



# CONTINUING EDUCATION IN TOXICOLOGIC PATHOLOGY REPRODUCTIVE SYSTEM



ORGANIZED BY SOCIETY FOR TOXICOLOGIC PATHOLOGY IN INDIA (STPI)

OCTOBER 29-31, 2010

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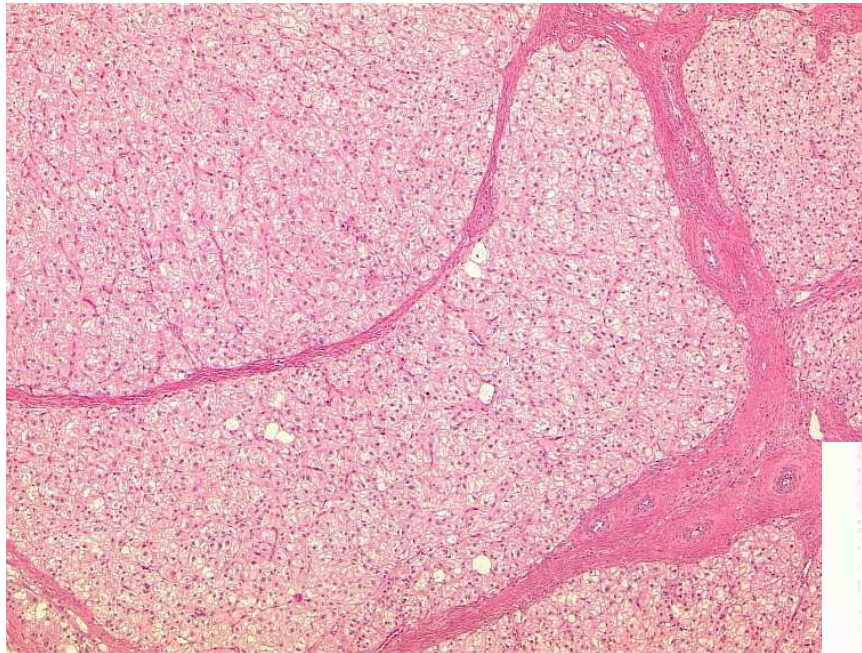
**Vishnu Traders**



**RCC**  
Linking science to progress

## Aromatase inhibitors - Letrozole

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**13-Week treatment:  
increased number,  
persistence/hypertrophy  
of corpora lutea**

**26-Week treatment:  
absence of large corpora  
lutea, follicular cysts,  
diffuse stromal cell  
hyperplasia**



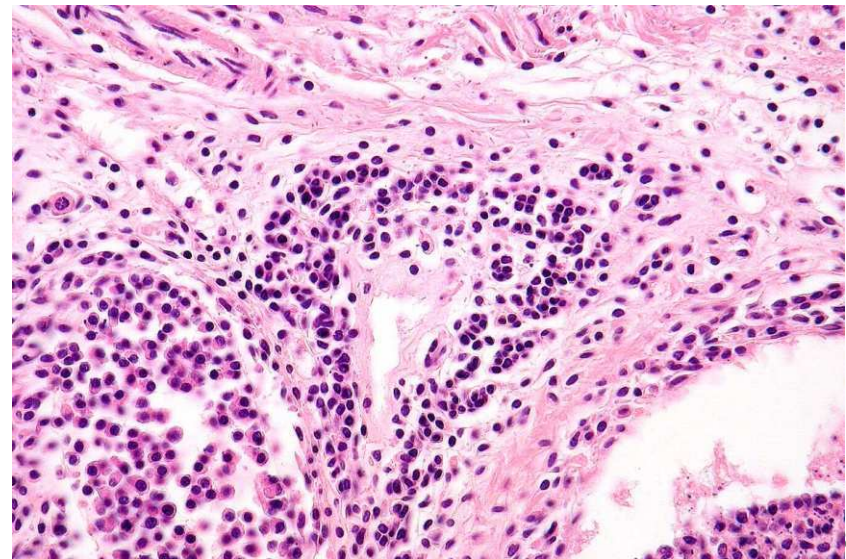
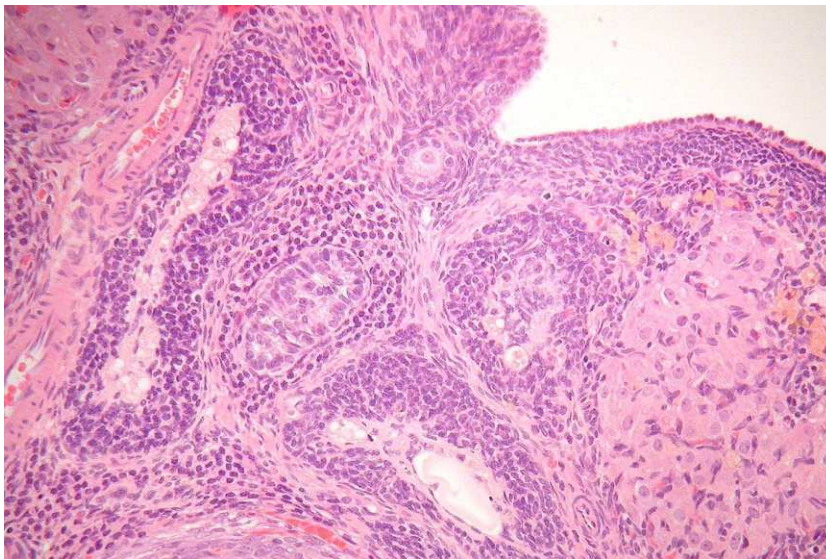
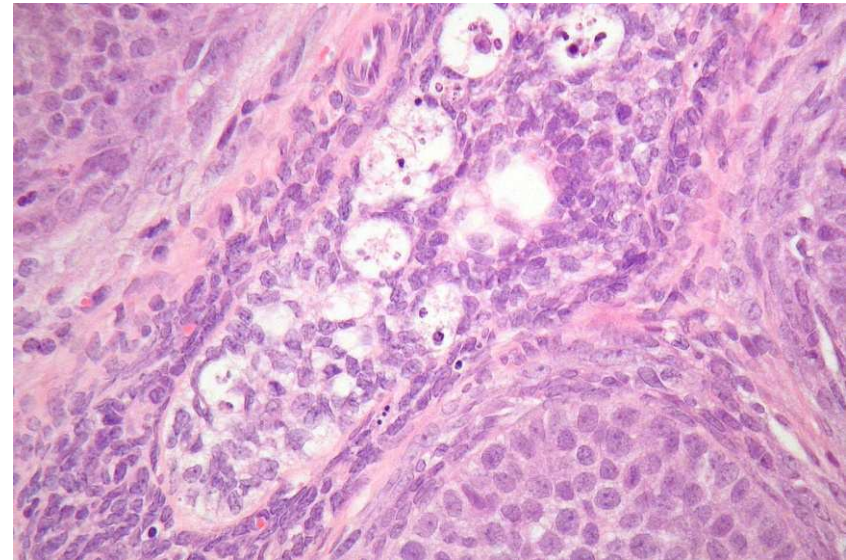
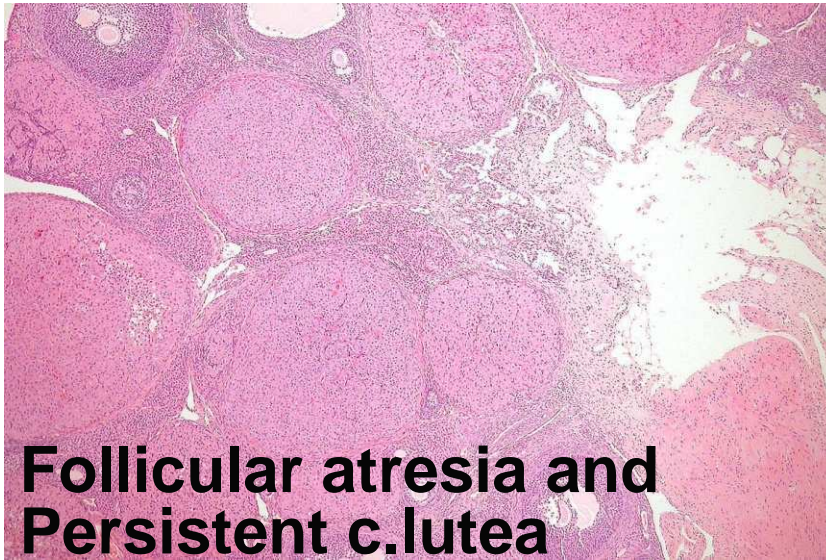
## Aromatase inhibitors - Letrozole

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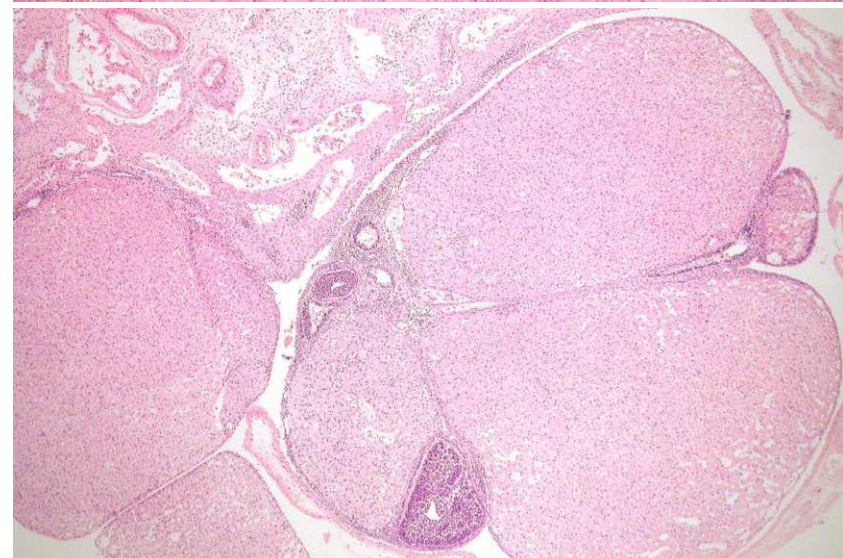
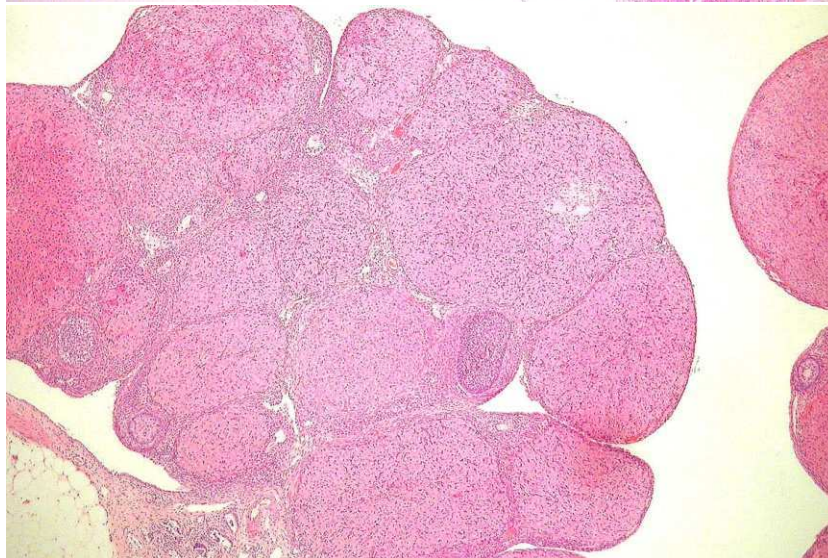
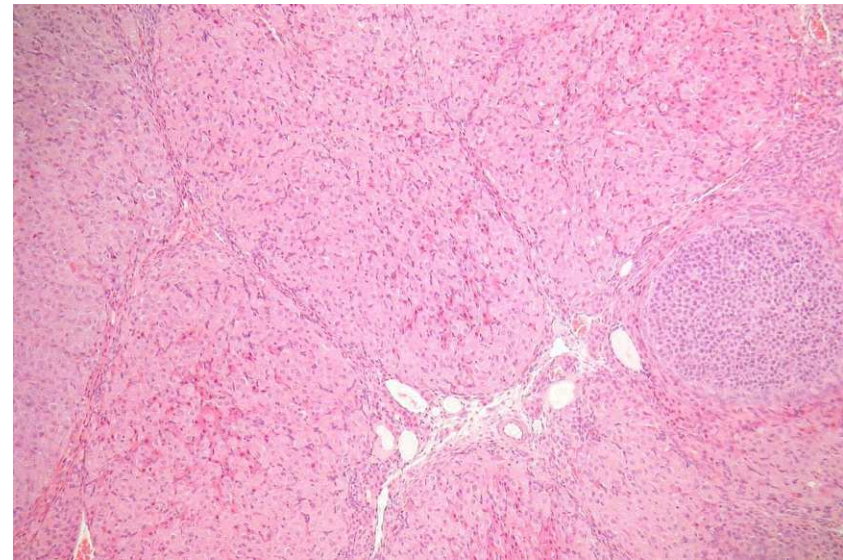
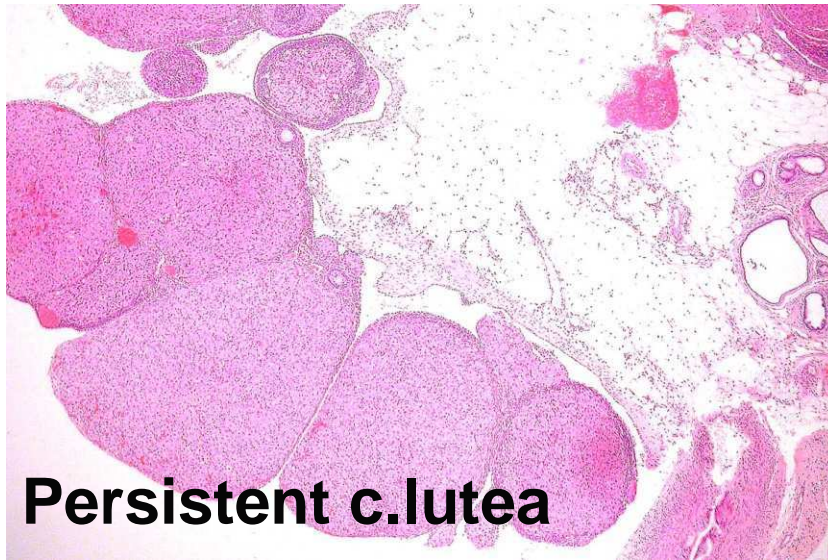


**26-Week treatment: atrophy**

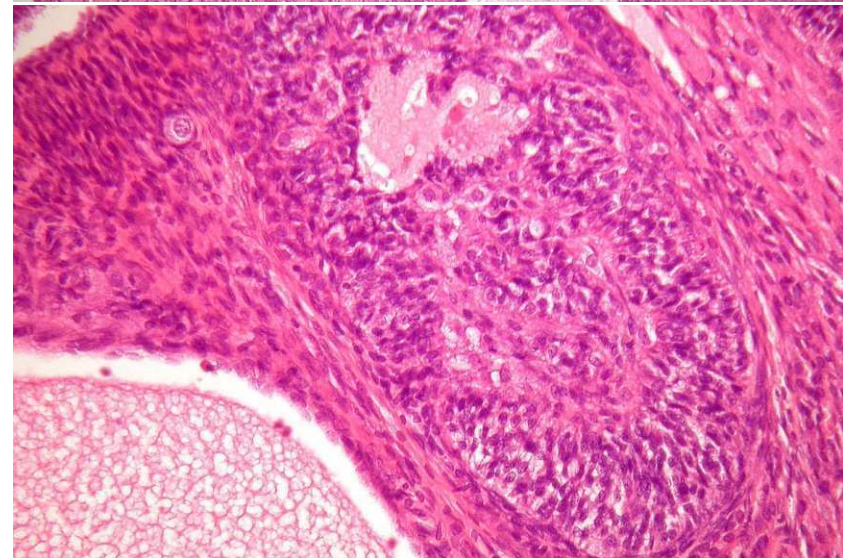
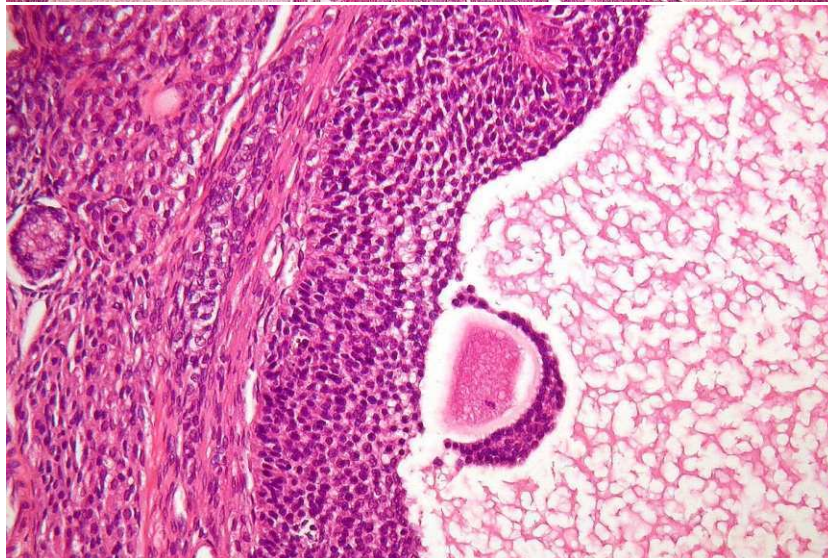
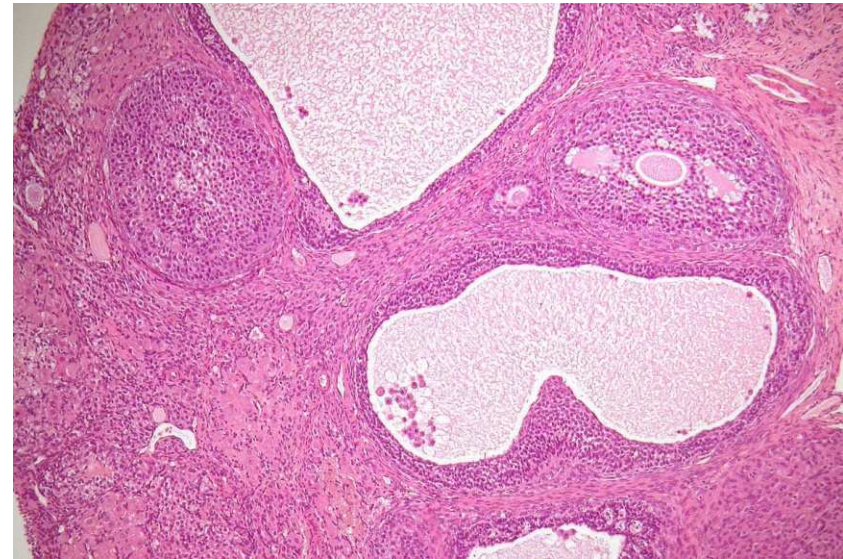
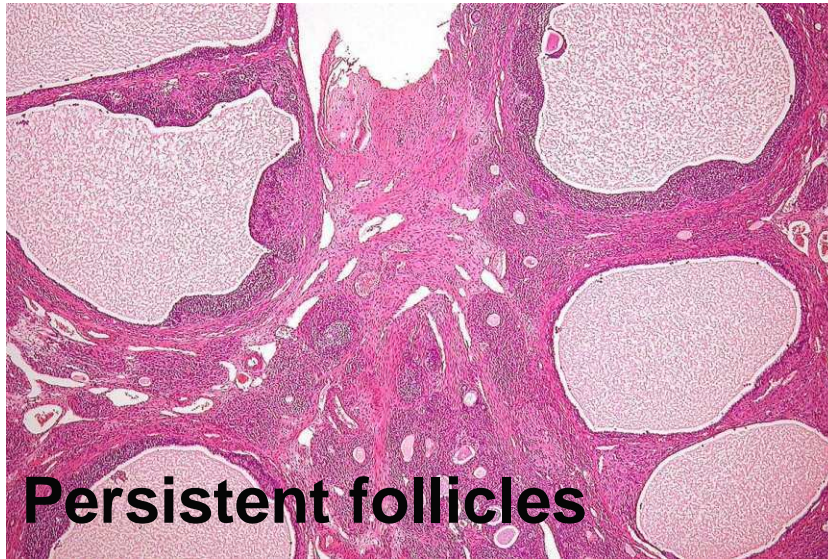
## Induced Cycle Interruption: Ovaries - PDE4 Inhibitors



## Induced Cycle Interruption: Ovaries – PDF4 Inhibitors



## Induced Cycle Interruption: Ovaries - rhGDF5



## EGFR Tyrosine Kinase Inhibitors

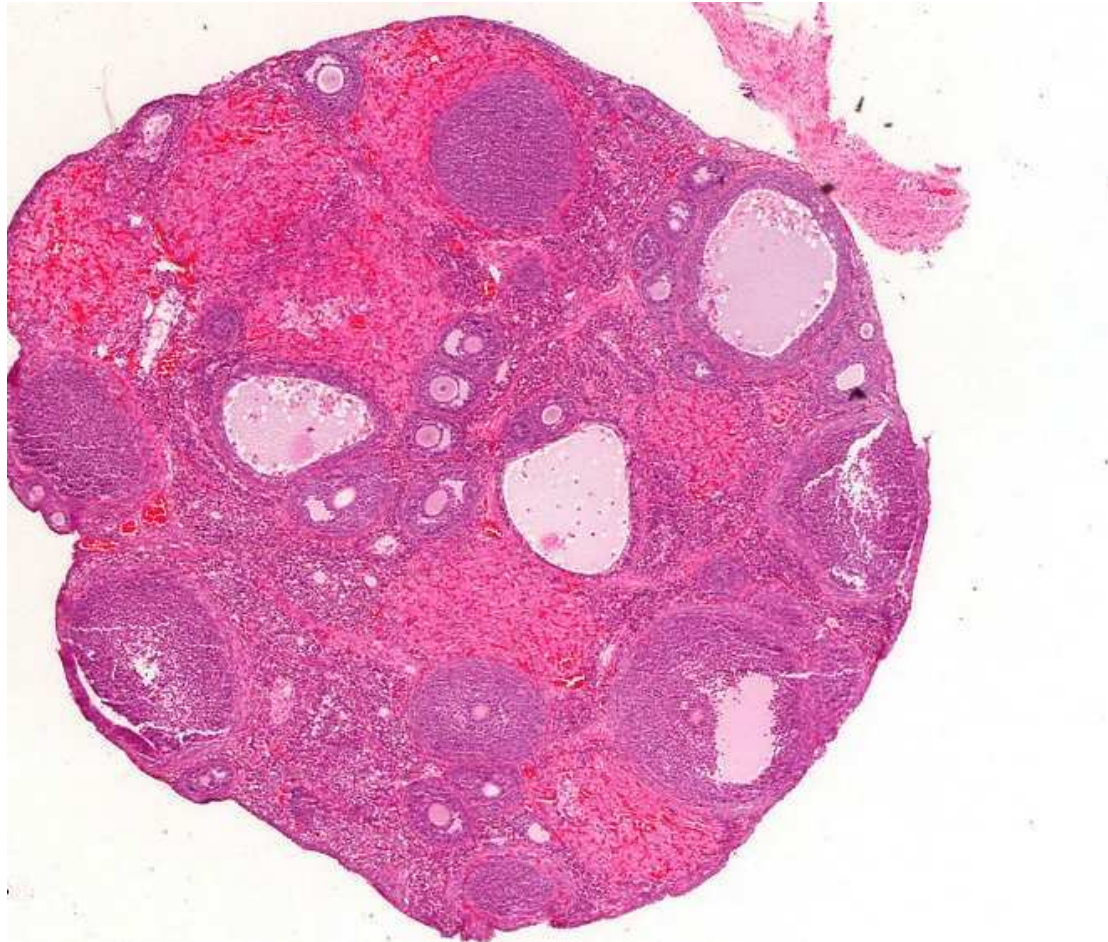
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- Treatment of solid tumour disease
- In rats, daily dosing for 14 days: atrophic changes in ovaries
- EGF has a role in the regulation of normal ovarian function and has an effect on many different ovarian cells
- Follicular development, and hence subsequent oestrogen production, involves granulosa cell proliferation and differentiation which is modulated by paracrine mechanism involving EGF and other growth factors

Pyrah I, Wadsworth P.: Classic Examples in Toxicologic Pathology (3rd Edition)

## EGFR tyrosine kinase inhibitors

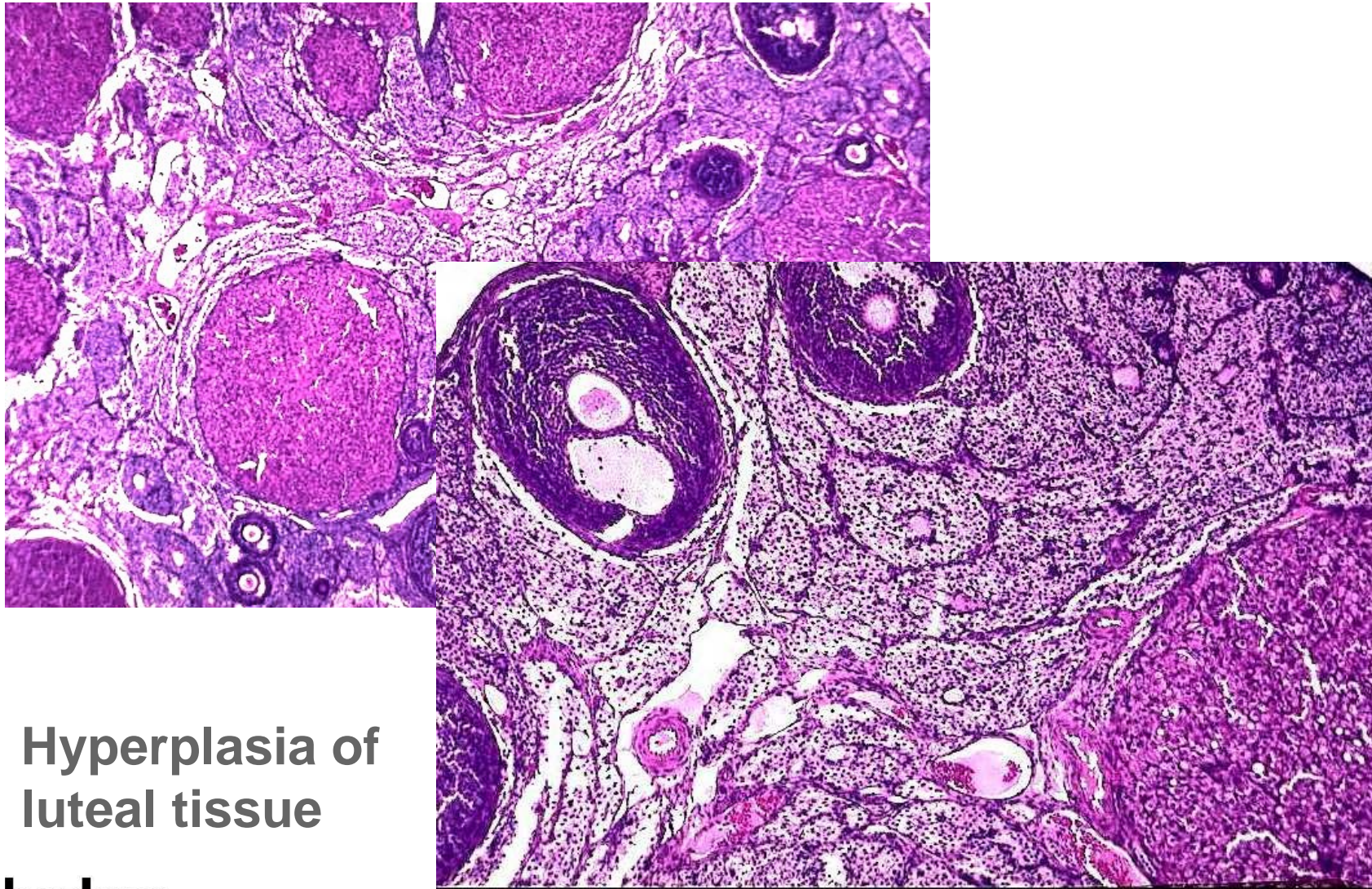
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**Absence of corpora lutea**



## Induced Cycle Interruption: Ovaries - Herbicide



Hyperplasia of  
luteal tissue

## Selective Estrogen Receptor Modulators (SERMs)

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- **Synthetic estrogen-like, non-steroidal, structurally diverse compounds binding to estrogen receptors (ER $\alpha$  and ER $\beta$ )**
- **Mixed agonist and antagonist effects in tissue specific manner**
- **Benefits include prevention of osteoporotic fractures and colorectal cancer**
- **Harms include coronary heart disease, stroke, thromboembolism, breast cancer (after long term therapy, i.e. over 5 years), cholecystitis**

Brander Weber P, Gasser JA, Germann PG:  
Classic Examples in Toxicologic Pathology (3rd Edition)

## Selective Estrogen Receptor Modulators (SERMs)

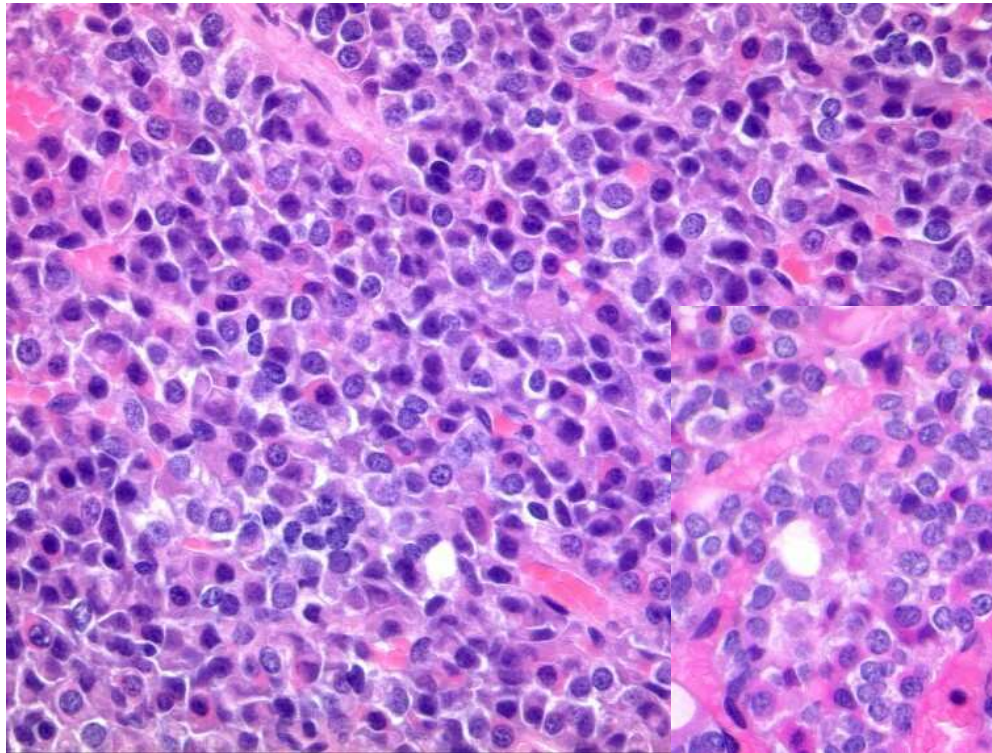
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### Experimental Design:

- Hypersecretion of gonadotrophs (FSH, LH) due to the removal of the negative feedback mechanism to the hypothalamic-pituitary-gonadal axis after ovariectomy.
- Prevention by substitution with  $17\alpha$ -ethinylestradiol, and partially prevented in animals treated with Raloxifene without dose-relationship.

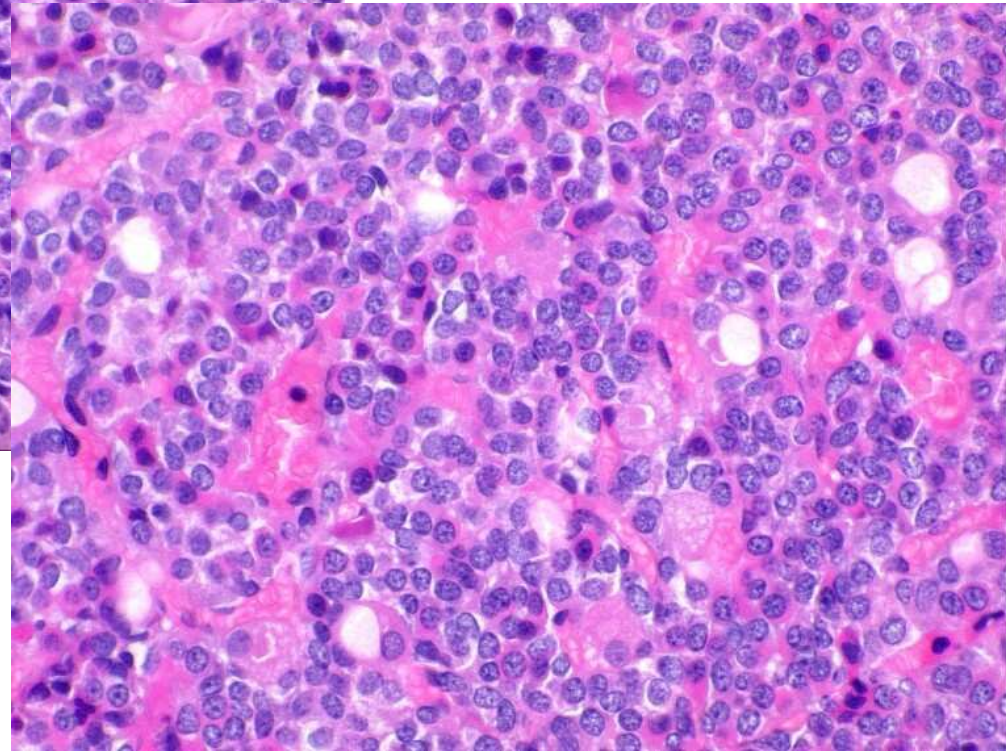
# Selective Estrogen Receptor Modulators (SERMs)

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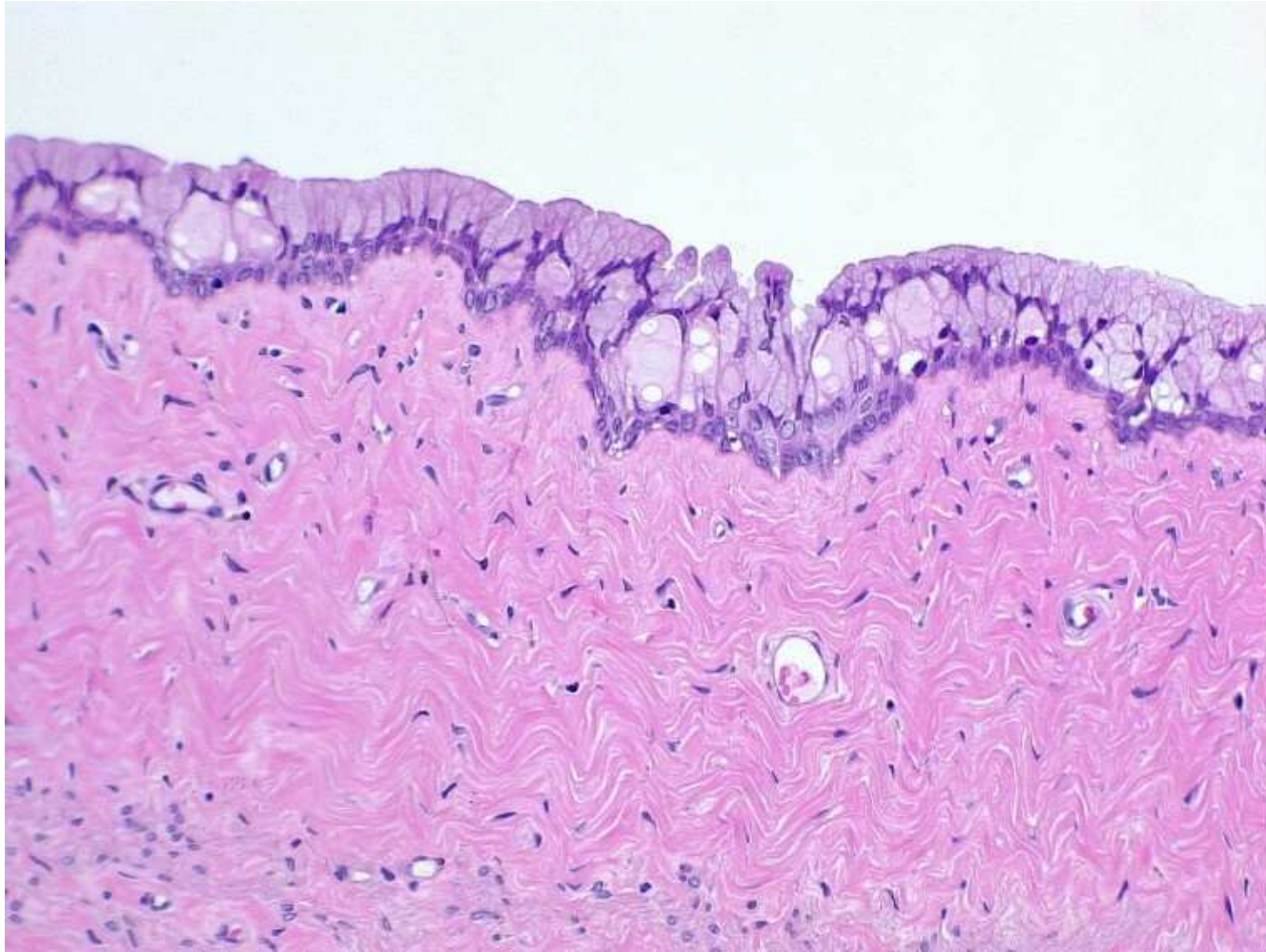
Pituitary: OVX

Pituitary:  
OVX + Raloxifene



## Selective Estrogen Receptor Modulators (SERMs)

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**Vagina: OVX + Raloxifene**

## Dopamine Agonists - Bromocriptine

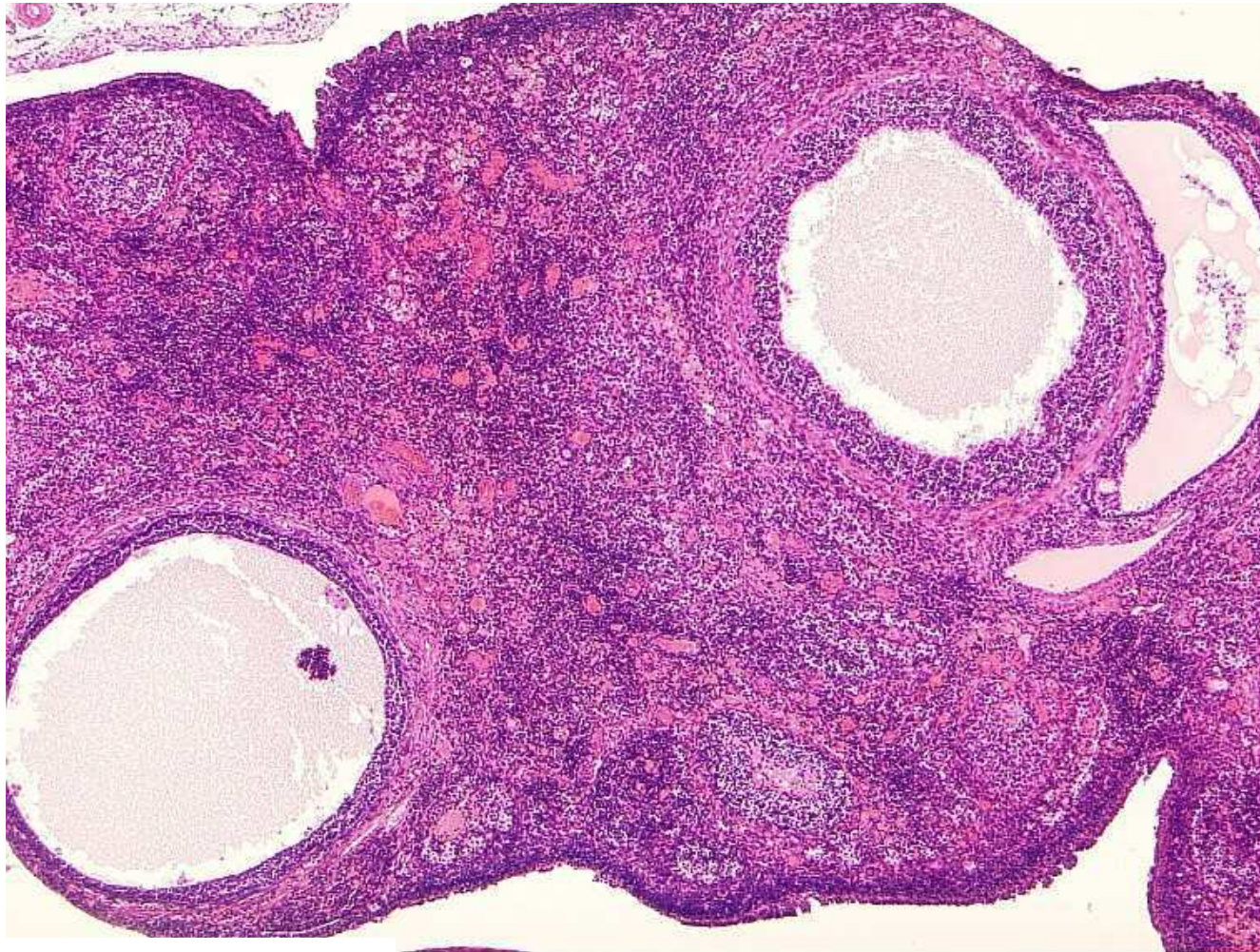
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- Endocrinological and neurological clinical indications
- Oral application to SD: OFA rats for 53 weeks
- Increased numbers of corpora lutea and cystic follicles in ovaries, associated with squamous metaplasia of uterine endometrium, pyometra and/or endometritis
- Bromocriptine does not lead to elevated estradiol levels per se, but is associated with higher estradiol to progesterone ratio

Ettlin RA, Junker U, Prentice DE:  
Classic Examples in Toxicologic Pathology (3rd Edition)

## Dopamine Agonists - Bromocriptine

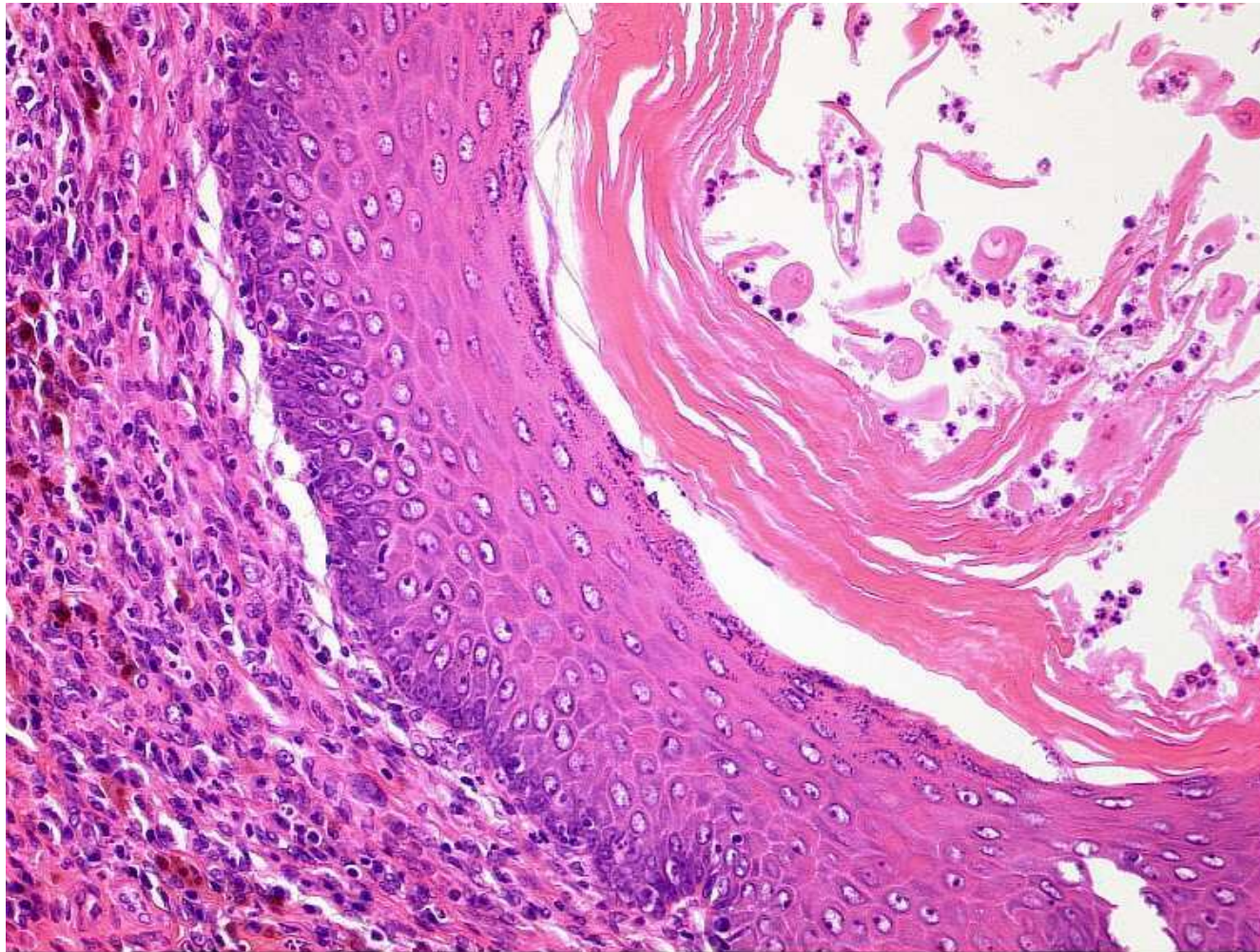
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**Cystic follicles, a consequence of the absence of the ovarian cycle**

## Dopamine Agonists - Bromocriptine

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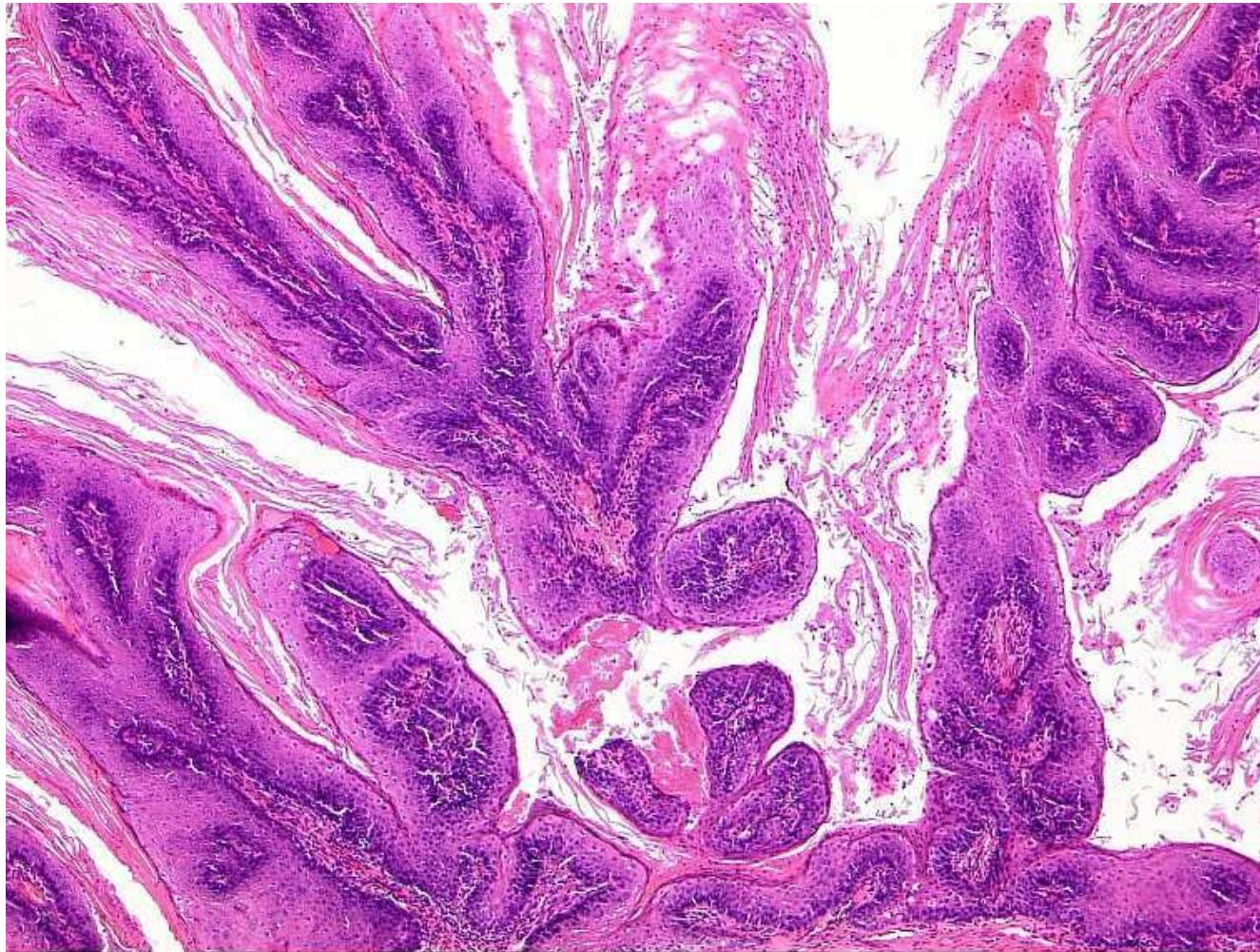


**Uterus: Squamous cell hyperplasia/polyp, a consequence of estrogen dominance and inflammation**



## Dopamine Agonists - Bromocriptine

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**Uterus: Squamous cell metaplasia and moderate inflammation of endometrium**

## **Progesterone receptor antagonists (Mifepristone)**

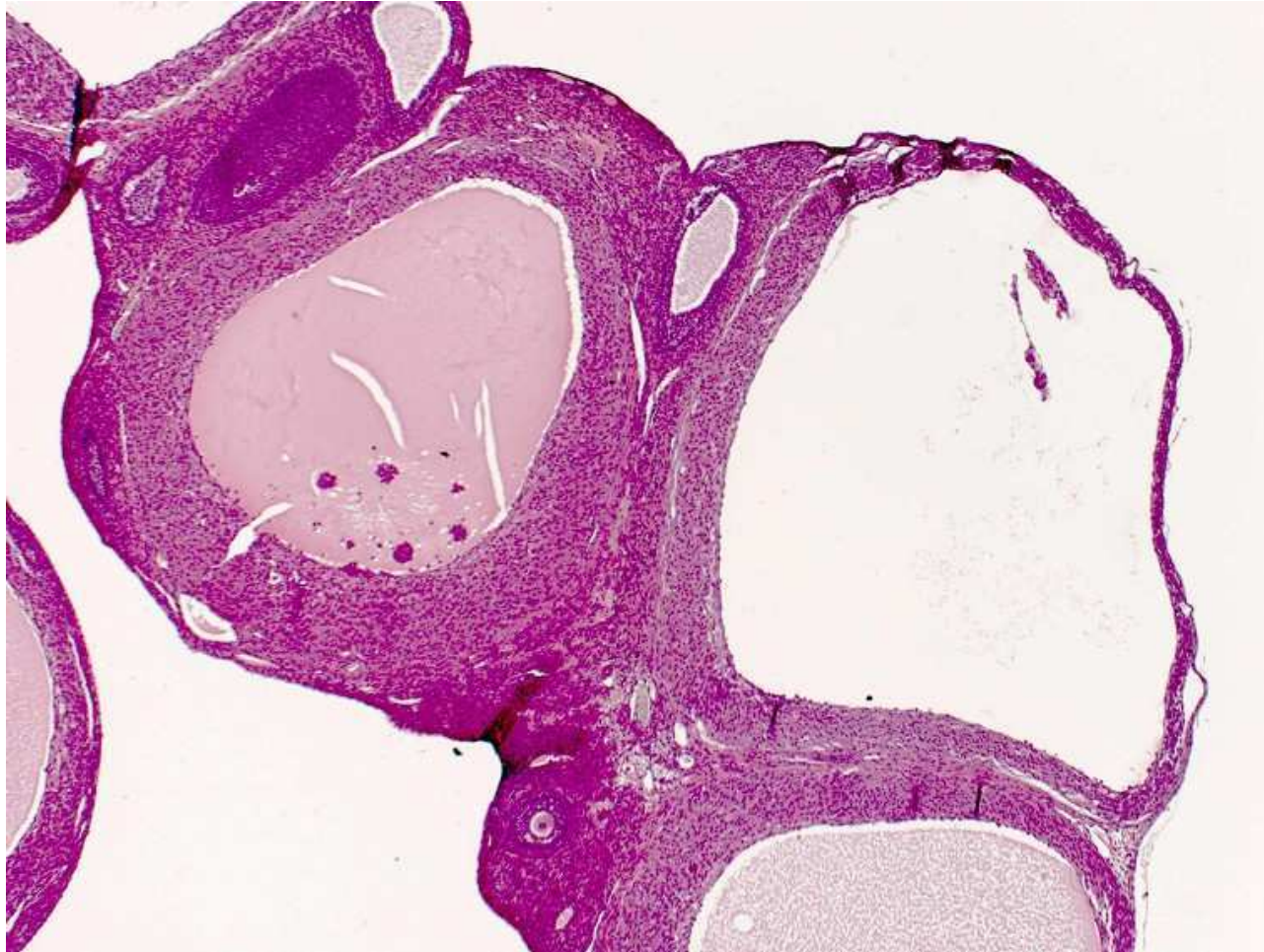
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- **Indications: contraception, menses induction, pregnancy termination and labor induction in late pregnancy**
- **Increase in progesterone plasma levels is in favor of a blockade of a progesterone negative feedback due to receptor antagonism**
- **No change in estrogen plasma levels, which leads to increased functional estrogen/progesterone level responsible for ovarian cysts, mammary changes and blockade in estrous phase**

Palazzi X: Classic Examples in Toxicologic Pathology (3rd Edition)

## Progesterone receptor antagonists (Mifepristone)

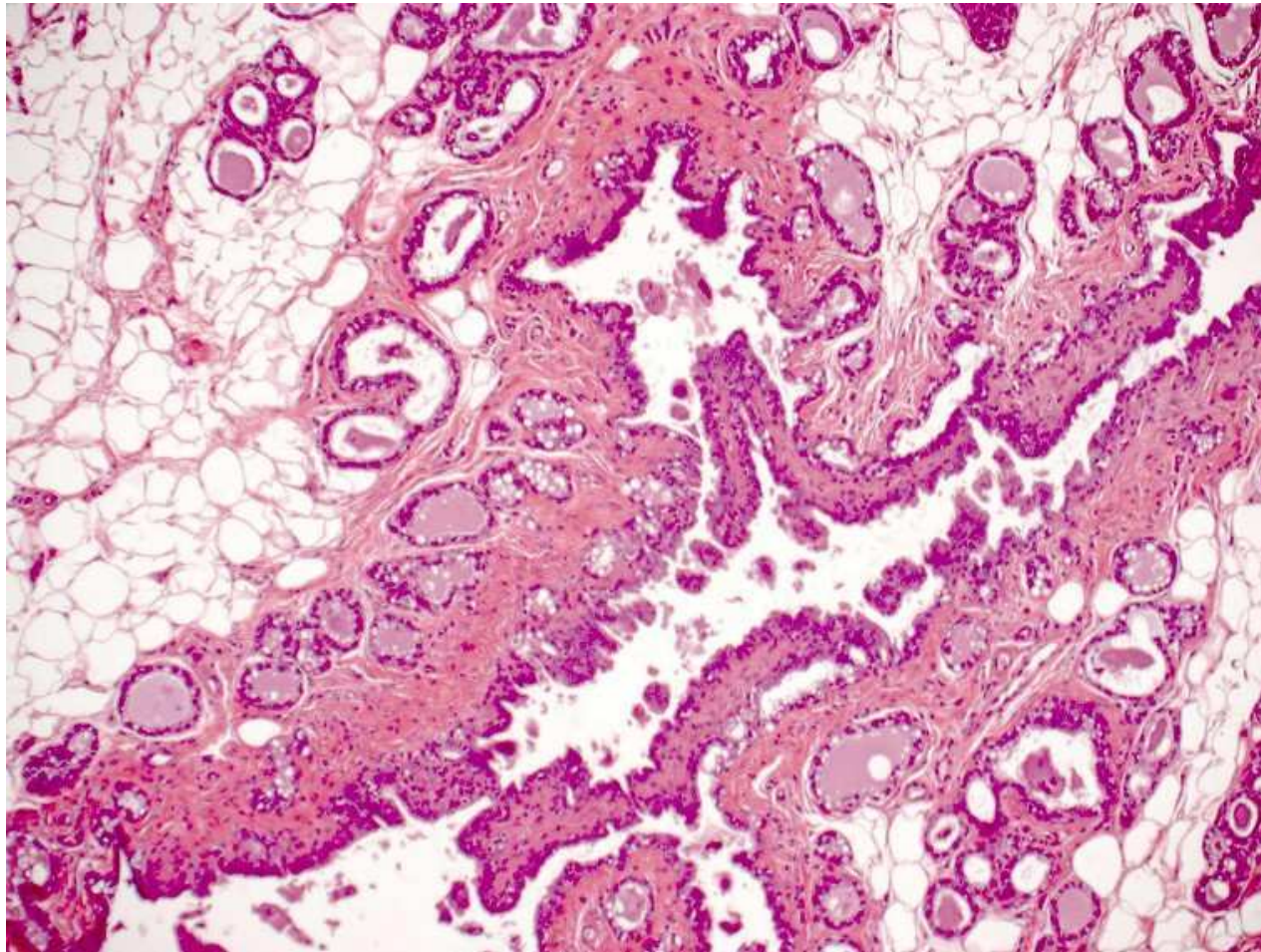
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**Ovary Day 15. Multiple fluid-filled cysts. Many of them show features of both follicular and luteal stages.** 18

## Progesterone receptor antagonists (Mifepristone)

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**Increased secretory activity in mammary gland,  
mild glandular development.**

## **$\beta_2$ -Agonists - Formoterol**

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- **Treatment of bronchospasms in patients with bronchial asthma.**
- **$\beta$ -agonists increase the intracellular cAMP content and therefore stimulate the steroidogenesis in steroid-producing cells (e.g. granulosa/theca cells)**
- **Sensitivity of theca cells towards physiological gonadotropines increase after treatment with  $\beta$ -agonists**
- **Likely that increased hyperplasias and tumors in the ovaries are consequence of pharmacological activity**
- **Also ovarian cyst might be induced by  $\beta$ -agonists, since ovulation in rodents is closely linked to the adrenergic system**

Junker U: Classic Examples in Toxicologic Pathology (3rd Edition)

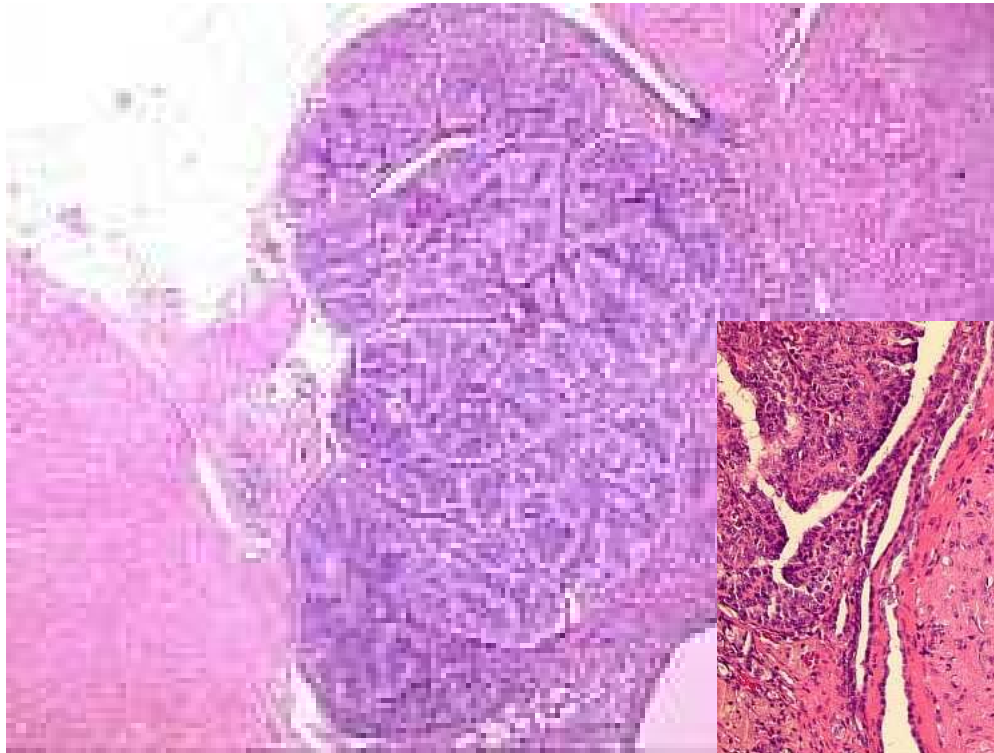
## **$\beta_2$ -Agonists - Formoterol**

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- Ovarian and mesovarian leiomyomas described with various  $\beta$ -agonists, almost exclusively in compounds with a predominant  $\beta_2$ -agonistic activity
- Hypothesis: tumors are a result of prolonged stimulation of  $\beta_2$ -receptors in the smooth muscle cells
- In rats only mesovarian smooth muscles are affected, in mice only the uterus.
- This species difference seems to reflect the differences in sensitivity of the tissues to the pharmacological effect.

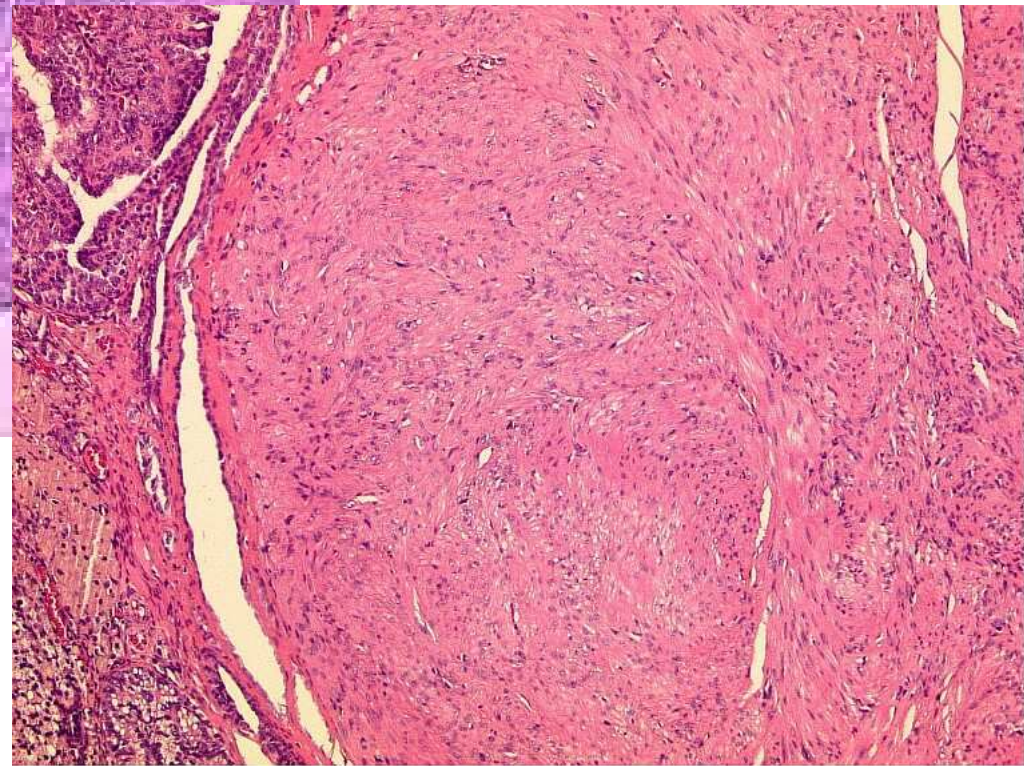
## $\beta_2$ -Agonists - Formoterol

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Ovary,  
13-Week treatment:  
granulosa cell tumor

Ovary,  
104-Week treatment:  
Mesovarian leiomyoma



## PAF

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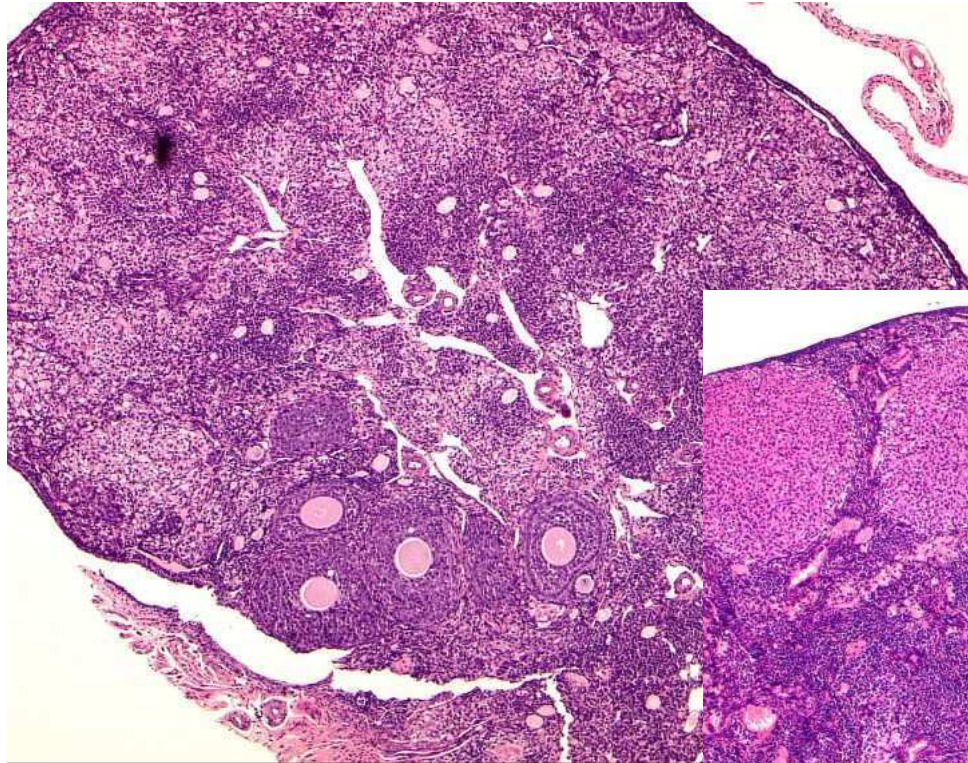
- **Key enzyme in inflammation**
- **Important influence on reproduction physiology, i.e. maturation of oocytes and ovulation**
- **PAF inhibitors able to inhibit ovulation**
- **In mice of the present study, but not in rats, there were persistent hypertrophic/hyperplastic corpora lutea.**
- **It was considered, that related increased progesterone production cause vaginal epithelial mucification**

Chevalier HJ, Weber K, Konrad D:  
Classic Examples in Toxicologic Pathology (3rd Edition)



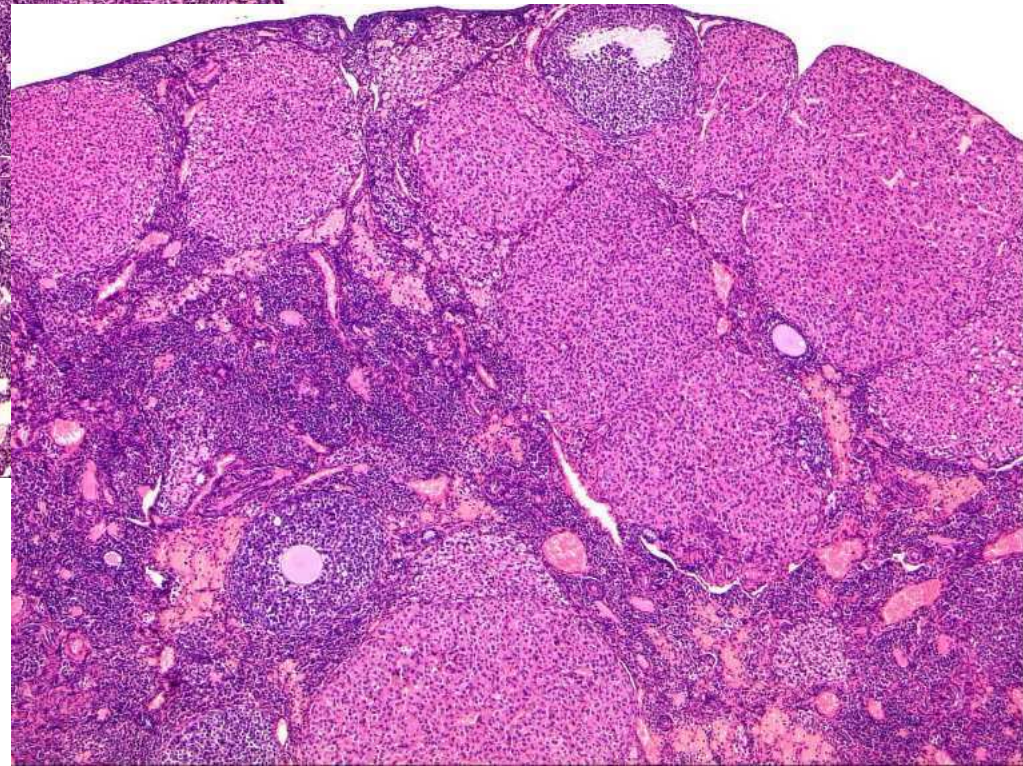
# PAF

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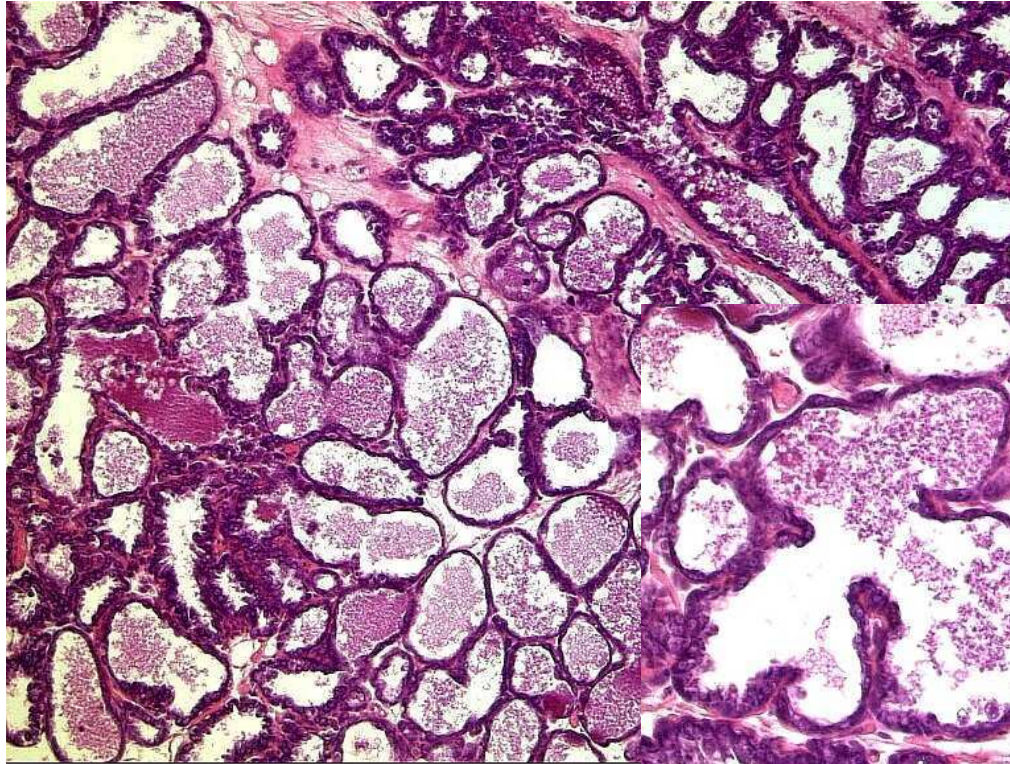
**Control mouse:  
senile atrophy,  
2-year study**

**Mouse, 2-year study:  
Persisten hypertrophic/  
Hyperplastic c.lutea**

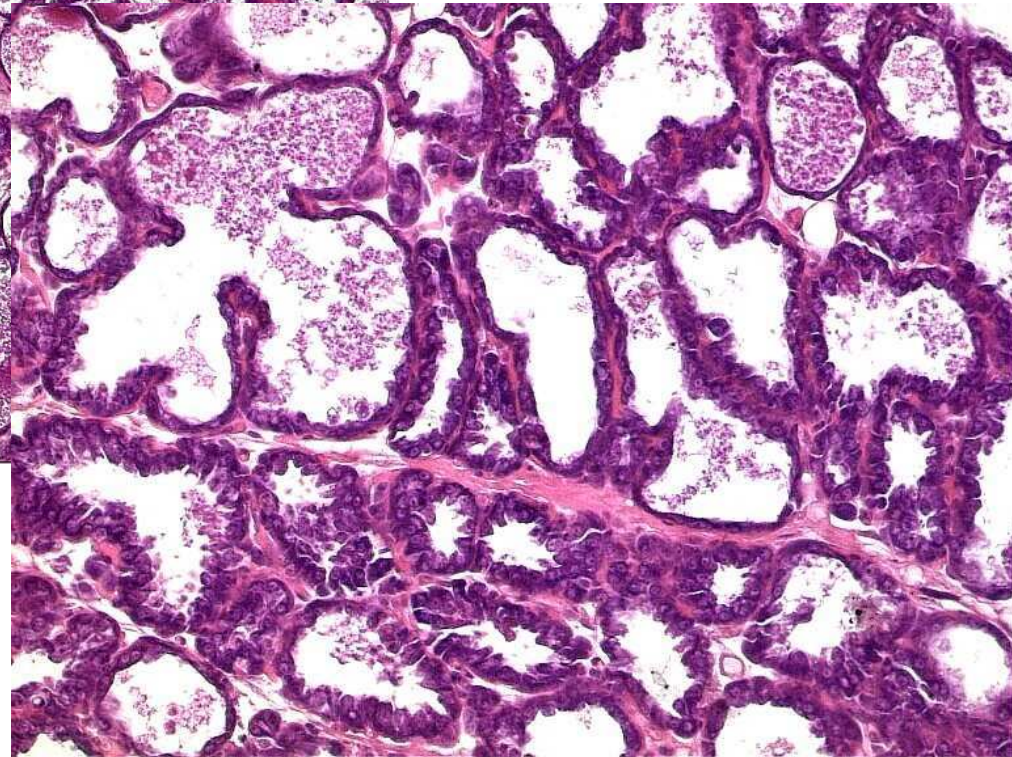


## Mammary Gland – Normal Alterations

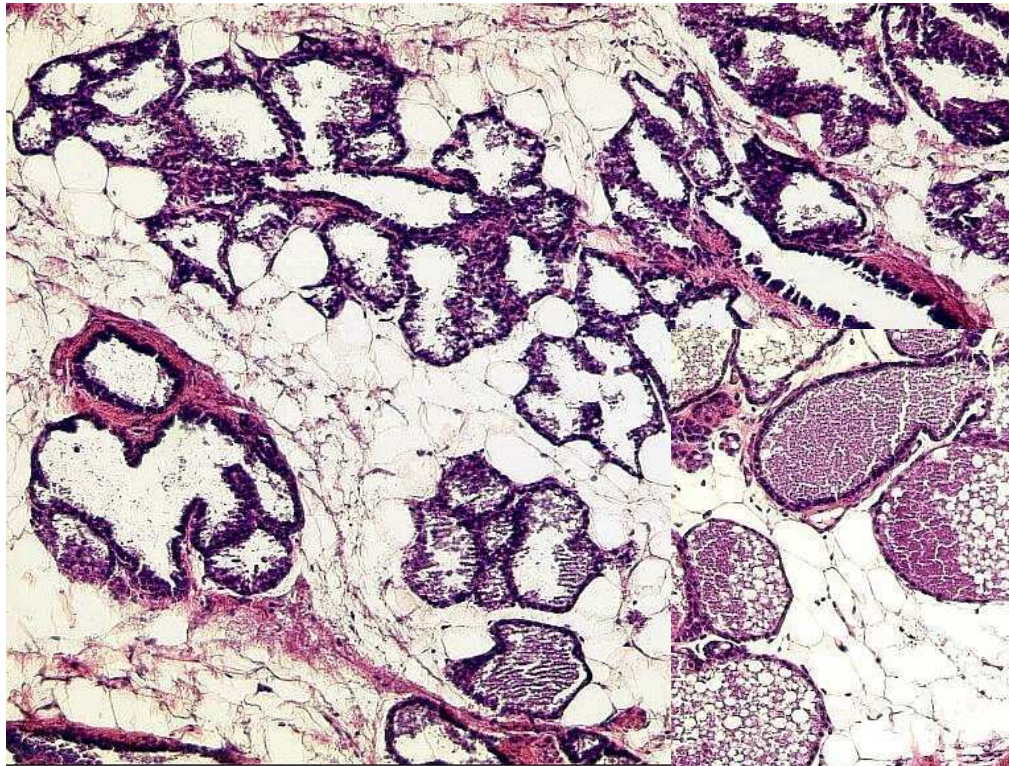
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Lactating Gland



## Mammary Gland – Reserpine



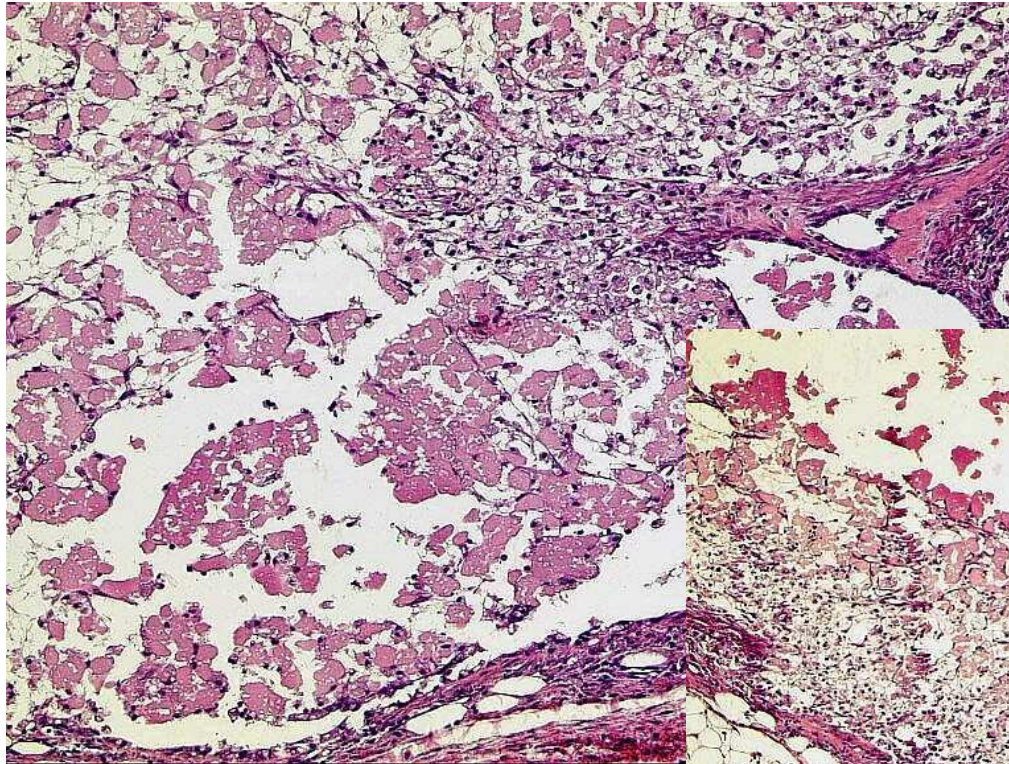
**Acinar hyperplasia  
and secretion**



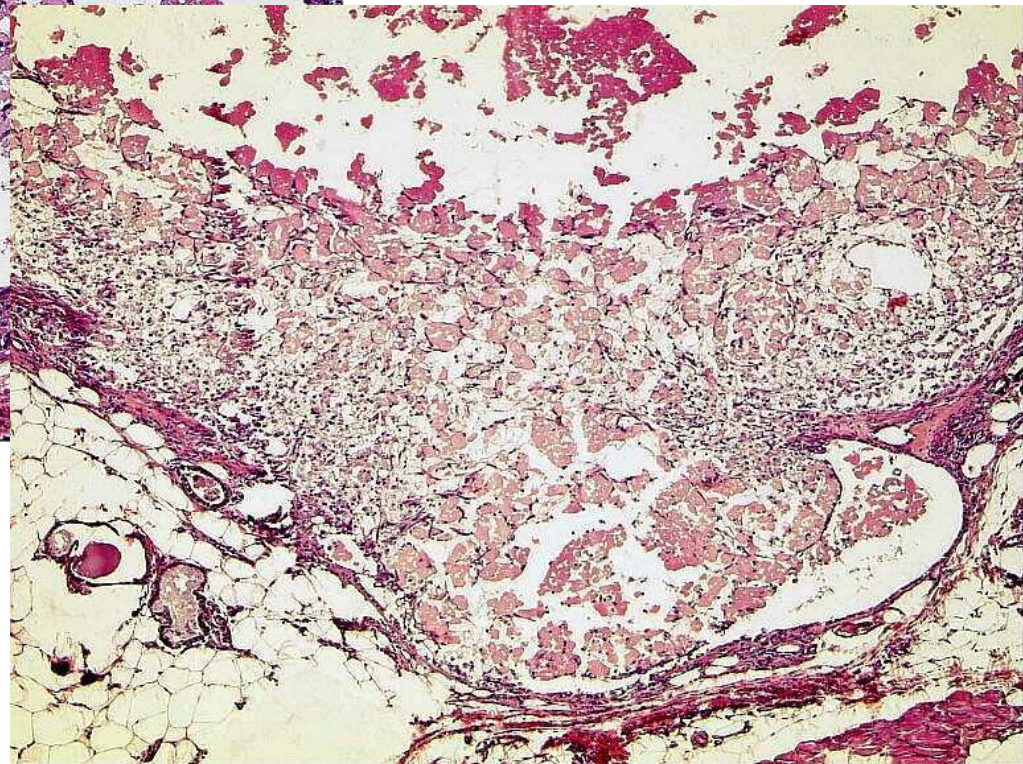
**Increase in  
dopamine cause  
increased prolactin**

## Mammary Gland – Antidepressant: 5-HT

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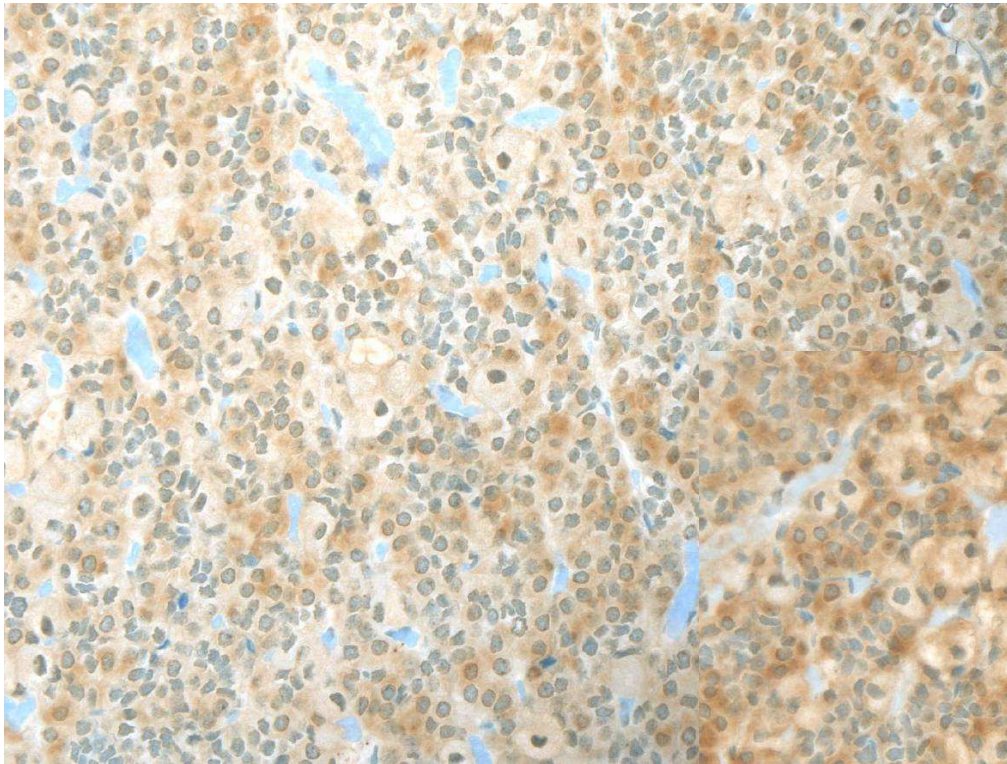
**Galactocoele**



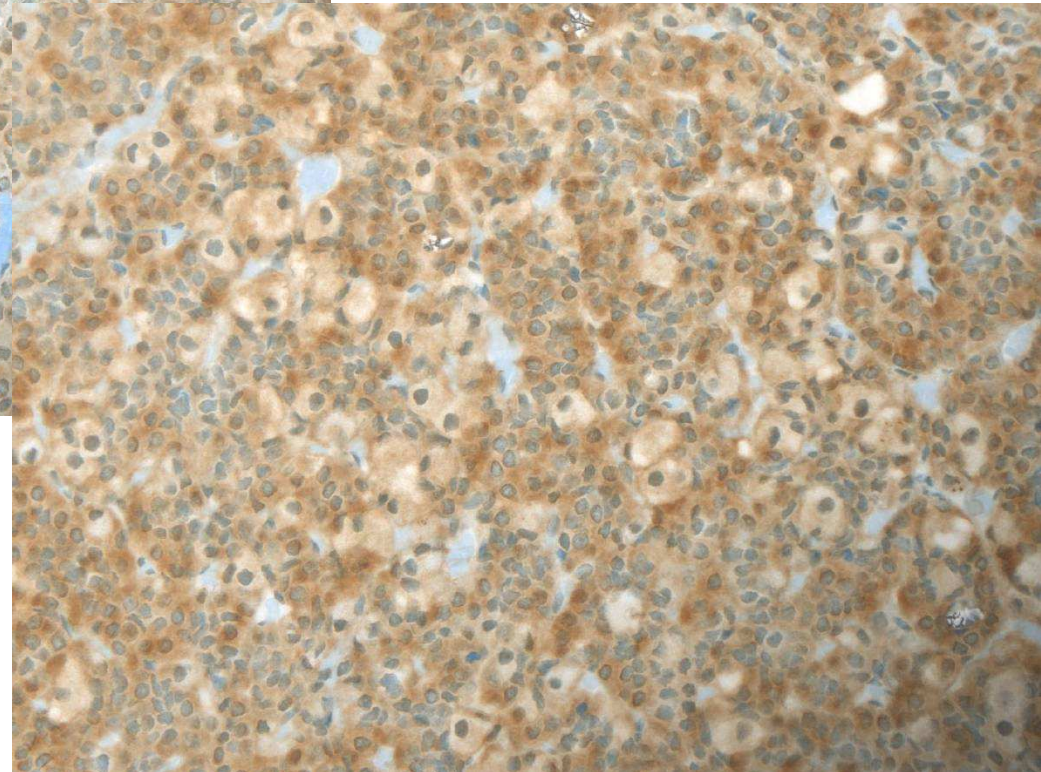
**Increase in  
serotonine cause  
increased prolactin**

## Mammary Gland – Pharmacological GH-Effect (Rat)

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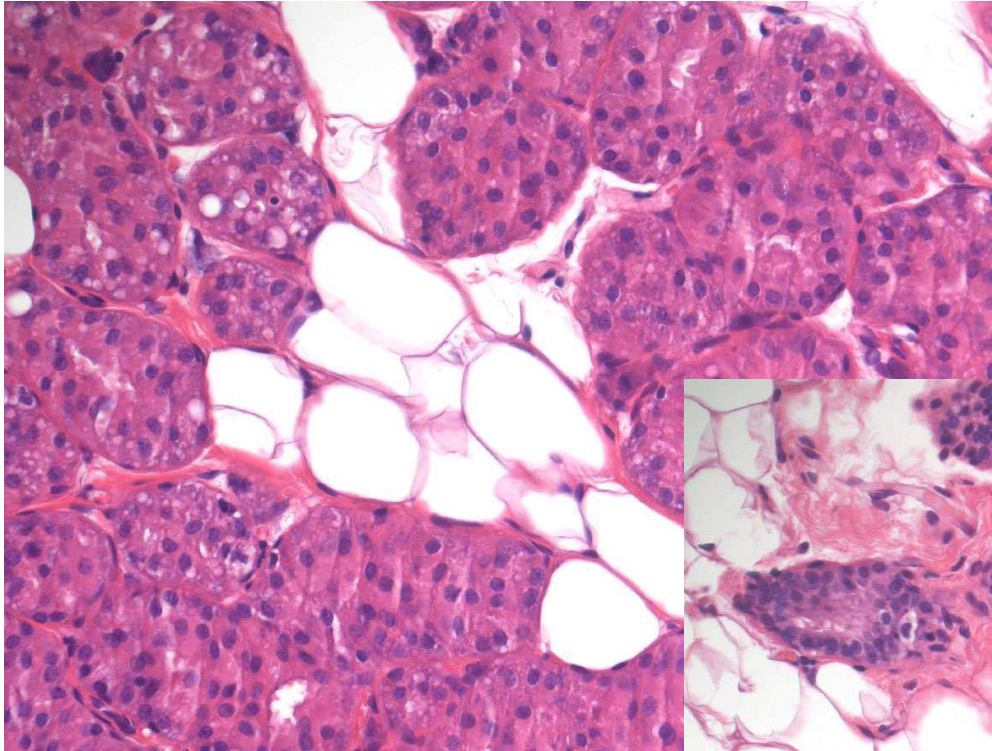
**Control Pituitary:  
GH**



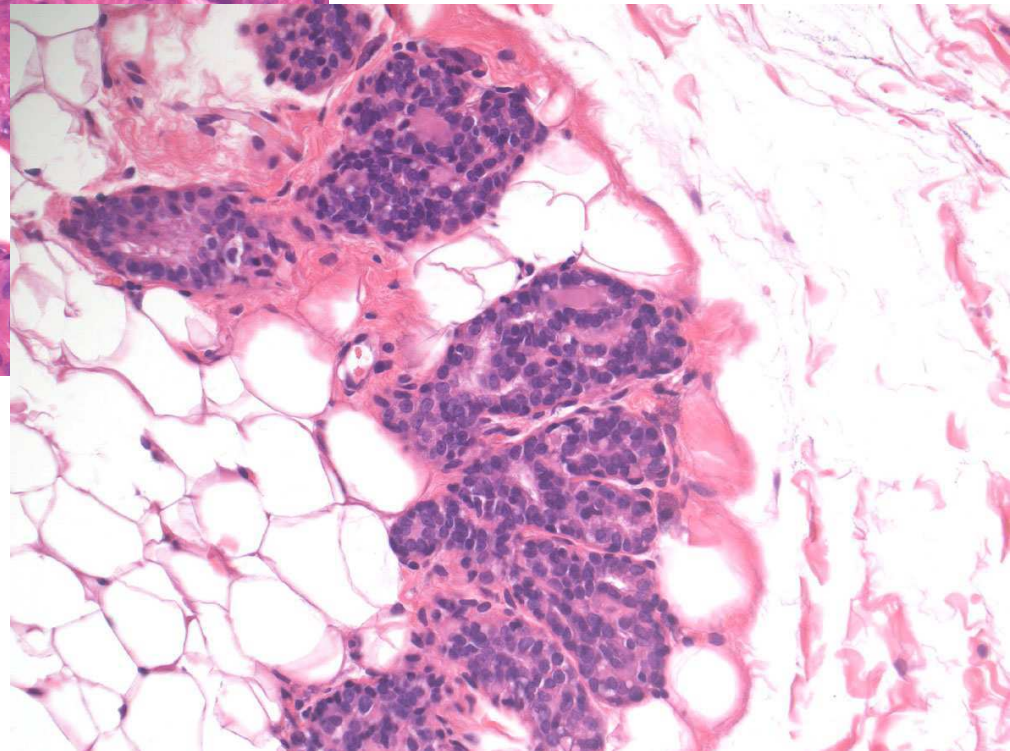
**Treated Pituitary:  
GH**

## Mammary Gland – Antimigraine: 5-HT Agonist

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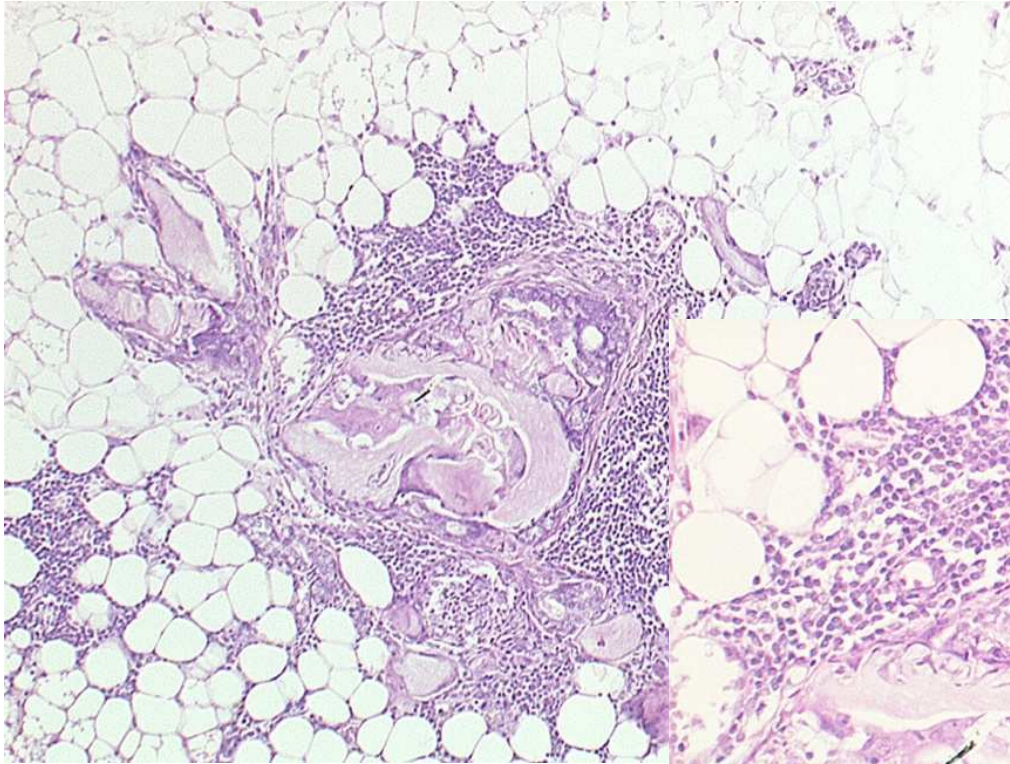


**Control male  
mammary gland**

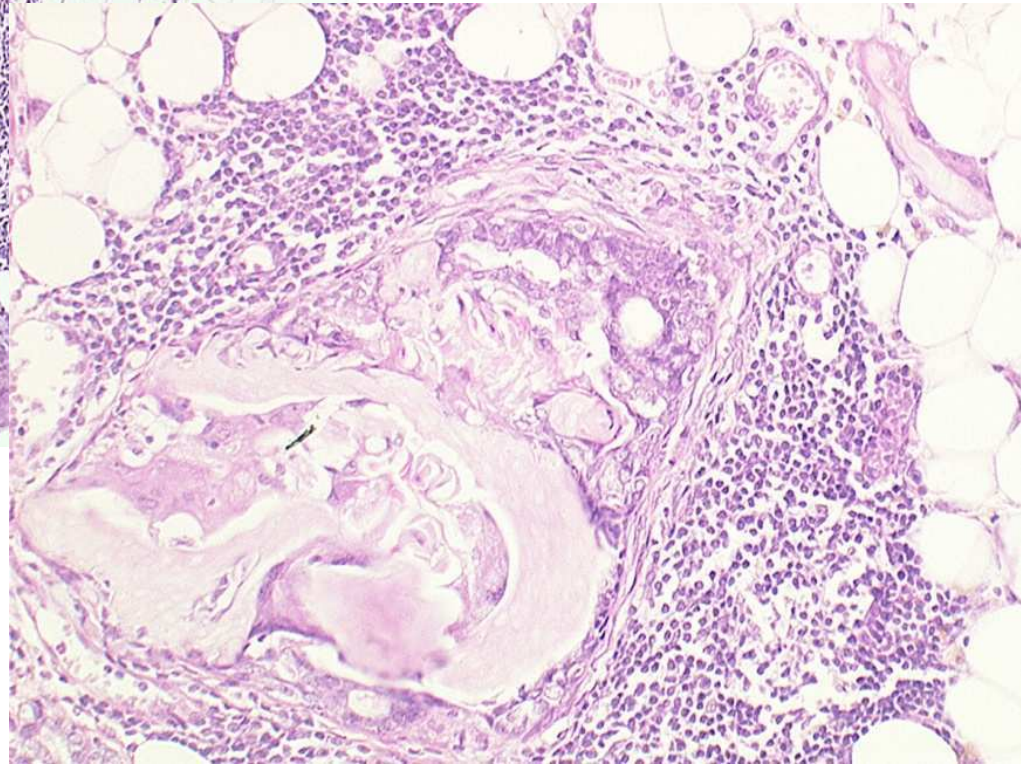


**Feminized treated  
Mammary gland**

## Mammary Gland – Antimigraine: 5-HT Agonist



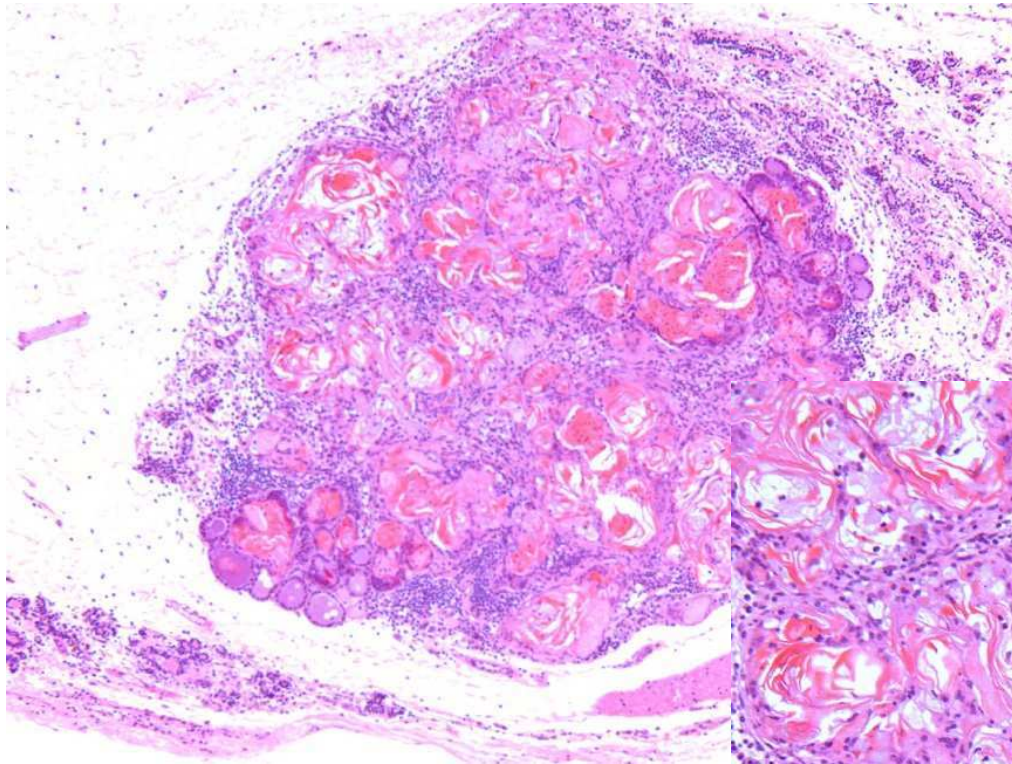
**Mouse:  
Ductular squamous  
metaplasia**



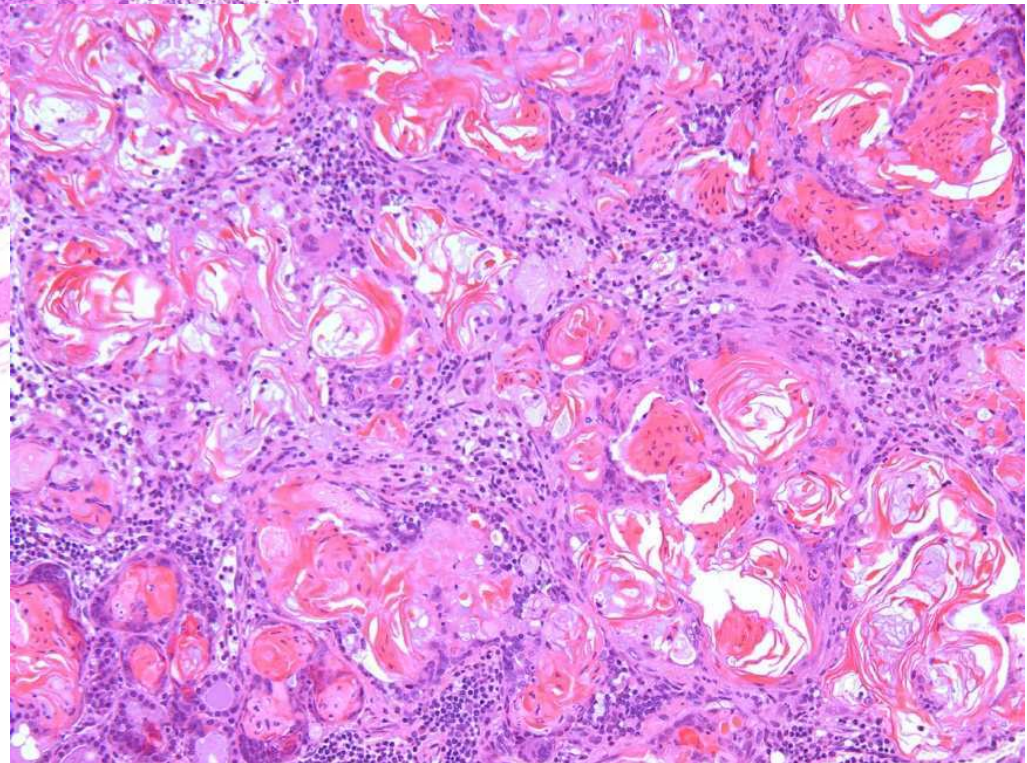
**Inflammation**

## Mammary Gland – Antimigraine: 5-HT Agonist

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**Mouse:  
Adenoacanthoma**





## Summary

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- **Physiology of female reproductive system implies anatomical rules**
- **A series of organs including mammaries, endocrinium etc.**
- **Compare to males**
- **Species differences are important**
- **Background lesions interfere with induced changes**
- **Not every alteration is a lesion**
- **Adverse vs Not Adverse need should be demonstrated by recovery**
- **Extra-polation to human is difficult**