UTERINE CERVIX

NORMAL HISTOLOGY

- Columnar mucous-secreting endocervix meets squamous-lined endocervix at the **cervical os**
- **PUBERTY:** squamocolumnar junction undergoes eversion
- Eventually, everted endocervical glands undergo squamous metaplasia
- Region where squamous transforms to column epithelium = **Transformation Zone**

TRANSFORMATION ZONE (TZ)

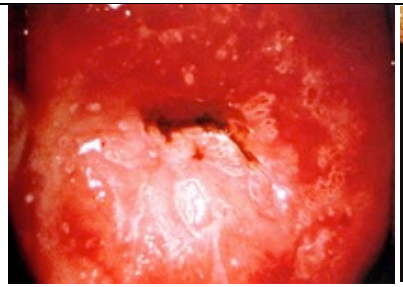
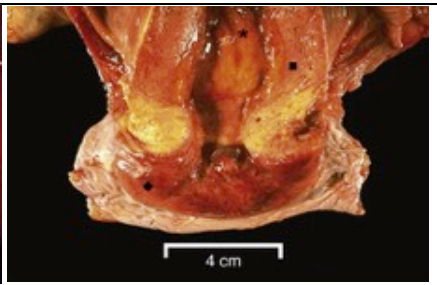
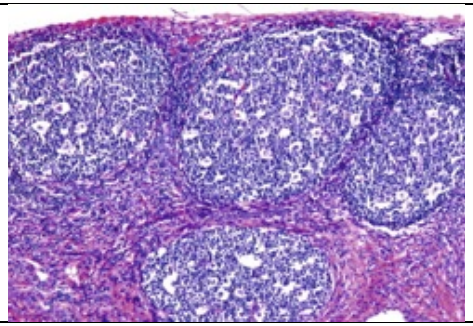
- **The area most at risk of neoplasia in all age groups**
- Note how location varies with age
  - SCJ and TZ are readily visible in younger women & may be quite large
  - SCJ migrates inward with aging & by menopause, it is usually within the canal & not visible
- The entire TZ must be sampled to maximize efficacy of the Papanicolaou smear

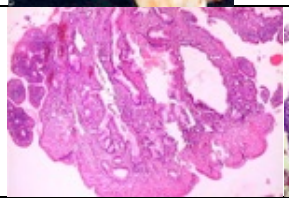
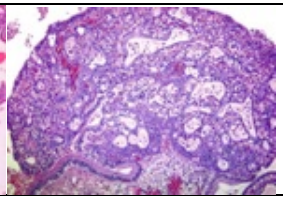
NORMAL ENDOCERVIX

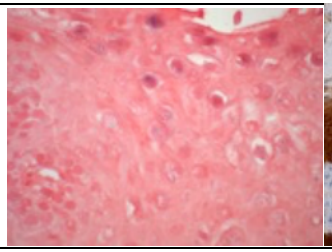
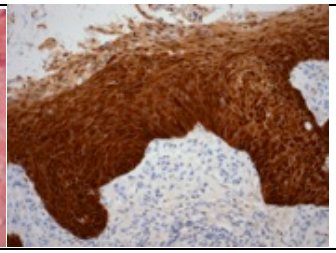
- Lined by columnar mucin-secreting epithelium that undergo squamous metaplasia
- Glands that undergo cystic change are called **Nabothian cysts**

NORMAL FLORA

- **LACTOBACILLI** are most important & keep pH below 4.5 & produce H_2O_2 suppressing growth of saprophytic & pathogenic organisms
- Alterations in pH (intercourse, bleeding, antibiotics) cause alterations in normal flora

1. CERVICITIS	
DEFINITION	Inflammation of uterine cervix; can be acute or chronic
CLINICAL	**ACUTE CERVICITIS: most common in POST-PARTUM period;** Staph & strep species responsible **CHRONIC CERVICITIS:** *inflammation, reactive changes*, columnar epithelium may undergo *squamous metaplasia*; **LEUKORRHEA** *(discharge of mucus from vagina)*
PATHOGENESIS	***Chlamydia trachomatis****, Ureaplasma urealyticum, T. vaginalis, Candida spp., Neisseria gonorrhea,* HSV-2, some strains of **HPV**
GROSS	  Chronic cervicitis typically begins at the SCJ of the cervix & can extend to involve ecto-cervival squamous epithelium;
MORPHOLOGY	 **FOLLICULAR CERVICITIS**
COURSE/ TREATMENT	***HPV is very important because of maternal-fetal transmission**

2. ENDOCERVICAL POLYPS	
DEFINITION	Benign growth arising in the **endocervical canal** & protrude through **cervical os**
CLINICAL	Bleeding after sex
GROSS	Can be sessile or polypoid 
MORPHOLOGY	  Proliferation of endocervical glandular epithelium that surround loose **myxoid stroma**
TREATMENT	Treated by curettage

3. HUMAN PAPILLOMA VIRUS (HPV) & CERVICAL CANCER	
DEFINITION	DNA virus; grouped into high & low oncogenic risks: – **HPV-16 & HPV-18 = HIGH RISK HPV → Malignancy (Squamous Cell Carcinomas)** – **HPV-6 & HPV-11 = LOW RISK HPV → Genital Warts (Condylomata accuminata)**
CLINICAL	HPV infection is detectable in most cases of **cervical cancer & CIN.** ***MOST HPV infections are asymptomatic**, transient, & cleared within months with no clinical consequence.*
PATHOGENESIS	**E6 inactivates p53 & E7 inactivates Rb** – HPV infects **BASAL LAYER OF TRANSITION ZONE (immature squamous epithelium)**, but replication of HPV DNA occurs in more mature cells ~20% of cervical cancers have somatic mutation in **LKB1**
MORPHOLOGY	  **KOILOCYTES** **p16+** (surrogate marker of hrHPV; accumulates in transformed cells)
RISK FACTORS FOR HPV-RELATED DISEASE & CANCER	– **Infectious** (**persistent infection** with high-risk HPV – HPV-16 & HPV-18) – **Environmental** (smoking) – **Sexual** (young age at sexual debut, **multiple partners**, multiparity) – **Immunosuppressive** (due to HIV or immunosuppressive therapy)
PREVENTION	**HPV Vaccine: *Guardasil* & *Cervarix*** – Both protect against HPV-16 & HPV-18; Cervarix also against HPV-6 & 11 – Prevent pre-cancerous lesions of the cervix

4. CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Peak age: 35 years old

DEFINITION

CIN is a **pre-cancerous epithelial lesion** that may progress to overt cancer; most commonly due to **HPV**

3 GRADES OF DYSPLASIA

CIN I (LSIL)

- Low-grade dysplasia involving **lower 1/3** of epithelium
- **Koilocytotic atypia** at **surface**

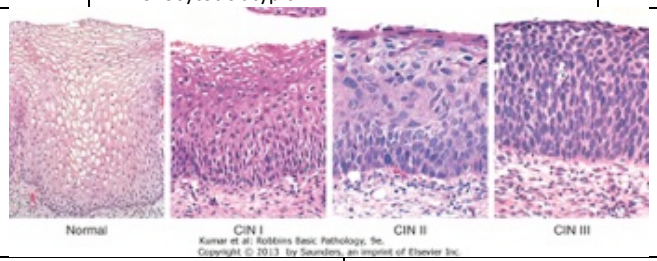
CIN II

- Dysplasia extending into **middle third**
- **Delayed maturation of keratinocytes**
- Variation in cell size & nuclear changes
- **Mitoses ABOVE basal layer**
- Koilocytotic atypic

CIN III

- Severe dysplasia or ***carcinoma in situ (CIS)***
- **Loss of maturation**
- Variation in cell size & nuclear size
- **Loss of cellular orientation**

NO INVASION



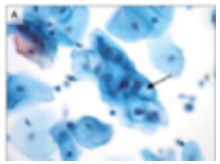
LOW GRADE vs. HIGH GRADE

LOW GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL)

Consists of CIN I

60% regress, 30% persist, 10% progress to HSIL

Cells with PERINUCLEAR HALOS, enlarged/hyperchromatic nuclei w/ irregular outlines

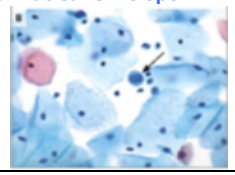


HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)

Consists of CIN II & CIN III

30% regress, 60% persist, 10% progress to carcinoma

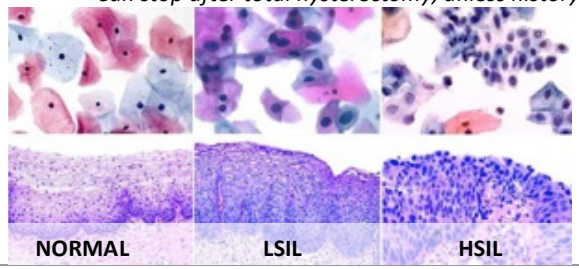
Abnormal isolated cell with a high N:C ratio, irregular chromatic distribution, & irregular nuclear envelope



DIAGNOSIS

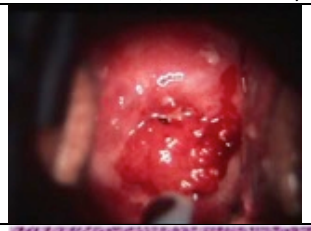
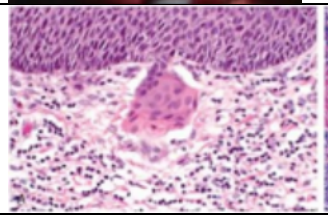
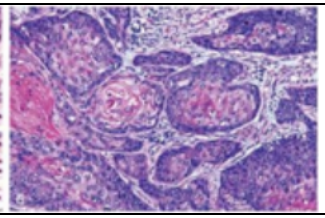
PAP SMEAR: May detect CIN long before gross changes are visible – *Most successful cancer screening method*

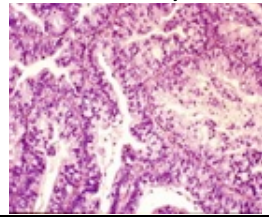
- **Begin 3 years after 1st vaginal intercourse, no later than 21**
- Before 30, screen every year with conventional Pap or every 2 years with liquid-based Pap
- After 30, if 3 normal results in a row → screen every 2-3 years with a Pap or every 3 years with a Pap + HPV test
- After 70, with >3 normal Pap & no abnormal Pap in previous 10 years → screening can be stopped
- *Can stop after total hysterectomy, unless history of CIN 2, 3, cervical cancer, or in utero DES exposure*

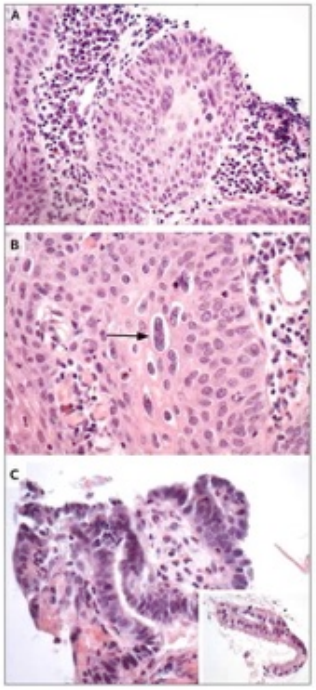


CLINICAL MANAGEMENT OF ABNORMAL PAP SMEAR:

- **LSIL & HSIL: colposcopy/biopsy**
- ASCUS *(atypical squamous cell of undetermined significance)*:
  - Repeat Pap smear 4-6 months
  - Colposcopy
  - Reflex HPV testing

5. CERVICAL SQUAMOUS CELL CARCINOMA Peak age: 45 years old (10 years after CIN)	
DEFINITION	75% of cervical caners; involves **TRANSFORMATION ZONE**;
CLINICAL	Vaginal bleeding after sex, **LEUKORRHEA** *(white discharge of mucus from vagina),* **dyspareunia**, dysuria
RISK FACTORS	**Cigarette smoking & HIV**
PATHOGENESIS	Development depends on highly variable course of high risk **HPV** infection + other mutations (such as LKB1) **Arises from HSIL**, extends locally to bladder or bowel, **invades underlying stroma**
GROSS	
MORPHOLOGY	 
TREATMENT	**Varies from cone biopsy to hysterectomy & LN dissection**
COMPLICATIONS	**RENAL COMPLICATIONS & FAILURE are a significant cause of morbidity**

6. Other Causes of Cervical Carcinoma:		
ADENOCARCINOMA Proliferation of malignant endocervical cells **Also caused by HPV** 	**ADENOSQUAMOUS CARCINOMA** Mixed glandular & squamous	**NEUROENDOCRINE** Similar to small cell of lung, but **positive for high risk HPV**

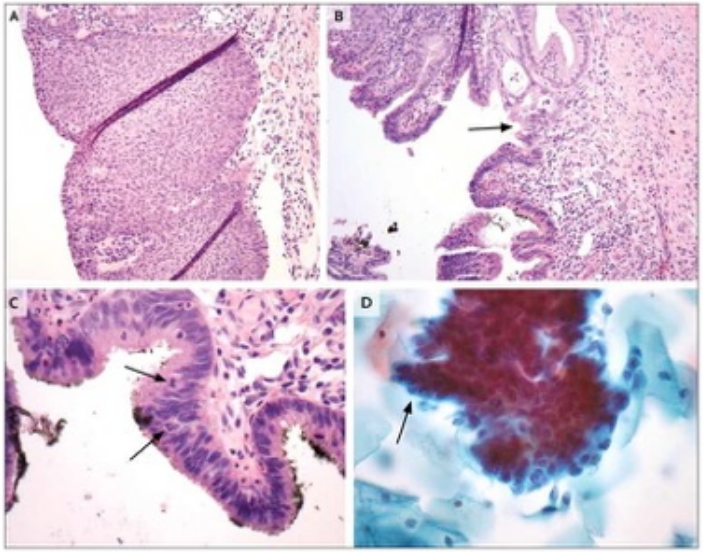


CERVICAL BIOPSY SPECIMEN

A) High-grade dysplasia with immaturity of the basal squamous cells extending into the midportion of the epithelium

B) In addition to the maturation abnormality, this area of the epithelium shows atypical cells with **perinuclear halos**, **nuclear enlargement**, and multinucleation, known as **koilocytosis** (arrow). These changes are indicative of HPV cytopathic effect.

C) Atypical endocervical epithelium is also present. The epithelium is **pseudostratified** and shows **enlarged nuclei** with **hyperchromasia**. This appearance is in contrast to normal simple endocervical epithelium (inset).



SPECIMEN FROM LOOP ELECTROSURGICAL EXCISION

A) Grade 3 CIN – abnormality of maturation of squeamous cells noted to ascend to involve near full thickness. No koilocytosis is present in this lesion since these cells are indicative of neoplastic, non-infectious process.

B) Endocervical adenocarcinoma in situ is present adjacent to the normal endocervical epithelium. The arrow points to the junction between adenocarcinoma in siti & normal-appearing cells

C) At higher magnification, the typical features of endocervical adenocarcinoma in situ are shown, including nuclear pseudostratification, enlargement, & hyperchromasia. Mitotic figures are prominent (arrows).

D) A hyperchromatic, crowded group of cells from the patient's original Pap smear has features that may be seen in both HSIL & endocervical lesions. A vague columnar appearance is present at one margin (arrow), suggesting an origin from endocervical cells, although the rest has more syncytial appearance, suggestive of HSIL.