



CONTINUING EDUCATION IN TOXICOLOGIC PATHOLOGY REPRODUCTIVE SYSTEM

Third Conference

ORGANIZED BY SOCIETY FOR TOXICOLOGIC PATHOLOGY IN INDIA (STPI)

OCTOBER 29-31, 2010

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Induced Lesions in the Female Reproductive System of Rodents

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Harlan Laboratories Ltd.
Switzerland

Problems Evaluating the Female Reproductive System?

- Xenobiotics and natural products may interfere with cycle
- If no moderate toxicity occurs, the cycle resembles normal diestrus
- Interaction of the nervous system, endocrinium and the reproductive system
- Mechanisms of toxicity are described

Types of Toxicity

- **Type I:** factors inducing inactivity in ovary, uterus, vagina, whereby the atrophy of the uterus and vagina is secondary to deficiency of ovarian steroids (absence or reduction of gonadotropins, impaired follicular development, impaired or altered steroidogenesis)
- **Type II:** factors inducing inactivity of ovaries but hyperactivity in uterus and vagina
- **Type III:** factors inducing hyperactivity in ovaries, uterus and vagina

Haschek WM, Wallig MA, Rousseaux C.: Fundamentals of Toxicologic Pathology. Second Edition, Academic Press Inc, San Diego, California (2009)

Types of Toxicity

- **Understanding the morphological details of different parts of the female reproductive system is the basis**

- **Summaries:**

Regan KS. et al.: Ovarian follicular counting in the assessment of rodent reproductive toxicity. *Toxicol Pathol.* 33: 409-412 (2005)

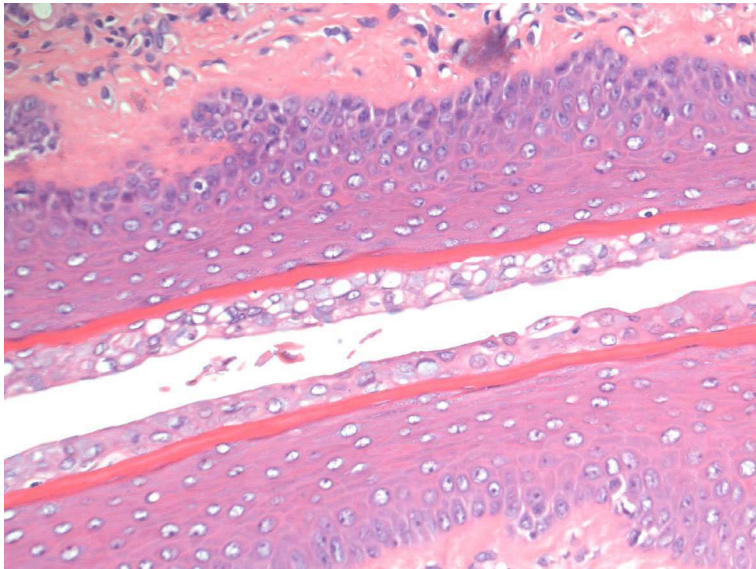
Westwood FR.: The Female Rat Reproductive Cycle: A Practical Histological Guide to Staging. *Toxicol Pathol.*, 36: 375-84 (2008)

- **Mammary gland may be affected under treatment**
- **Male and female mammary glands differ morphologically, but changed hormone levels can alter sexual dimorphism**

Lucas JN et. al. The rat mammary gland: morphologic changes as an indicator of systemic hormonal perturbations induced by xenobiotics. *Toxicol Pathol.*, 35:199-207 (2007)

Normal Cycle: Rat - Proestrus

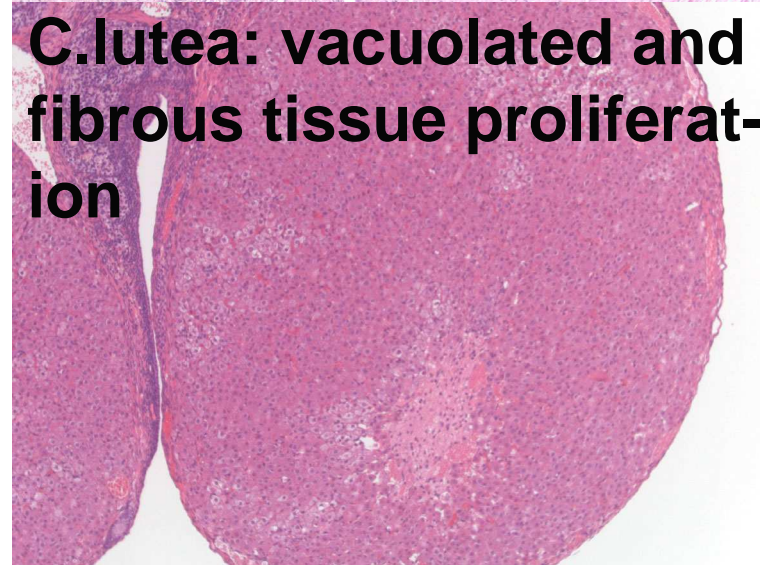
Vagina:
Mucification overlaying
cornified layer, thick ger-
minative epithelial layer



Horn: dilated

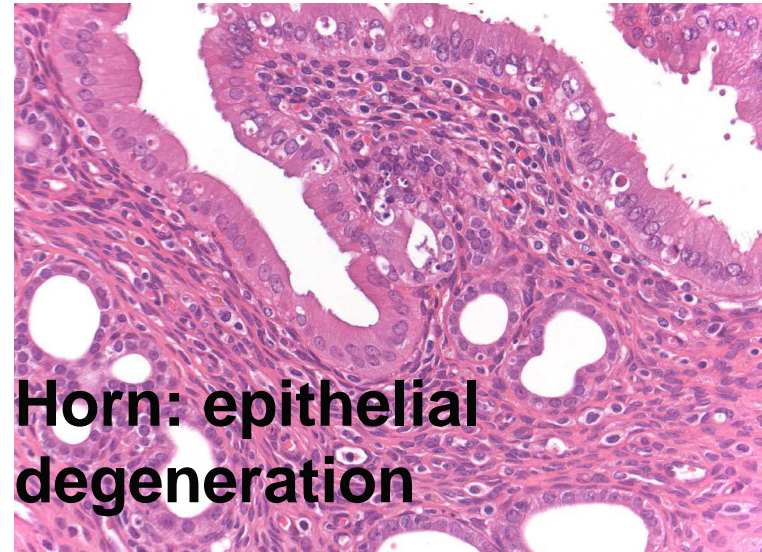
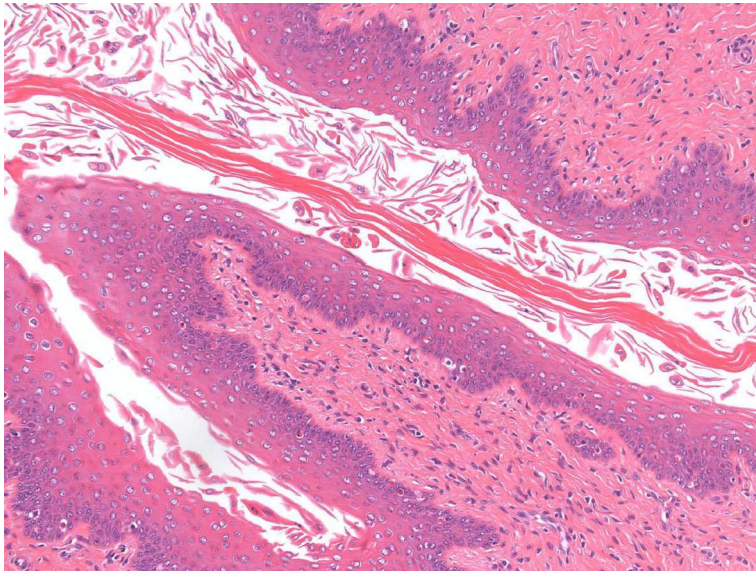


**C.lutea: vacuolated and
fibrous tissue proliferat-
ion**



Normal Cycle: Rat - Estrus

Vagina:
Shedding of cornified layer



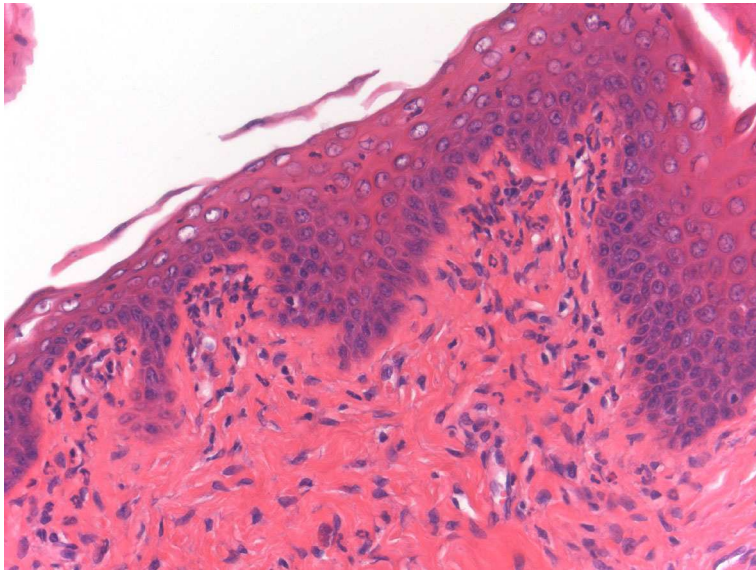
Horn: epithelial degeneration



C.lutea: basophilic with Fluid filled cavities

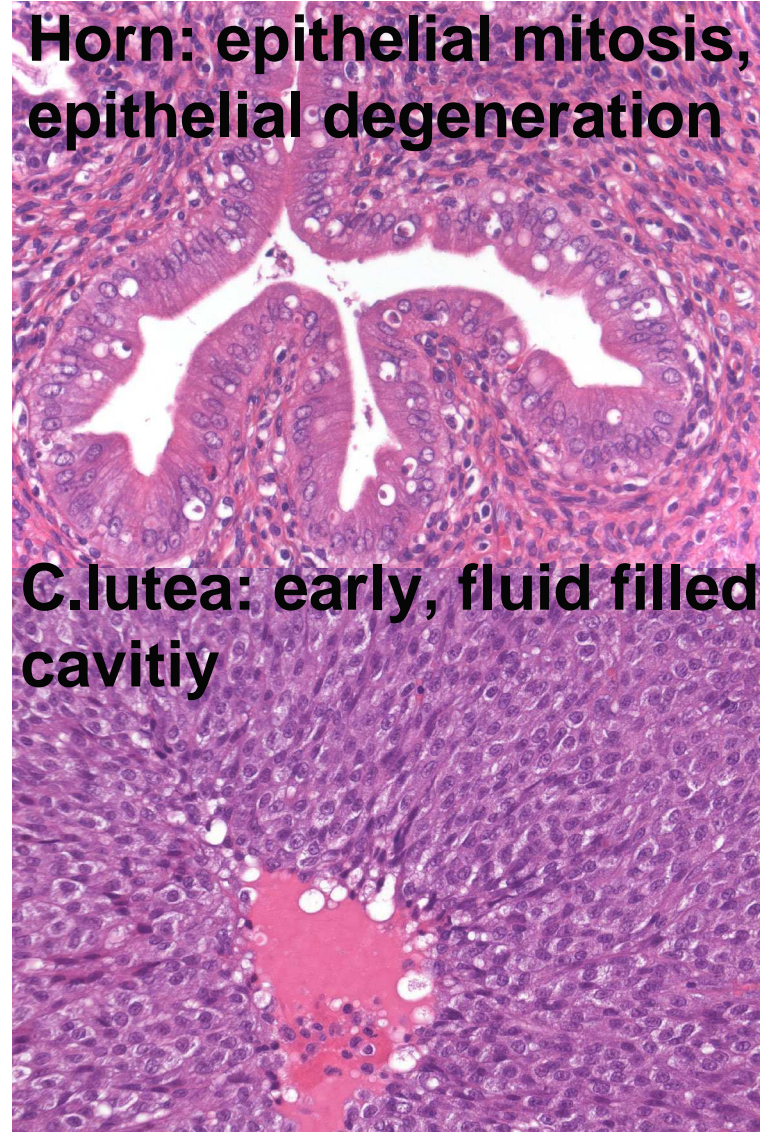
Normal Cycle: Rat - Metestrus

Vagina:
Shedding of cornified layer
and infiltration with
granulocytes



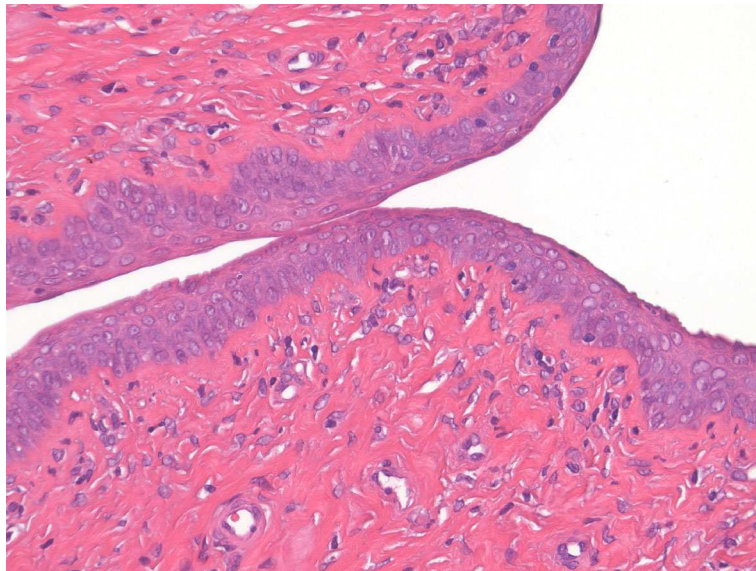
**Horn: epithelial mitosis,
epithelial degeneration**

**C.lutea: early, fluid filled
cavitiy**

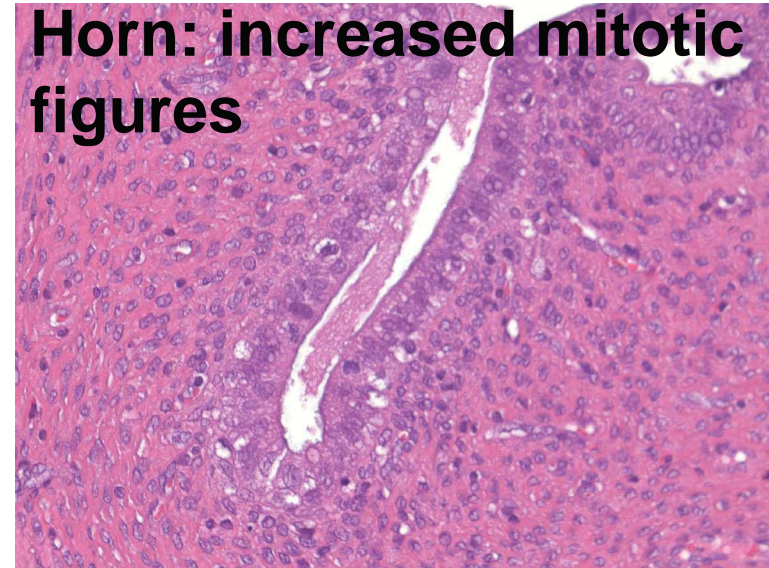


Normal Cycle: Rat - Diestrus

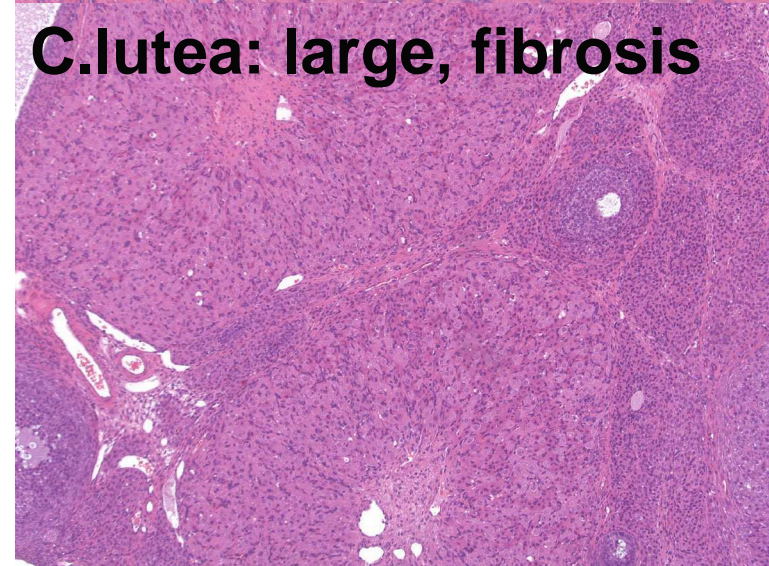
Vagina:
thick stratified epithelium,
No stratum granulosum



Horn: increased mitotic figures



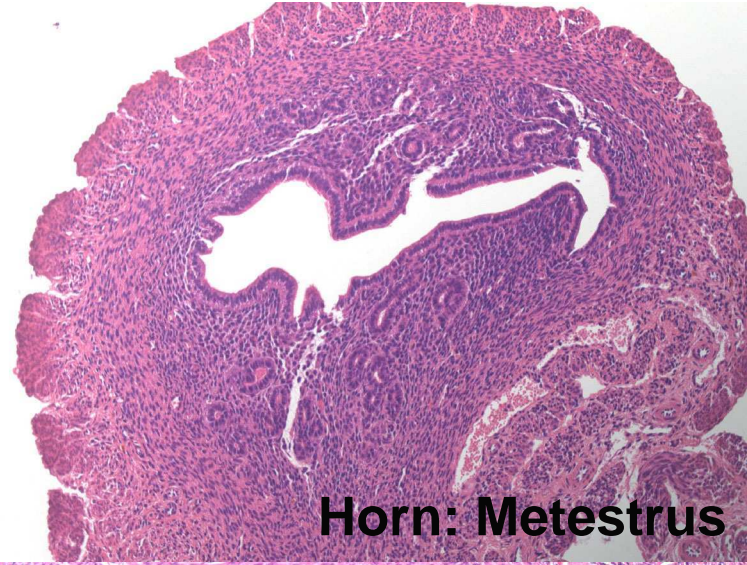
C.lutea: large, fibrosis



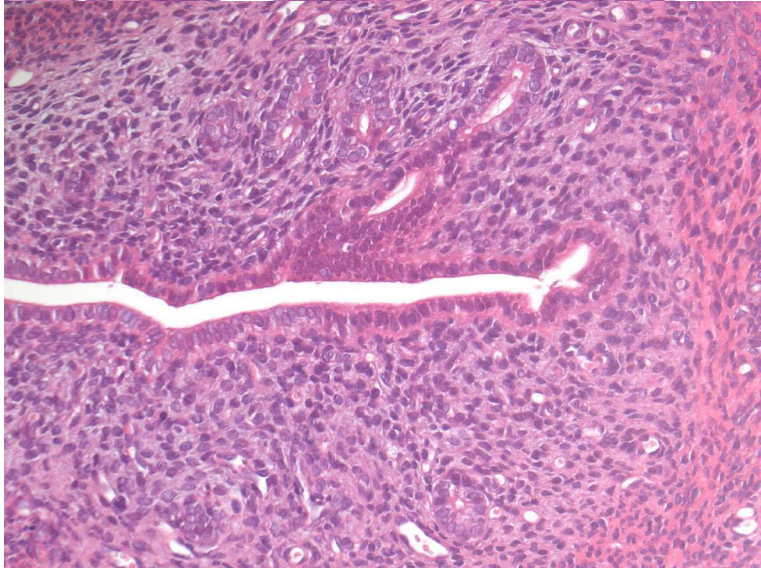
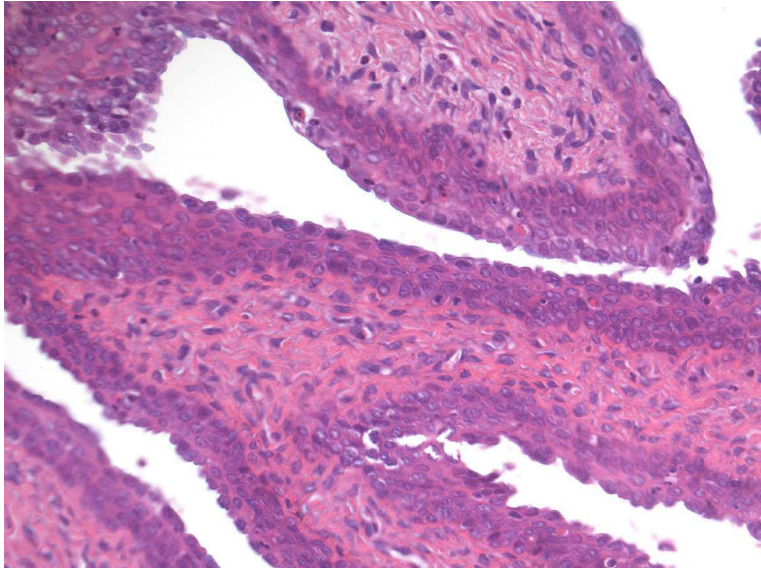
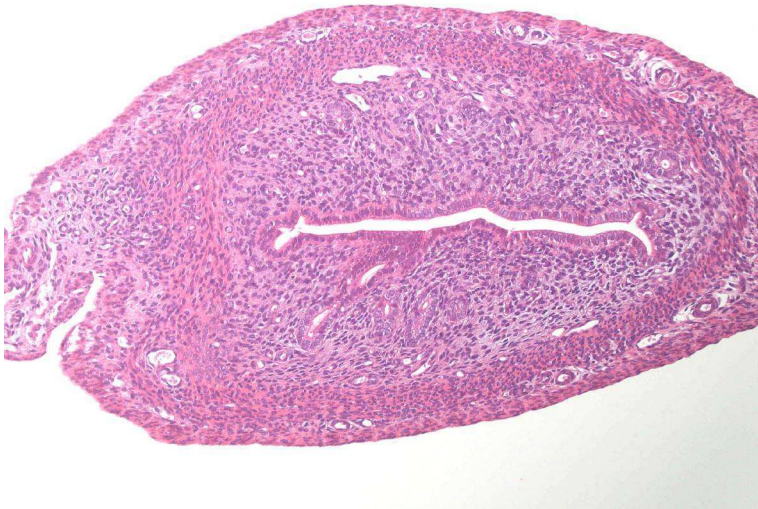
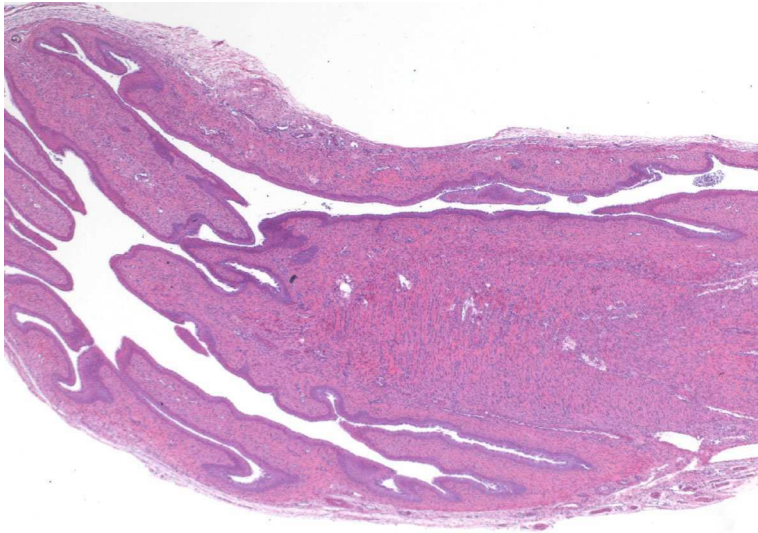
Normal Cycle: Mouse



Normal Cycle: Mouse

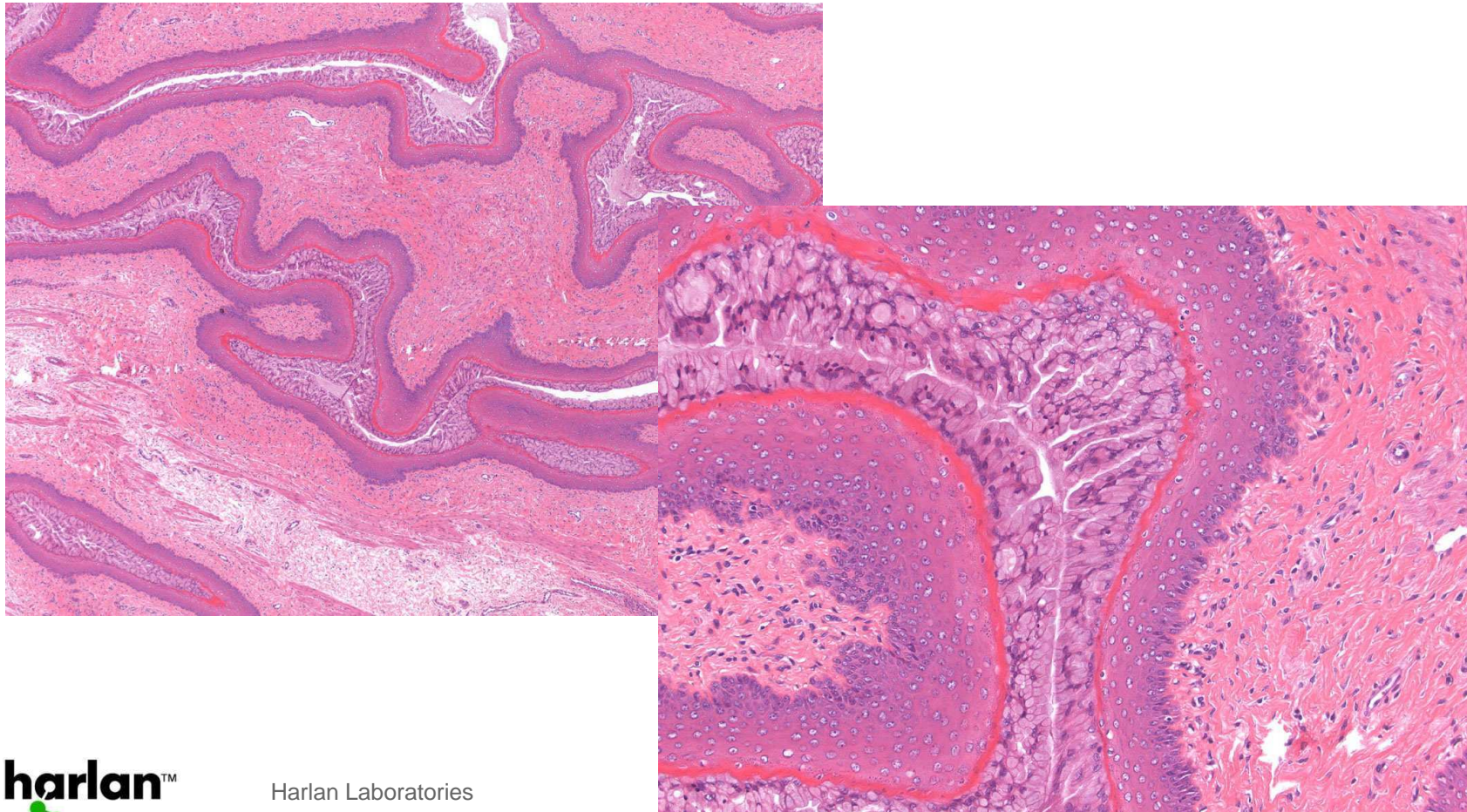


Immature Animal: Rat



Naturally Occurring Cyclic Changes: Rats

Vagina: Proestrus after Pregnancy with moderate mucification



Naturally Occurring Cyclic Changes: Rats



Problem: Lactational Diestrus

- **Food restriction during lactation results in increased progesterone levels**
- **Ability of food restriction to extend the length of lactational diestrus is mediated, in part, by a decrease in sensitivity to the positive-feedback effects of oestrogen**
- **Therefore high circulating concentrations of progesterone which apparently reduce the ability of oestrogen to induce progesterone receptor expression**

Abizaid A, Service G, Woodside B. Food restriction during lactation results in prolonged hyposensitivity to the positive-feedback effects of oestradiol.

J Neuroendocrinol. 15:1037-45 (2003)

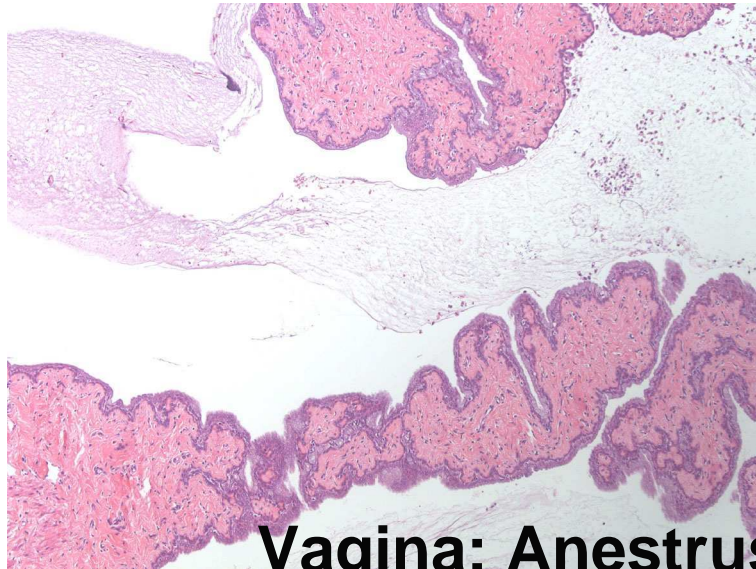
Woodside B. Effects of food restriction on the length of lactational diestrus in rats. Horm Behav. 25:70-83 (1991)

Problem: Lactational Diestrus

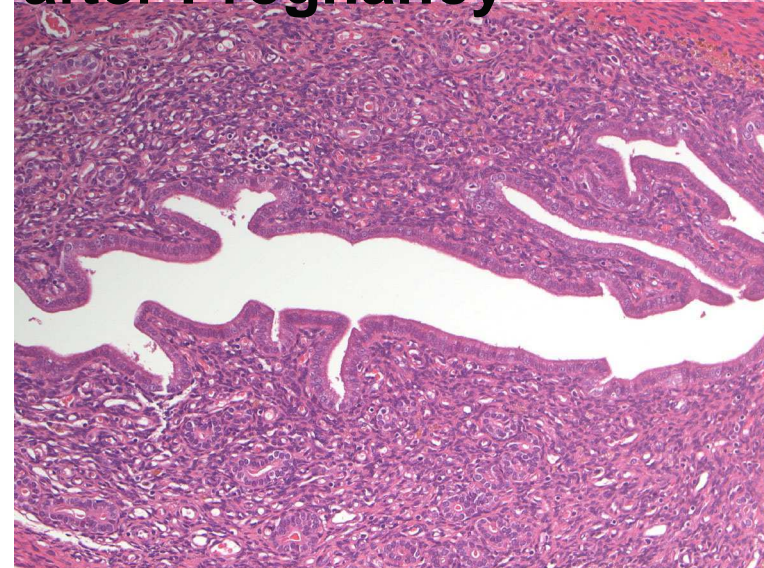
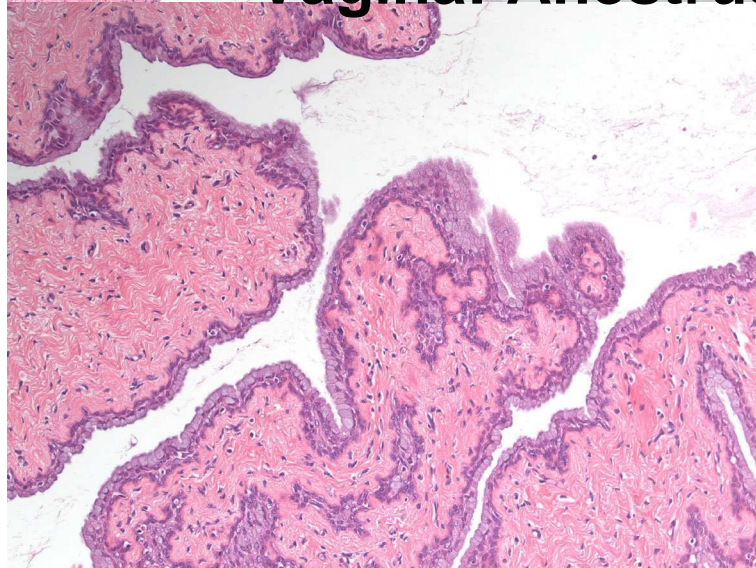
- **Lactational diestrus is morphological similar to anestrus**
- **Lactational diestrus often reveal focal/multifocal hypertrophic sialic acid containig surface epithelia**
- **Lactational diestrus mucosa may be atrophic**

- **Anestrus: Mucosa atrophic (1-2 epithelial layer)**
- **Anestrus: Often superficial layer is mucified**

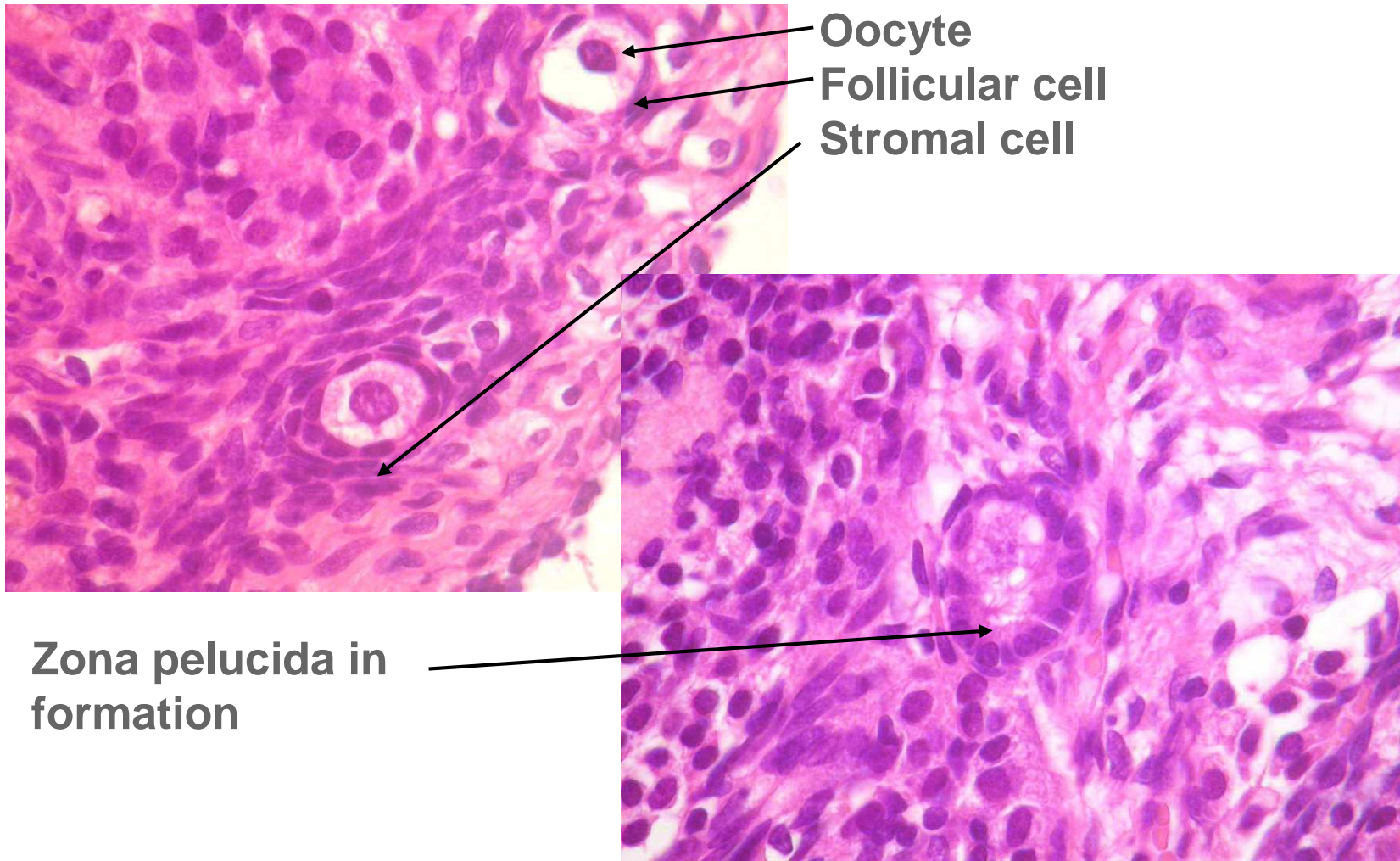
Naturally Occurring Cyclic Changes: Rats



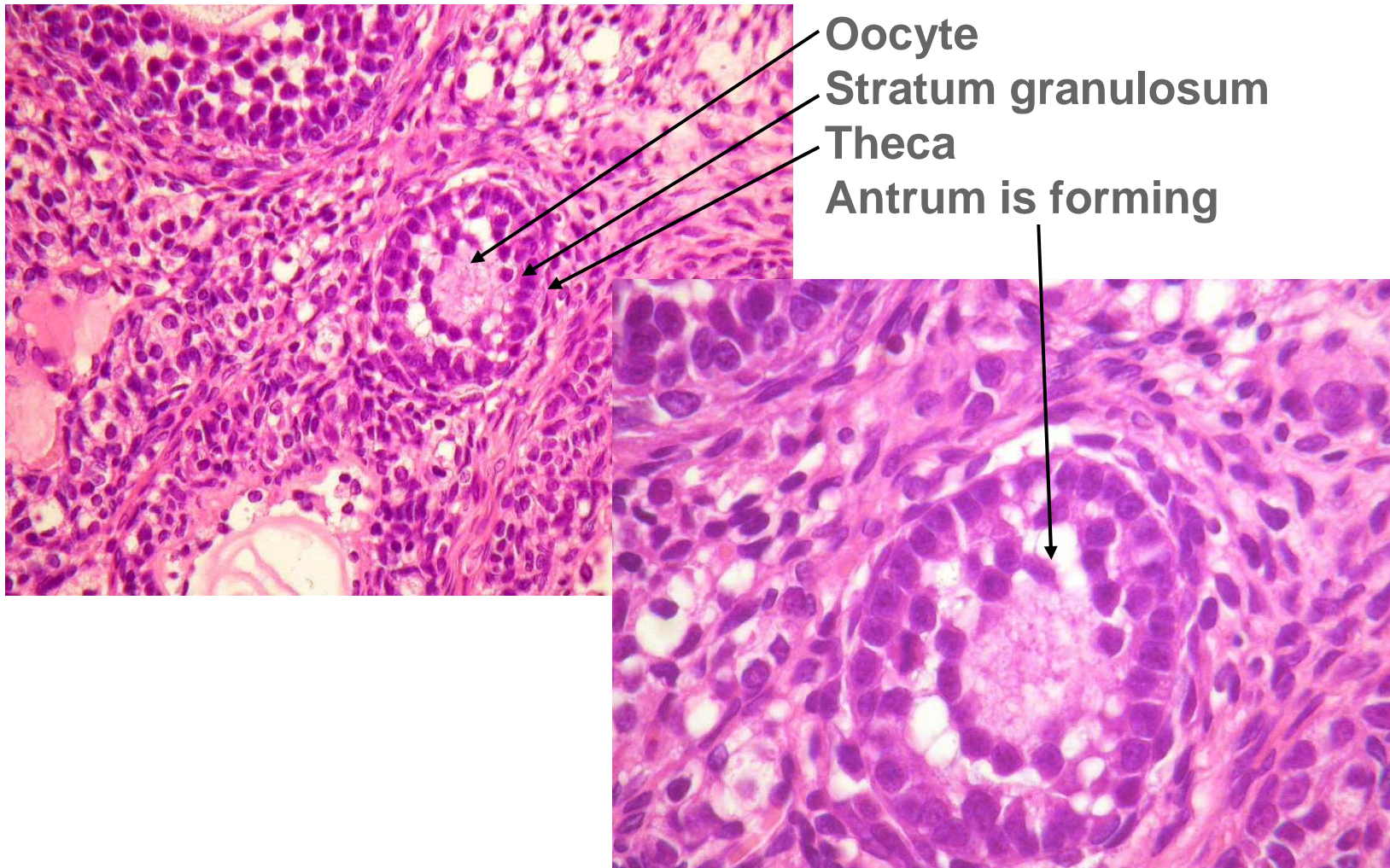
Vagina: Anestrus after Pregnancy



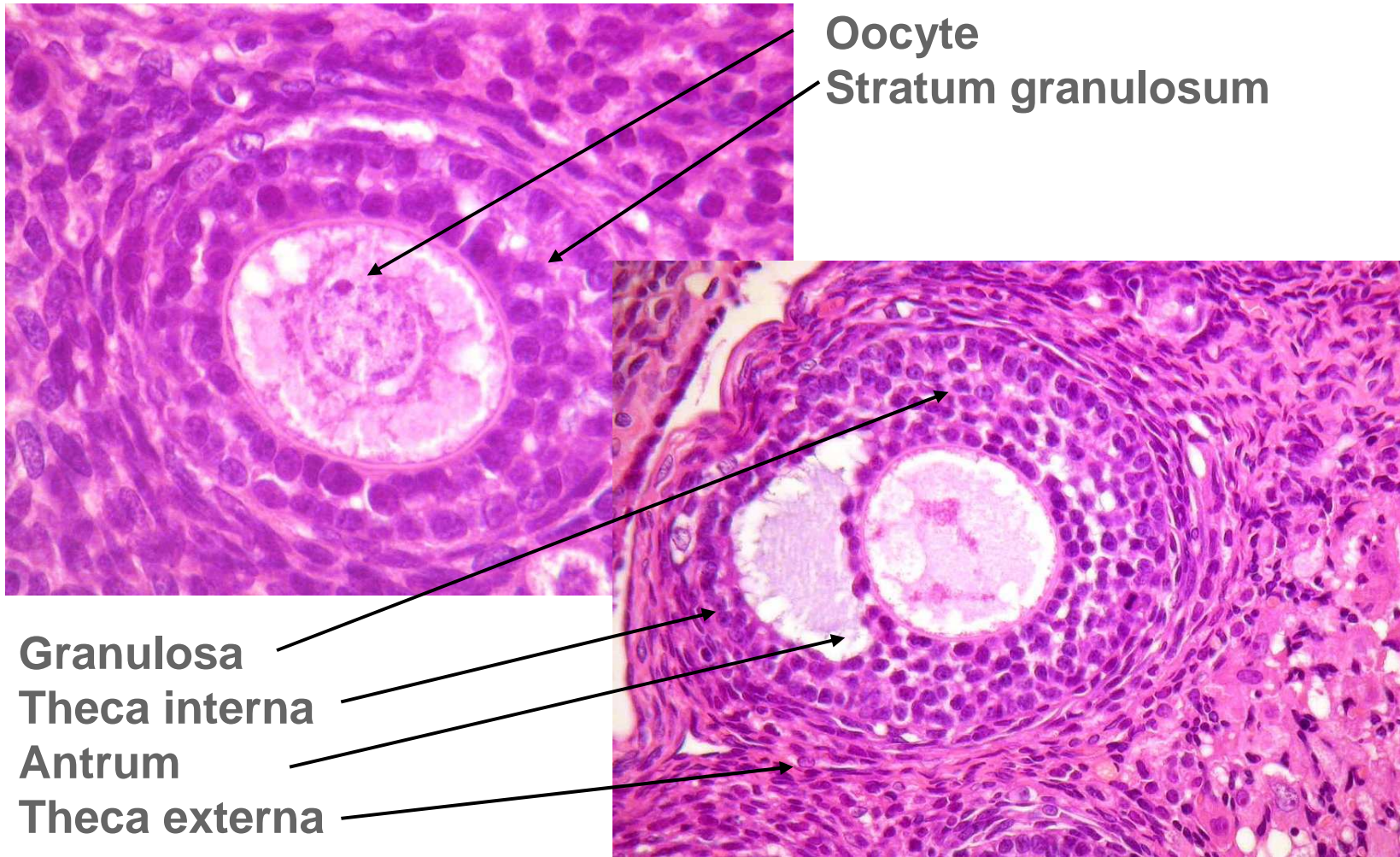
Normal Ovarian Structures: Primordia and Primary follicles



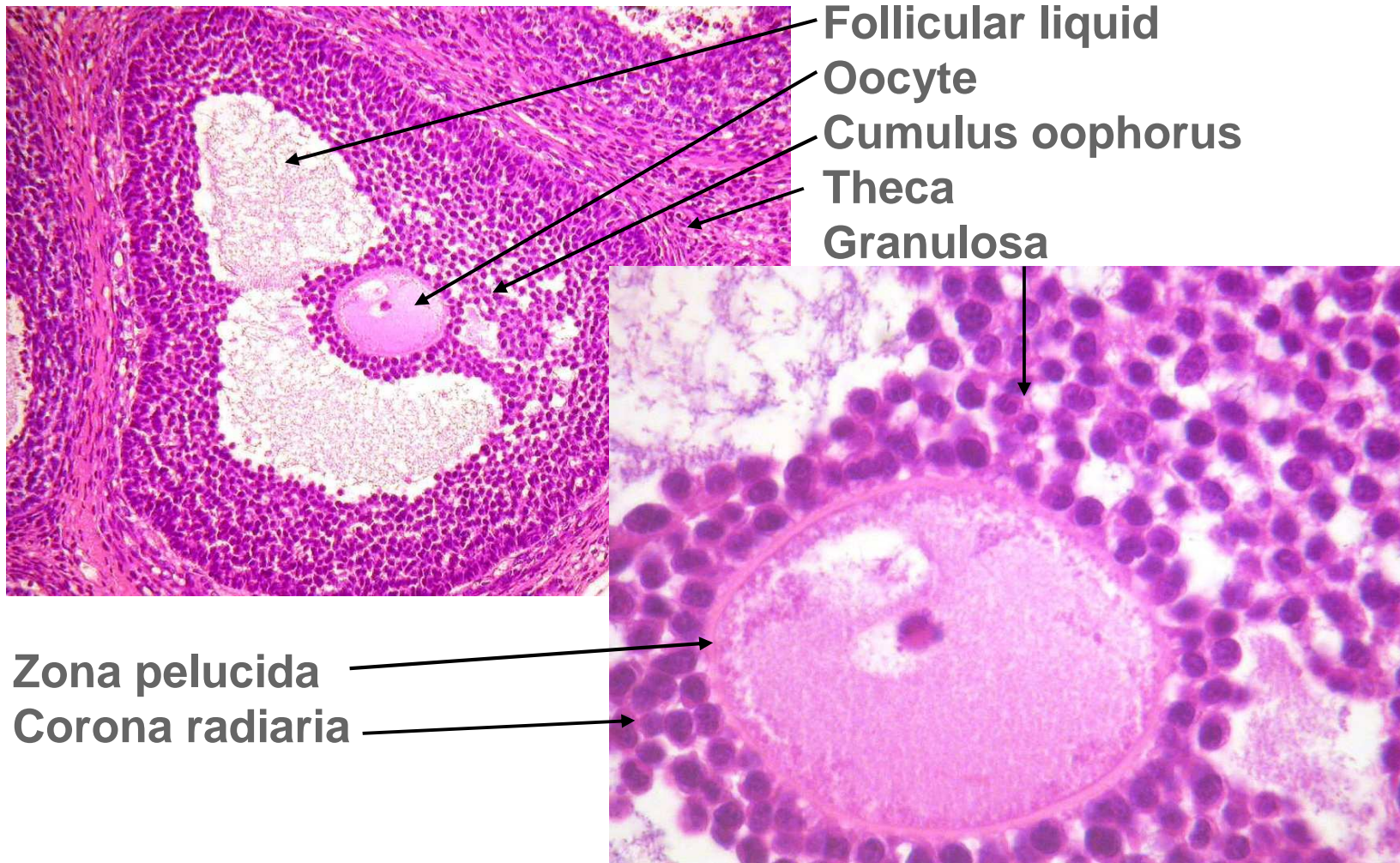
Normal Ovarian Structures: Growing Primary Follicle



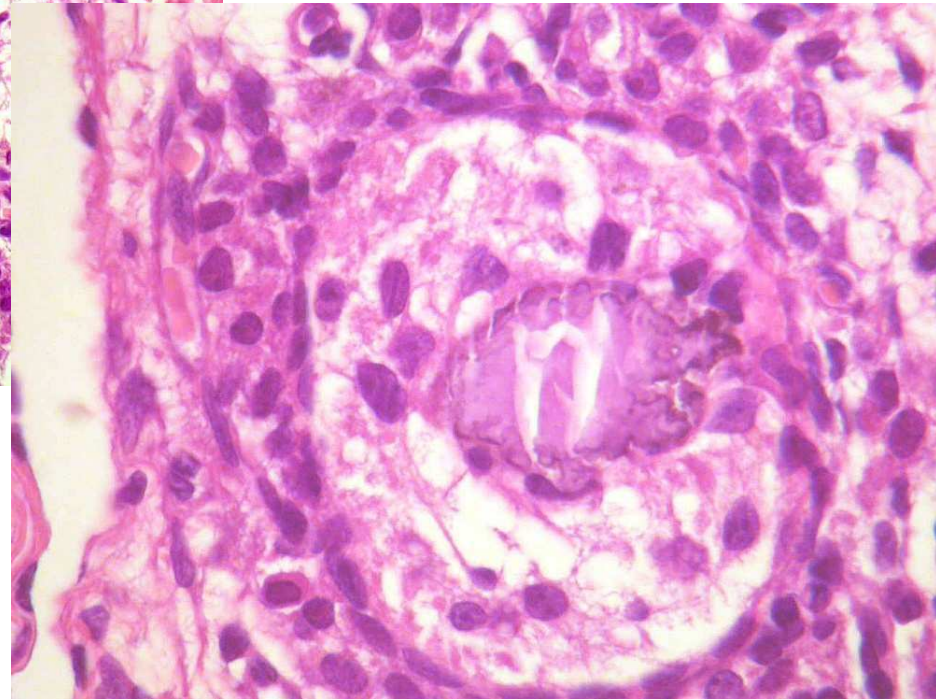
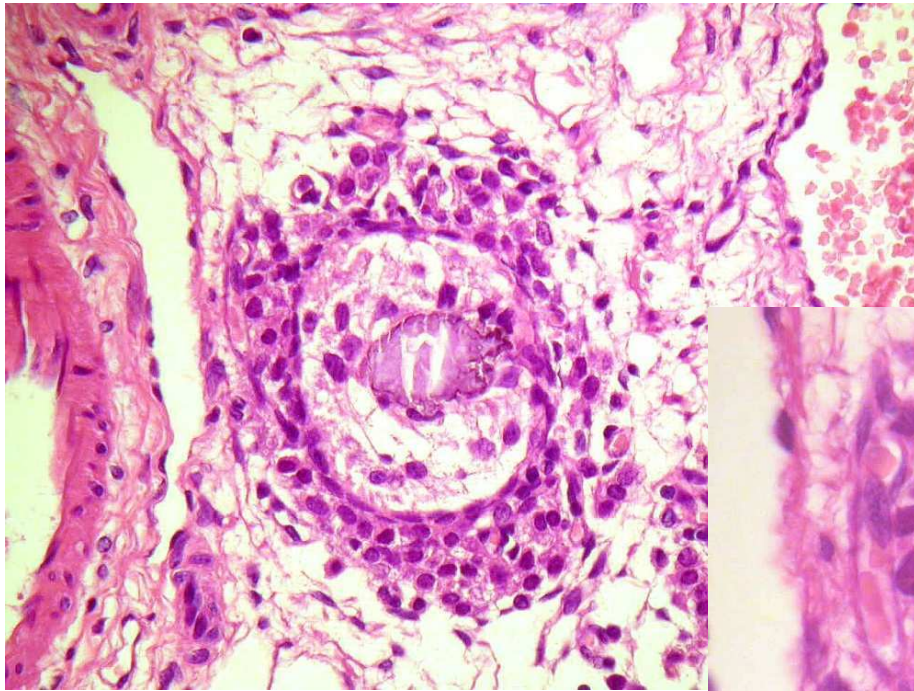
Normal Ovarian Structures: Growing Follicle (Secondary)



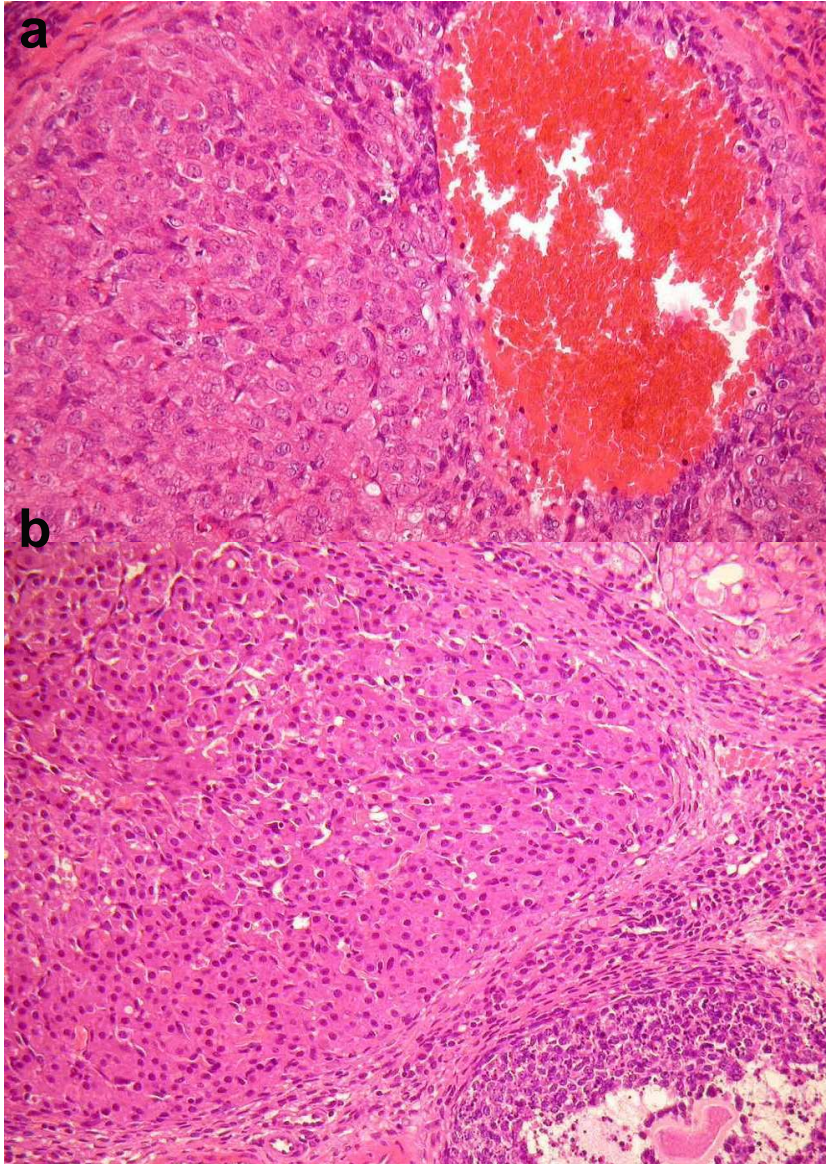
Normal Ovarian Structures: Antral Follicle (Tertiary)



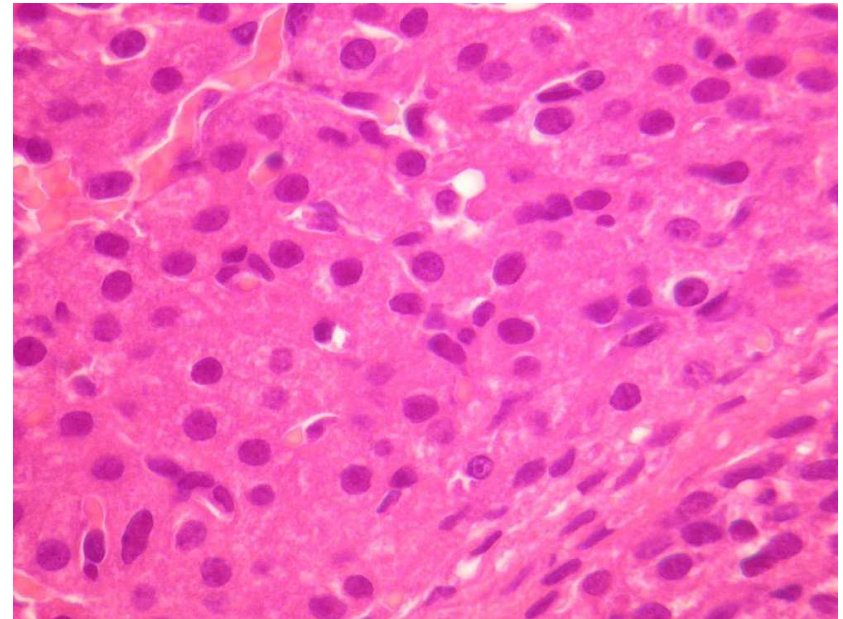
Rare Normal Ovarian Structures: Atretic Follicle



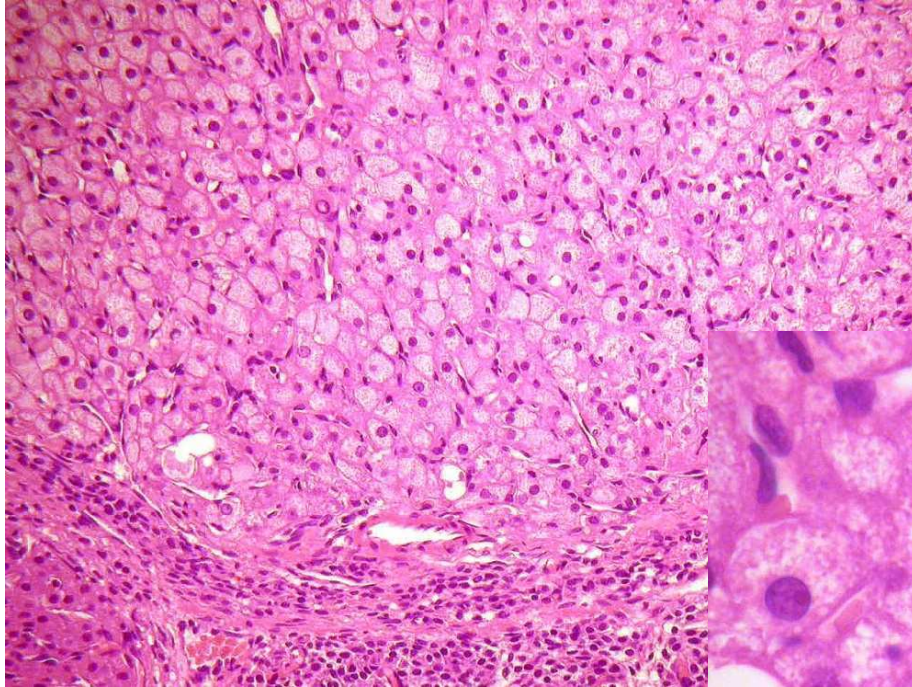
Normal Ovary Structures: Corpora lutea



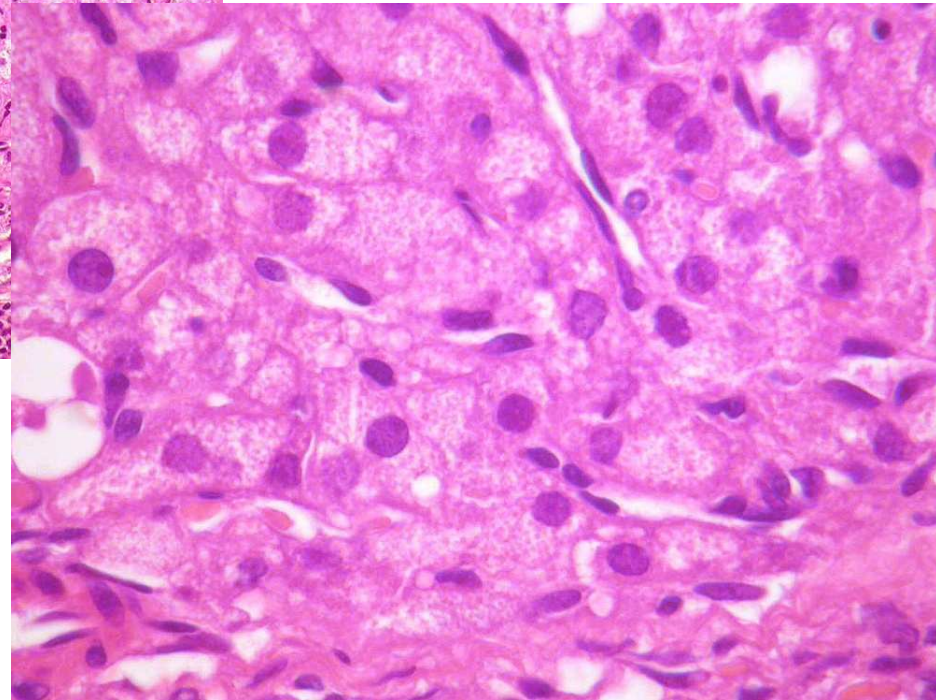
Corpus rubrum (a)
Young Corpora lutea (b. c)
(Estrus)



Normal Ovarian Structures: Corpora lutea



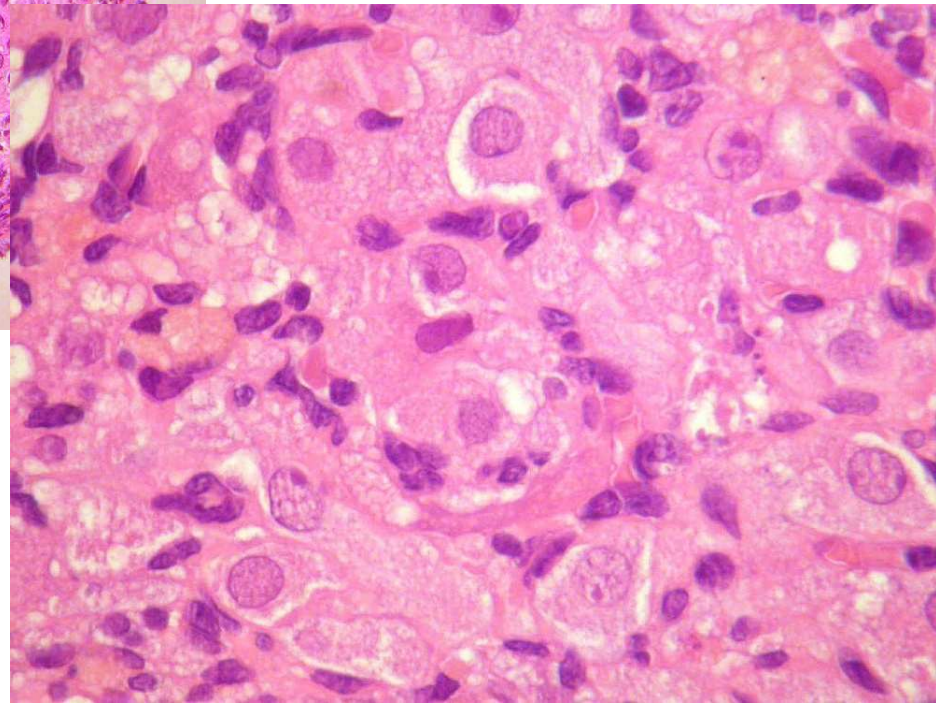
Luteinization (Diestrus)



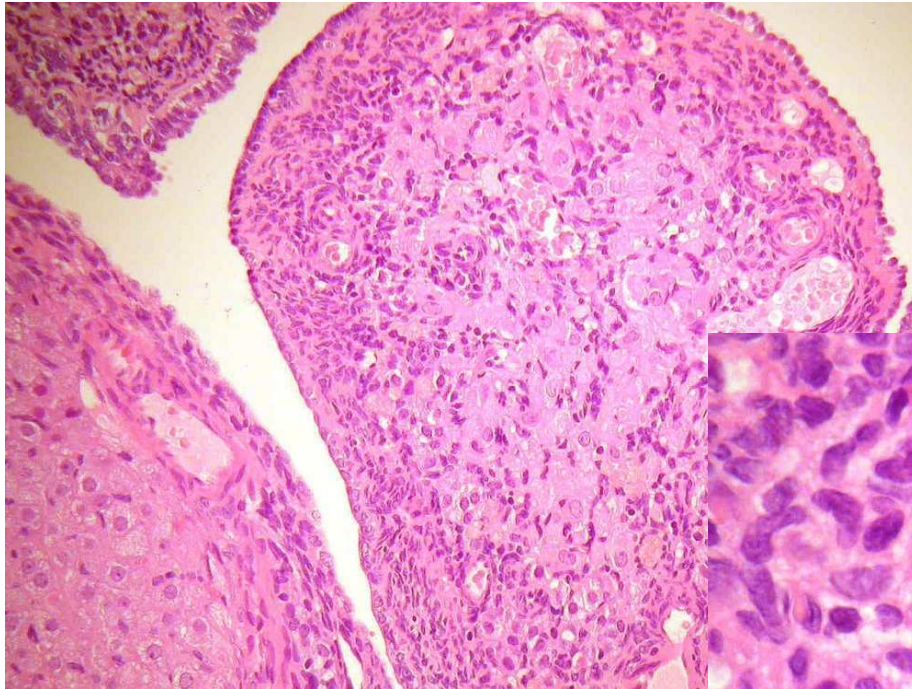
Normal Ovarian Structures: Corpora lutea



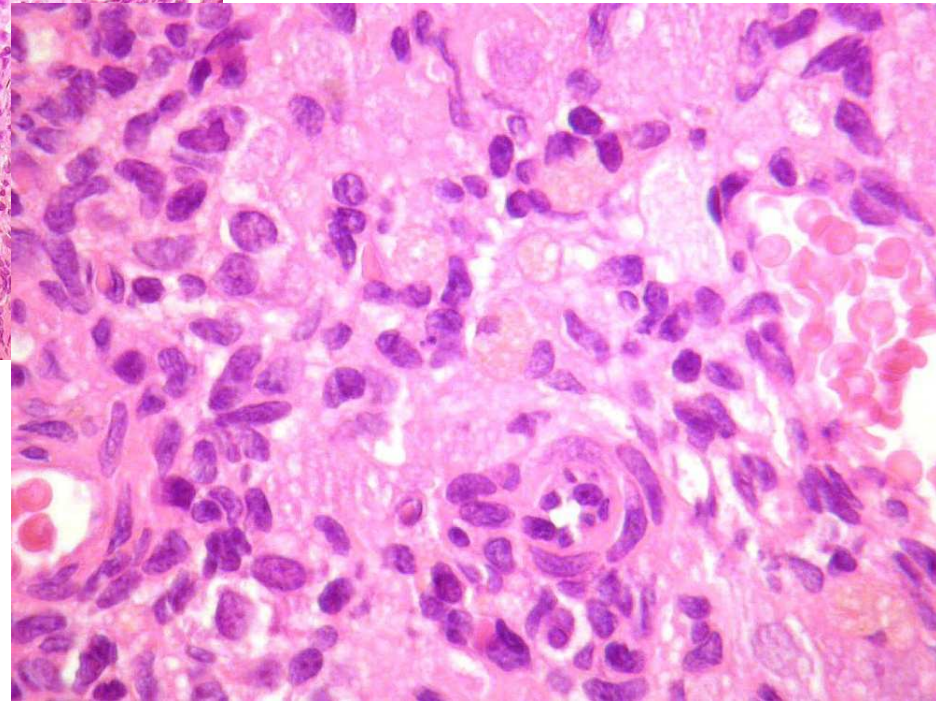
Atretic corpus luteum



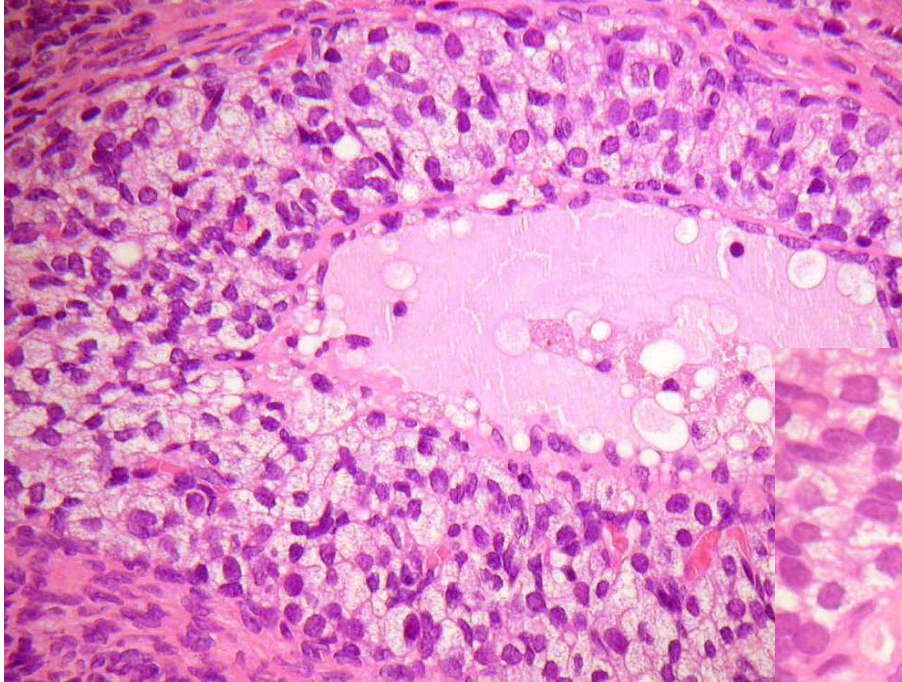
Normal Ovarian Structures: Corpora lutea



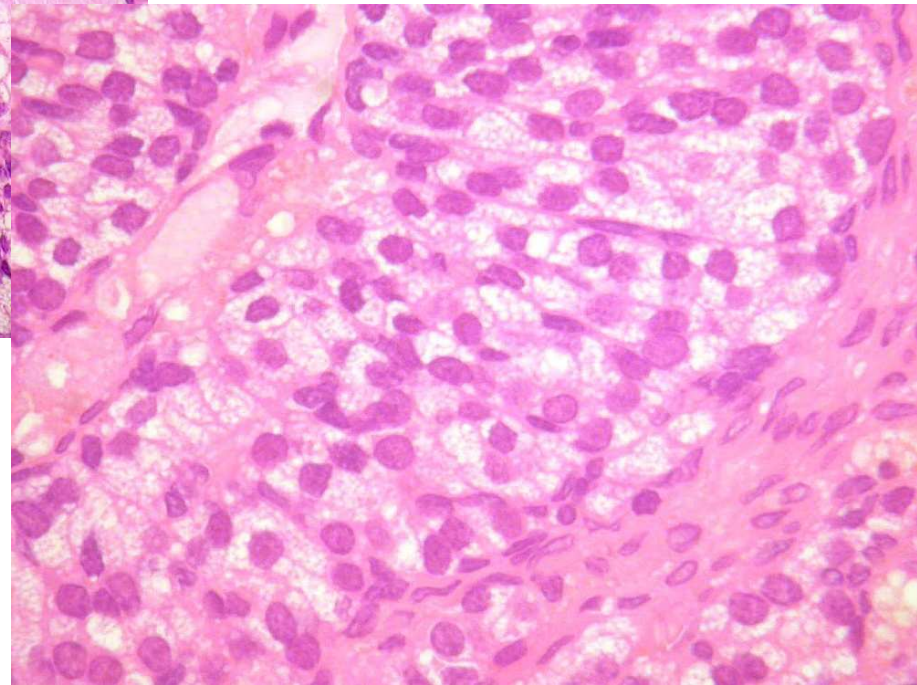
**Atretic corpus luteum
(Remnant)**



Normal Ovarian Structures: Corpora lutea



**Corpora albicantes
(remnants, interstitial
glands)**



Placenta

Decidua: endometrium during pregnancy that forms maternal part of the placenta

- **Discoidal placenta**
- **Hemochorial placentation (invasion of maternal tissue by the trophoblast cause disappearance of maternal blood vessels)**
- **Direct contact with maternal blood**

2 structures:

1. Choriovitellinae placenta:

- **Trophoblasts adhered to basement membrane**
- **Associated with decidua capsularis**
- **Degenerates and disappears by day 14 of gestation**

Placenta

2. Chorioallantoic placenta:

- Develops before degeneration of choriovitellinae placenta in mesometrial uterine region
- Two zones:
 - a) Junctional zone adjacent to decidua basalis consisting of outer giant cells (trophoblasts) and maternal vascular channels (trophospongium with highly packed basophilic spongioblast cells)
In decidua basalis, maternal blood spaces lined by cytotrophoblast and syncytiotrophoblast.

Trophospongium contains necrotic areas.