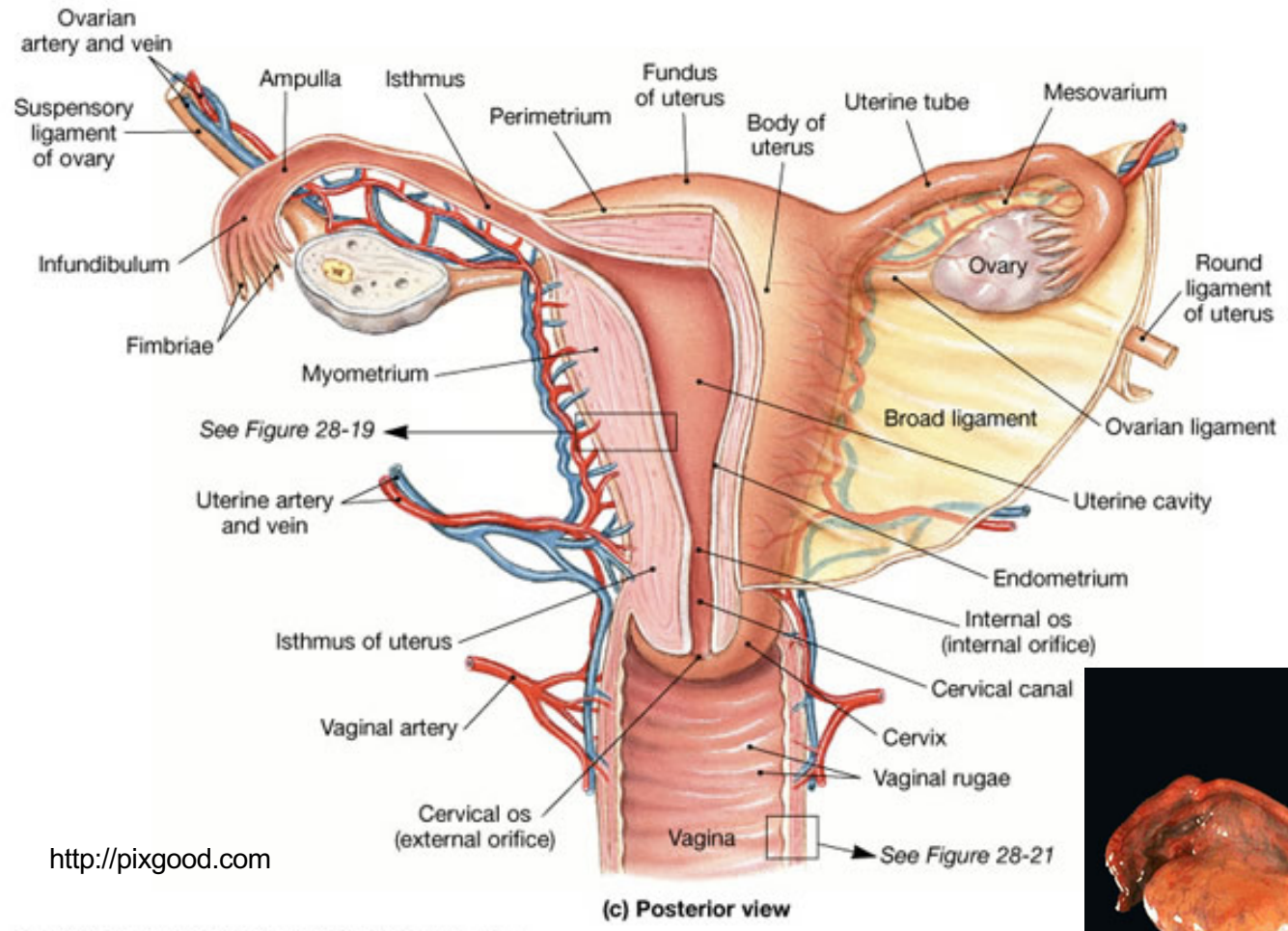
Endometrial hyperplasia, uterine cancer and fibroids

Reference: Robbins & Cotran Pathology and Rubin's Pathology

Uterus with bilateral tube and ovaries, posterior view



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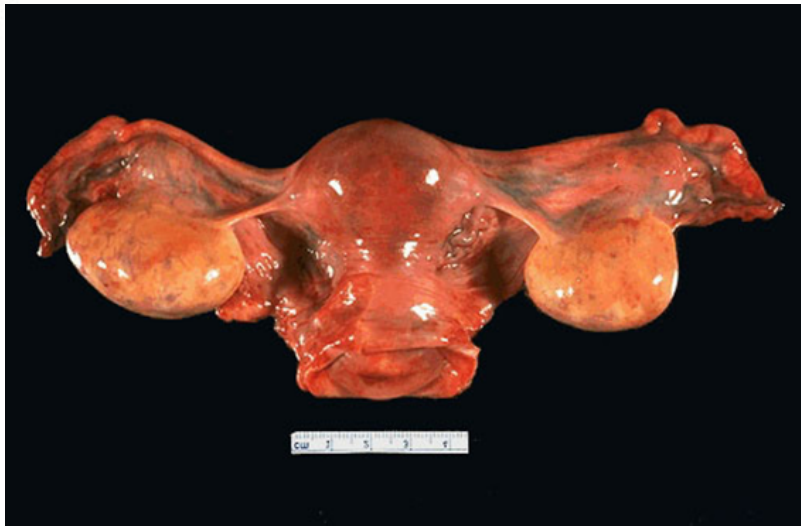

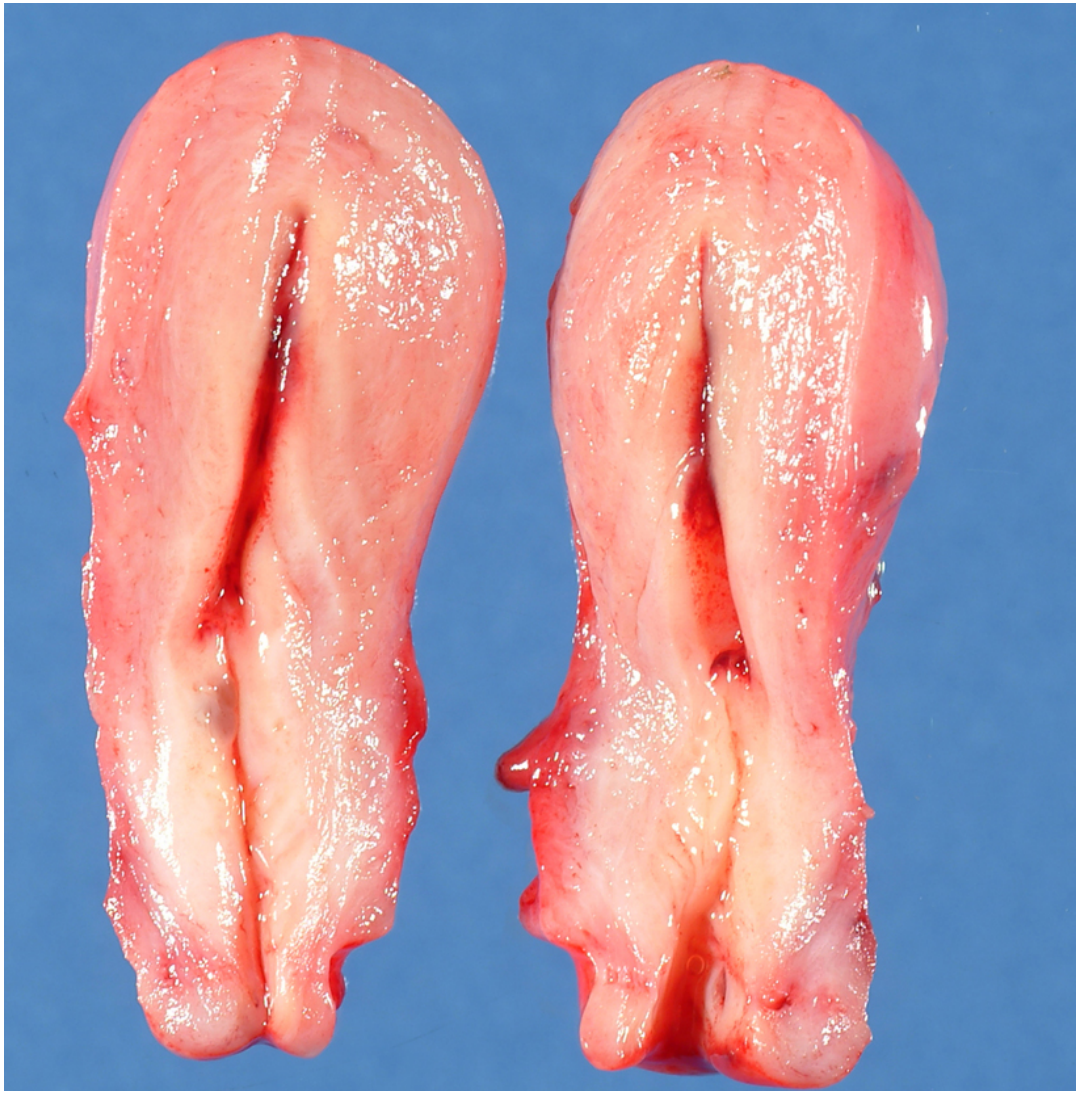

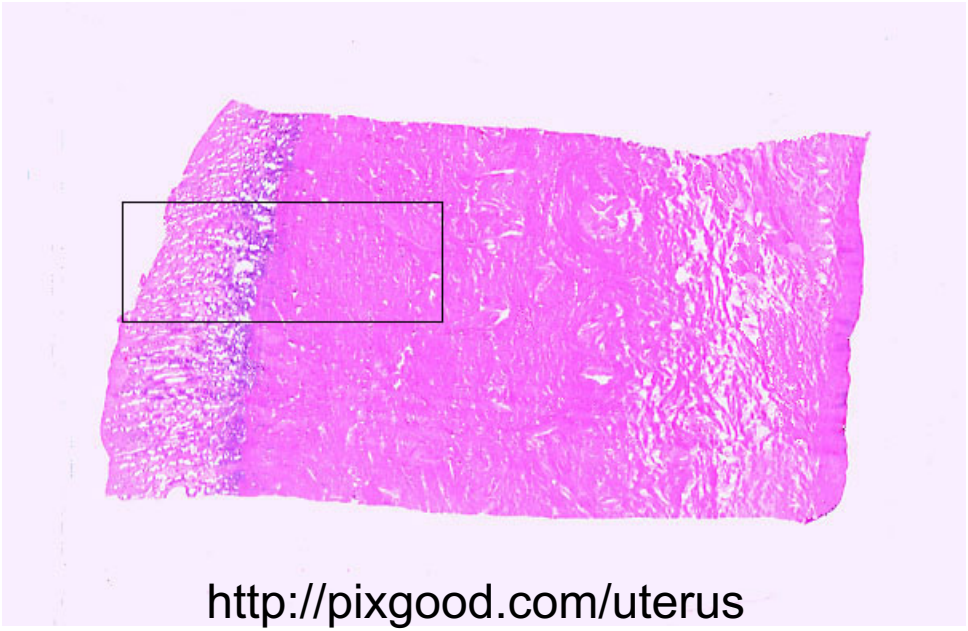

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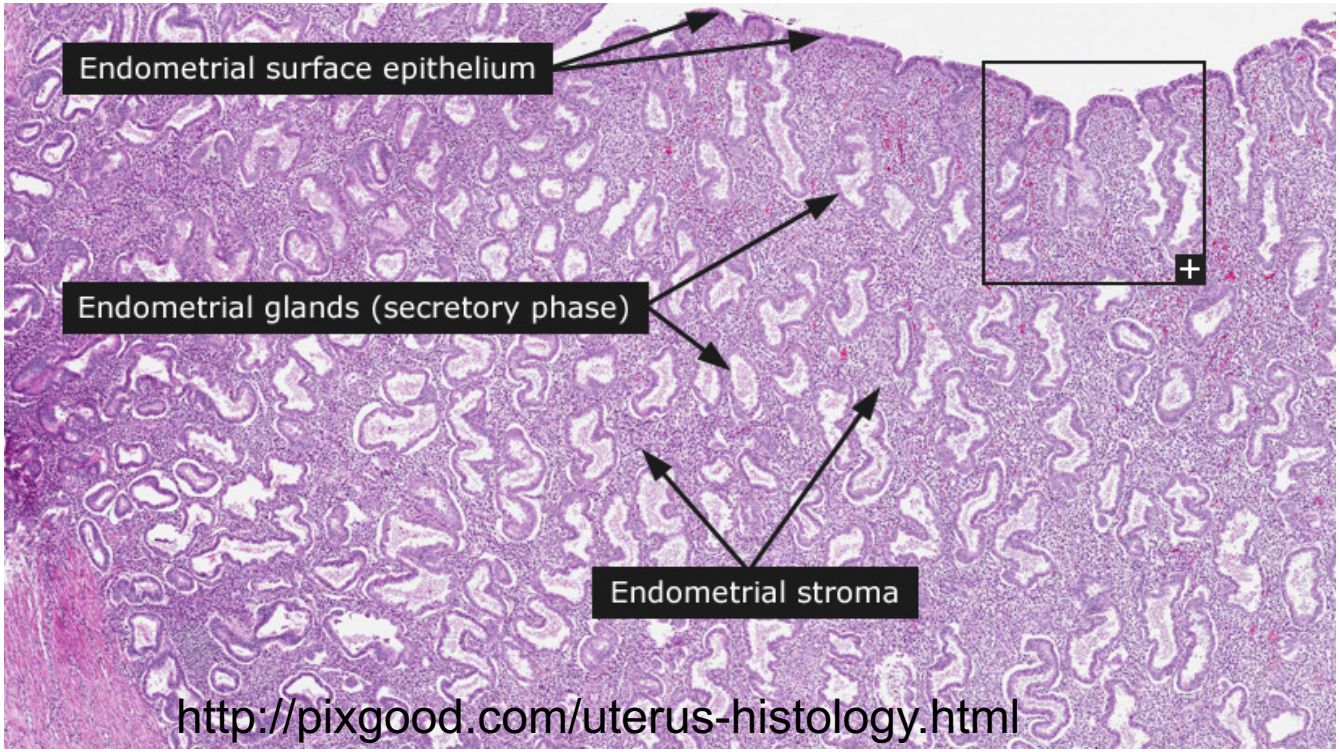

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Lecture Outline

Lecture: Endometrial hyperplasia, uterine cancer and fibroids (leiomyomas).

At the end of this lecture, the student should know:

Lesions of endometrium of uterus: know the risk factors, clinical presentation, macroscopic and histological features of:

- **Endometrial hyperplasia.**
- **Endometrial carcinoma.**

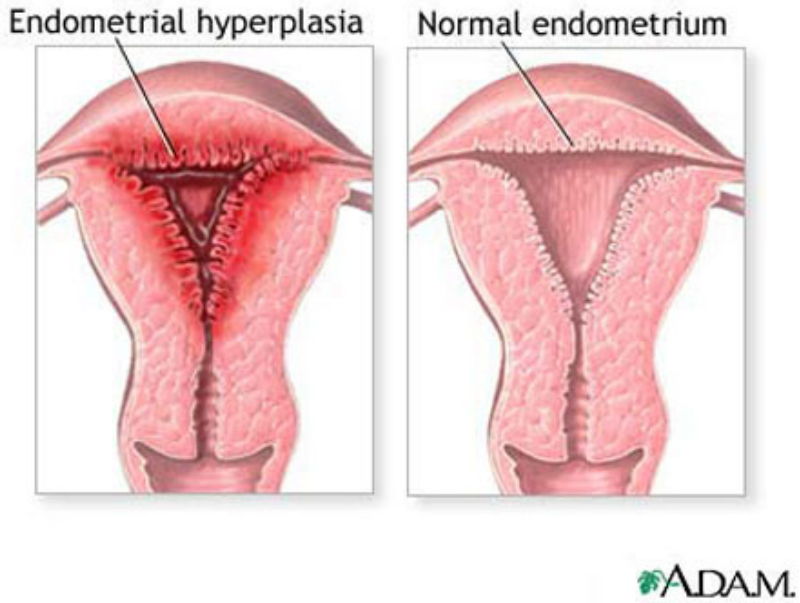
Lesions of myometrium of uterus:

- **Leiomyoma :** understand the pathology and clinical features of uterine leiomyomas and aware that leiomyoma (fibroid) is the commonest neoplasm arising in the female genital tract.
- **Leiomyosarcoma.**

Endometrial Hyperplasia

Endometrial Hyperplasia

- Endometrial hyperplasia is a process in which there is a proliferation of endometrial glands resulting in an **increase in the gland/stroma ratio** of the endometrium when compared to normal.
- The endometrial **hyperplasia may progress to endometrial carcinoma.**
- The risk of developing carcinoma depends on the level and duration of the **estrogen excess**, the severity of the endometrial hyperplasia and associated cellular atypia.



Endometrial Hyperplasia: causes

Causes of Endometrial Hyperplasia: **persistent, prolonged stimulation of the endometrium by high levels of estrogen** (**any condition in which there is high estrogen level can lead to endometrial hyperplasia) e.g.**

a. Anovulatory menstrual cycles (failure of ovulation).
b. Excessive endogenous production of estrogen (by the body) e.g. in
    - polycystic ovary syndrome (Stein-Leventhal syndrome).
    - granulosa cell tumors of the ovary.
    - cortical stromal hyperplasia (excessive ovarian cortical function).
c. Exogenous administration or intake of estrogenic steroids without counter balancing progestin, over a long period of time.

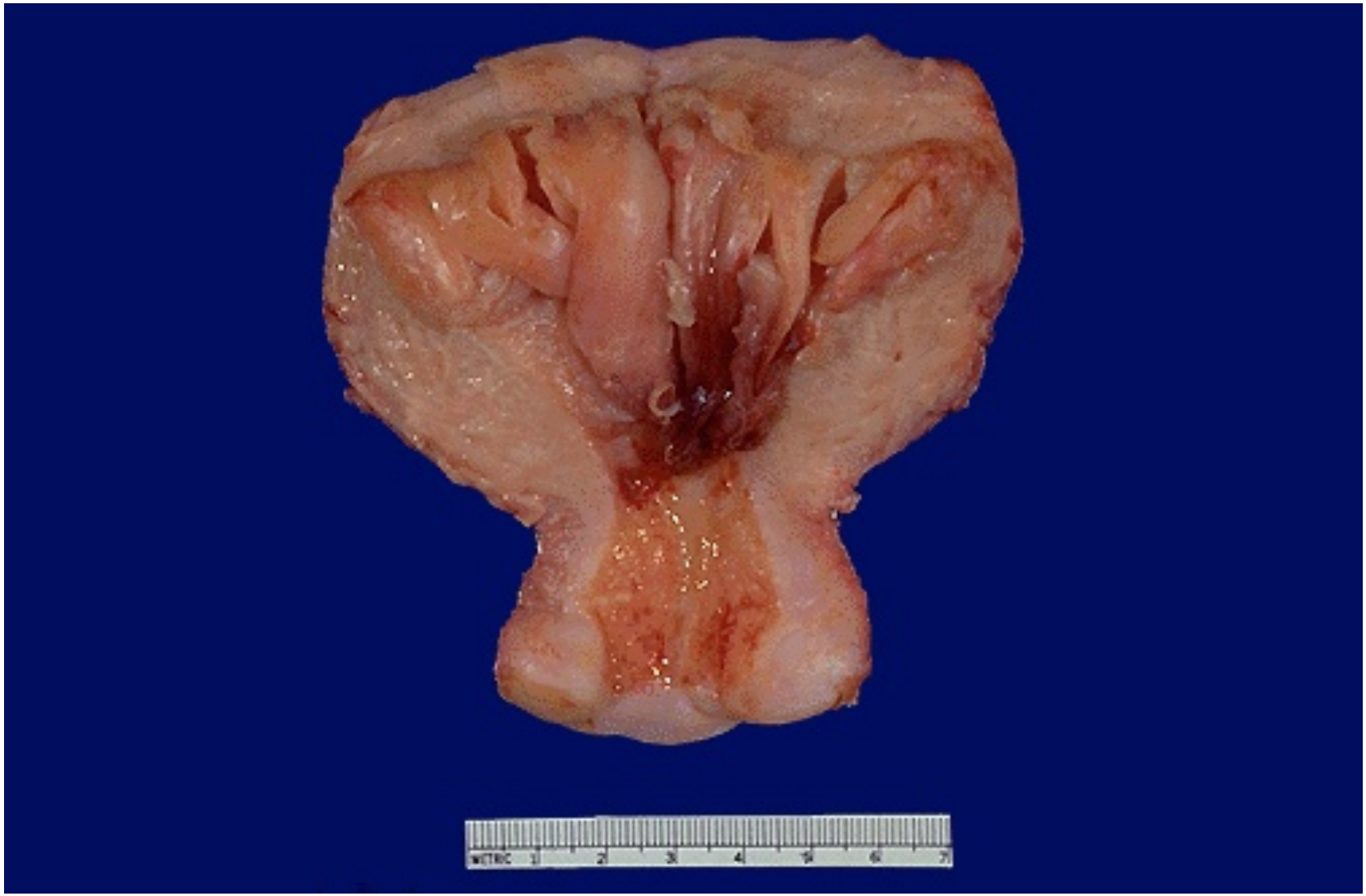
Endometrial Hyperplasia: clinical

- Mild type of hyperplasia tends to occur in younger patients. Most of the mild hyperplasia cases regress, either spontaneously or after treatment.

- The more severe type of hyperplasia occur mainly in perimenopausal or postmenopausal women. This form has a significant **premalignant potential.**

- Patients with endometrial hyperplasia usually present with **abnormal uterine bleeding.**

Endometrial hyperplasia



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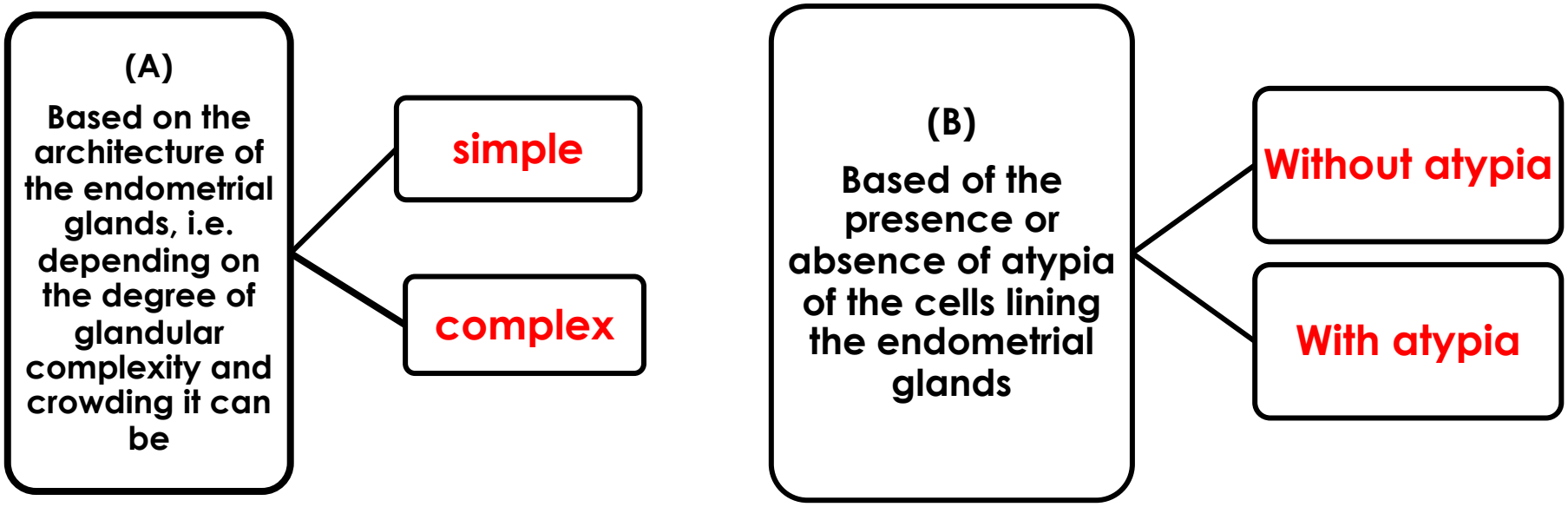
Endometrial Hyperplasia: classification

In endometrial hyperplasia there is proliferation of both glands and stroma but the proliferation of the glands is much more leading to over crowding of glands. Endometrial hyperplasia is classified based on (A) and (B):



CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA:

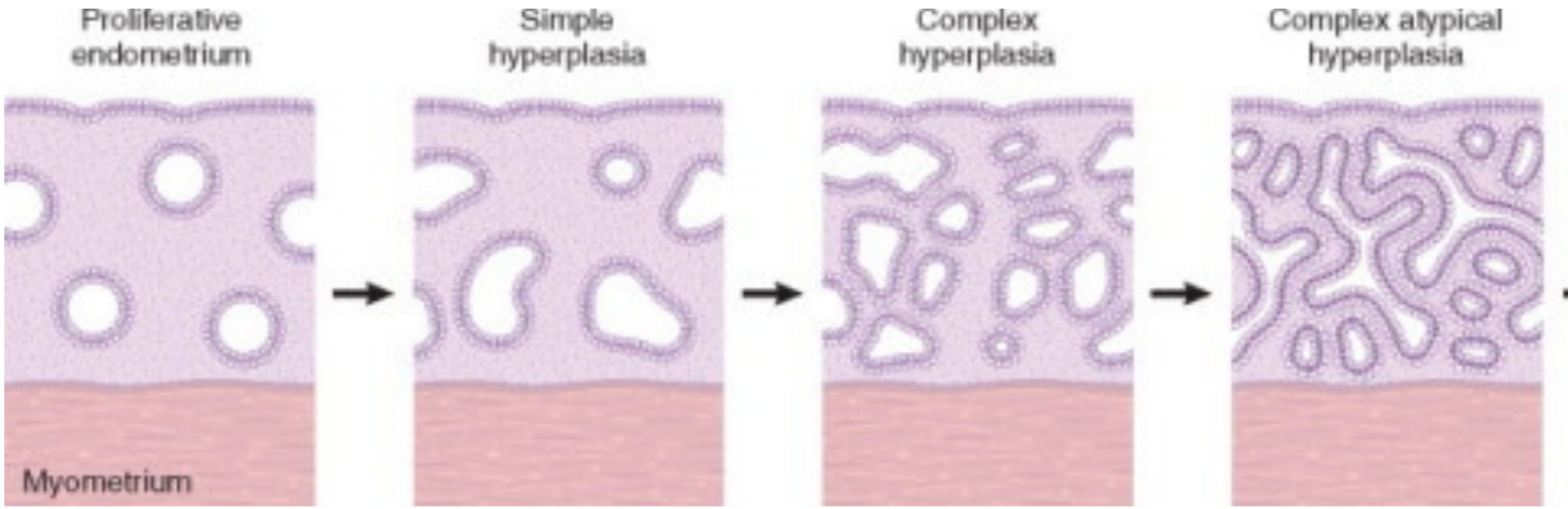
I. Simple hyperplasia

- Without atypia
- With atypia

II. Complex hyperplasia

- Without atypia
- With atypia

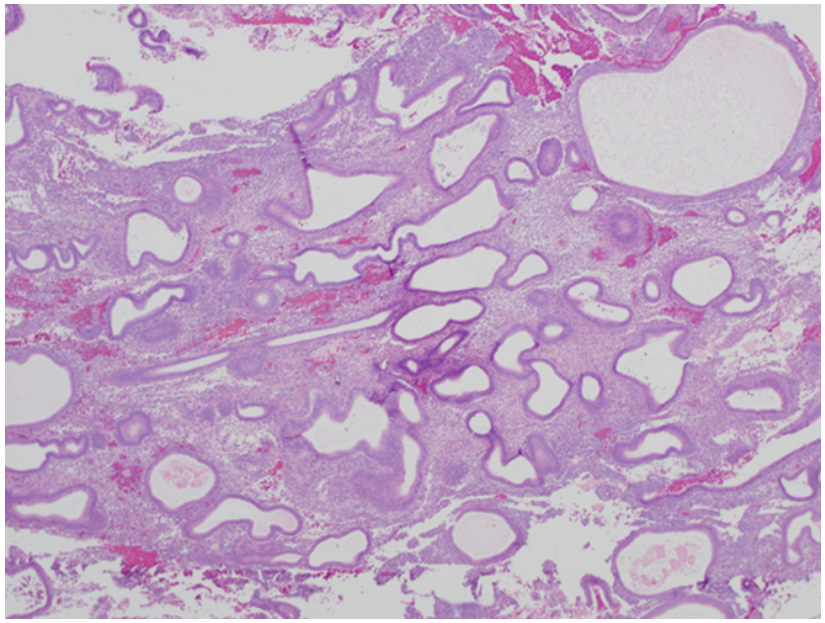
Note: atypia/ pleomorphism = loss of polarity, vesicular nuclei, prominent nucleoli, rounded cells.



http://quizlet.com/22858165/srwk3

Simple hyperplasia without atypia

- Simple hyperplasia (cystic hyperplasia): glands are variably shaped and sized and cystically dilated with abundant cellular stroma and give a "Swiss Cheese" appearance.
- There is a mild increase in the gland-to-stroma ratio.
- These lesions rarely progress to adenocarcinoma.
- Simple hyperplasia may progress to cystic atrophy.



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Gisela Dallenbach-Hellweg
Dietmar Schmidt · Friederike Dallenbach

Atlas of Endometrial Histopathology

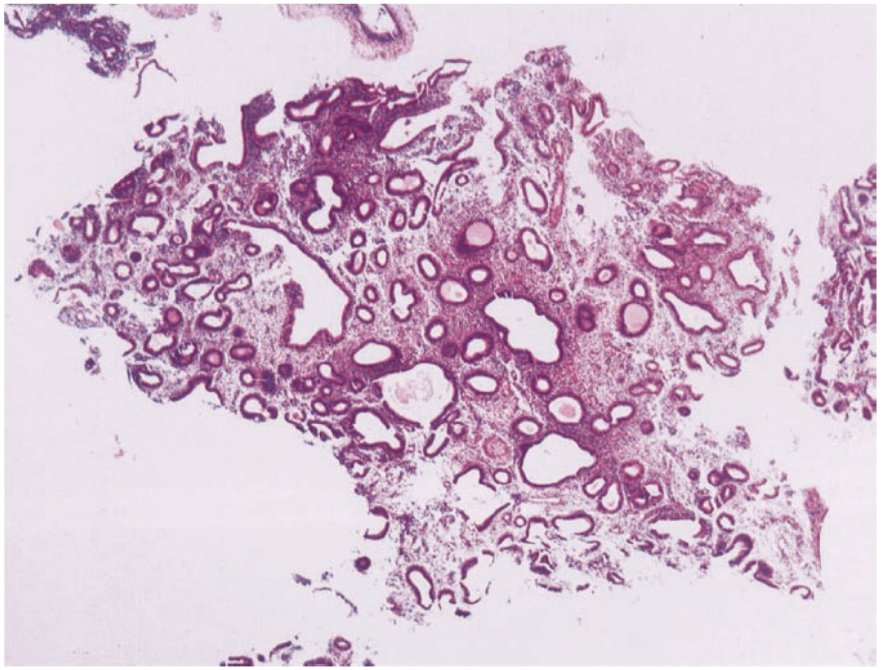


Fig. 6.15 Simple hyperplasia, early stage. H & E, ×25

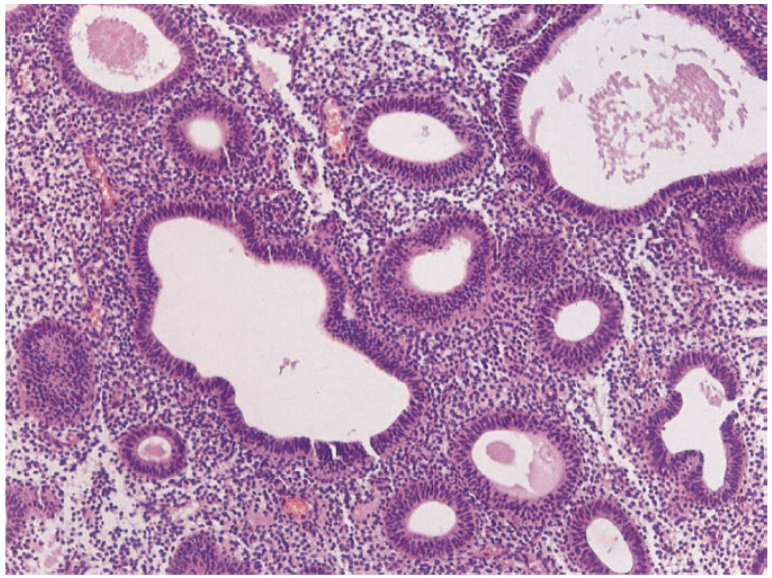
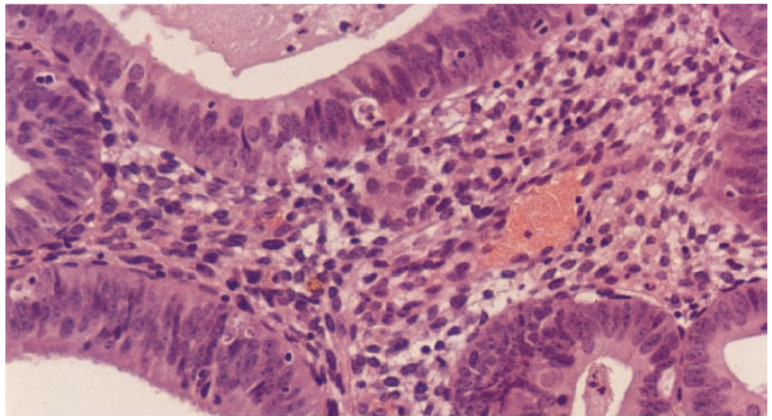


Fig. 6.18 Simple hyperplasia, advanced stage. H & E, ×100

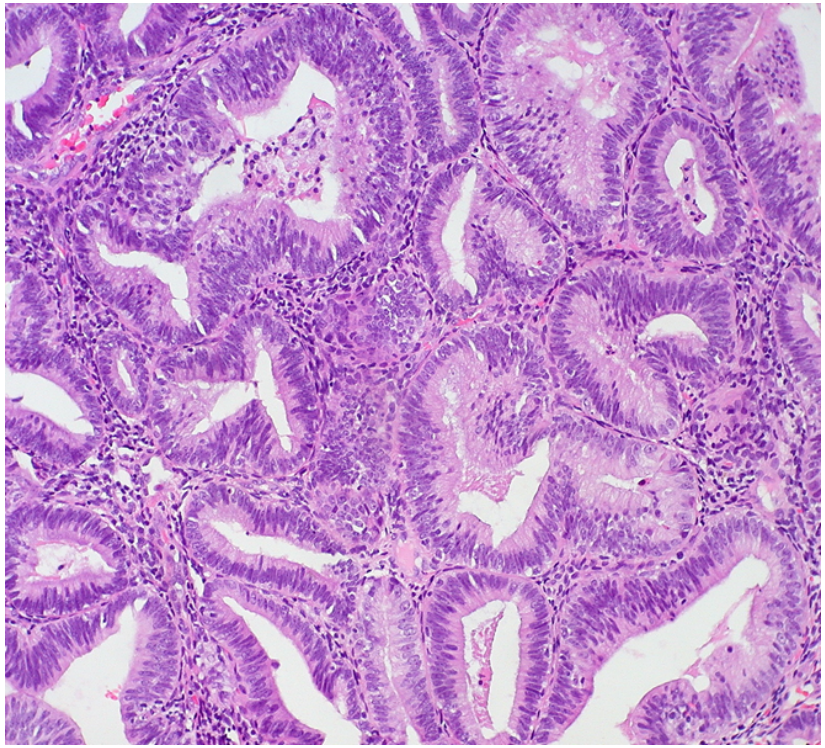


Simple hyperplasia with atypia

- Uncommon.
- It has the Architecture of simple hyperplasia, but there is cytological atypia within the glandular epithelial cells.
- 10% of such lesions progress to carcinoma.

Complex hyperplasia without atypia

- Proliferation of endometrial glands resulting in complex crowded glands with papillary infoldings and irregular shapes. The crowded glands are back-to-back with very little intervening stroma.
- The epithelial cells remain cytologically normal.
- 3% progress to carcinoma.



http://upload.wikimedia.org/wikipedia/commons/a/a2/Complex_Hyperplasia_of_the_Endometrium_%28no_atypia%29_%284746311706%29.jpg

Michael T. Mazur
Robert J. Kurman

Diagnosis of Endometrial Biopsies and Curettings

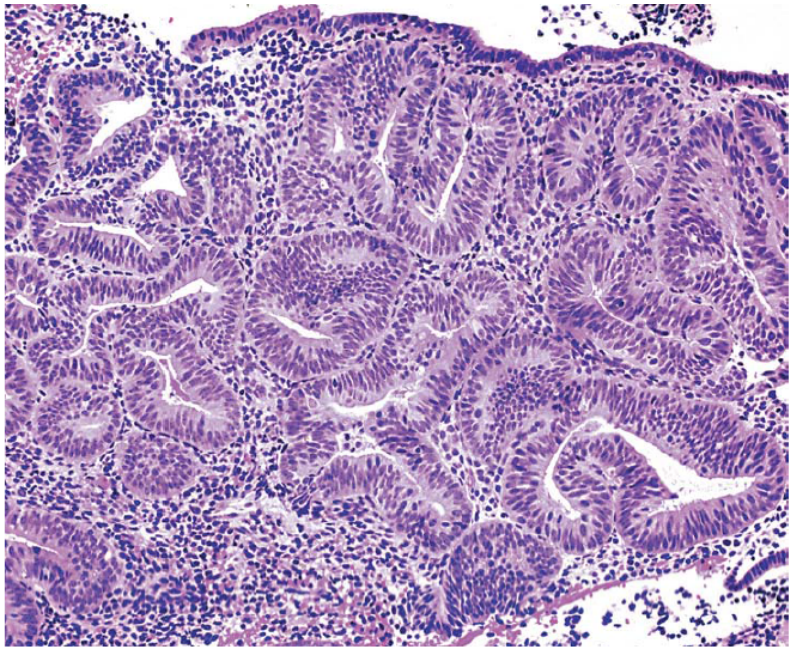


FIGURE 9.3. Complex hyperplasia. The glands are closely packed, lacking the abundant stroma seen in a simple hyperplasia. There is no atypia.

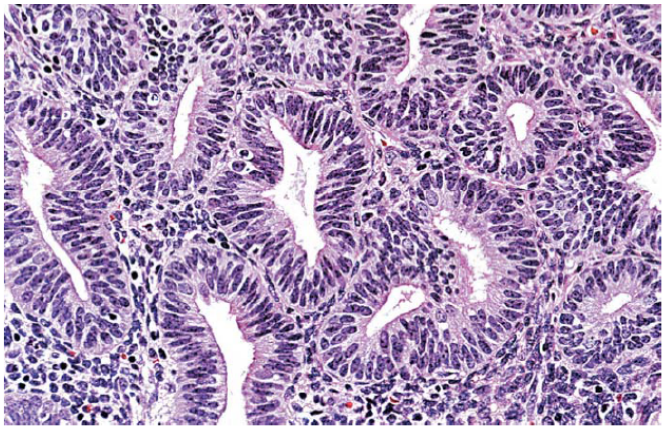
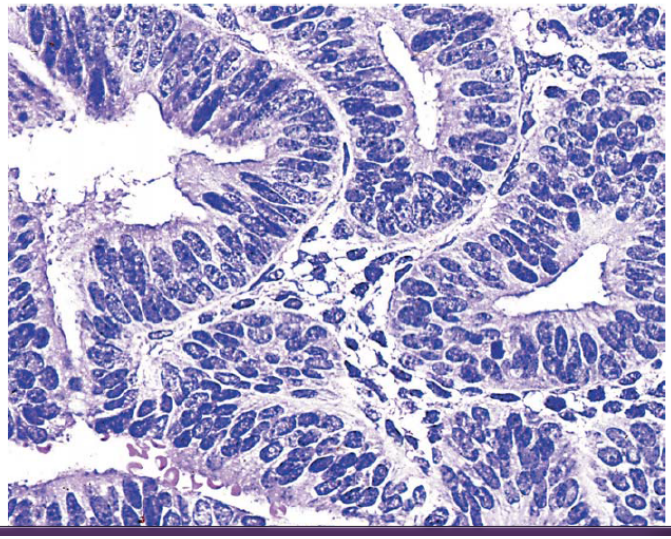
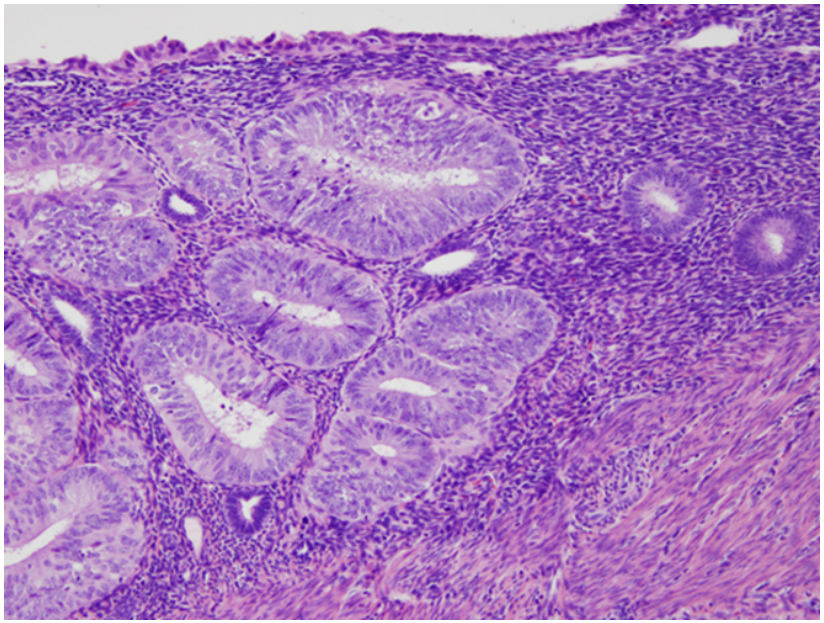


FIGURE 9.4. Complex hyperplasia without atypia. The glands vary in size and are separated by only a small amount of stroma. Nuclei are oval and pseudostratified. There is no atypia.



Complex hyperplasia with atypia

- Complex proliferation of endometrial glands (back-to-back irregular glands) with atypia.
- **The nuclei show loss of polarity and are enlarged and rounded and may have irregular nuclear membranes.**
- Commonly about 30% of women with this diagnosis have carcinoma somewhere in the uterus when a hysterectomy is performed.
- About 30% progress to carcinoma.



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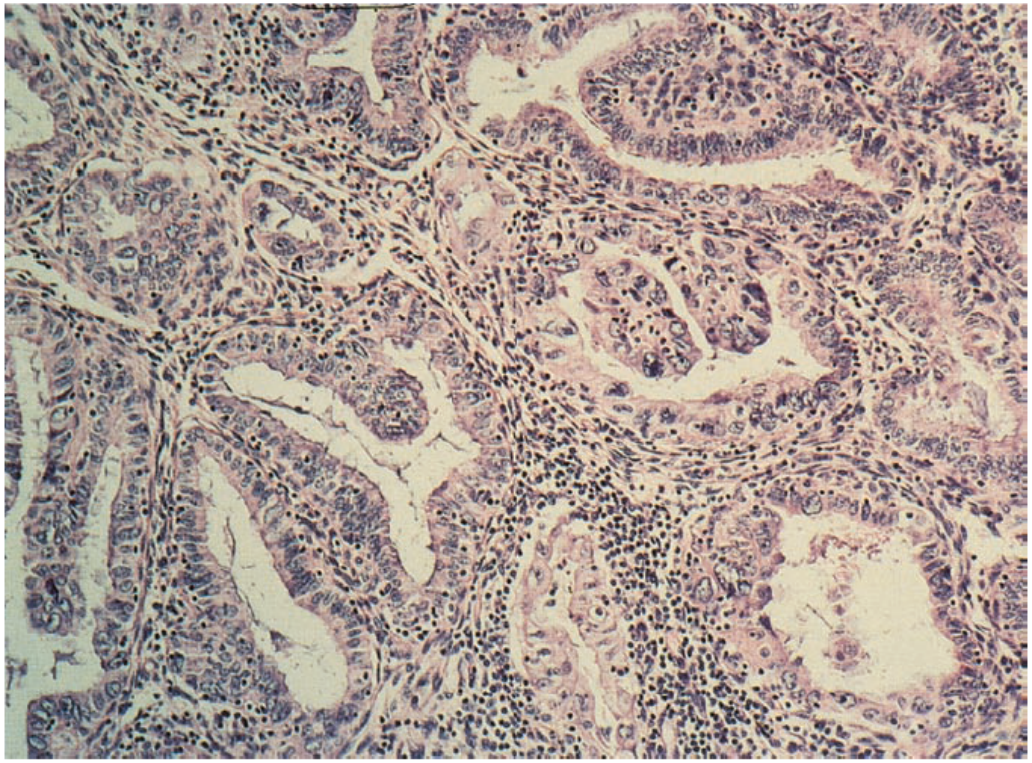


Fig. 6.31 Atypical hyperplasia with cytologic atypia. H & E, ×100

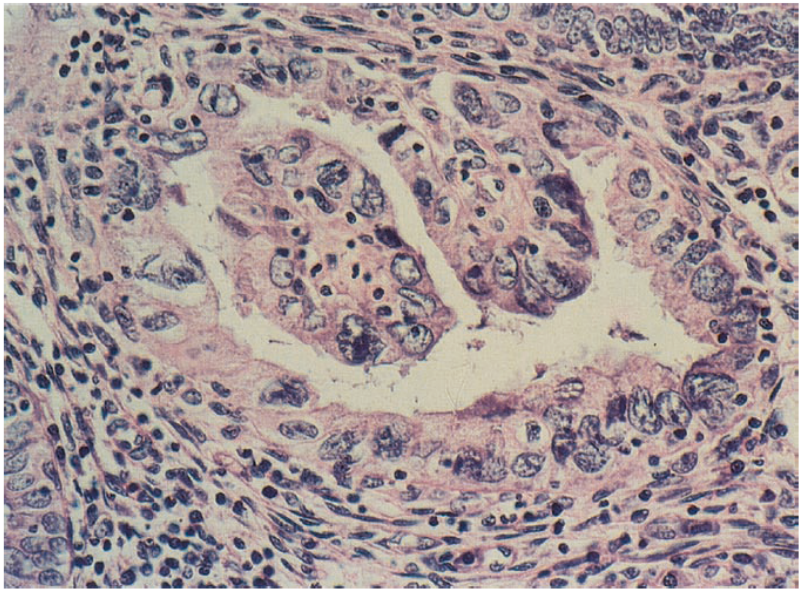
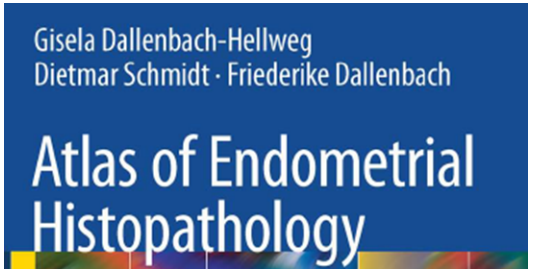


Fig. 6.32 Higher magnification of Fig. 6.31. H & E, ×350



Endometrial Hyperplasia: Clinical behavior and premalignant potential

- Some endometrial hyperplasia revert to normal spontaneously or with medical treatment, others persist as hyperplasia, and a few progresses to endometrial adenocarcinoma.

- The risks for developing adenocarcinoma in each are as follows:
  - Simple hyperplasia without atypia — 1%
  - Complex hyperplasia without atypia — 3%
  - Simple hyperplasia with atypia (simple atypical hyperplasia) — 10%
  - Complex hyperplasia with atypia (complex atypical hyperplasia) — 30%

- Atypical hyperplasia in postmenopausal women appears to have a higher rate of progression to adenocarcinoma.

- **Non atypical endometrial hyperplasia.**

- **Atypical endometrial hyperplasia /Endometroid intraepithelial neoplasia (EIN).**

  - Higher risk of progression to endometrial carcinoma than non atypical endometrial hyperplasia.

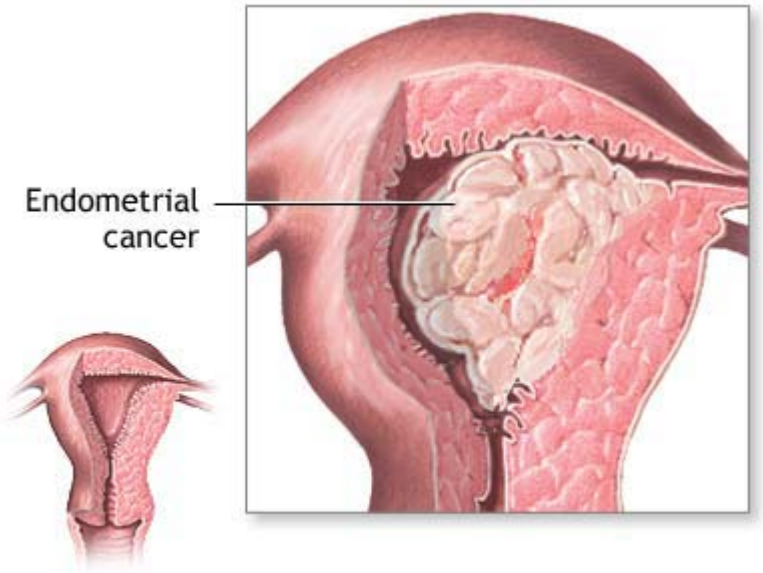
Endometrial Hyperplasia, Risk Factors

- Obesity.
- Western diet.
- Nulliparity.
- Diabetes Mellitus.
- Hypertension.
- Hyperestrinism.

Endometrial adenocarcinoma

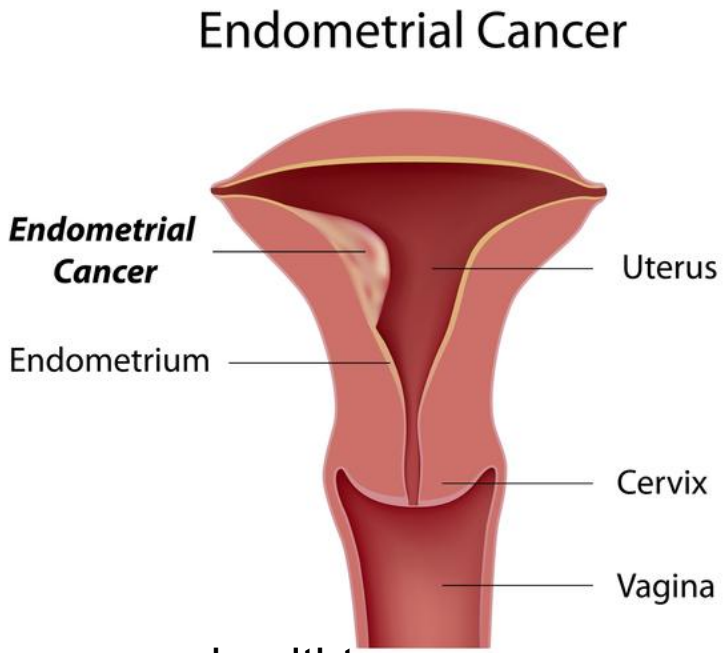
Endometrial adenocarcinoma

This is a common neoplasm in women. Overall it is the fifth commonest cancer in women.



- Endometrial cancers arise mainly in **postmenopausal** women.
- They cause **postmenopausal bleeding.**
- Early detection and cures are possible.

- These tumors are classified into two broad categories:
  - **Type I carcinomas (also known as endometrioid carcinoma):** accounts for 80% of endometrial cancers. It is the most common type. e.g.→ endometrioid adenocarcinoma and its variants.
  - **Type II carcinomas:** they are papillary **serous** carcinoma and clear cell carcinoma. Papillary serous is the more common form of type II carcinoma.

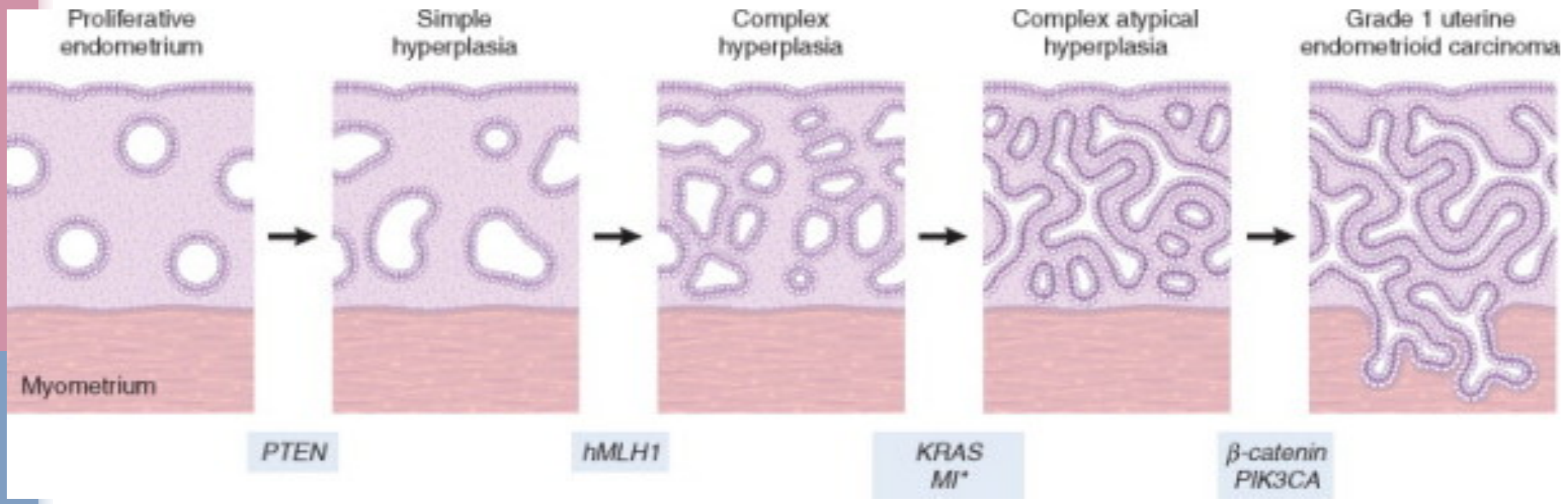


Type I endometrial carcinoma, endometrioid carcinoma

- Endometrioid carcinoma is associated with **estrogen excess** and **endometrial hyperplasia**. The majority of the carcinomas are well differentiated.
- Endometrial hyperplasia is a precursor to endometrioid carcinoma
- Risk factors for type I are they same as that of endometrial hyperplasia and include:
  - Obesity.
  - Western diet.
  - Nulliparity.
  - Diabetes Mellitus.
  - Hypertension.
  - Hyperestrinism.
  - Estrogen therapy.
  - chronic anovulation.
  - Late menopause.
  - Tamoxifen therapy.
  - High socioeconomic status.

The disease may follow atypical hyperplasia but may occur independently of it especially in older patients.

Usual sequence of events in Type I endometrioid carcinoma



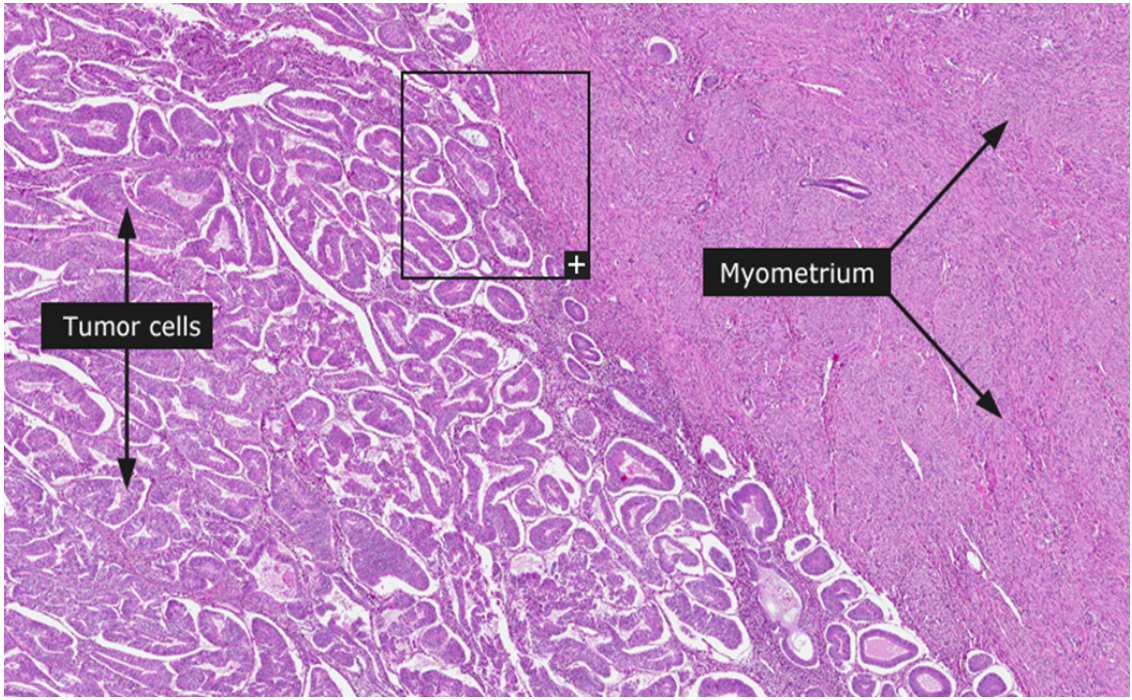
http://quizlet.com/22858165/srwk3

Type I endometrioid carcinoma: genetics

1. Majority of endometrioid carcinomas have PTEN gene mutations.

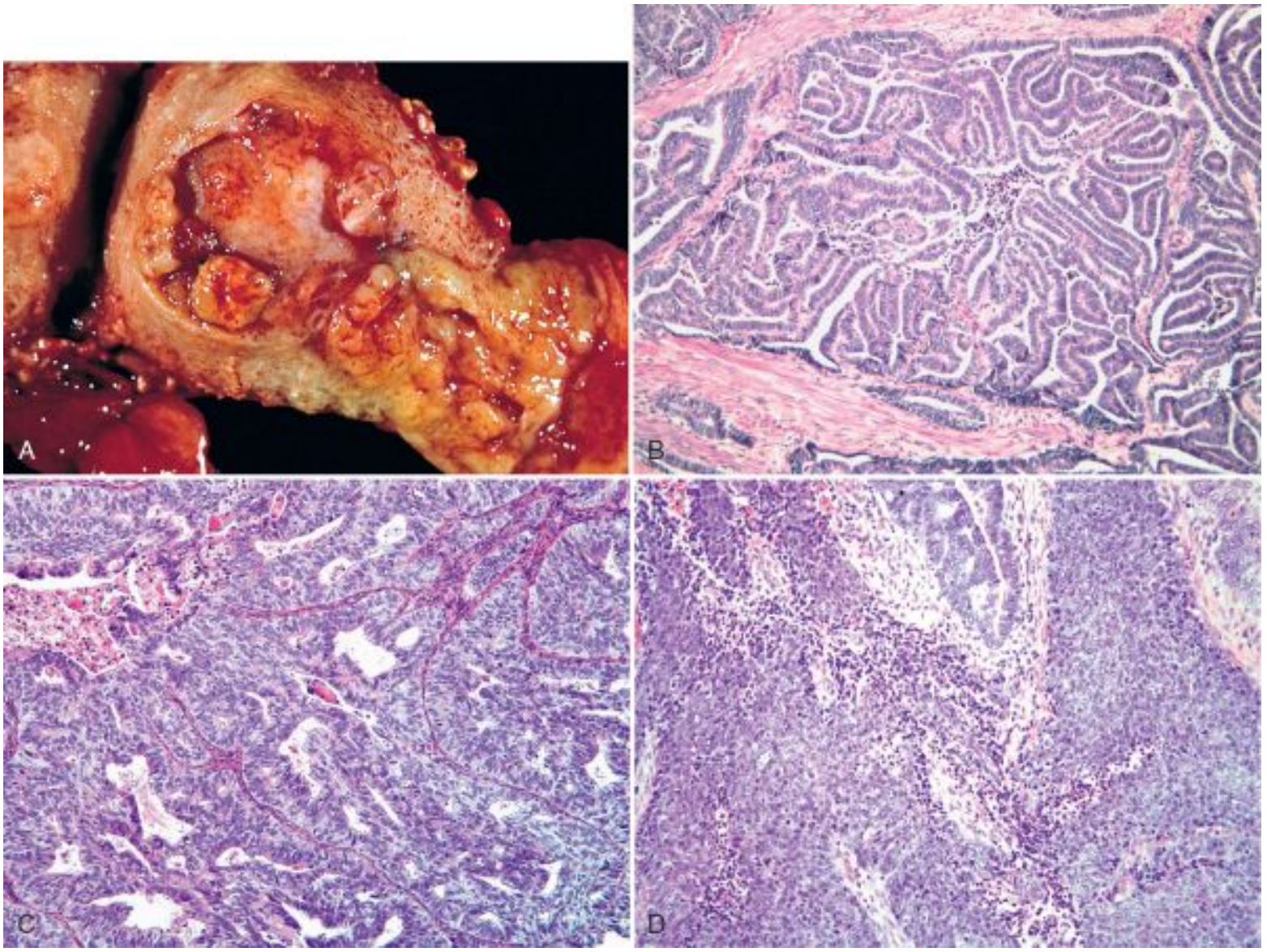
2. Also there may be inactivation of DNA mismatch repair genes.

3. *P53 mutations* is seen in half of the poorly differentiated endometrioid carcinomas.



http://www.proteinatlas.org/images_dictionary/endometrial_cancer__1__figo_1__overview.jpg

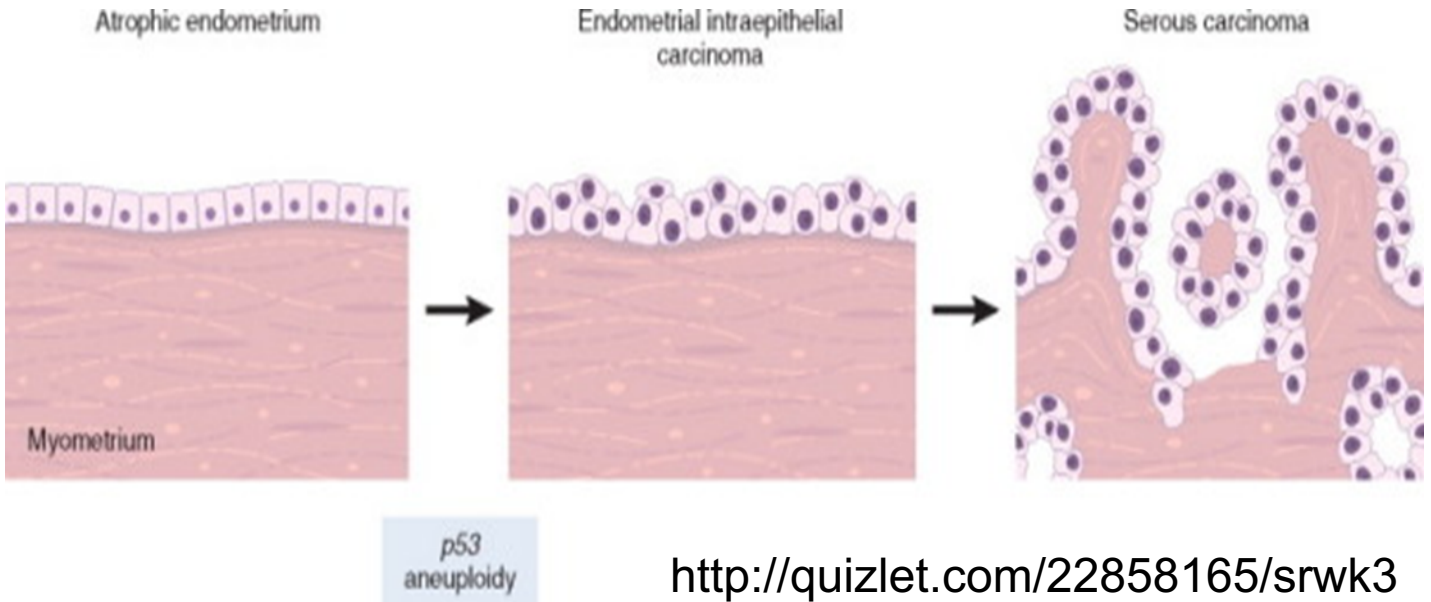
Endometrial carcinoma



Picture Taken from Robbins and Cotran Pathologic basis of disease. 8th edition, Chapter 21, 2010 Sanders

Type II endometrial carcinomas: Serous carcinoma

- *Serous carcinoma* arises in older women, with endometrial atrophy (small atrophic uterus).
- They occur in late in life, about one decade later than type I carcinoma.
- There is no association with hyperestrinism or preexisting hyperplasia.
- They represent 15% of cases of all endometrial carcinoma.
- Mutations in *P53* are present in at least 90% of serous endometrial carcinoma
- The precursor of serous carcinoma is endometrial intraepithelial carcinoma (its like carcinoma in situ)
- These tumors are large bulky poorly differentiated tumors which invade early into the myometrium and have a poor prognosis. Extrauterine extension is common.



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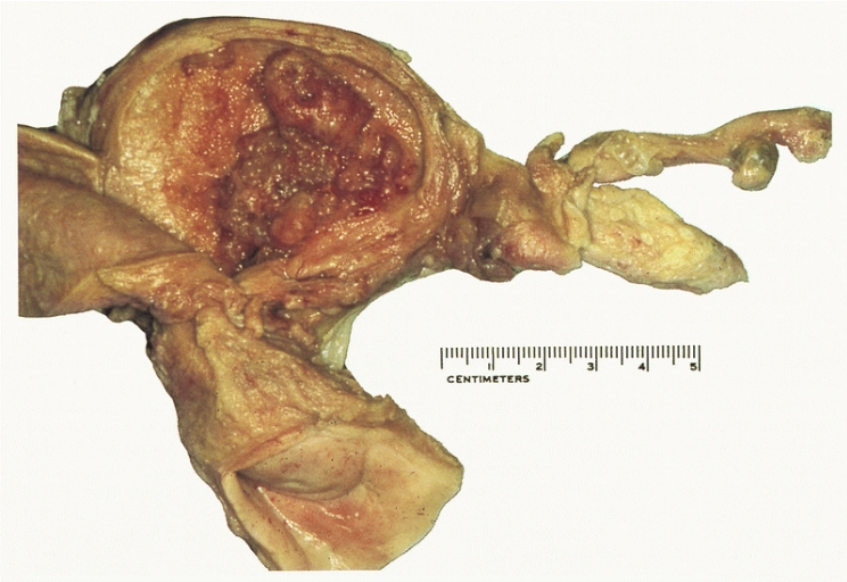
CHARACTERISTICS OF TYPE I AND TYPE II ENDOMETRIAL CARCINOMAS

FEATURES	TYPE I	TYPE II
HISTOLOGIC TYPE	Endometriod adenocarcinoma	Serous or clear cell carcinoma
AGE	Premenopausal and perimenopausal (50-60 yrs)	Post menopausal (~ 70 yrs)
UNOPPOSED ESTROGEN	Present	Absent
PRECURSOR LESION	Hyperplasia with atypia	Endometrial intraepithelial carcinoma
GROWTH	Slow growing	Rapidly progressing
GRADE	Low	High
MYOMETRIAL INVASION	Usually superficial	Usually deep
PROGNOSIS	Favorable	Poor
GENETIC ALTERATIONS NOTED	PTEN, microsatellite instability	P53 mutations

Endometrial adenocarcinoma: clinical features

- Most patients are between 50 and 60 years.
- Many of the patients tend to be nulliparous and obese.
- Patients have **abnormal vaginal bleeding** and excessive leucorrhea.
- Elderly women present with **postmenopausal bleeding**.
- The diagnosis of endometrial cancer must be confirmed by biopsy or curettage and histologic examination of the tissue.



http://upload.wikimedia.org/wikipedia/commons/0/00/Endometrial_hyperplasia.jpg

Endometrial carcinoma: basic morphology

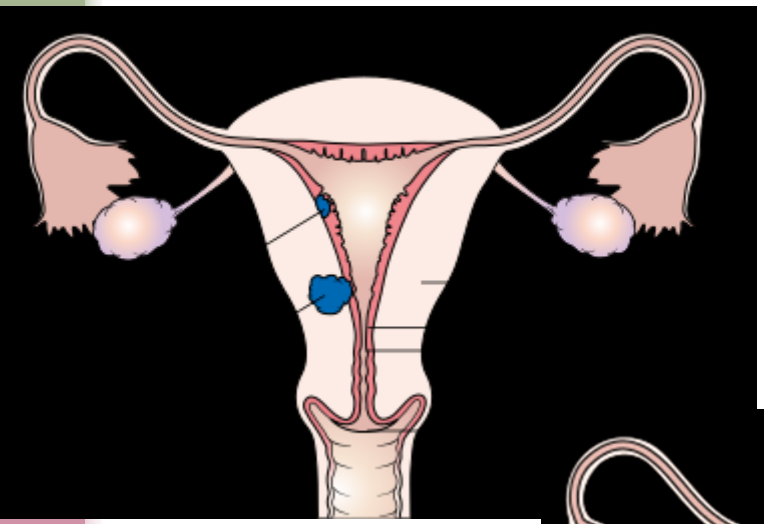
- **Grossly:**
  - May look close to normal or exophytic or infiltrative.
- **Microscopy:**
  - Both type I and II are adenocarcinomas.
  - In both cases tumors originate in the endometrium and can eventually infiltrate the underlying myometrium, enter vascular spaces and metastasize to lymph nodes.
  - Serous carcinoma has much greater cytological atypia and are more poorly differentiated and is therefore more aggressive.
- **Tumor spreads by:**
  - Direct myometrial invasion with extension to the periuterine structures.
  - Through lymphatics to lymph nodes.
  - In the late stages, metastasize to the lungs, liver, bones, others.

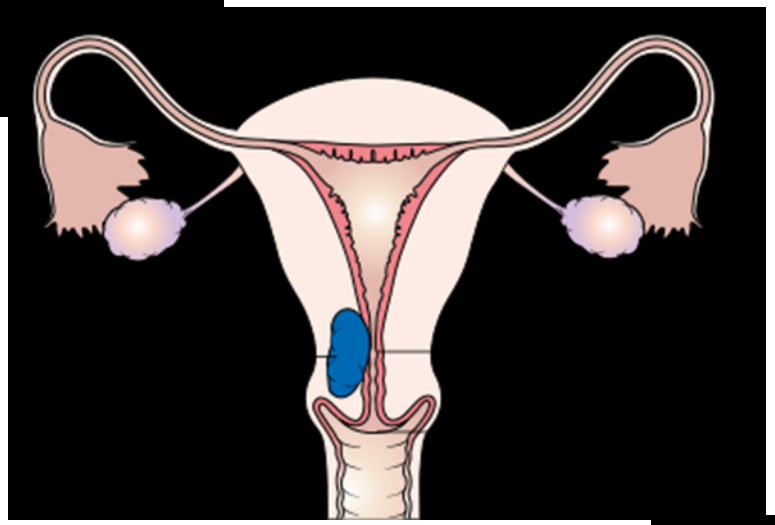
Endometrial adenocarcinoma: prognosis

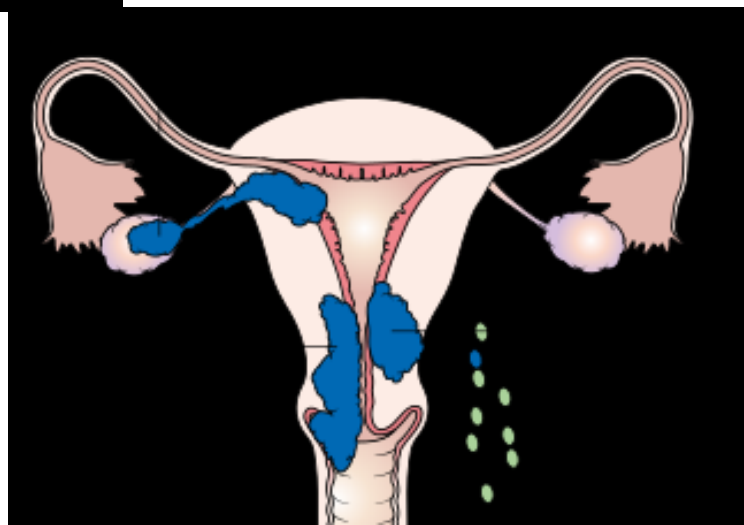
- Clinical behavior of endometrial adenocarcinoma depends on the histologic type, the grade (degree of differentiation) and the stage (extent of spread).
- Endometrioid carcinoma (type I) has a better prognosis than the other histologic types.
- Serous carcinoma (type II) has poorer prognosis.
- Stage is the major determinant of survival.

How endometrial carcinoma can spread

(stages 1, 2 and 3 of endometrial carcinoma)







Leiomyoma

Leiomyosarcoma

Leiomyoma (fibroid) of uterus

- Leiomyoma is a benign tumor of smooth muscle origin.
- It is the most common neoplasm of the female genital tract and probably the most common neoplasm in women.
- The tumor is estrogen responsive. Estrogen stimulates their growth. Leiomyomas often increases in size during pregnancy and decrease in size after menopause.
- About 40% of leiomyomas have an associated chromosomal abnormality.
- They are benign tumors with no appreciable malignant potential (incidence of malignant transformation to sarcoma is 0.1-0.5%).

Leiomyoma (fibroid) of uterus

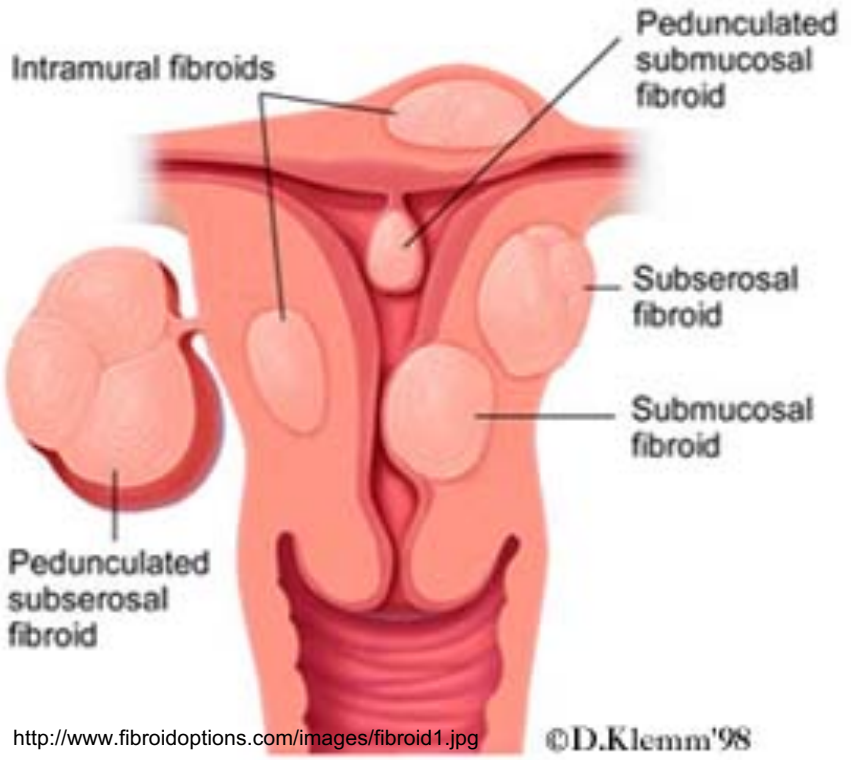
Clinical features

- It can be single or multiple (mostly multiple).
- Irregular abnormal bleeding and sometimes pelvic pain.
- It may cause anemia from heavy bleeding.
- Can have urinary frequency if the fibroid is compressing the urinary bladder.
- It may interfere with implantation and therefore cause infertility.
- In pregnant women it may cause abortion, obstructed labor, post partum hemorrhage etc.
- *Alternatively it maybe* entirely asymptomatic.

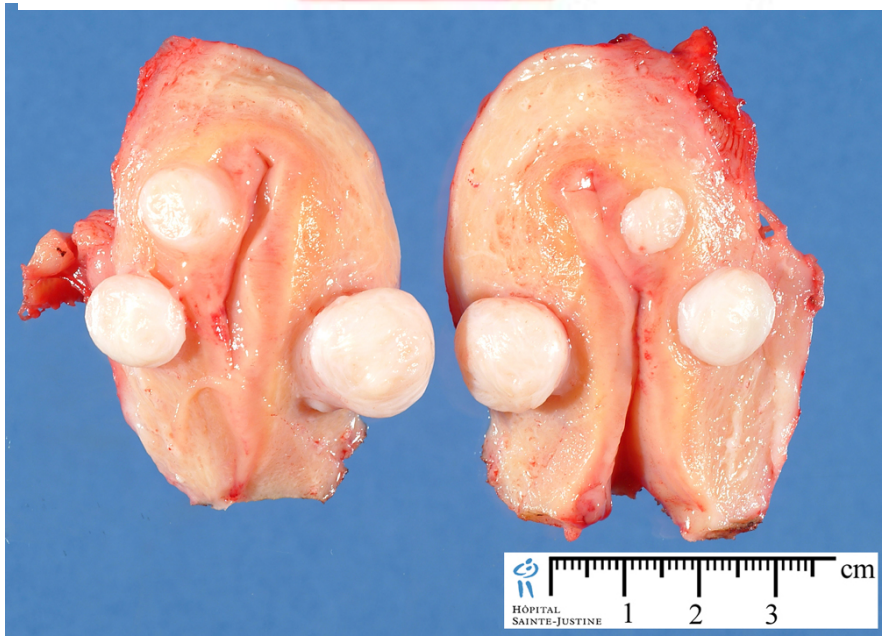
Uterine Leiomyoma

Leiomyoma may be located anywhere in the myometrium:

- **Submucosal** tumors are present immediately below the endometrium.
- **Intramural** tumors, the most common, lie within the myometrium.
- **Subserosal** fibroids lie beneath the serosal surface of the uterus or are pedunculated and attached to the serosa.
- **Pedunculated** ones may loose their connection to the uterus forming a "parasitic leiomyoma".



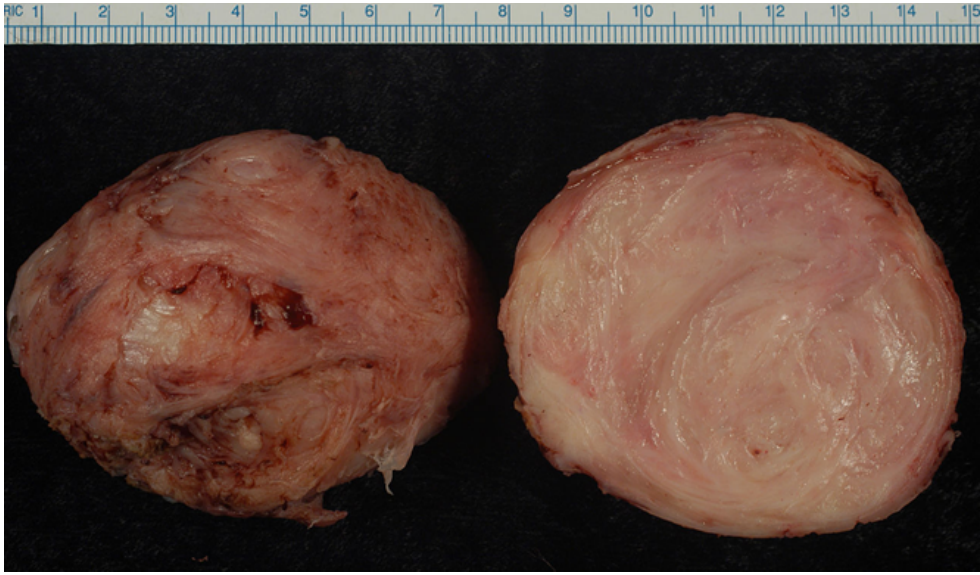
http://www.fibroidoptions.com/images/fibroid1.jpg



http://www.humpath.com/IMG/jpg/uterine_leiomyoma_0412_3.jpg

Leiomyoma gross:

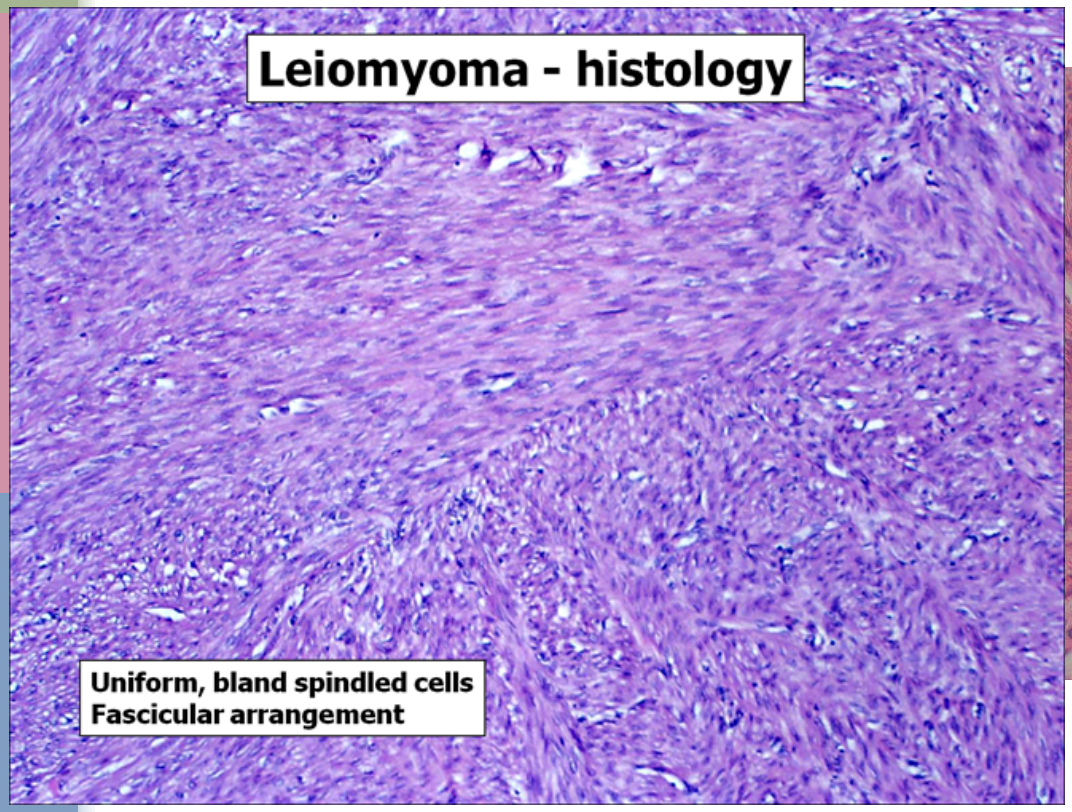
- Well circumscribed, spherical, dense and firm-to-hard masses.
- Cut section shows whorled, tan-white cut surfaces.



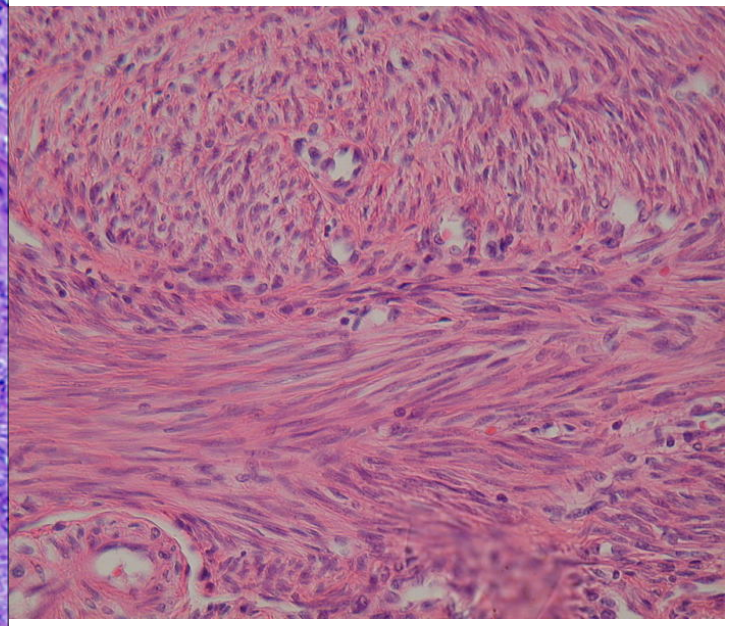
"Leiomyoma" by Ed Uthman from Houston, TX, USA - Leiomyoma. Licensed under CC BY 2.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Leiomyoma.jpg#/media/File:Leiomyoma.jpg

Leiomyoma, Microscopically:

there are interlacing bundles of smooth muscle cells with collagenous stroma between bundles. The individual muscle cells are uniform in size and shape. They have the characteristic oval to elongated nucleus. Mitotic figures are few.



http://pixgood.com/leiomyoma-histology.html



http://pixgood.com/myometrium.html

Leiomyosarcoma

- It is the malignant tumor of the smooth muscle with increased mitosis and necrosis.
- It is rare.
- Sites include the uterus and soft tissue
- Poor prognosis.