Female Genital System

Part 2: Uterine Corpus

These photos are from the Galapagos Islands

APPROVED

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Goals for Today

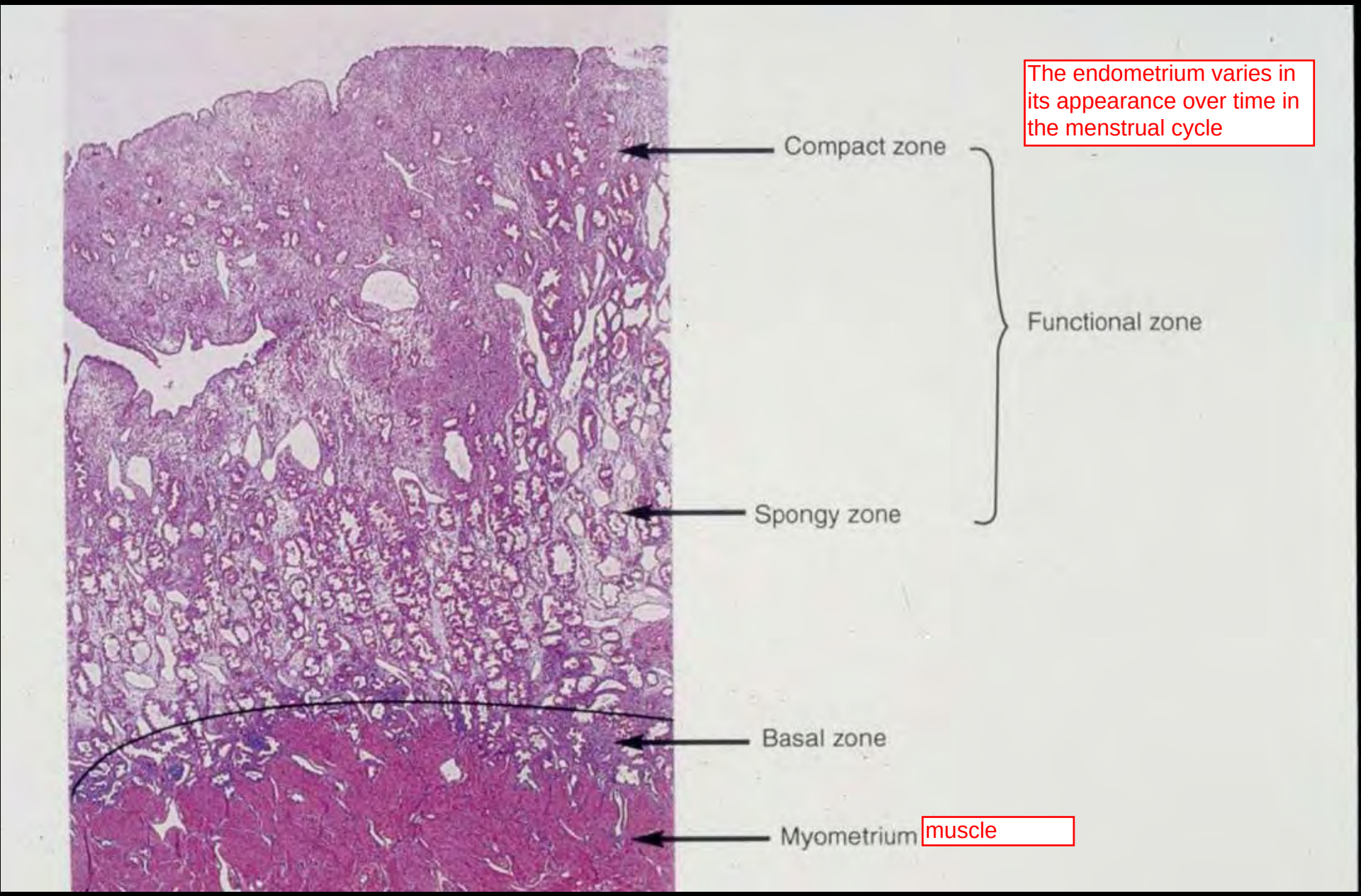
Read

At the end of today's lecture you will be able to:

- List the common pathologic causes of abnormal endometrial bleeding
- Explain the relationship of endometrial hyperplasia to endometrial cancer
- Explain the role of estrogens in the development of endometrial hyperplasia and cancer
- Recognize the typical appearance of a leiomyoma
- Recognize and describe the pathology of endometrial disorders

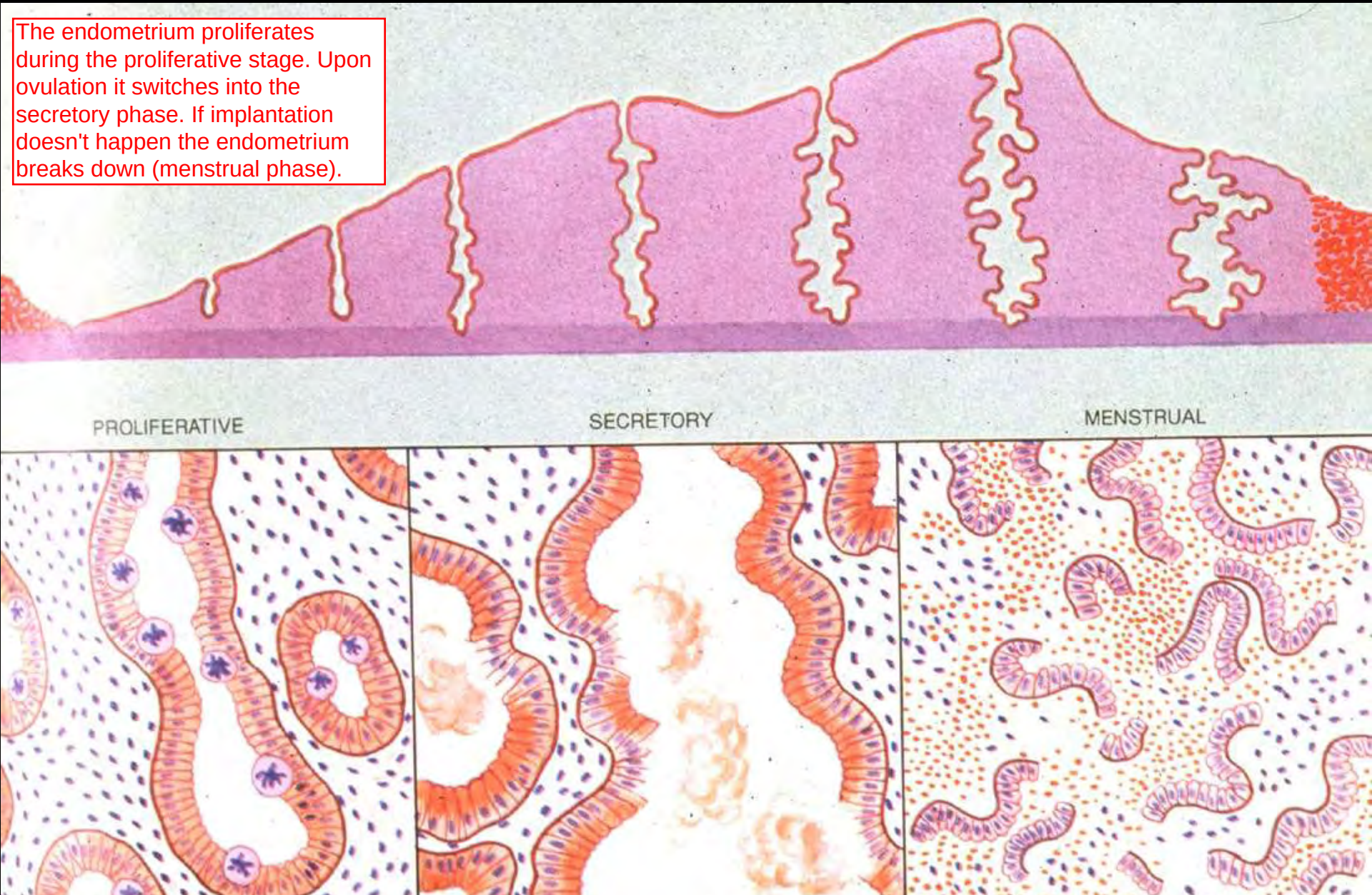
common issue

Normal Endometrium



Endometrium-Menstrual Cycle

The endometrium proliferates during the proliferative stage. Upon ovulation it switches into the secretory phase. If implantation doesn't happen the endometrium breaks down (menstrual phase).



Uterine Fundus: The Main Players

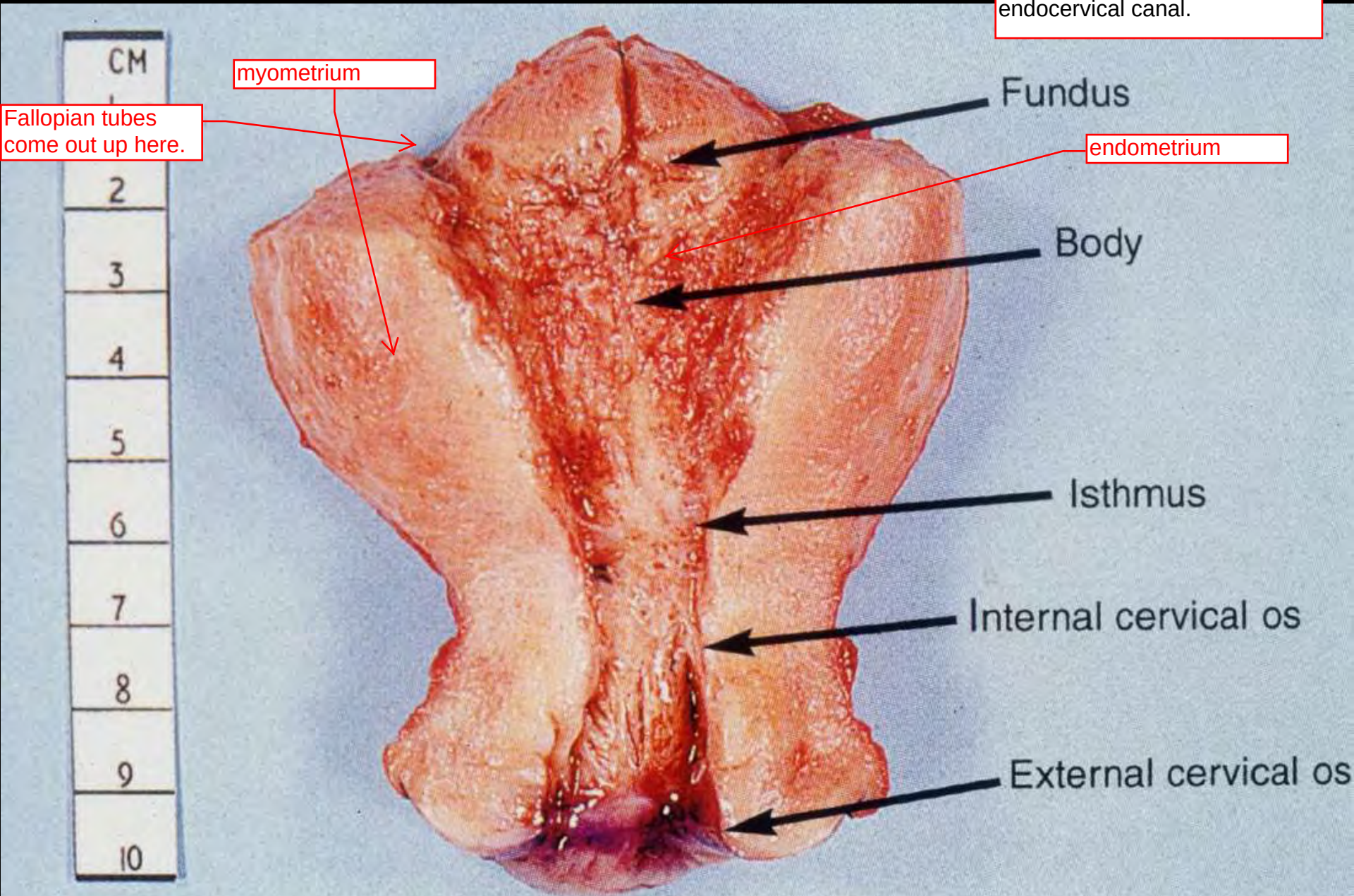
Summary of what we will cover

- Endometrium
  - Developmental
  - Endometritis
  - Endometriosis
  - Polyps
  - Dysfunctional Uterine Bleeding (DUB)
  - Hyperplasia
  - Carcinoma
- Myometrium
  - Adenomyosis
  - Leiomyoma (fibroids)
  - Leiomyosarcoma

rare

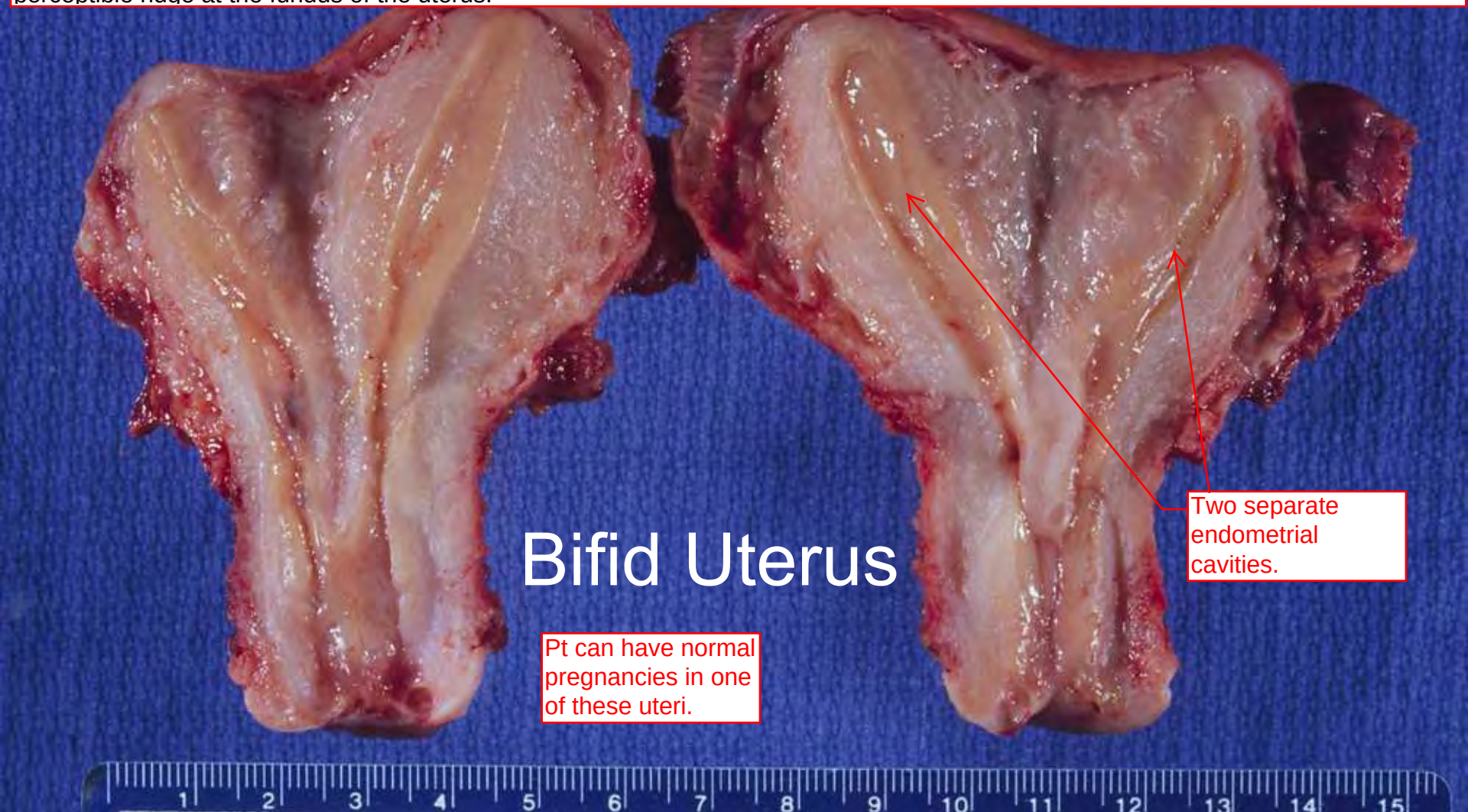
Normal uterus

This uterus has been cut in half coronally to reveal the endometrial cavity and endocervical canal.



Developmental Abnormalities

Many variations of fusion defects can be seen. Complete failure of the Mullerian ducts to fuse gives rise to two separate uteri ("uterus didelphys"), each with a cervix and single fallopian tube, and sometimes connecting to two separate vaginas. Partial fusion gives rise to bifid (also known as bicornuate) uterus, as seen above, and in the most minimal forms of fusion defect to a barely perceptible ridge at the fundus of the uterus.



Endometritis

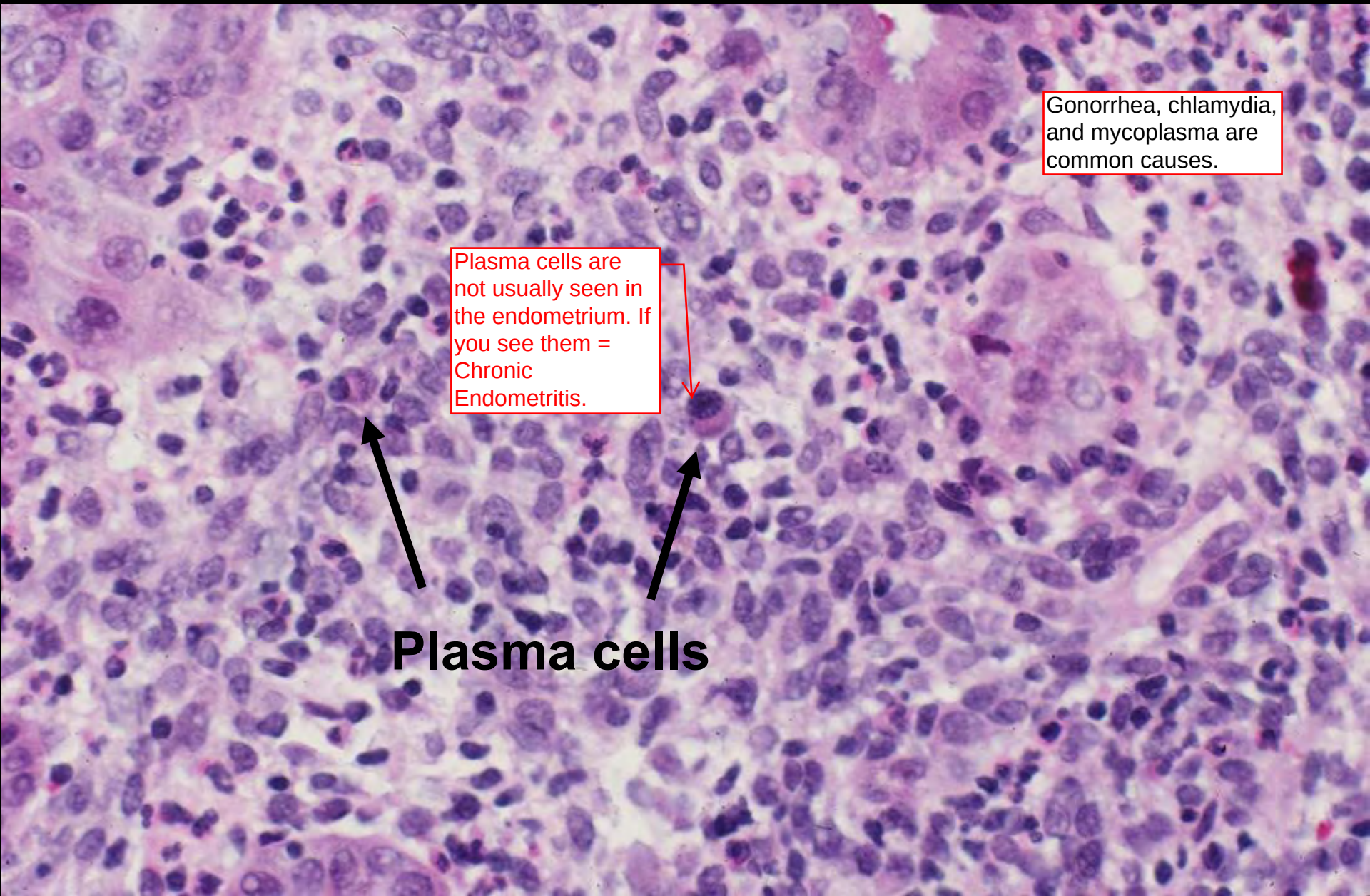
Infections, relatively infrequent.

- Acute
  - Unusual, usually retained products of conception
  - Typically cured by removal of dead tissue.
- Chronic endometritis
  - STD's
    - Often associated with pelvic inflammatory disease
  - IUD's
    - Actinomyces
  - Treat infection and/or remove IUD

Seen in Pt w STD's. If the STD continues out into the pelvic cavity Pt can get Pelvis inflammatory disease.

Intrauterine devices. Actinomyces is a common infection in Pt with IUD's.

Chronic Endometritis



Very Common

Endometriosis

- Ectopic endometrium outside the uterus
- Major cause of pelvic pain, dysmenorrhea, and infertility
  - 5.5 million women in U.S. affected
  - Half of infertility patients
- Common sites
  - Ovaries
  - Fallopian tubes
  - Pelvic peritoneum
- Less common sites: lung, lymph nodes, bowel, etc

+ many more undiagnosed

Also seen in the Lung, lymph nodes, bowel, skin -> it is very diverse, it can be almost anywhere. Unlike cancer it stops growing eventually.

This means you menstruate out of your mouth?

Endometriosis

- **Etiology**
  - **?Regurgitation**
  - **?Metaplasia**
  - **?Vascular dissemination**
- **Mechanism of injury**
  - **Repeated bleeding with menstrual cycle**
    - **Inflammation**
    - **Fibrosis, adhesions, and scarring**
    - **Formation of large "chocolate" cysts (esp. in ovary)**
      - **May require surgical management**

Theories on how it occurs. Endometrium is broken down monthly, some of it gets into the pelvic cavity.

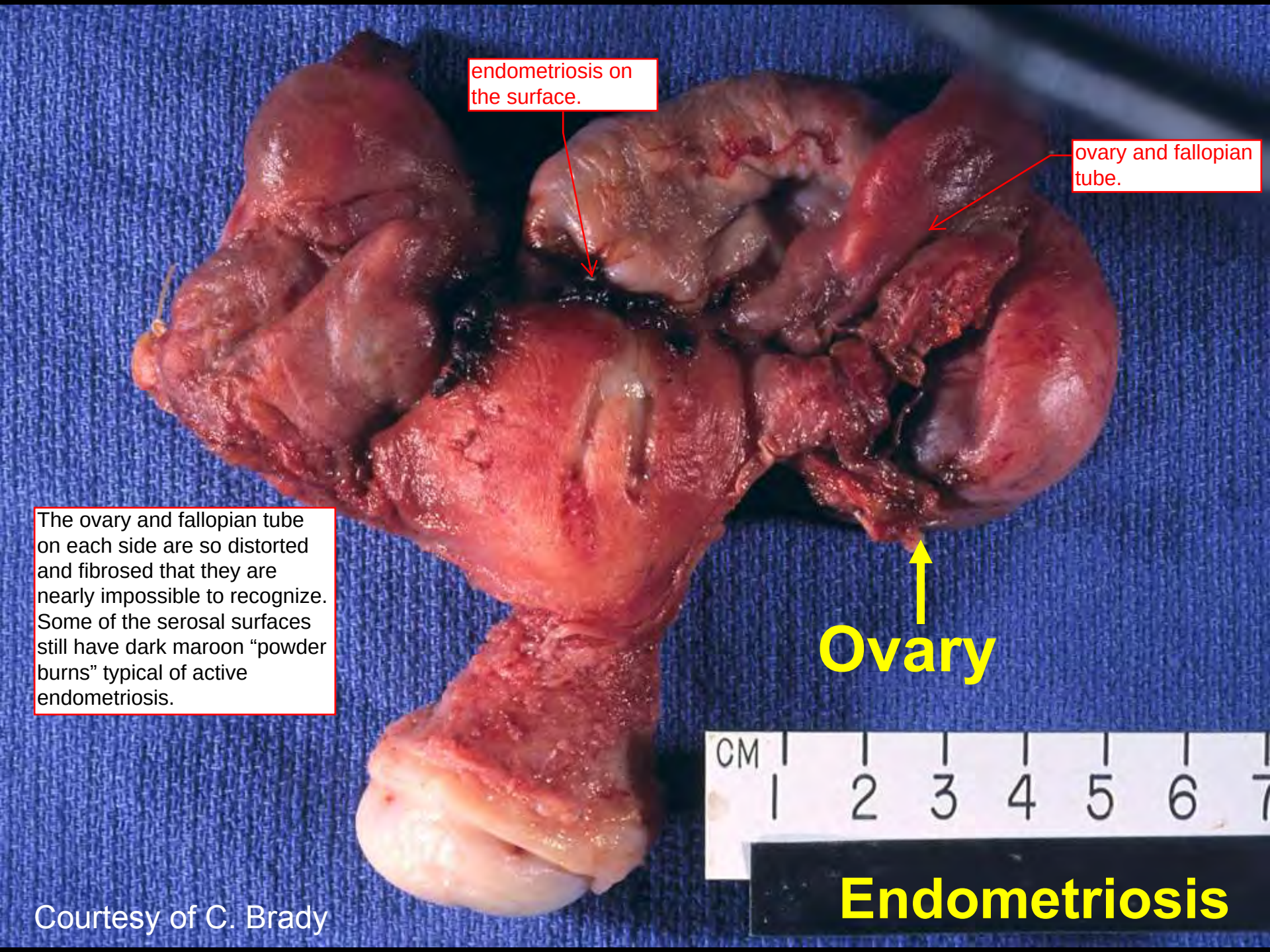
Under the influence of hormones a lot of structures in the endometrium are capable of undergoing de novo development.

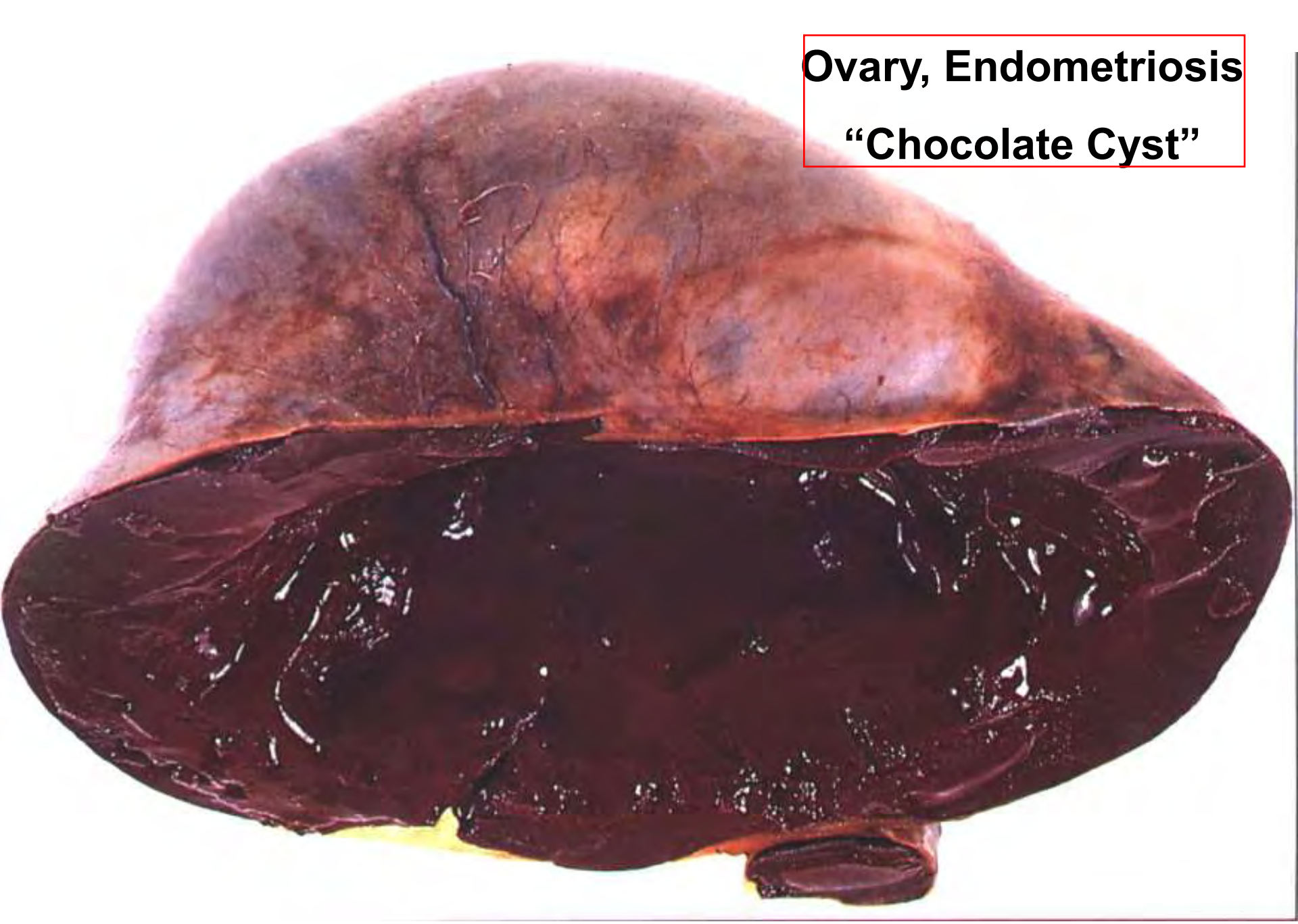
Some of these lesions (like in the brain) may have gotten there via the vasculature (but we dont know how).

These pieces of endometrium undergo cycles of proliferation and breakdown. This cycle results in all of these ->

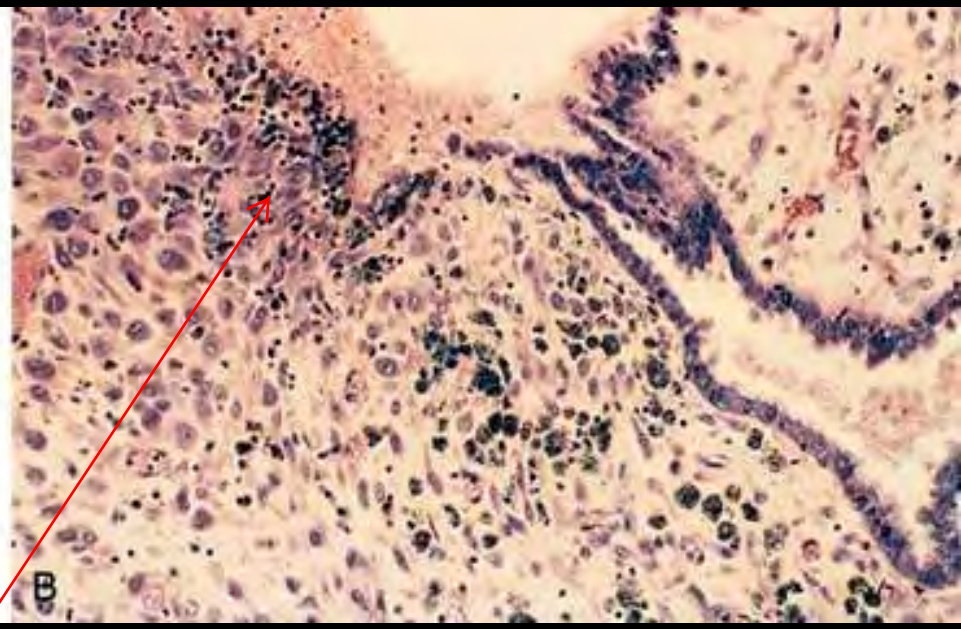
Disorts surrounding tissue

15-20 cm in size.


endometriosis on the surface.
ovary and fallopian tube.
The ovary and fallopian tube on each side are so distorted and fibrosed that they are nearly impossible to recognize. Some of the serosal surfaces still have dark maroon “powder burns” typical of active endometriosis.
Ovary
CM
1
2
3
4
5
6
Endometriosis
Courtesy of C. Brady


Ovary, Endometriosis
"Chocolate Cyst"

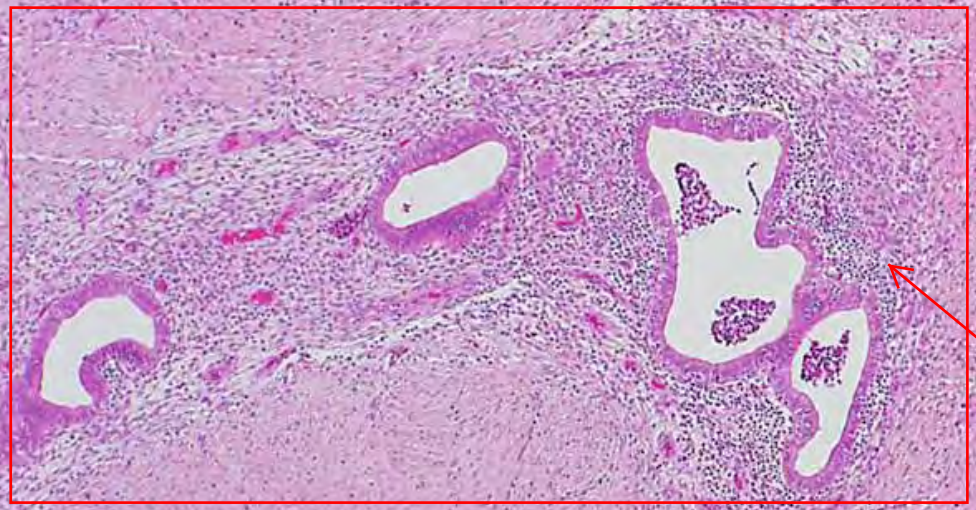
Chocolate cyst



The pigment is hemosiderin from broken down RBS's.

Endometrium lining chocolate cyst

Endometriosis in Scar



Looks like endometrium, except it is in a location it shouldn't be in.

This patient developed a painful mass in a C-section scar, and the pain was worse each month during her menses.

Endometriosis--Treatment

- **Hormonal tx:**
  - **Progestins, oral contraceptives, pregnancy**
  - **GnRH analogs, menopause**
- **Surgical excision of lesions**
- **Laser tx**
- **Pain meds (NSAIDs)**

If you can get pregnant, endometriosis regresses.

Menopause helps.

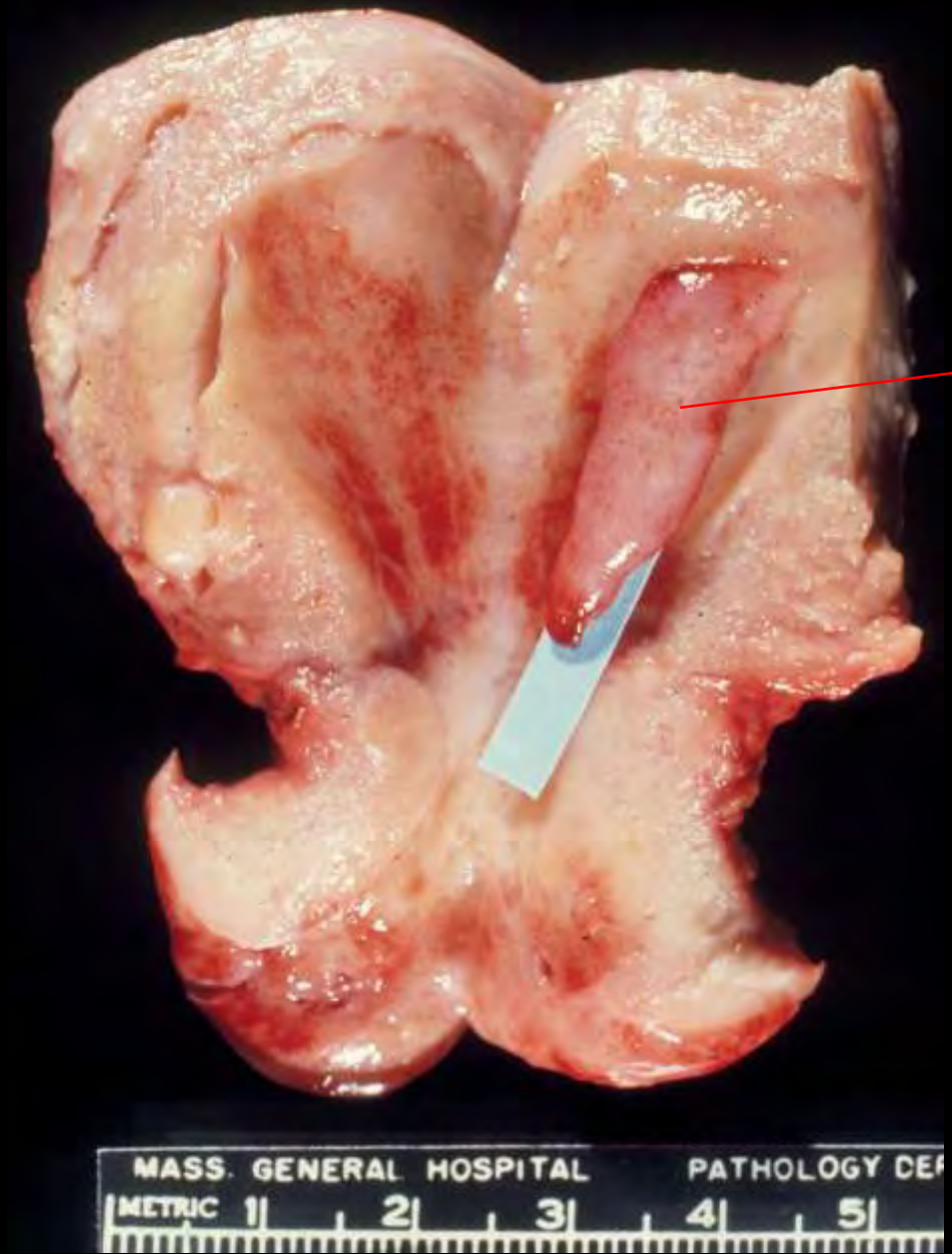
Destroy the lesions.

symptoms management.

Endometrial Polyps

- Sessile or pedunculated mass
- Composed of normal endometrium and fibrous stroma
- Common cause of abnormal bleeding in menopause and older
- Account for 25% of pts with abnormal bleeding

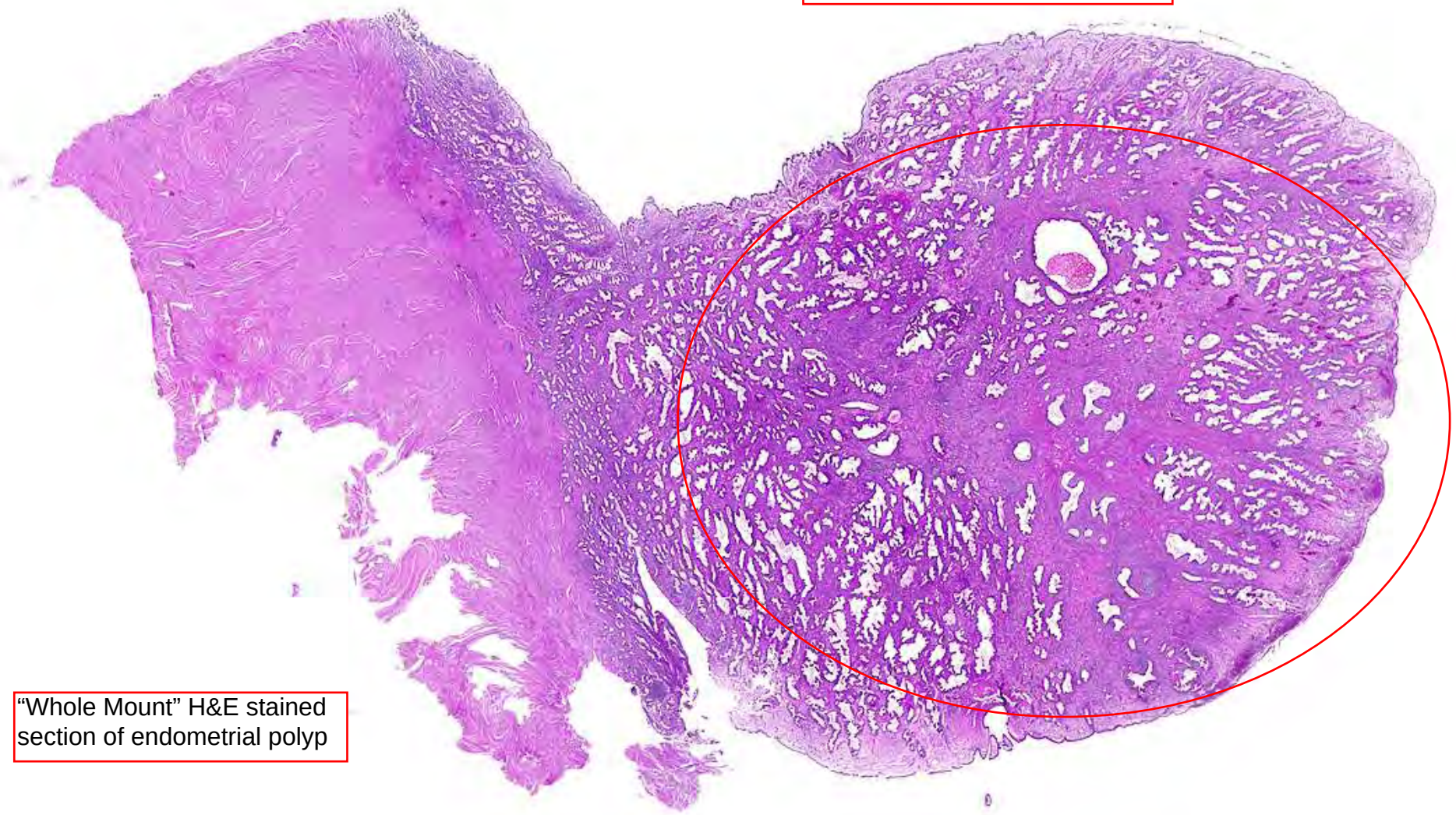
Stroma is replaced by fibrous tissue. These polyps are benign, but they cause bleeding. Bleeding is otherwise a sign of endometrial cancer.



Endometrial Polyp

Endometrial Polyp

totally benign



"Whole Mount" H&E stained section of endometrial polyp

Abnormal Uterine Bleeding

- Abnormal amount or timing of bleeding
  - Menorrhagia: bleeding too much or too long at time of period
  - Metrorrhagia: bleeding between periods
  - Menometrorrhagia: both!
- One of most common reasons women seek medical attention
- Experienced by most women at some point

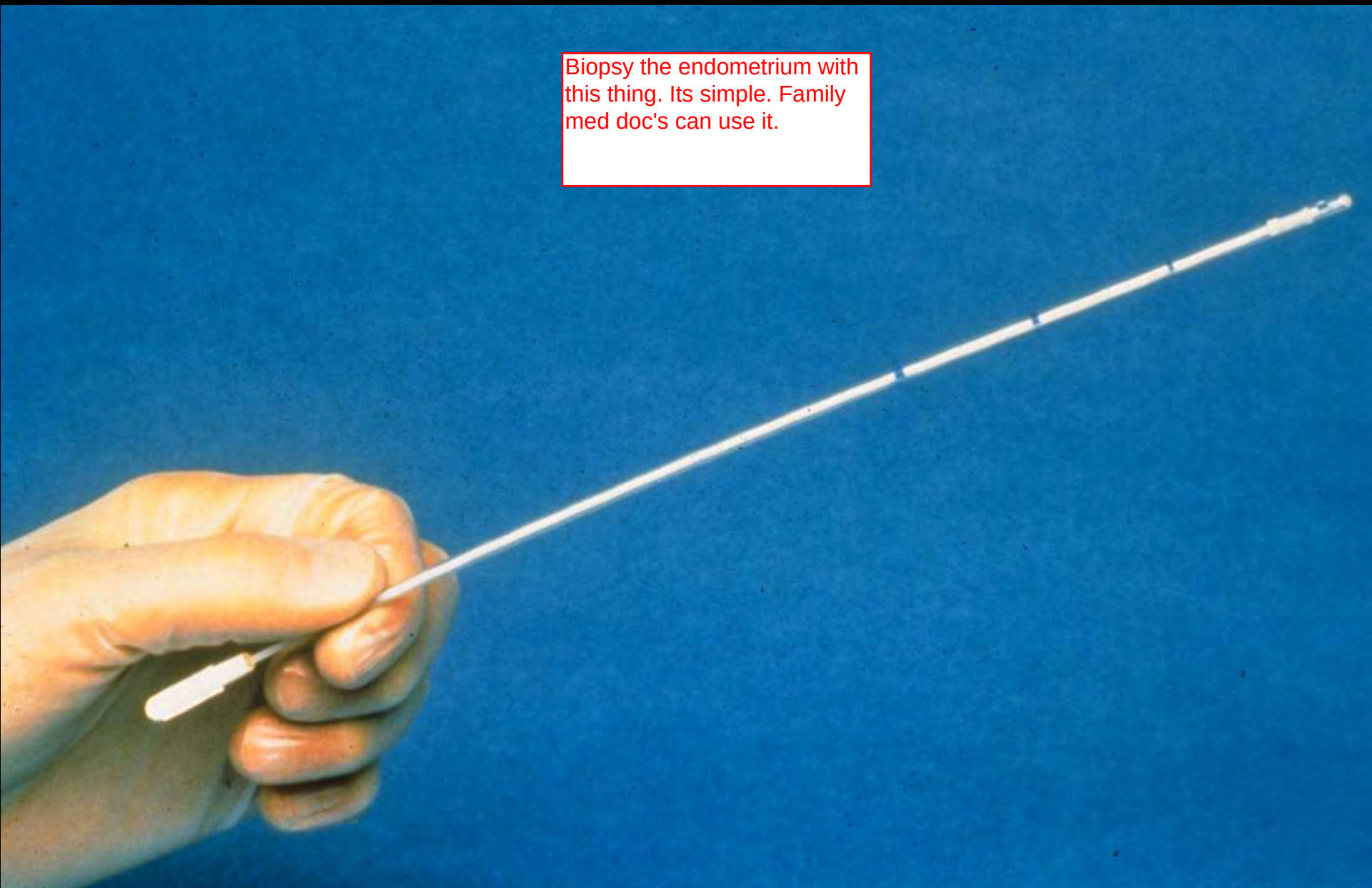
Abnormal Uterine Bleeding

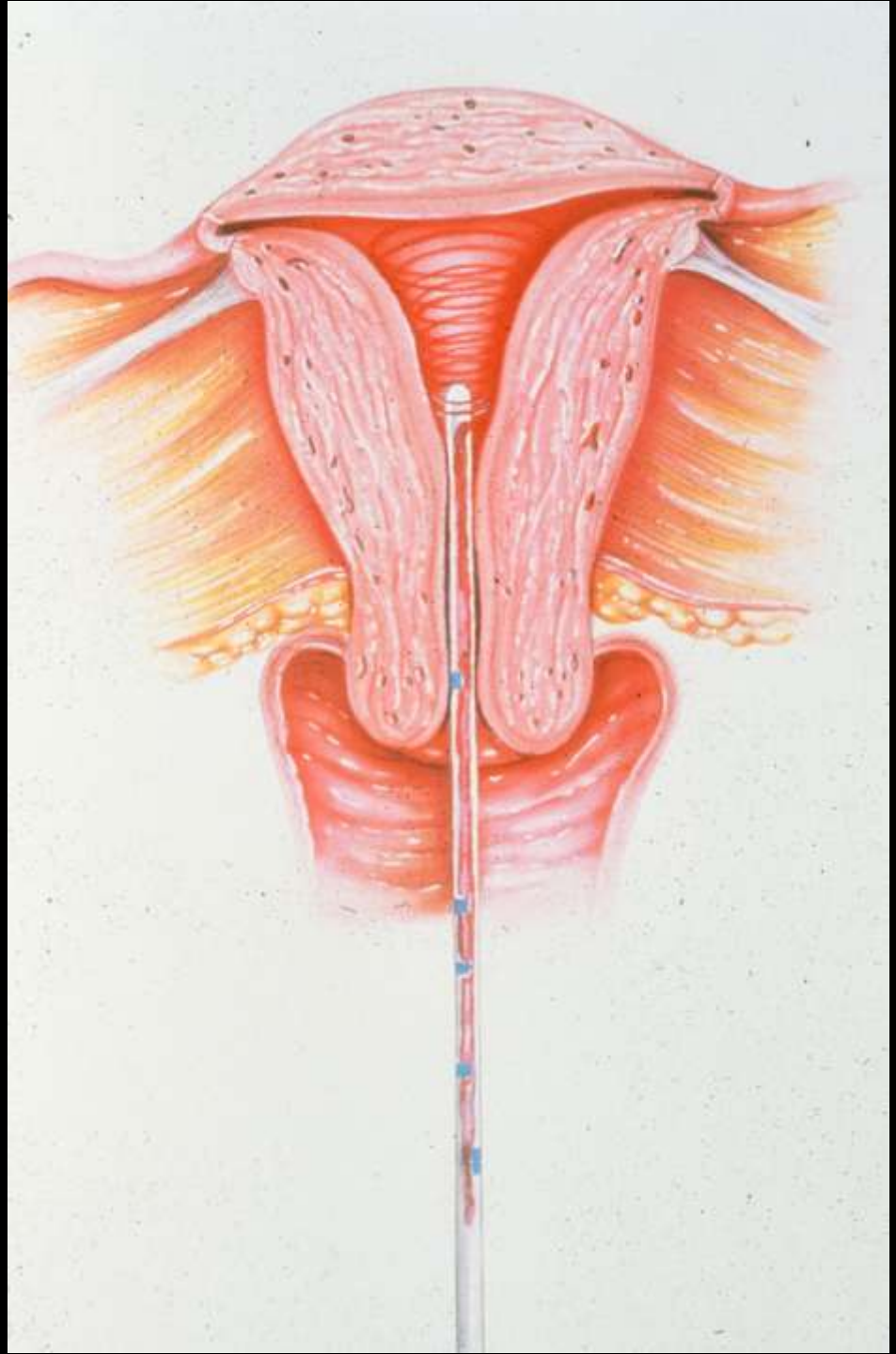
Large number of causes

- Leiomyomas
- Polyps
- Endometritis
- Hyperplasia/carcinoma
- Hormonal disorders (pituitary/hypothalamic)
- Complications of pregnancy
- Atrophy
- Coagulation disorders

These are the most common causes of bleeding.

Endometrial Pipelle





One would slip it right in, pull on a piston that sucks in some tissue for sampling.


Sample.

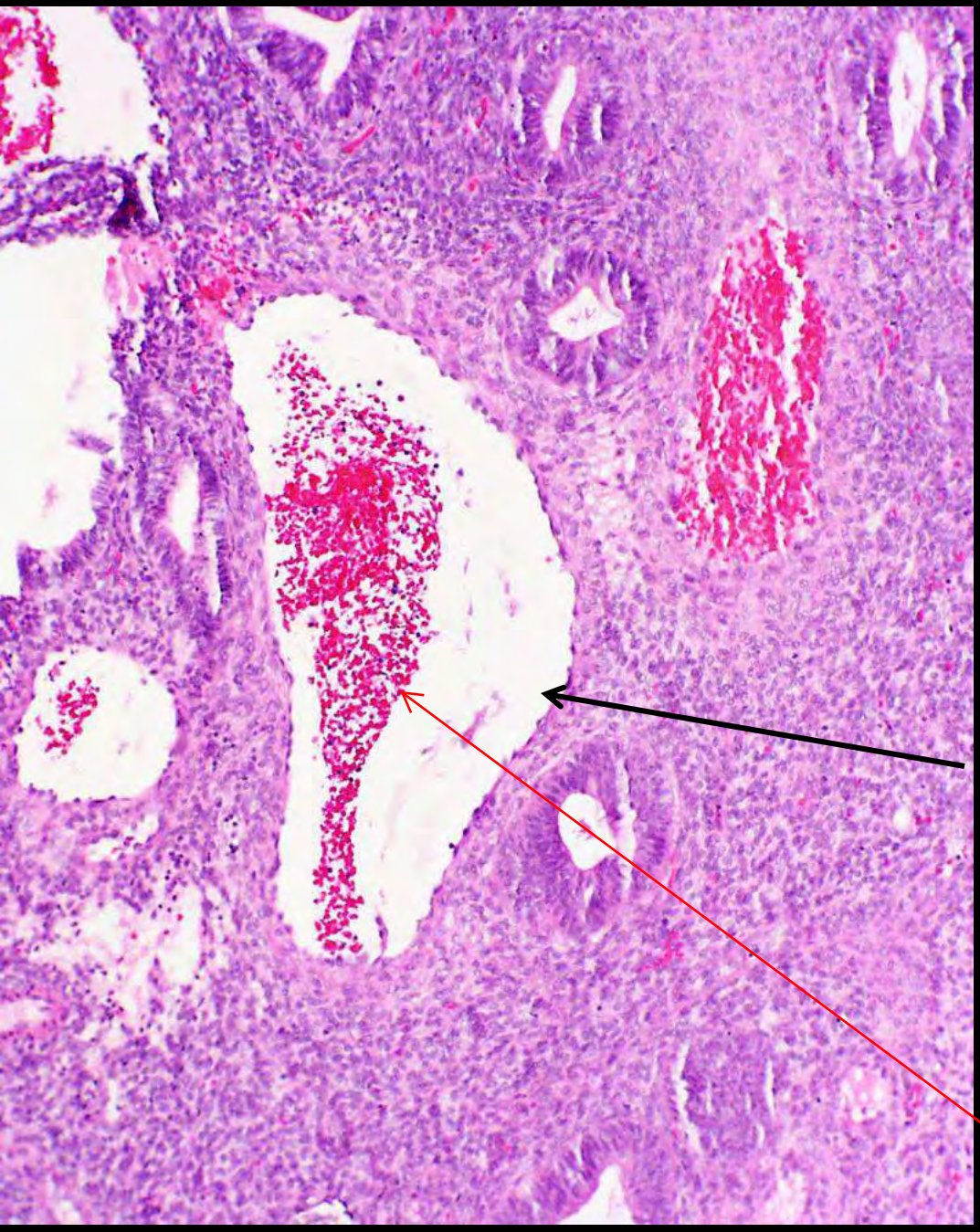
Dysfunctional Uterine Bleeding

- **"DUB": abnormal bleeding with no identifiable "organic" cause**
- **Most related to anovulatory cycles**
  - **Continuous estrogen stimulates endometrium to grow.**
  - **Outstrips ability of stroma to support and breaks down, with bleeding.**

Most DUB Pt's are anovulatory. They have follicles, but no ovulation. Can persist for a while. Pt is exposed to continuous estrogen but little progesterone. Estrogen makes the endometrium grow. Eventually the endometrium starts falling apart because it gets to big.

Anovulation

- Persistent proliferation leads to disordered growth of glands



Anovulation

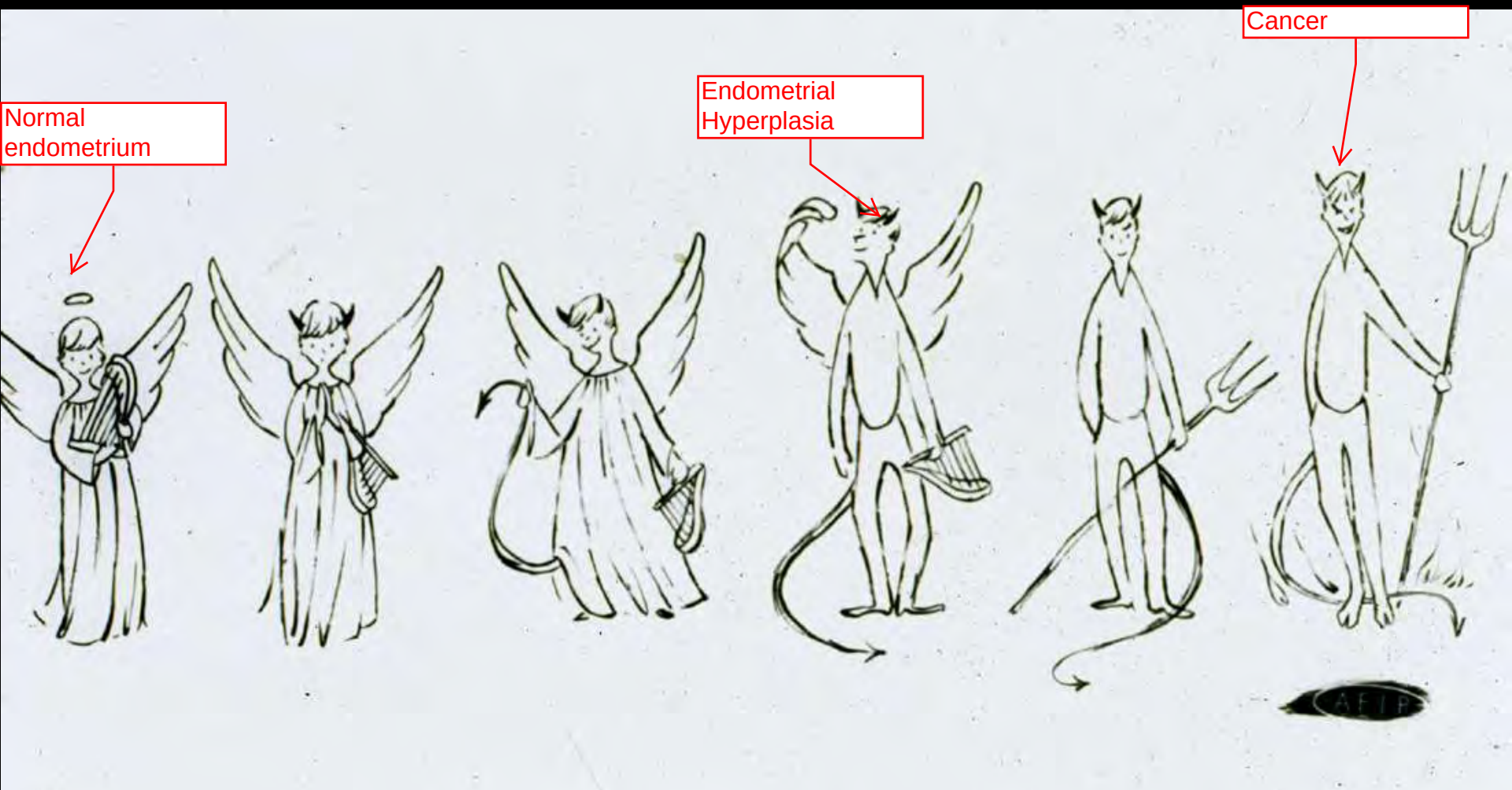
- Persistent proliferation leads to disordered growth of glands
- **And large ectatic vessels that bleed (and bleed, and bleed…)**

Abnormal vessels, no muscle in the wall. Without muscles the vessels cant constrict when bleeding starts.


Anovulation can be a result of :
Normal due to menopause
Hypothalamic/Pituitary dysfunction
Low weight women
No understandable reasons

Endometrial Hyperplasia:

Precursor to Adenocarcinoma



Endometrial Hyperplasia

- Estrogen stimulates endometrial proliferation
- Hyperplasia caused by continuous estrogen exposure without progestin ("unopposed" estrogen)

Endometrial Hyperplasia

- **Risk factors:**
  - **Anovulation**
  - **Obesity**
  - **Diabetes Mellitus**
  - **Hypertension**
  - **Exogenous unopposed estrogenic agents (including tamoxifen—a weak estrogen agonist in the endometrium)**
  - **Estrogen secreting tumors**

Peripheral estrogen conversion

Tamoxifen is a weak estrogen agonist in the endometrium.

Endometrial Hyperplasia

Protective Effect of Progestins in Hormone Replacement Therapy

Risk of having hyperplasia after 5 years of hormonal therapy.

Estrogen	Progestin	Hyperplasia
+	-	56%
+	+	0%

The original thought was: Estrogen helps with the symptoms, so lets give Pt's only estrogen.
Result: 5 yrs later most Pt's had hyperplasia (Bad).

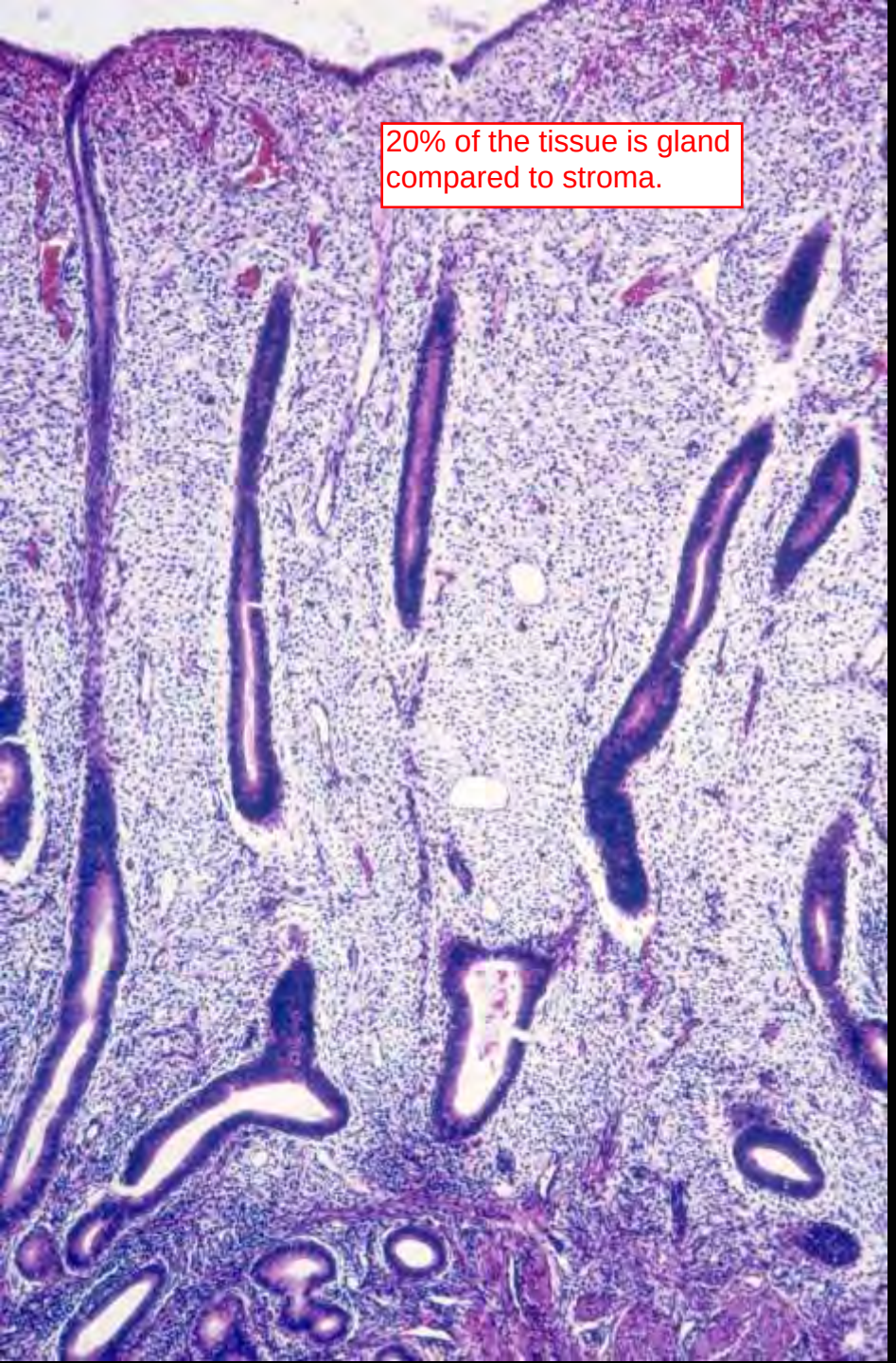
Endometrial Hyperplasia Classification

ARCHITECTURE

- Simple
  - No atypia
  - With atypia
- Complex
  - No atypia
  - With atypia

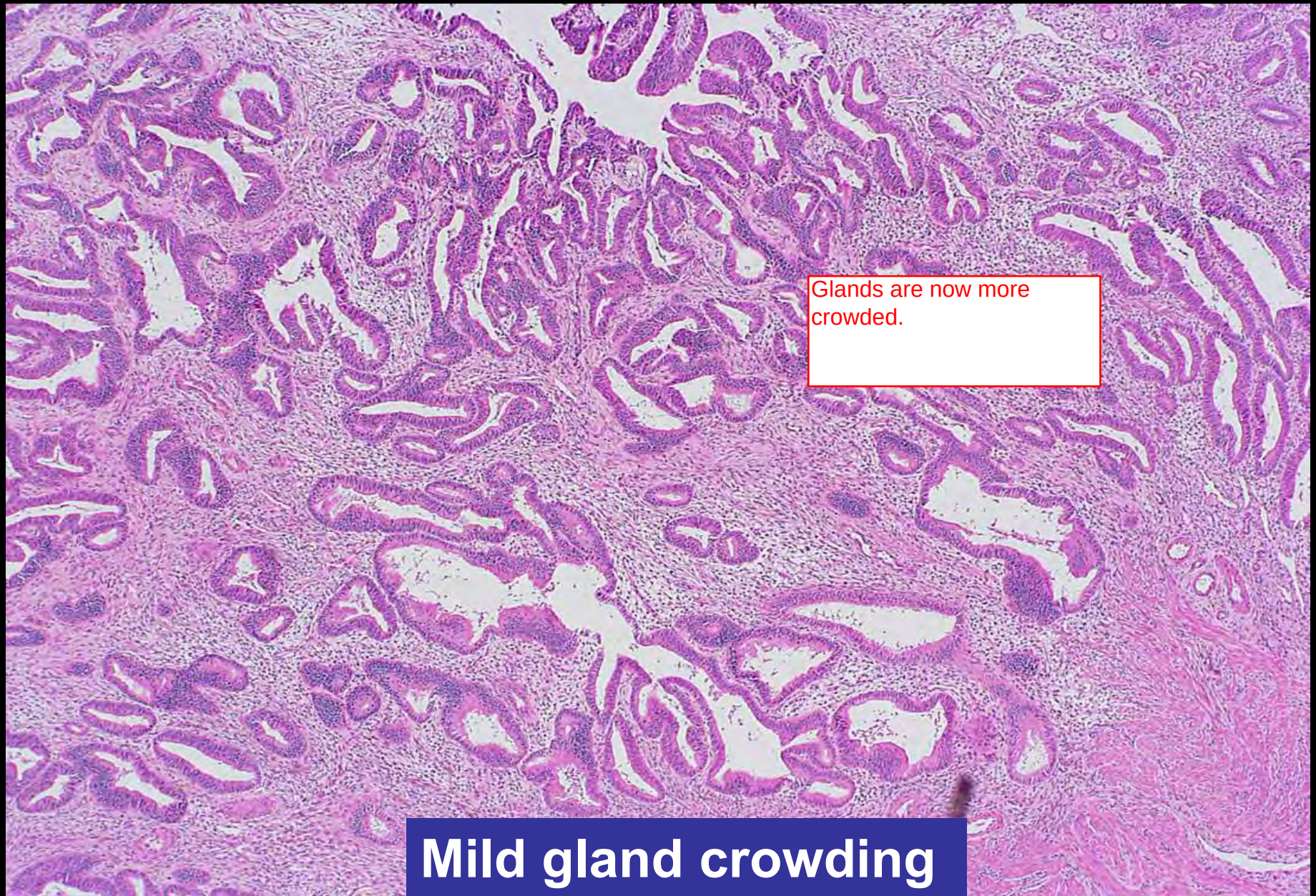
Endometrial Hyperplasia

- Endometrial Intraepithelial Neoplasia (EIN) is alternate concept/terminology
- EIN encompasses all of the atypical hyperplasias



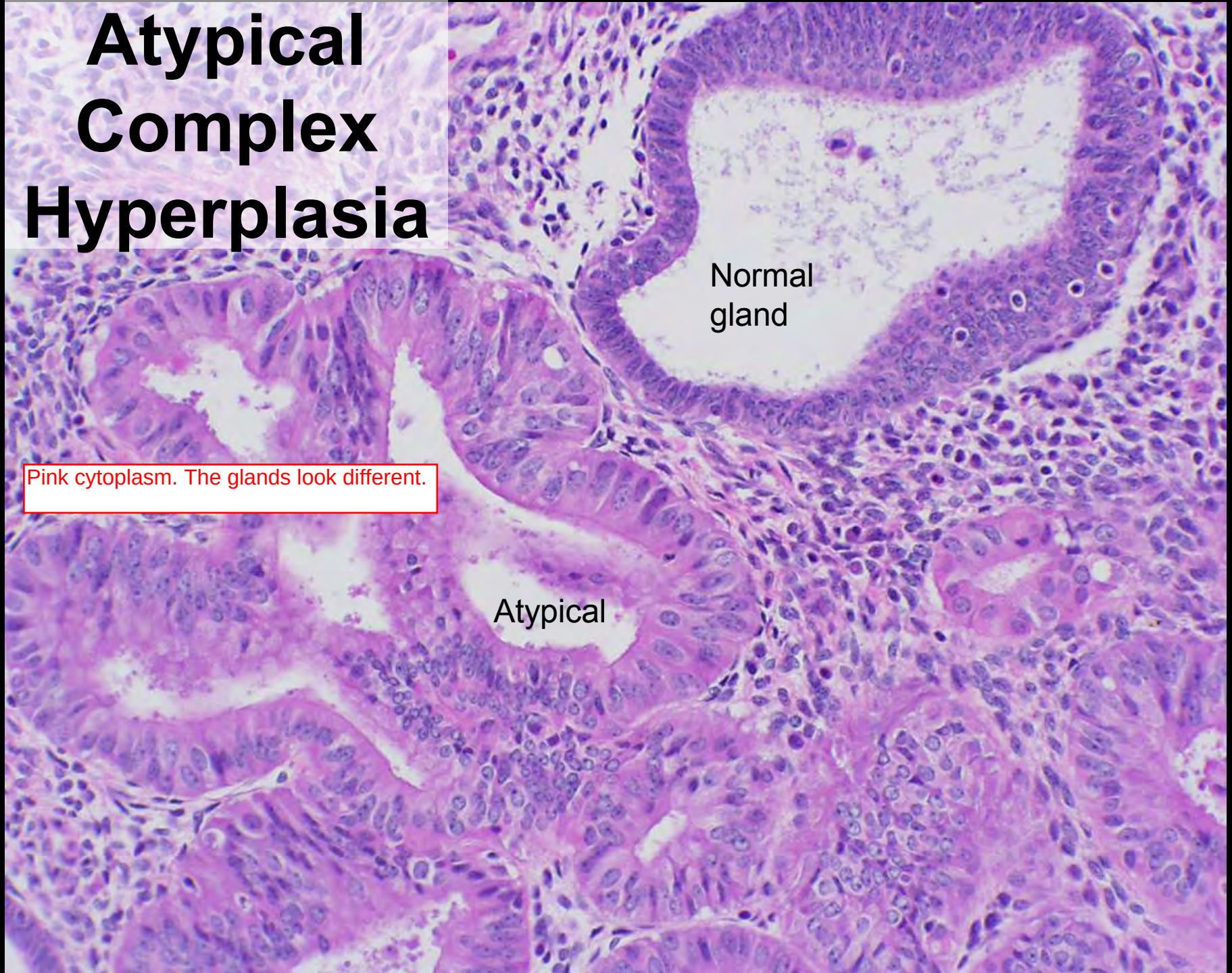
Normal Proliferative Endometrium

Simple Hyperplasia



Complex Hyperplasia

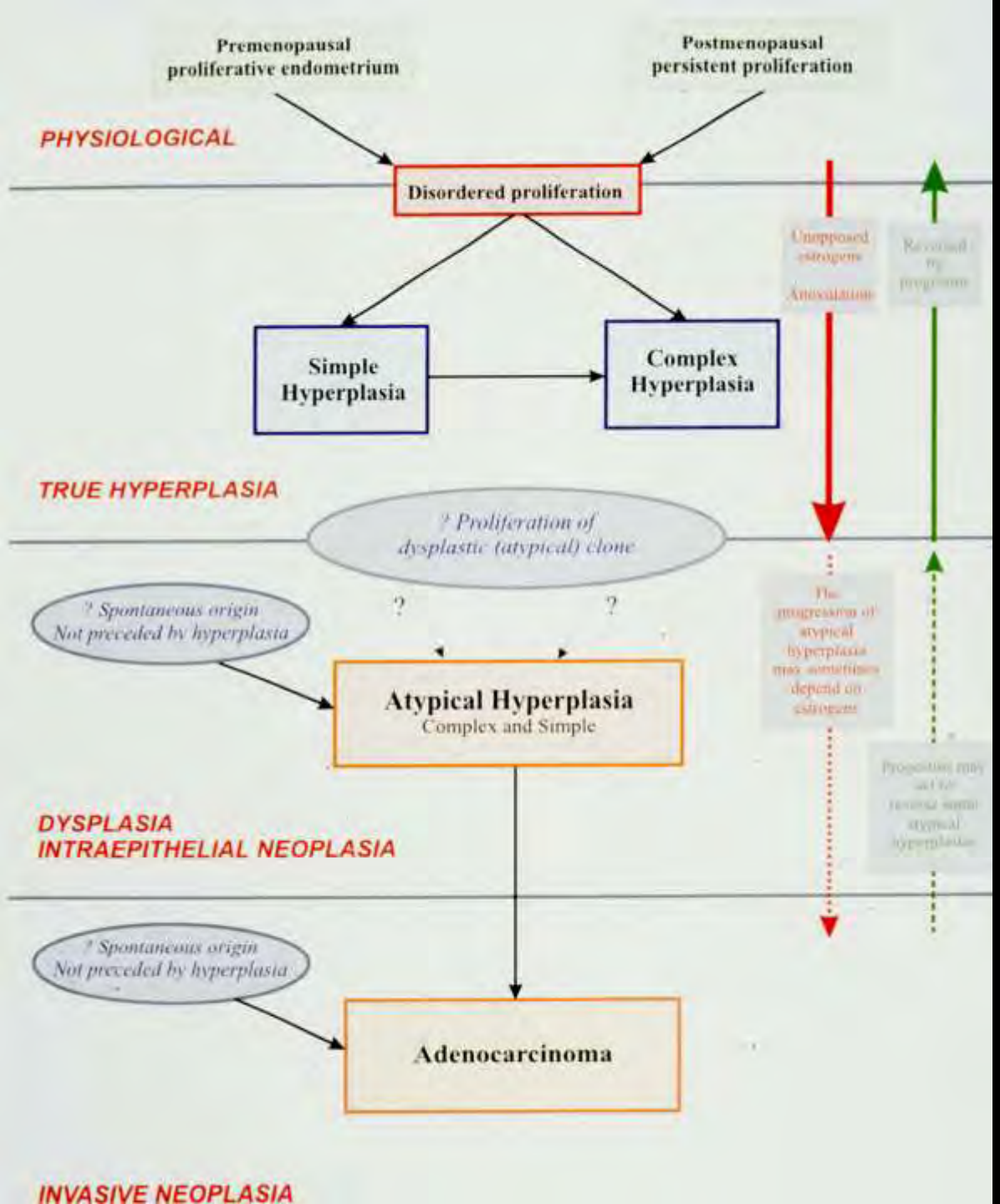
Atypical Complex Hyperplasia



Natural History Endometrial Hyperplasia

Rate of progression to adenocarcinoma on long term follow-up (10-20 years).

	Progress to carcinoma
No atypia — Simple/Complex Hyperplasia	2%
Yes atypia — Atypical hyperplasia	23%



Summary:

Pathogenesis of Endometrial Carcinoma

*We start out with Proliferative endometrium. We then go on to disorder and hyperplasia. The cells then begin looking atypical. Finally we develop adenocarcinoma.
*Estrogens drive the entire process.
*We can reverse the lesions with progestins. There are even a few adenocarcinomas that can be cured with progesterins.
*The ability to cure lesions with progestins declines as the lesions progress towards cancer.

Endometrial Cancer

U.S. Gyn Cancers - 2008

Most common site.

Most common cause of death

	New cases	Deaths
Corpus	40,100	7,470
Ovary	21,650	15,520
Cervix	11,070	3,870
Vulva	3,460	870
Vagina/ other	2,210	760

Endometrial Carcinoma

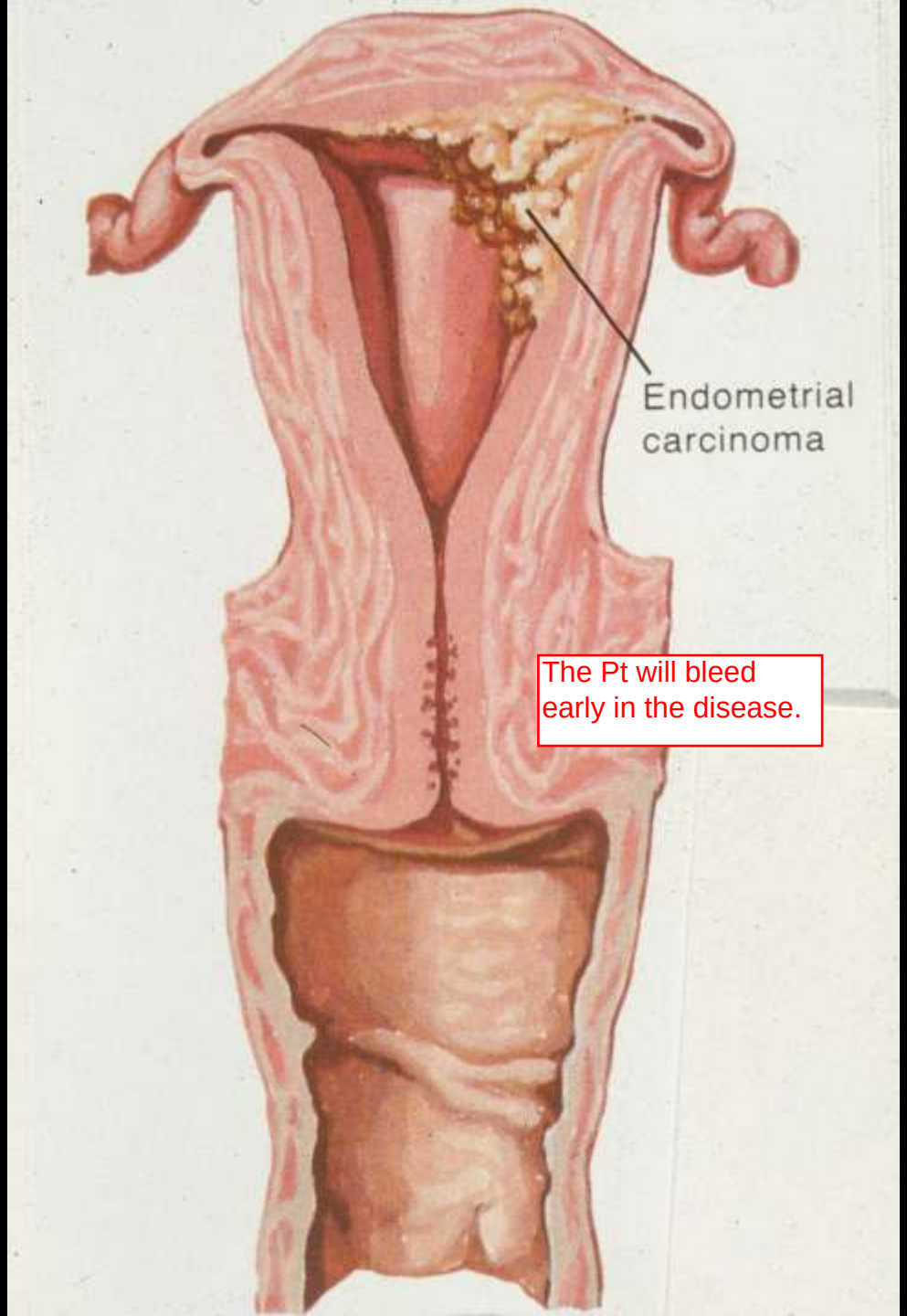
- "Endometrioid" type most common
- Peak age 55-65; rare <40
- Most arise from hyperplasia
- Risk factors similar to hyperplasia
- 2nd most common cancer in HNPCC (mismatch repair defects, Lynch syndr.)

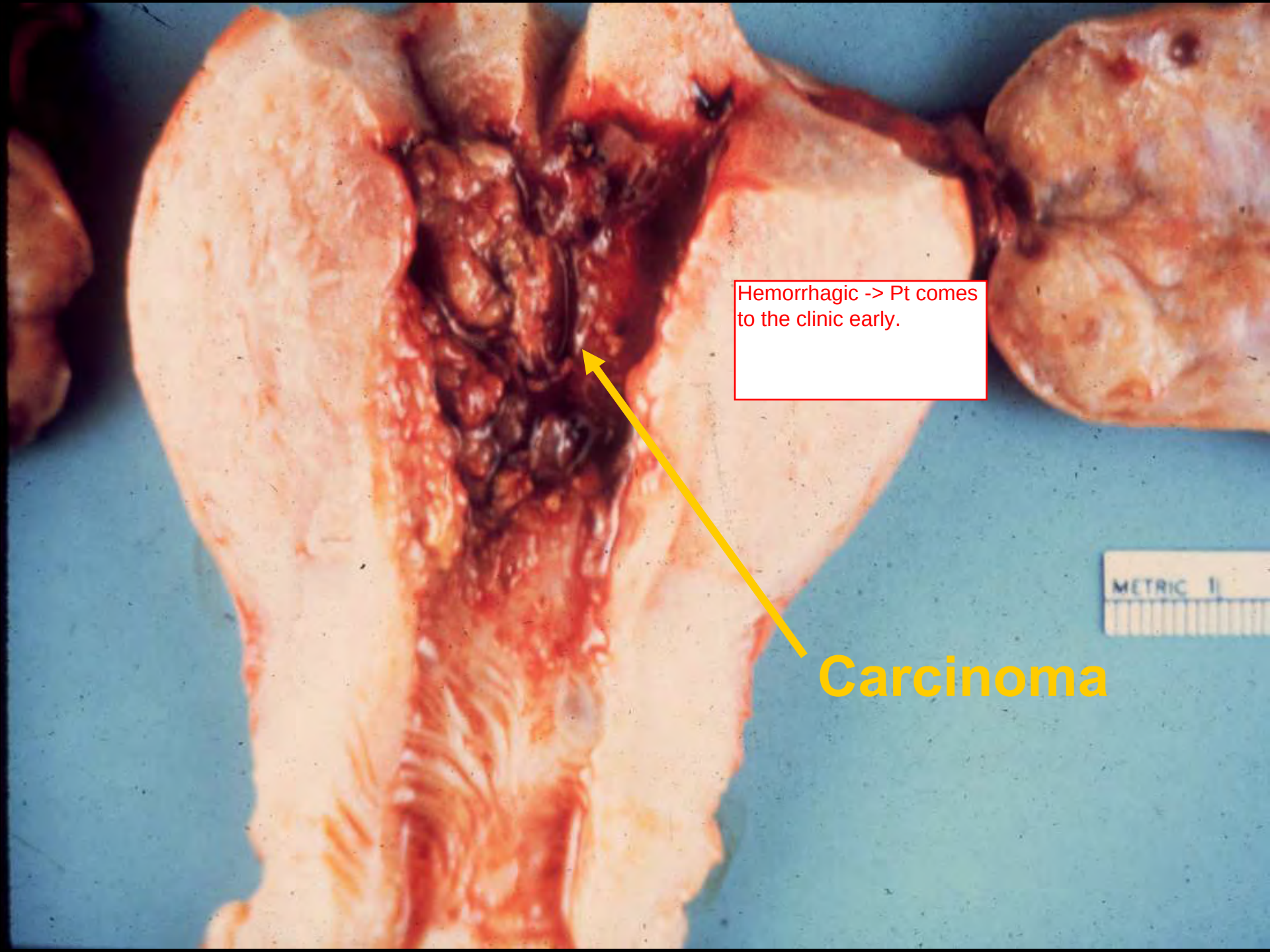
Generally in post menopausal women.

Hereditary nonpolyposis colorectal cancer syndrome: results from a mismatch repair defect. Pt with endometrial cancer or colon cancer should be screened for this defect.

Endometrial Carcinoma

- Important feature of endometrial carcinomas is tendency to bleed
- This results in the patients coming to clinical attention early
- Most endometrial cancers are found at an early stage!

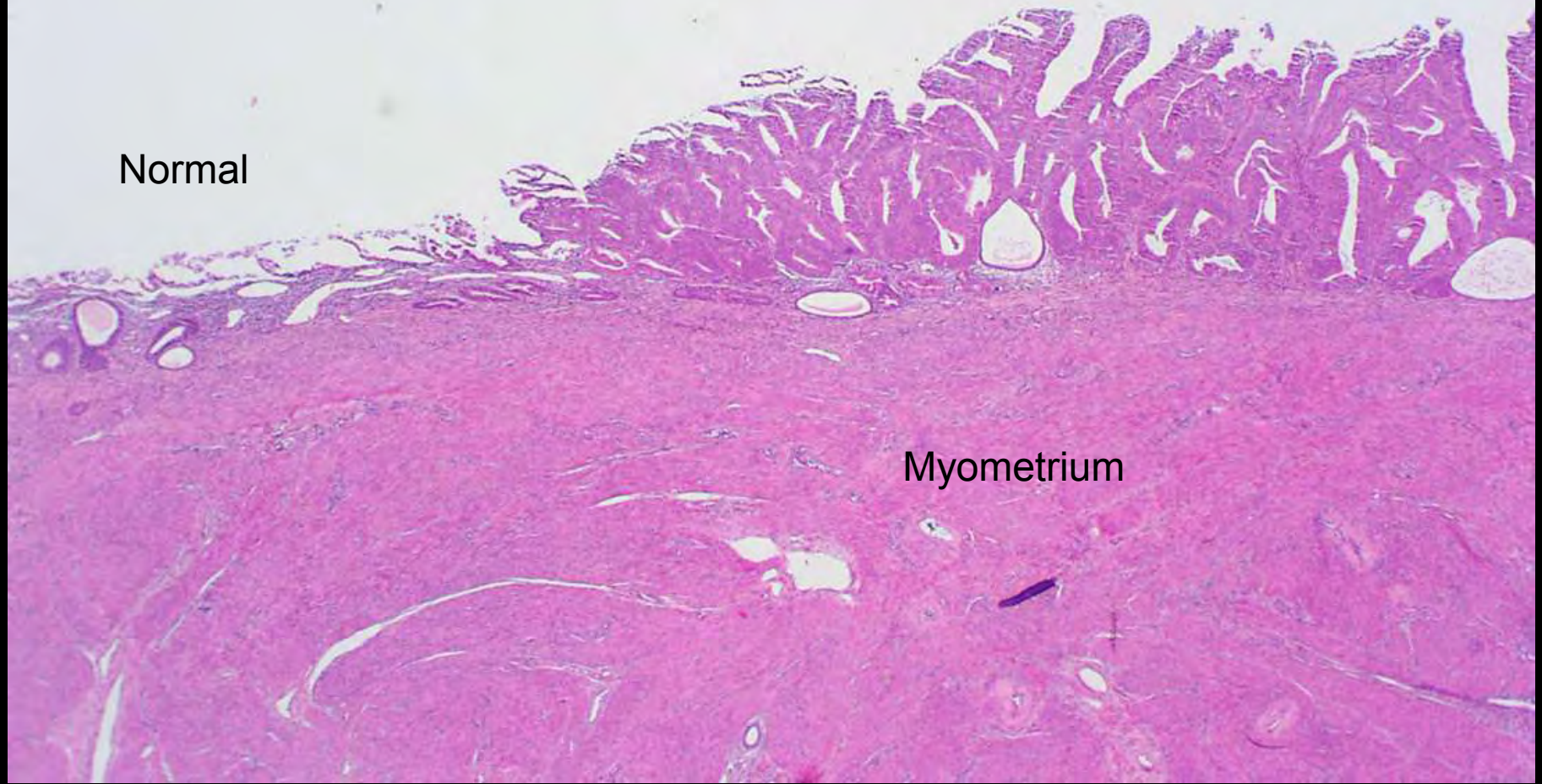



Hemorrhagic -> Pt comes to the clinic early.
Carcinoma
METRIC

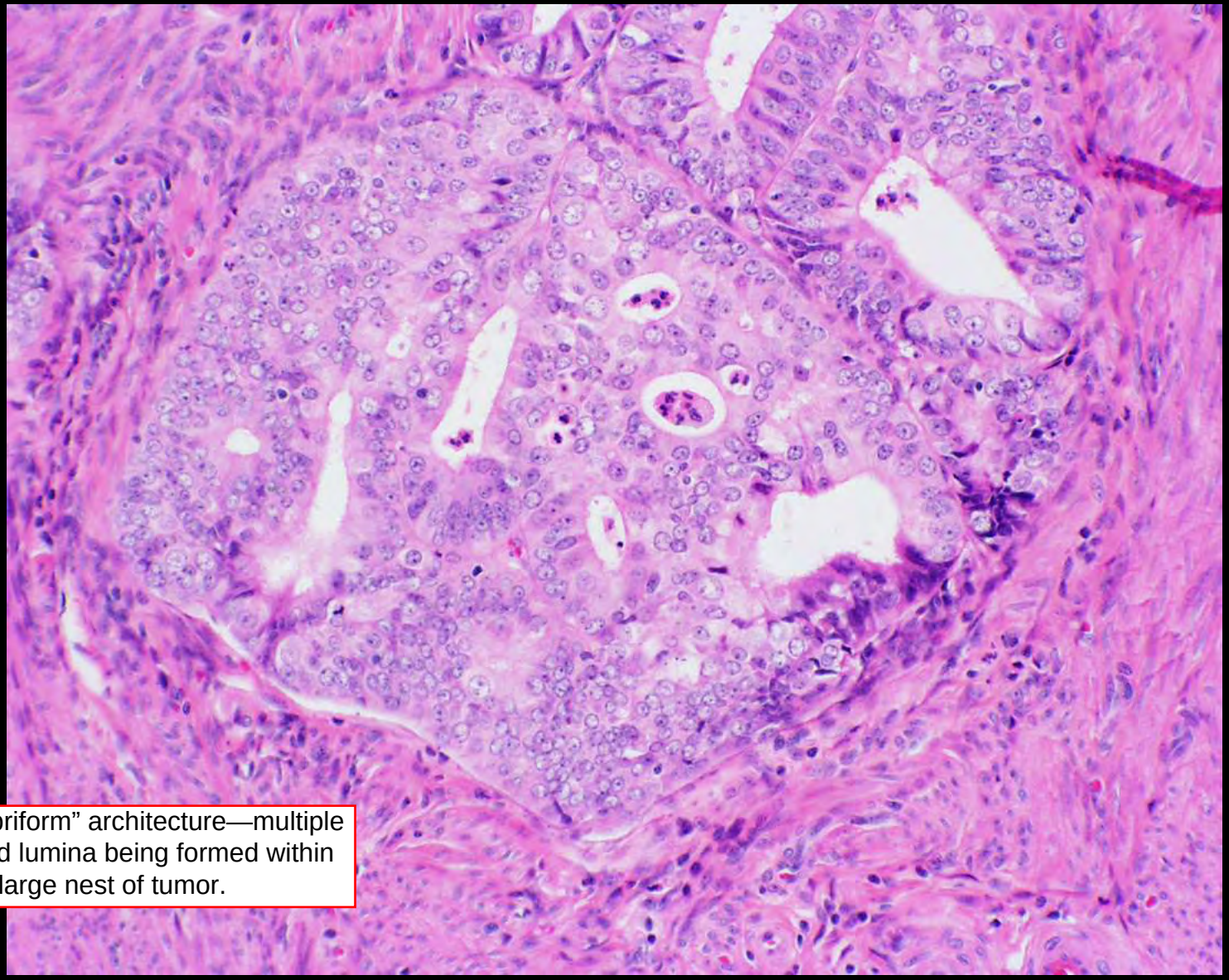
Endometrioid Adenocarcinoma

In this example, the cancer has replaced the endometrium in the right side of the photograph, but there is no invasion into underlying myometrium.

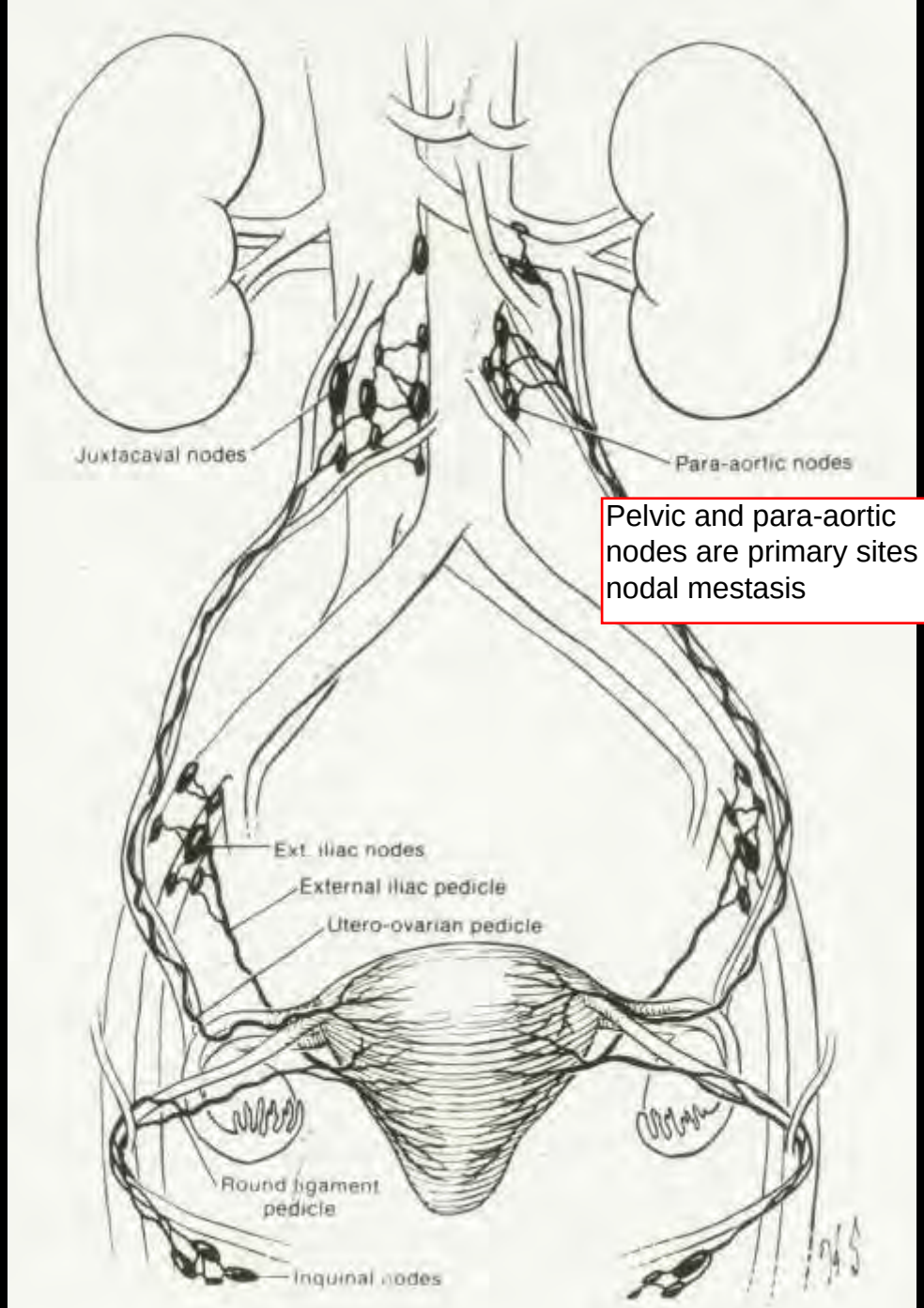
Growing along the surface. The majority of endometrial cancers are caught in this early stage.



Endometrioid Adenocarcinoma



"Cribriform" architecture—multiple gland lumina being formed within one large nest of tumor.



Pelvic and para-aortic nodes are primary sites of nodal mestasis

Endometrial Cancer

Mode of Spread

Endometrial Cancer

5 year survival

Stage = How big is the tumor? Does it invade anything?

Grade= level of differentiation.

Note that both stage and grade are strong predictors of survival for endometrial cancer.

	Grade		
Stage	-1-	-2-	-3-
IA	97%	66%	57%
IB	82%	71%	44%
II	80%	42%	12%
III/IV	25%	33%	17%

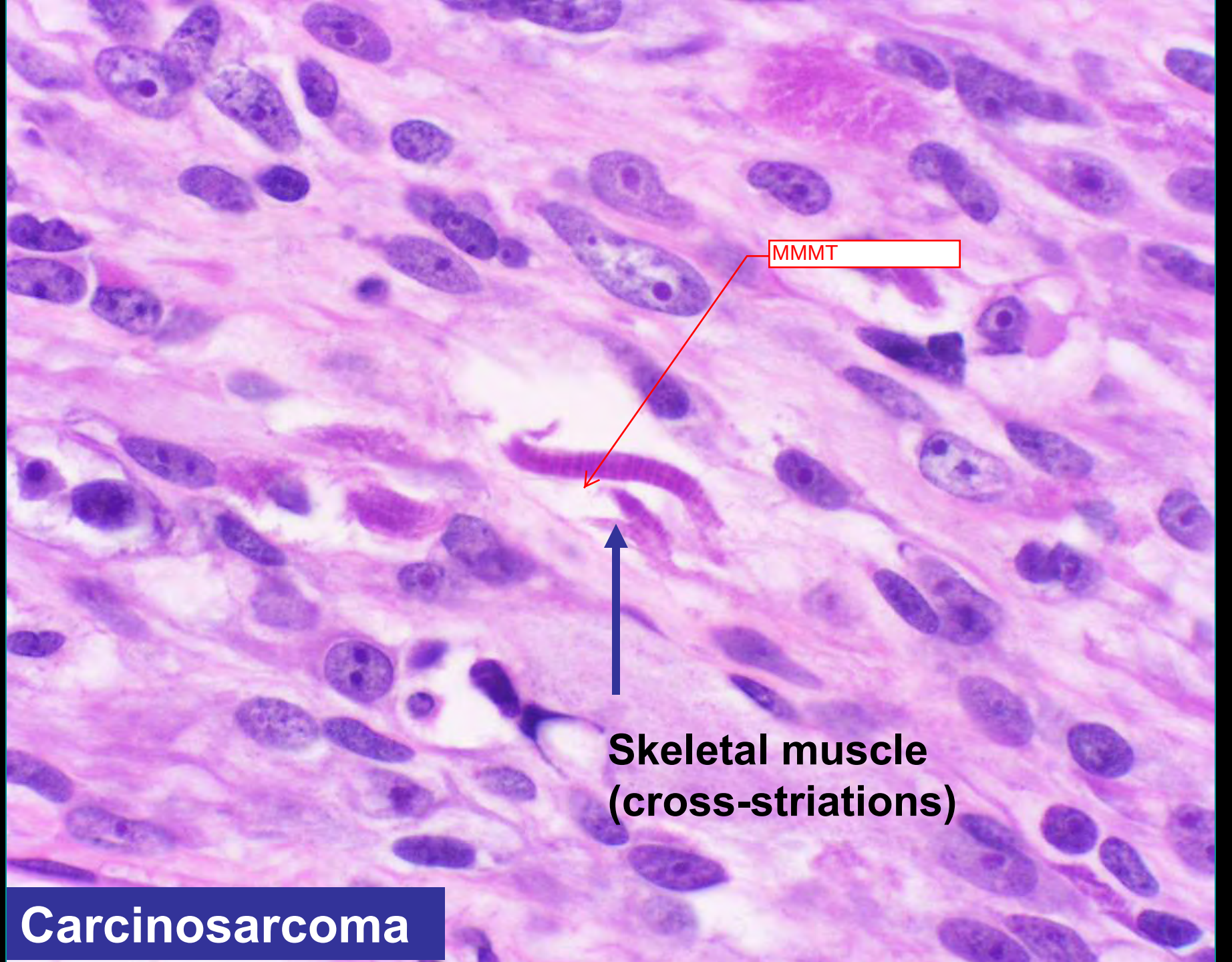
Type II Carcinomas

Not dependent on estrogens. They are aggressive.

- Papillary Serous and Clear Cell
- Not associated with Estrogen use
- Older population
- High grade aggressive tumors with much worse prognosis even when low stage.
- 5-10% of endometrial cancers are in this category

Carcinosarcoma

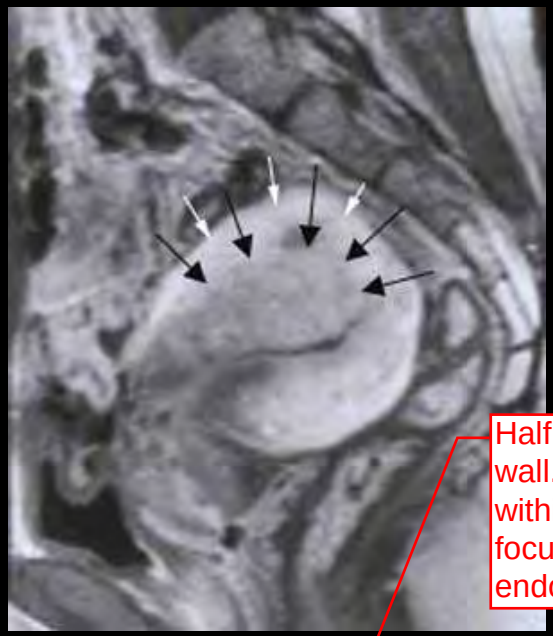
- Also known as Malignant Mixed Mullerian Tumor (MMMT)
- Very poorly differentiated carcinoma that has undergone differentiation into a mesenchymal cell type (skeletal muscle, fat, cartilage, etc)
- Mixture of carcinoma and sarcoma
- Very aggressive tumor with poor prognosis.



Carcinosarcoma

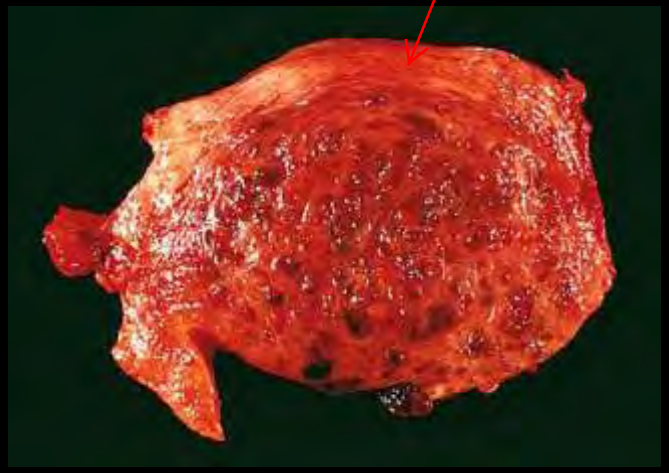
Myometrium

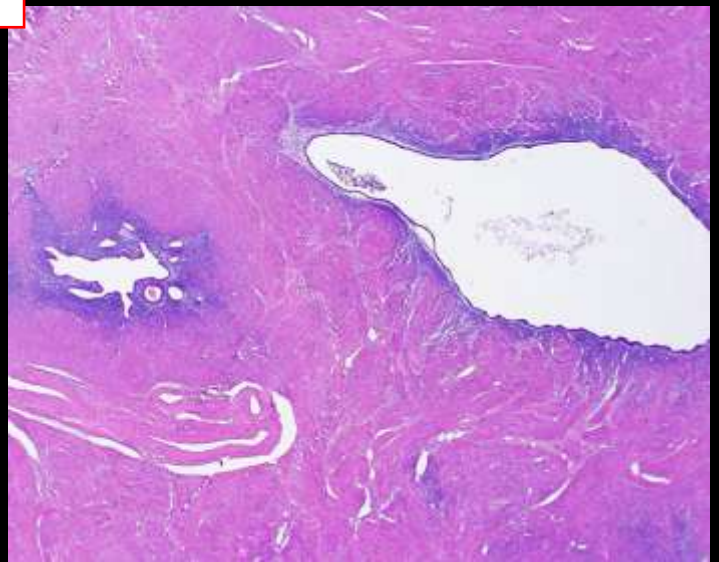
Adenomyosis



- Extension of endometrium into myometrium
- Myometrium thickened
- Common cause of dysmenorrhea ← Pain with a period
- 20% of women

Half of the uterine wall. The cysts within the wall are focus of endometrium.





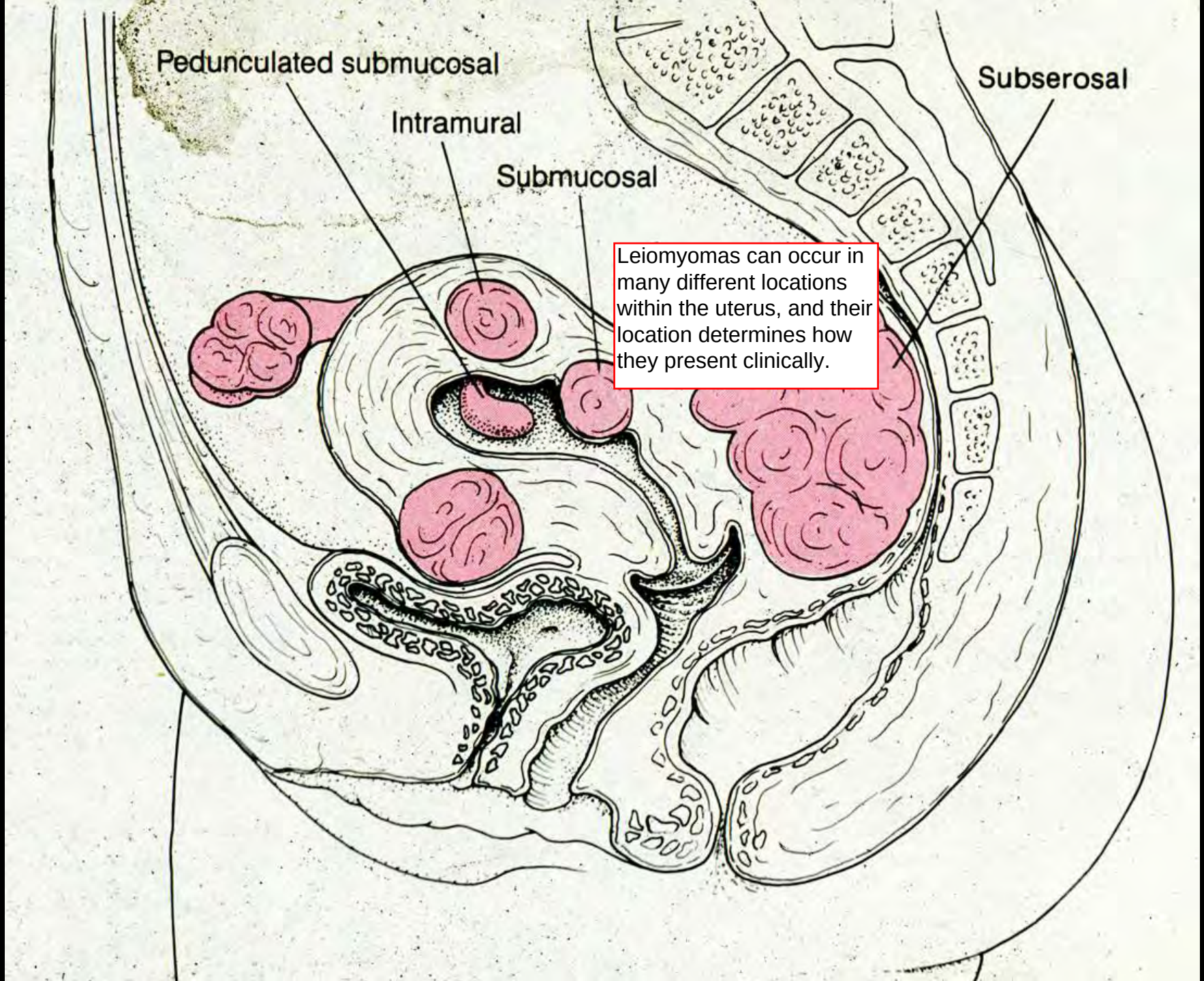
Adenomyosis

Whole Mount

Leiomyomas ("Fibroids")

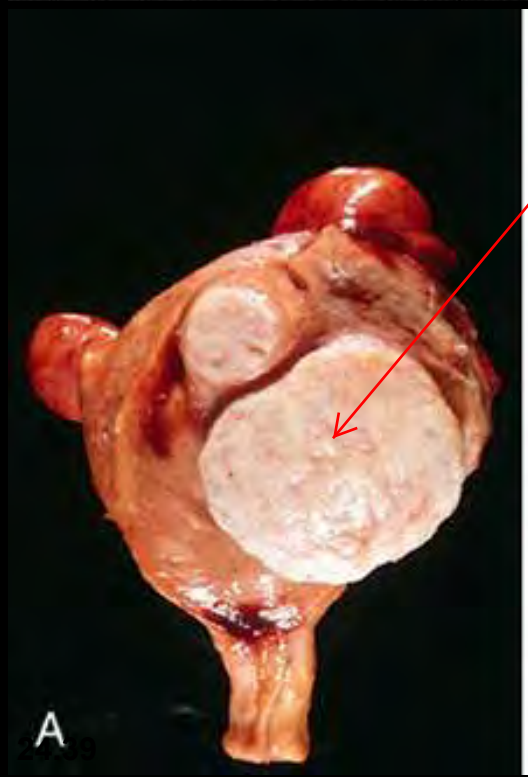
80% of women in the 40s will have at least one Leiomyoma in the uterus. A leading cause of hysterectomy.

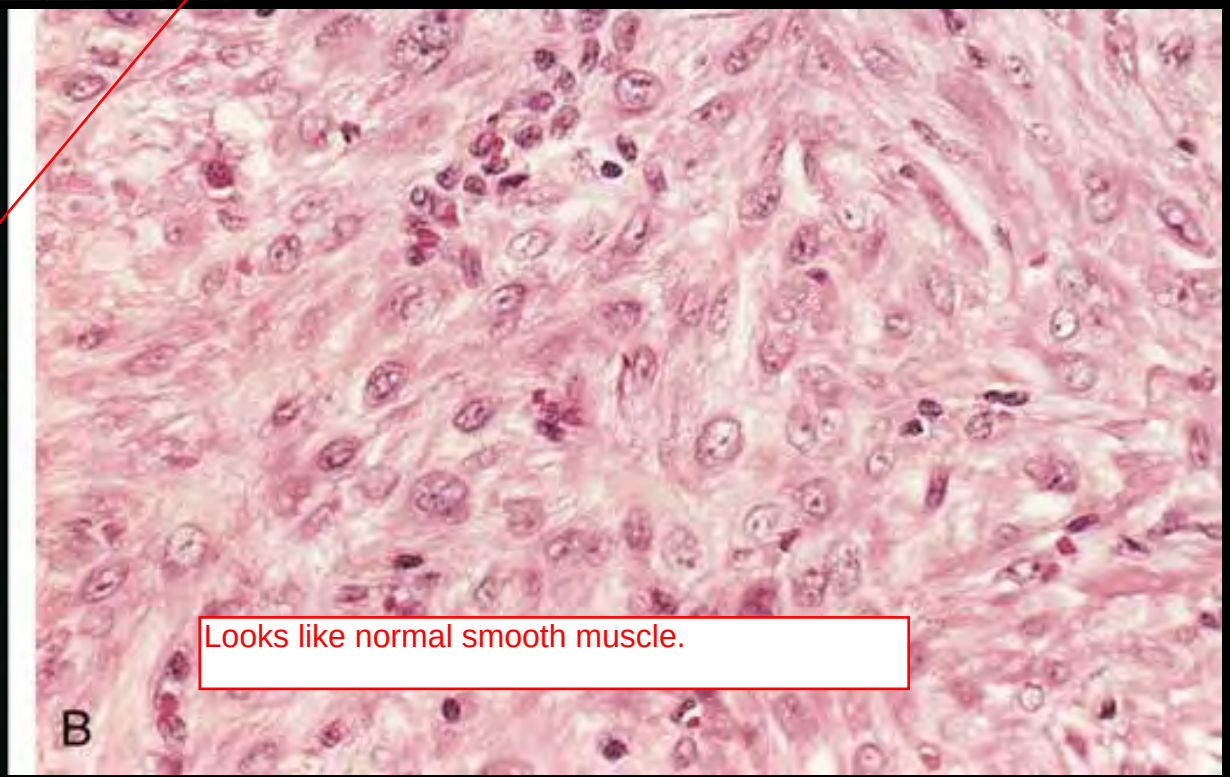
- Benign neoplasms of smooth muscle
- 30's and 40's peak age
- Often multiple and very large
- Extremely common
  - Present in 80% of uteri in peak age ranges
  - 25% of women symptomatic
  - Major indication for hysterectomy


Pedunculated submucosal
Intramural
Submucosal
Subserosal
Leiomyomas can occur in many different locations within the uterus, and their location determines how they present clinically.

Leiomyomas

Leiomyoma: Large pelvic mass on CT; typical white, whorled gross appearance, with the tumor bulging over the cut surface; and microscopic appearance—closely resembles normal smooth muscle.





Looks like normal smooth muscle.

Multiple Leiomyomas

Large Leiomyoma!

"When I said leiomyomas can be very large, I wasn't kidding!"

Leiomyomas

Clinical presentation

- Abnormal bleeding
- Pelvic pain/pressure
- Infertility

Lots of presentations

Treatment

- Hormone suppression
- Embolization
- Myomectomy
- Hysterectomy

Pop out the leiomyoma.

Leiomyosarcomas

- Rare (0.1% of leiomyomas)
- Distinguished from leiomyomas by high mitotic rate, necrosis, and marked nuclear atypia.
- Behave like other high grade sarcomas
  - Local invasion
  - Distant blood-borne metastases
  - Poor prognosis

Much less common then leiomyoma. It is not clear if leiomyomas develop into leiomyosarcomas.

Summary

- Reviewed common non-neoplastic causes of abnormal uterine bleeding
- Defined endometriosis and described some of the common complications
- Described the progression of endometrial hyperplasia to adenocarcinoma
- Discussed the basic epidemiology of endometrial adenocarcinoma
- Described common pathologic lesions in the myometrium

The End

Gyn Part 2