrane.
  - **Hypernuclelosis**- large nucleoli are usually present in nuclei.
- **Mitotic activity –** (increased, abnormal, beyond the usual proliferative compartment)



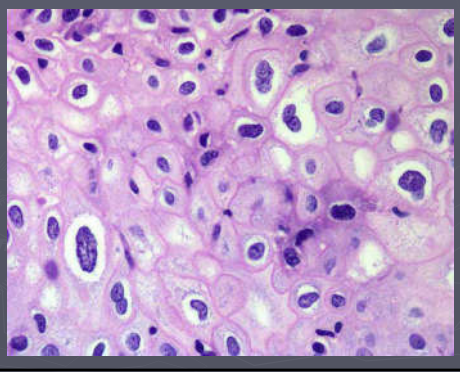
CIN- morphology

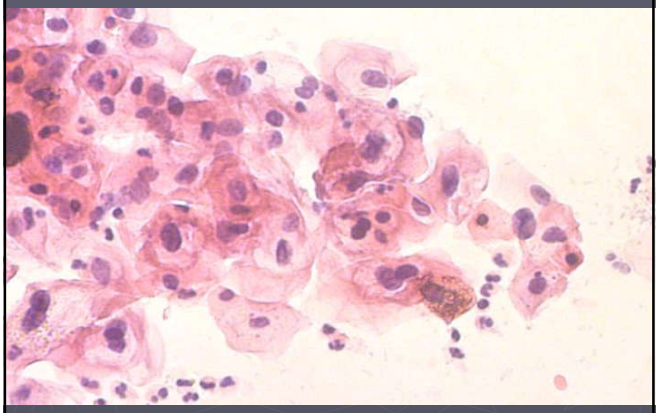
- **CIN I** (mild dysplasia): This lesion is characterized by dysplastic changes in the lower third of the squamous epithelium and koilocytotic changes mostly in the superficial layers of the epithelium. **Koilocytosis** is composed of nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV.



CIN I

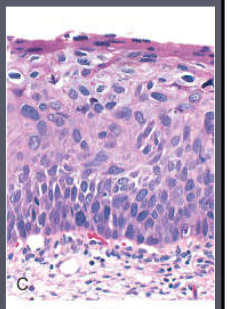
Koilocytes: cells with nuclear hyperchromasia and angulation with perinuclear vacuolization produced by cytopathic effect of HPV





CIN- morphology

- **CIN II** (moderate dysplasia): in CIN II the dysplasia is more severe, it extends to the middle third of the epithelium.
- It is associated with some variation in cell and nuclear size, heterogeneity of nuclear chromatin and mitoses above the basal layer.
- The superficial layer of cells shows some differentiation, and in some cases it shows the koilocytotic changes



CIN II
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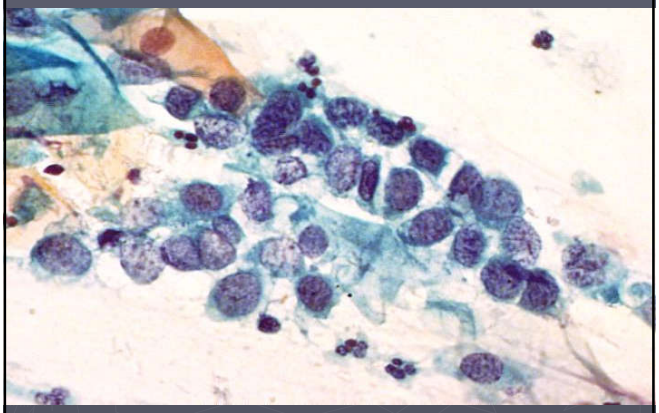
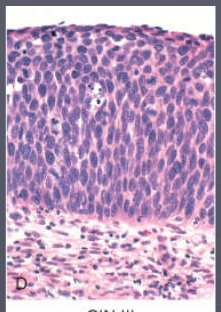


Cervical intraepithelial neoplasia - CIN

- As the spectrum evolves, there is progressive loss of differentiation with involvement of more and more layers of the epithelium, untill it is totally replaced by immature atypical cells exhibiting no surface differentiation – **CIN III (high dysplasia, preinvasive carcinoma)**

CIN III (praeinvasive carcinoma) - morphology

- Loss of regular arrangement and polarity of cells involving entire thickness of the epithelium
- Features of cellular atypia (particullary hyperchromasia) and mitotic figures in all levels of the epithelium
- The cells differ in size and shape
- The surface layer do not show any flattened cells



CIN III
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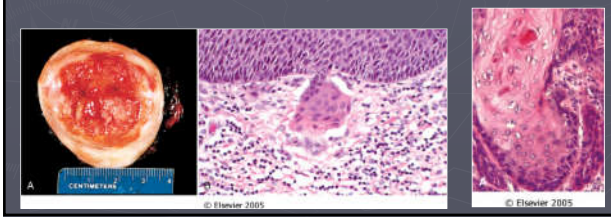
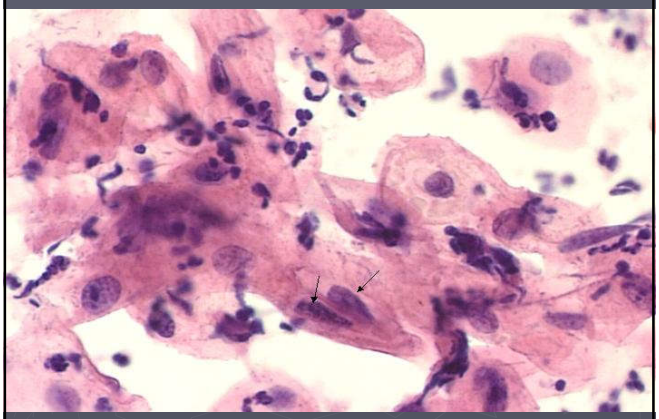
CIN III (carcinoma in situ) with diffuse atypia and loss of maturation.

Invasive squamous cell carcinoma

Ma:
- with exophytic growth into the lumen of the vagina
- endophytically into the cervical wall (with ulceration)

Mi: SCCs range from well-differentiated squamous cell neoplasms showing keratinization with keratin pearls and intracellular bridges to poorly differentiated neoplasms having only minimal residual sqamous cell features.





Invasive cervical carcinoma

- The most common cervical carcinomas are **squamous cell carcinomas (75%),** followed by adenocarcinomas and adenosquamous carcinomas (20%), and small-cell neuroendocrine carcinomas (<5%).
- The squamous cell lesions are increasingly appearing in younger women, now with a peak incidence at about 45 years, some 10 to 15 years after detection of their precursors.
- Invasive carcinomas of the cervix develop **in the region of the transformation zone** and range from microscopic foci of early stromal invasion to grossly conspicuous tumors encircling the os. Thus, the tumors may be invisible or exophytic.

Invasive squamous cell carcinoma

The prognosis depends upon the clinical stage at admission.
5-years survival rate equals in:

- **Stage 0** (preinvasive, CIN III) – 100%
- **Stage I** (with microinvasion, to 7mm beneath the basement membrane) – 90%
- **Stage II** (ca involves up to 1/3 of the uterus, infiltrates vagina or parametrium but does not reach the wall of true pelvis) – 82%
- **Stage III** (infiltration of true pelvis, uterus, vagina, ureters) – 35%
- **Stage IV** (massive infiltration of true pelvis, urinary bladder, rectal mucosa) – 10%