FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

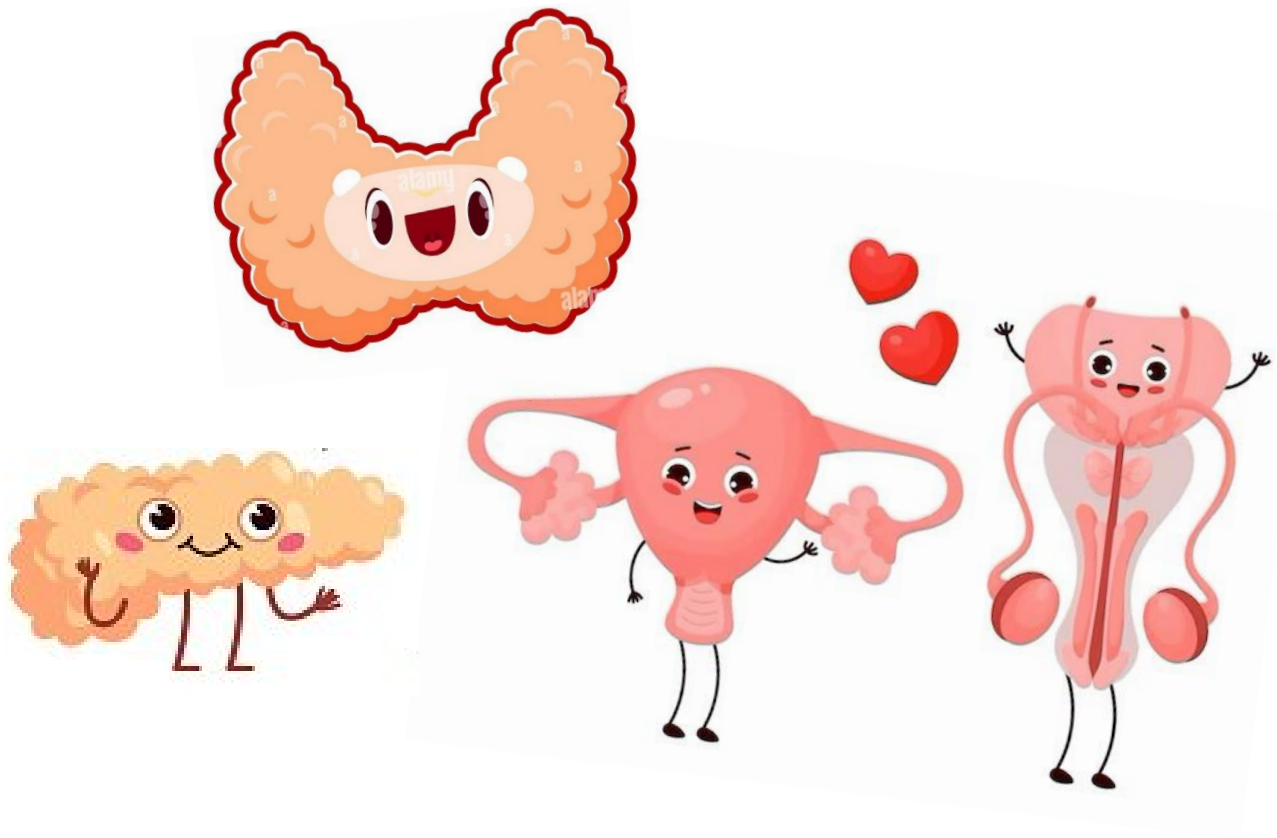
SEMESTER 4

STAFF OF MANSOURA NATIONAL UNIVERSITY

2024

Table of Contents

Subject	Page
Physiology	1
Anatomy	116
Histology	202
Pathology	277
Microbiology	403
Pharmacology	465
Biochemistry	530
Parasitology	564



FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

PHYSIOLOGY

Endocrine glands

- The **endocrine glands** are group of cells that secrete certain chemicals called **hormones**.
- They are also called **ductless glands** because they release their hormones **directly** in the **circulating blood**.

Hormones

- The secretory product of endocrine glands.
- Secreted in a catalytic amount (very small amounts) into blood stream to reach specific target cells (which have a specific hormone receptors), where they produce physiologic, morphologic and biochemical changes.

Endocrine glands

1- Hypothalamus: which has 2 endocrinal functions:

a) Controls the secretion of the anterior pituitary gland, by:

i- Releasing and release inhibiting hormones for: growth hormone, prolactin and melanocyte stimulating hormone.

ii- Releasing hormones for: thyrotropin, corticotropin and gonadotropin.

b) Releases the posterior pituitary hormones: antidiuretic hormone and oxytocin.

2- Pituitary gland: which is formed mainly of 2 lobes:

a- Anterior lobe:

i- Its own primary hormones: growth hormone, prolactin and melanocyte stimulating hormone.

ii- Trophic hormones which regulate the functions of all the other endocrine glands except parathyroid glands, pancreas and adrenal medulla.

b- Posterior lobe: which releases antidiuretic and oxytocin hormones.

3- The thyroid gland which releases: thyroxin, tri-iodothyronine and calcitonin hormones.

4- The parathyroid glands which release parathormone hormone.

5- The suprarenal glands. Each is formed of cortex and medulla:

a) Cortex, which is the outer part of the gland and releases:

- Mineralocorticoid hormones e.g. aldosterone hormone.
- Glucocorticoid hormones e.g. cortisol.
- Androgenic corticoids e.g. dehydro-epiandrosterone.

b) Medulla, the inner part of the gland, which releases the catecholamines epinephrine and norepinephrine, together with some dopamine.

6- The endocrine portion of the pancreas (islets of Langerhans):

a) Alpha cells release glucagon hormone.

b) Beta cells release insulin hormone.

c) Delta cells which secrete somatostatin hormone.

d) F cells which release pancreatic polypeptide

7- The primary sex organs:

a) The testes (male gonads) which release the male sex hormone, testosterone.

b) The ovaries (female gonads) which release estrogen and progesterone hormones.

8- The thymus gland which releases thymosin hormone.

9- The pineal gland which releases melatonin hormone.

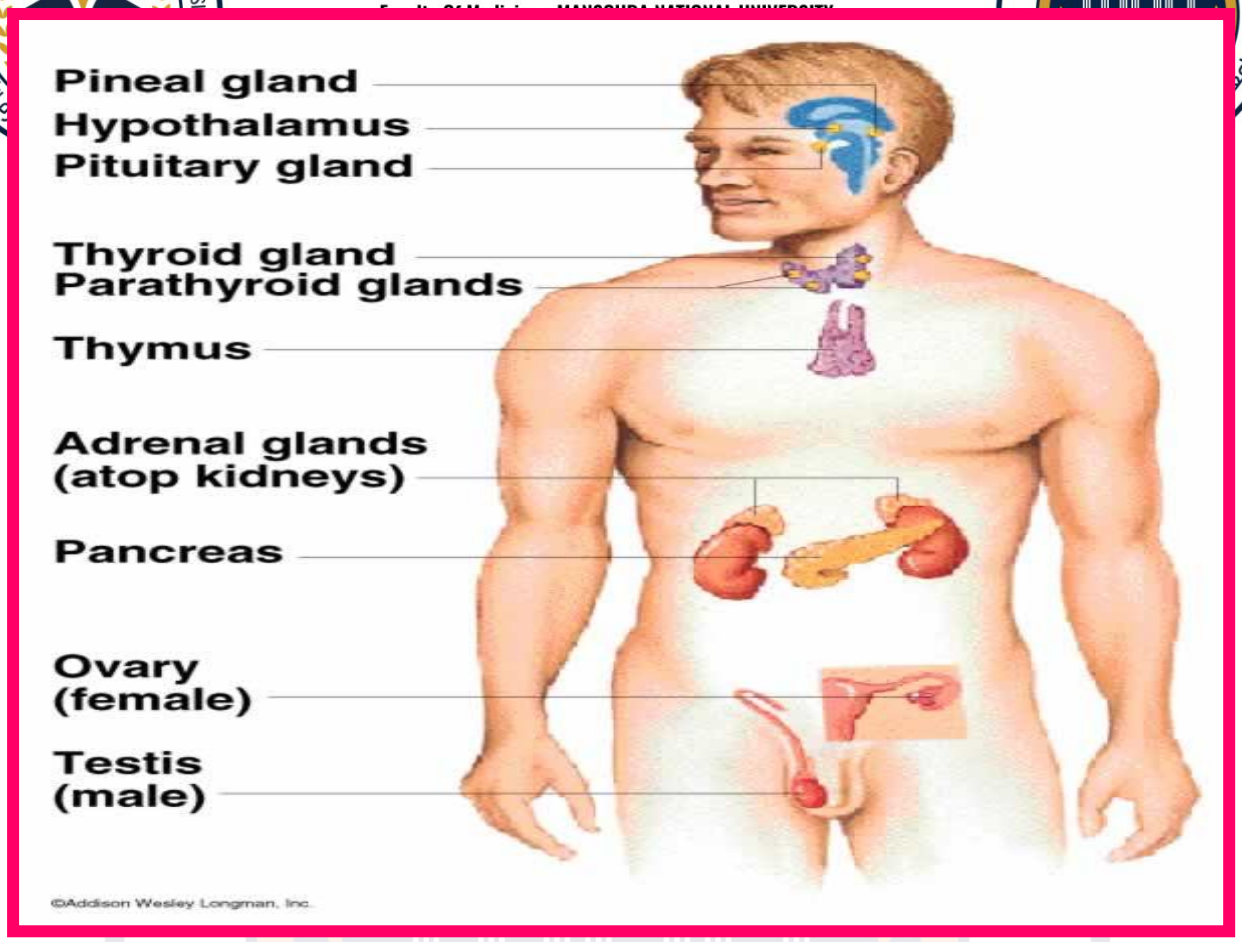


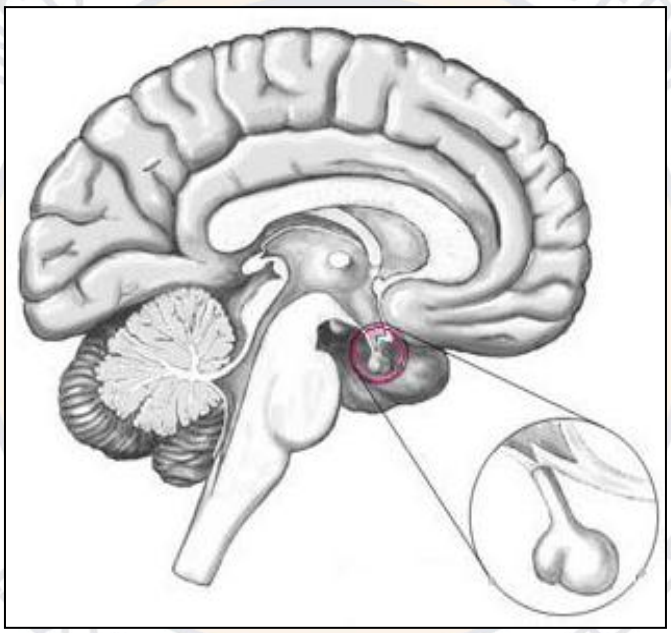
Figure: Endocrine glands

Pituitary gland (Hypophysis Cerebri)

• **Shape:** ovoid.

• **Weight:** 500 – 600mg.

• **Site:** at the base of brain in a small cavity called ***sella tursica*** (***pituitary fossa***), which is covered by extension of the dura matter (***the diaphragma sellae***), through which the ***pituitary stalk*** passes connecting the gland to hypothalamus.



N.B. Hypothalamic connections to pituitary gland:

1-Vascular connection: hypothalamo-hypophyseal portal circulation between hypothalamus & anterior pituitary.

2-Neural connection: hypothalamo-hypophyseal tract between hypothalamus & posterior pituitary.

Anterior pituitary (Adenohypophysis)

-Weight: 75% of weight of pituitary gland.

-Color: dark red color.

- Hormones:

A) Primary hormones:

1-growth hormone.

2-Prolactin.

3-Melanocyte stimulating hormone (MSH).

B) Trophic hormones:

4-Thyroid stimulating hormone (TSH).

5-Adrenal cortico tropic hormone (ACTH).

6-Gonadotropins:

a) Follicle stimulating hormone (F.S.H).

b) Luteinizing hormone (L.H).

- Cells:

(1) Chromophils (50%):

a) Acidophil cells (30-40%)➔

- Somatotropes that secrete Growth hormone.
- Mamotropes that secrete Prolactin.

b) Basophil cells (10-20%)➔

- Thyrotropes that secrete T.S.H.
- Gonadotropes that secrete F.S.H & LH.
- Corticotropes that secrete ACTH and □-M.S.H.

(2) Chromophobes (50%): Small cells with no granules (inactive).

N.B.: the anterior pituitary gland is called the master gland as it secretes trophic hormones that control all other endocrine glands **except parathyroid, supra-renal medulla & pancreas**.

- Control of secretion of ant. pit:

1) Hypothalamic control:

*The hypothalamus influences the release and synthesis of anterior pituitary hormones by **hypothalamo-hypophyseal portal circulation**.

Hormone	Hypothalamic control
• Growth hormone (GH).	• GH releasing hormone (GHRH). • GH release inhibitory hormone (GHRIH)
• Prolactin.	• Prolactin releasing hormone (PRH). • Prolactin release inhibitory hormone (PRIH) = (dopamine)
• Melanocyte stimulating hormone (MSH) (Melanotropin)	• Melanotropin releasing hormone (MRH). • Melanotropin release inhibitory hormone (MRIH).
• Thyroid stimulating hormone or thyrotropin.	• Thyrotropin releasing hormone (TRH).
• Adrenocortico trophic hormone (ACTH) or corticotropin.	• Corticotropin releasing hormone (CRH).
• Gonadotropins: Follicle stimulating hormone (F.S.H) & luteinizing hormone (LH).	• Gonadotropin releasing hormone (GRH).

2) Negative feedback control:

- ***Thyroxine*** ➔ inhibit TSH secretion from A. pit. and TRH secretion from hypothalamus (mainly A. Pit.).
- ***Estrogen or cortisol*** ➔ inhibit gonadotropin or ACTH secretion from A. pit & Gn RH or CRH secretion from hypothalamus (mainly hypoth.).

Growth Hormone (GH)

(Somatotropic hormone or somatotropin)

• Source: acidophil somatotrop cells.

• Nature: protein hormone (190 aa).

• Blood levels:

- **3 ng/ml.**
- High in newborn
- Total amount secreted/day = **0.5 mg**

• Functions:

(1) On growth: Responsible for **50% of linear growth** of the body.

a) ↑ weight & bulk of soft tissues by powerful protein anabolic effect (***except gonads, adrenals and thyroid***, which are controlled by A. pit. trophic hormones)

b) ↑ length of bones by:

- Stimulating proliferation of epiphyseal cartilage.
- Formation of more protein bone matrix.
- Increase the precipitation of minerals in bones.

* **Anabolic effect is promoted by insulin** ➔ glucose oxidation ➔ energy needed for building up tissue proteins.

(2) On metabolism:

a) Protein metabolism:

- ↑ amino acids transport across cell membrane.
- ↑ protein synthesis by ribosomes.
- ↑ RNA formation.
- Inhibit protein catabolism.

b) Carbohydrate metabolism: GH has an anti-insulin action:

- It inhibit hexokinase enzyme ➔ ↓ glucose uptake by tissues.
- ↑ gluconeogenesis.
- Stimulate glucagon release ➔ ↑ glycogenolysis.

c) Fat metabolism:

- Lipolysis ➔ ↑ free fatty acids (FFA) ➔ energy during stress e.g. starvation & hypoglycemia.

d) Electrolyte metabolism:

- ↑ Ca^{2+} absorption from GIT.
- ↓ Na^{+}, K^{+} & $PO_4^{=}$ excretion by kidney.

• Mechanism of action of GH:

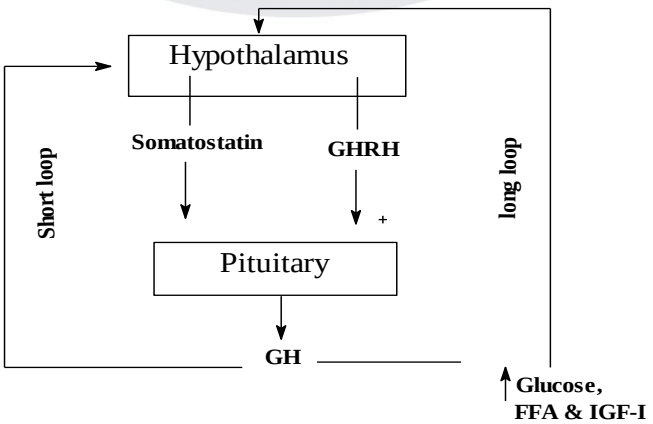
- GH has **no direct anabolic actions**.
- Growth promoting actions of GH are mediated by a group of intermediary polypeptide substances called **somatomedins**.
- Somatomedins are formed in the **liver, and bone**.
- Structurally **similar to proinsulin**, so called insulin like growth factors (IGF), **e.g.** IGF-I (somatomedin-C) & IGF-II.
- They bind to **specific membrane receptors**. These receptors can also bind insulin and proinsulin but with much less affinities.

• Control of GH secretion:

(1) Hypothalamus releases:

- ❖ GH releasing hormone ➔ increase GH secretion.
- ❖ GH release inhibiting hormone ➔ decrease GH secretion.

(2)–ve feedback: GH ➔ inhibition of secretion of GHRH from hypothalamus (– ve FB).



(3) Other factors:

Stimulators	Inhibitors
- Hypoglycemia. - Decrease FFA. - Increase aa e.g. arginine. - Starvation. - Stress. - Sleep. - Exercise. - Estrogen and dopamine. - □ – adrenergic agonists.	- Hyperglycemia. - Increase FFA. - Increase cortisol - Increase GH. - Obesity.

NB: GH has a ***regular nocturnal peak*** which occurs ***1- 2 hours after the onset of deep sleep***.

• Disorders of growth hormone:

(I) Gigantism:

-Def: A disease resulting from ↑ secretion of GH before union of epiphysis.

-Cause: tumour or hyperplasia of somatotrope cells.

-Characters:

1. Marked elongation of **bones**, but in a **relative proportion** (span does not exceed the height). The final height may reach 2.6 meters.

2. Overgrowth of **soft tissues** **e.g** muscles and viscera.
3. **Hyperglycemia** and increased **metabolic rate**.
4. **hypogonadism:** overgrowing somatotropes encroach on gonadotropes cells ➔ ↓ gonadotropins ➔ gonads and accessory sex organs are **under developed**.
5. **Headache** and **visual disturbances** due to local pressure of the growing tumour on the sella tursica and optic chiasma, respectively.
6. **Mentally retarded** and unless treated, **die** before the age of 20 years.

(II) Acromegally: (**acro**=extremity & **megally**=enlargement)

-Def: A disease resulting from ↑ secretion of GH in adults after union of epiphyses.

-Characters:

1. **Bones** become thick and deformed.
2. **Muscles** and **viscera** enlarge.

3. **General coarsening of features due to:**
    - Thickening of **skin** and **subcutaneous tissues**.
    - Enlargement of **head, hands and feet**.
    - **Lower jaw** hypertrophies and protrude forward (prognathism) and **teeth** become widely separated.

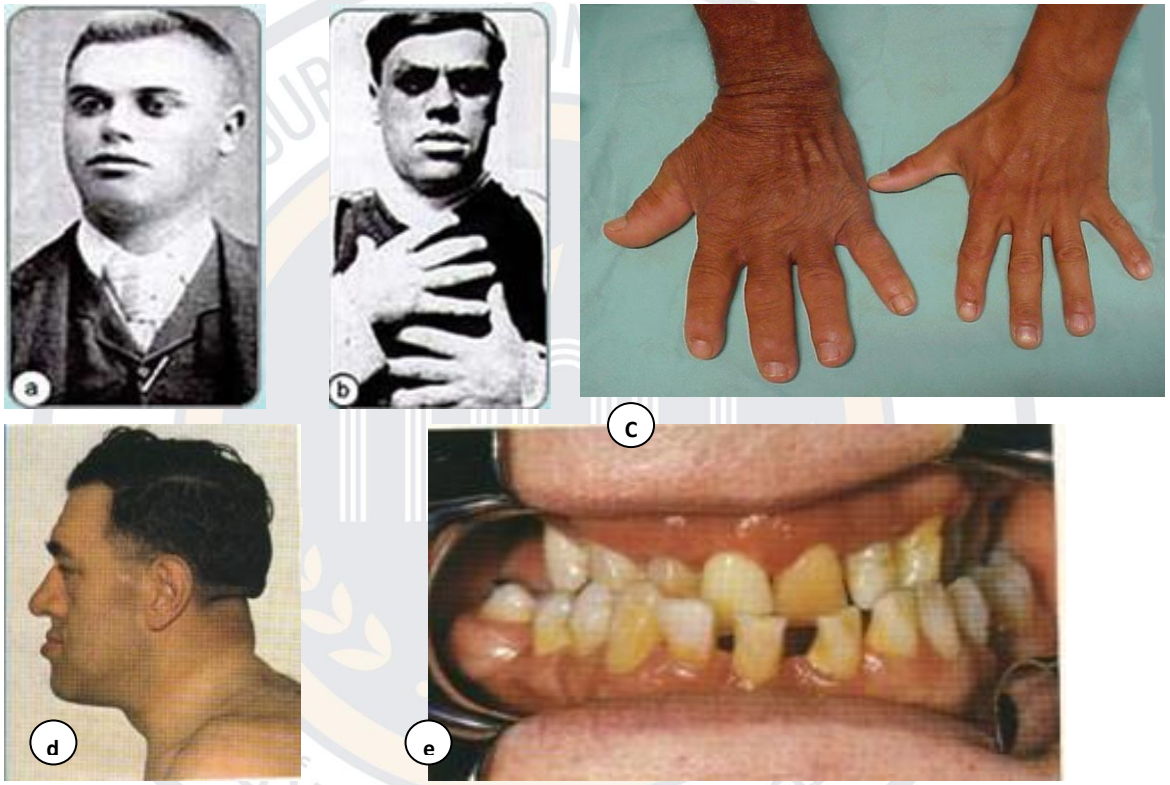


Fig. 11: ***Acromegaly in an adult. a) Normal subject before acromegaly; b) The same subject after development of acromegaly; c) Enlargement of hands in acromegaly; d) Coarseness of the facial features; e) Protruded mandible and separated teeth.***

4. **Kyphosis** due to thickening of the vertebrae.
5. **↑ BMR**.
6. **Hyperglycemia** and **glucosuria**.
7. **Hypogonadism**.
8. **Headache** & **vomiting** due to increase ICT.
9. **Visual disturbances** due to pressure on optic chiasma.

10. **Gynaecomastia** and **galactrorrhea** due to:
    - Lactogenic effect of GH.
    - Secretion of Prolactin by tumour cells.
11. **Hirsutism**.

*** Treatment:** Surgical removal of tumour or destruction by irradiation.

(III) Dwarfism:

- Def: ↓ secretion of GH in children.

-Characters:

1. ↓ **bone growth** ➔ **proportionate** reduction of all body features ➔ short stature.
2. ↓ **soft tissues growth**. **Mild obesity** is common. Patient looks much **younger than his age**.
3. ↓ **metabolic rate**.
4. **Hypoglycemia** due to lack of insulin antagonism from G.H..
5. **Mental growth** is normal.
6. **Sexual maturation** is reached (Dwarfism + hypogonadism = **Infantilism**).

Physiology of growth:

- Body growth is a **continuing process** throughout childhood and adolescence.
- It is **rapid** in **1st 2 years** of life, and **less** during **middle years** of childhood.
- **Later**, there is a **2nd phase of rapid growth** at puberty followed by **cessation** of growth when adult height is reached.
- **Factors affecting growth:**

1.Hormones:

a) **Growth hormone:** promotes growth in infancy, where its plasma level is elevated.

b) Thyroid hormone:

- Stimulate physical growth by potentiating the action of somatomedins.
- Essential for mental and sexual growth.

c) Insulin:

- Potentiate growth.
- Importance for formation of somatomedins.
- Juvenile DM ➔ stunted growth.

d) Glucocorticoids:

- Physiological conc ➔ facilitate growth.
- Pharmacological doses ➔ inhibiting GH ➔ ↓ growth.

e) Androgens and estrogens:

- Responsible for 2nd phase of rapid growth at puberty due to their anabolic effect.
- Growth is initially stimulated then stops as they cause fusion of epiphyseal cartilage of long bones.

f) **Parathormone and vit D** ➔ essential for normal skeletal ossification.

2.Extrinsic factors:

a) **Balanced diet** rich in proteins and vitamins is necessary for growth.

b) **Stress** e.g. infections ➔ suppression of growth.

3.Genetic factors: ***determines:***

a) Growth rate. b) Age of puberty. c) Adult height.

Prolactin

(Lactogenic hormone or mammotropin)

-Nature: polypeptide hormone (198 amino acids) [similar to GH].

-Source: mammotrope cells.

-Plasma conc: Men = 5ng/ml. Women = 8ng/ml.

-Functions:

1. **Development of breast:**
   a) **Pre and post pubertal:** Prolactin (with estrogen, progesterone, cortisol & GH) ➔ stimulation of proliferation and branching **of milk ducts** in female breast.
   b) **During pregnancy:** Prolactin (with estrogen and progesterone) ➔ development of **milk alveoli**.
   c) **After labor:** Prolactin stimulates **milk synthesis and secretion**.
2. **Inhibits LHRH release** ➔ ↓ LH ➔ prevent ovulation in women. This accounts for amenorrhea during postpartum lactation.
3. **Stimulates lymphocyte proliferation**.

- **Control of Prolactin secretion:**

1. **Hypothalamic control:**
   - PRH ➔ increase Prolactin.
   - PRIH (similar to dopamine)➔ decrease Prolactin.
2. **Drugs:**
   - **L-DOPA** ➔ ↑ dopamine ➔ ↓ Prolactin.
   - **Apomorphine and bromocriptine** ➔ stimulate dopamine receptors ➔ ↓ Prolactin.
   - **Chlorpromazine** ➔ block dopamine receptors ➔ ↑ Prolactin.
3. **Feed back mechanism:**
   - Prolactin ➔ ↑ dopamine release at median eminence ➔ ↓ prolactin (***–ve FB***).
4. **Pregnancy:**
   - Prolactin increase during pregnancy.
   - **Cause:** ↑ estrogen ➔ stimulate hyperplasia of prolactin producing cells.
5. **Suckling:**
   - Sucking of the offspring ➔ stimulation of nipples ➔ afferent impulses arise from receptors in nipple ➔ inhibition of PRIH ➔ ↑ prolactin.
6. **Others:**
   - Sleep, stress, oxytocin, VIP, subs. P and AII ➔ ↑ prolactin.

- **Disorders of prolactin:**
  - **Decrease prolactin** ➔ inability to lactate in women.
  - **Increase prolactin:**
    a. **Cause:** hypothalamic dysfunction or pituitary tumour.
    b. **Characters:** increase prolactin ➔ -ve FB effect on Gn ➔

Women	Men
• anovulation. • Amenorrhea. • Infertility. • Galactorrhea. • Decreased libido.	• ↓ Testosterone. • ↓ Sperm production. • Breast development and lactation. • ↓ libido. • Impotence. • Infertility.

Melanocyte-Stimulating Hormone (MSH) (Melanotropin)

- Nature: polypeptide hormone

- Source: anterior pituitary.

- Importance: It controls the ***skin color*** by alteration of the dispersion of ***melanin*** containing granules in the melanocytes of the skin in response to the amount of light to which the animal is exposed.

- Types: alpha, beta and gamma. **Gamma MSH** is secreted by corticotrop cells which secrete ACTH. **Beta MSH** is secreted by human pituitary gland.

- Structure: Each of the 3 types of MSH is formed of a sequence of amino acids which is structurally similar to part of the 39 amino acid polypeptide chain of ACTH. This explains the marked **MSH activity of ACTH**.

- e.g. in hypofunction of suprarenal cortex (Addison's disease) ➔ ↑ ACTH level due to ↓ cortisol release ➔ hyperpigmentation of skin & mucous membranes.

Panhypopituitrism (Simmond's Disease)

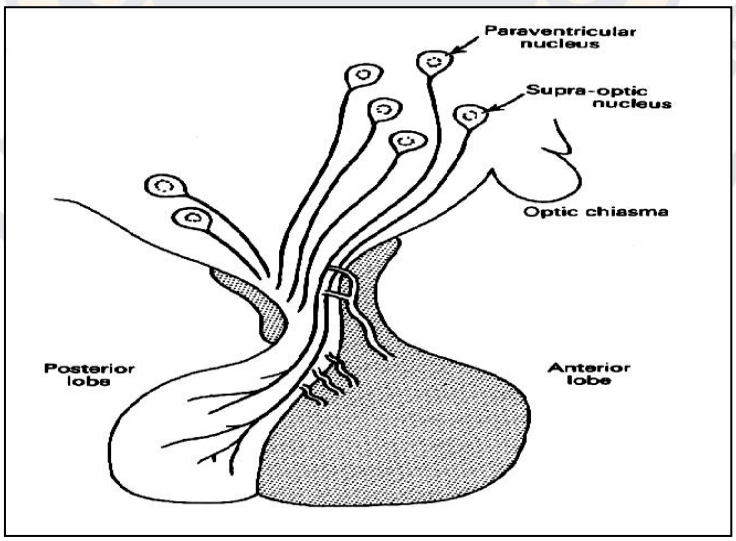
-Cause: destruction of anterior lobe of pituitary gland ➔ severe ↓ of its hormones ➔ atrophy of the thyroid and supra-renal glands & of the gonads.

-Manifestations:

1- **In children:** infantilism i.e failure of growth and of sexual maturity.
2- **In adults:** the lack of trophic hormone ➔ hypofunction of their target glands together with relative hyperinsulinism.
   a) ***Hypofunction of the thyroid gland*** (Myxoedema).
   b) ***Hypofunction of the adrenal cortex*** (hypocortisism or "Addison's disease').
   c) ***Hypofunction of the gonads*** (hypogonadism).
   d) ***Loss of weight and sever wasting of muscle*** **(cachexia)** due to**:**
      * Loss of appetite (anorexia).
      * Absence of anabolic effect of growth hormone and androgens.
   e) ***Premature senility (progeria):*** The skin becomes dry and wrinkled with early graying of hair so that the patient looks older than his age.
   f) ***Hypoglycemia*** due to relative ↑ in insulin level due to lack of antagonistic hormones.
   g) ***Skin colour*** becomes lighter due to anemia and ↓ ACTH and beta-MSH.

Neurohypophysis (posterior pituitary)

- ***ADH*** is formed in ***supra optic nucleus***, whereas ***oxytocin*** is formed in ***paraventricular nucleus*** of hypothalamus.
- These neurons constitute the ***hypothalamo hypophyseal tract*** which terminates in the posterior pituitary.
- ***ADH and oxytocin are synthesized in*** cell bodies of these neurosecretory neurons and incorporated into granules with a binding protein (***neurophysin***) [***neurophysin 1 for oxytocin& neurophysin 2 for ADH***].
- ***The granules*** pass down the axons of hypoth. hypoph. tracts to dilated nerve endings **(Hering bodies)** in post pit, from which the hormones enter the blood.
- ***Release of hormone:*** Depolarization of supraoptic and paravent nuclei ➔ generation of nerve impulse which reach the nerve terminal ➔ Ca^{2+} influx ➔ fusion of secretory granules with knob membrane ➔ **exocytosis** of ADH and oxytocin to the adjacent capillaries.



Antidiuretic hormone (ADH)

• Functions:

(1) Renal effects:

- **Reabsorption of free water** from glomerular filtrate in **DCT and CDs**.
- **Mechanism:** ADH binds to a specific plasma memb. receptor on capillary side of cell ➔ activate adenyl cyclase ➔ ↑ intra cellular cAMP ➔ activate protein kinase on luminal side of cell ➔ phosphorylation of membrane protein ➔ ↑ luminal membrane permeability to water ➔ back diffusion of water along an osmotic gradient from hypotonic tubular urine (that emerge from LH) to hypertonic interstitial fluid of renal medulla.

(2) Extra renal effects: systemic administration of large doses ➔ contraction of smooth muscles particularly in the blood vessels ➔

i. Increase ABP.
ii. Coronary VC.
iii. Splanchnic VC (so, used in controlling GIT bleeding).

(3) On the anterior pituitary: ↑ secretion of ACTH as it may **function as CRH**.

• Control of secretion:

(1) Osmotic regulation: ↑ **plasma osmolarity** (1-2%) (↑ H_2O loss, ↓ water intake, administration of solutes as Na^+) ➔ loss of intracellular water from osmoreceptor neurons ➔ their stimulation ➔ ↑ ADH release ➔ ↑ water reabsorption from tubular fluid in kidney ➔ dilution of ECF ➔ return to normal osmotic composition.

(2) Blood volume:

- **Arterial baroreceptors** (carotid and aortic) and stretch receptors in walls of left atrium ➔ tonic inhibition of ADH release.
- **Hypovolemia** ➔ ↓ stimulation and discharge of inhibitory impulses from these pressure receptors ➔ ↑ ADH release.

- Also, **renin** release from juxta glomerular apparatus (JGC) ➔ ↑ A II ➔
  - ❖ Stimulate thirst.
  - ❖ ↑ ADH release.

(3) Other factors:

Inhibitors of ADH release	Stimulators of ADH release
- Diuretics. - Chronic water loading. - PGE. - Cortisol. - ↓ K^+ and ↑ Ca^{2+}. - Cold weather. - Ethanol.	- Sulfonyl ureas. - Nicotine. - Barbiturates. - Opiates. - Estrogen. - Progesterone. - Increase temperature

• Disorders of ADH:

(1) Diabetes insipidus:

***Causes:** -↓ ADH release (central type)

- Inability of kidney to respond to ADH (nephrogenic type).

***Characters:**

i. **Polyurea:**

* **Volume:** increase markedly (25L/day).

* **specific gravity:** very low (1001-1003).

* **Due to:** failure of facultative water reabsorption by DT.

ii. **Polydipsia:** Drinking large amounts of water, 2ry to polyuria which produce intense thirst.

iii. **Anorexia and general weakness:** due to loss of vitamins.

***Treatment:** ADH administration.

(2) Syndrome of Inappropriate ADH hypersecretion (SIADH):

***Manifestations:**

i. ↑ ECF volume.
ii. ↑ plasma volume ➔ ↑ ANP ➔ ↑ Na^+ excretion.
iii. Hyponatremia ➔ headache, drowsiness, nausea, and coma.
iv. ↑ urine osmolarity.

Oxytocin Hormone

-Mech. of action: ↑ intracellular Ca^{2+}.

-Transport: unbound ➔ half life =5 minutes

-Functions:

1. **Milk-letting effect:**
   - By stimulation of **myopithelial cells** of alveoli of mammary glands ➔ force milk into ducts.
   - **This action is:**
   - ***potentiated by***: estrogen.
   - ***inhibited by:*** catecholamines.
   - ***Suckling reflex:*** suckling of breast by infant ➔ stimulate touch receptors at nipple and areola ➔ send afferent impulses to hypoth. ➔ release of oxytocin and prolactin.
2. **Contraction of uterus:**
   - By **lowering threshold** for depolarization of myometrial muscles.
   - **This action is:**
     - ***potentiated by:*** estrogens.
     - ***inhibited by:*** progesterone.

- **Importance:**

- Initiate labour.
- Post partum contractions ➔ haemostasis after evacuation of the placenta.
- Involution of uterus after delivery.

3.Transport of sperms in uterus during intercourse: by the end of intercourse ➔ oxytocin release ➔ uterine contractions➔

i. Orgasm sensation. ii. Suck of sperms into uterus.

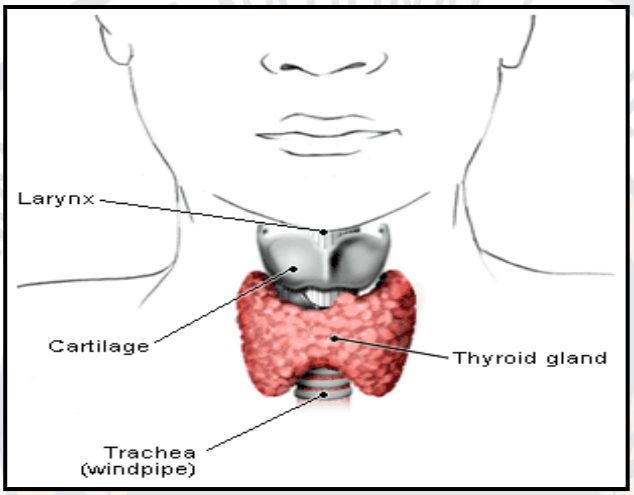
4.In males: discharge of sperms from semineferous tubules and epididymis to vas deferens.

5. Sweat secretion: from sweat glands at axilla, nipples, groin and perineum ➔ sex attraction esp. in animals.

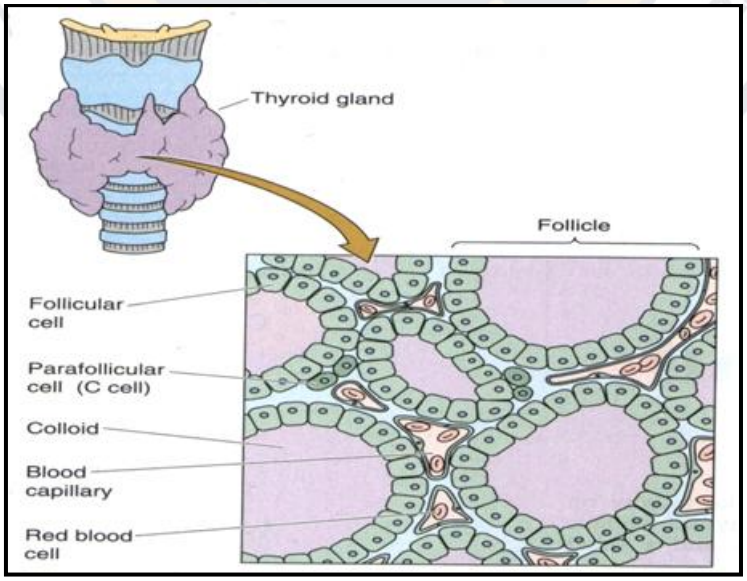
Thyroid gland

• Gross anatomy:

- Thyroid gland is formed of **2 lobes** lying on either side of **lower larynx & upper trachea (weighing 20 grams)**.
- **Not essential for life**.



• Histology:



1- **Thyroid follicles:** a hollow spherical unit:
   - Lined with hormone secreting cuboidal cells carrying microvilli.
   - Filled with thyroid colloid which contains thyroglobulin protein.
2- **Para follicular cells:** between the follicles.

• **N.B:**

- When the gland is **inactive**, follicles are **large**, colloid is **abundant** & follicular cells are **flat**.

- When the gland is **active**, follicles are **small**, colloid is **little** & follicular cells are **columnar**.

• Thyroid hormones:

1- **Thyroid follicles: ➔ produce:**
   - Tetraiodothyronine (T4) (thyroxine).
   - Tri iodo thyronine (T3).
2- **Para follicular cells ➔ produce**
   - Calcitonin.

• *T3 and T4:* T_3 is **3-5 times more active** than T_4 at cellular level **although T_4:**
   - Constitute **90%** of thyroid output.
   - Persists in blood **longer** time than T_3.

• Synthesis of T3 and T4:

(1) Iodide (I^-) uptake from plasma by active pump ➔ (I^- conc in thyroid acinar cells is 10 times its plasma conc)

a. **Accelerated by** ➔ TSH.

b. Inhibited by:
   - Thiocyanate .
   - Perchlorate.

(2) Oxidation of I^- to iodine (I_2)

$$I^- \xrightarrow[\text{(oxidation)}]{\text{Thyroid peroxidase enz}} I_2$$

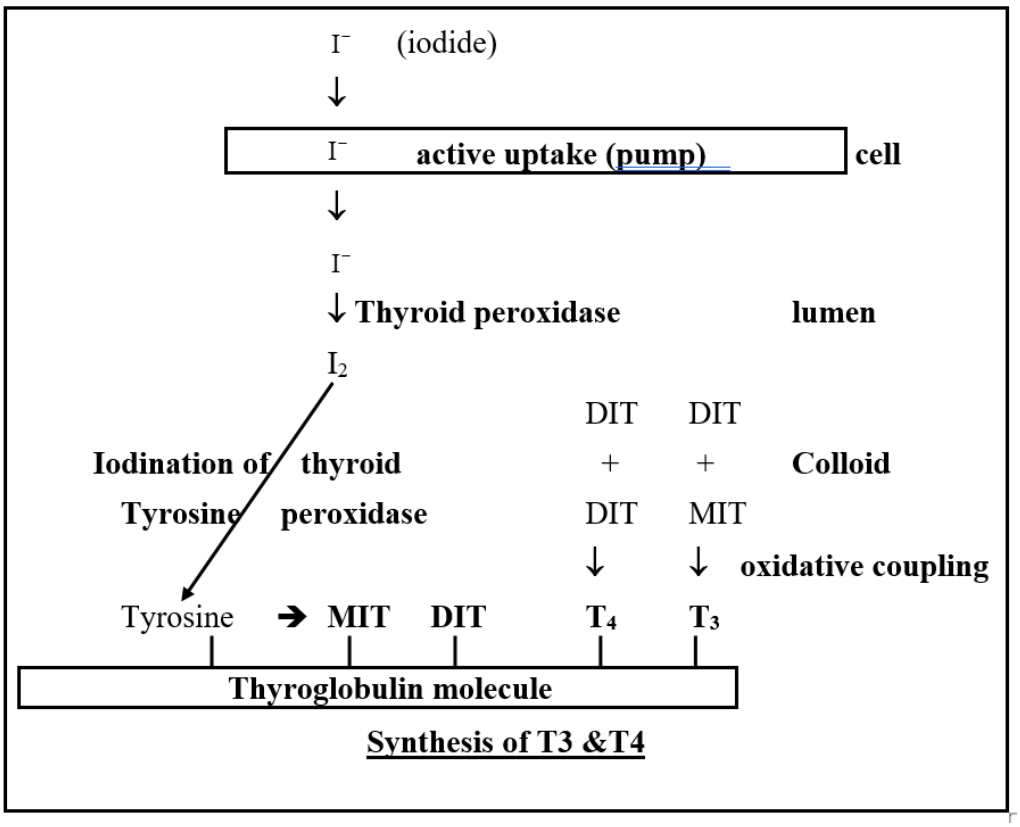
(3) Iodination of tyrosine ➔ Mono iodo tyrosine (MIT) and di iodo tyrosine (DIT).

(4) Oxidative coupling:

- DIT + DIT ➔ T_4.
- DIT + MIT ➔ T_3.

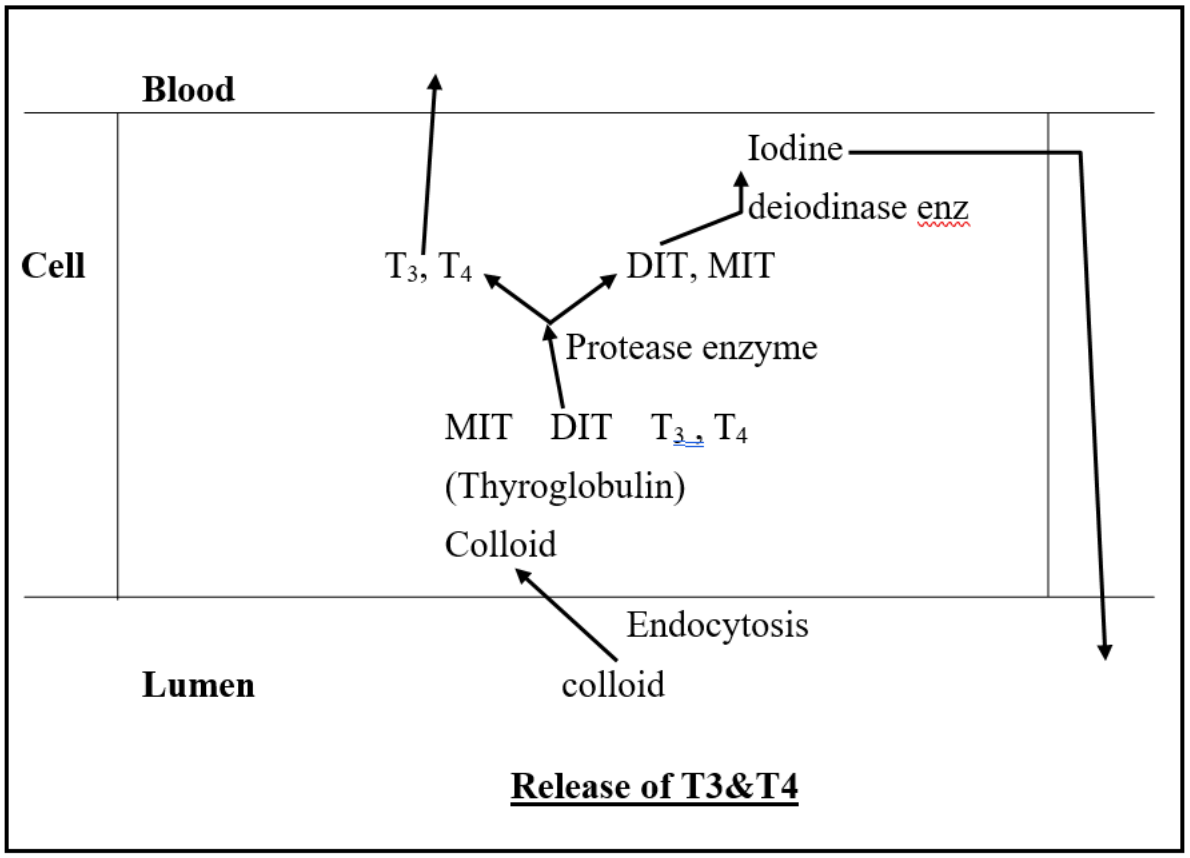
* Oxidation of I^-, iodination of Tyrosine and oxidative coupling ➔ require **thyroid peroxidase enz**.

* **Block of this enzyme by thiocarbamide group** e.g thiouracil and carbimazole ➔ inhibit these reactions ➔ so used in treatment of **hyperthyroidism**.



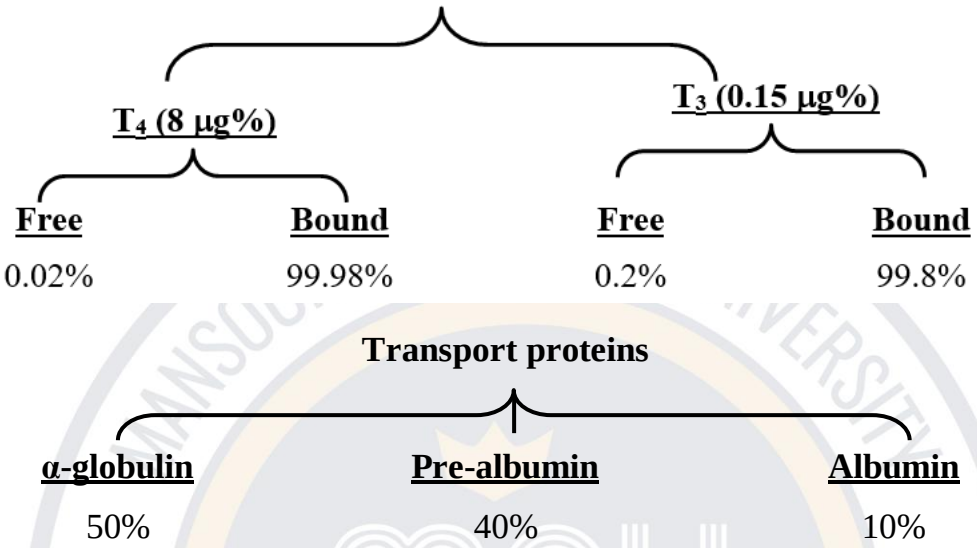
Synthesis of T3 &T4

- **I_2 requirement:**
  - **1mg / week**.
  - Areas far from sea (**e.g.** oases) are supplied by iodized tablet to prevent I_2 ↓.
- **Storage:** T_3 and T_4 are stored in colloid in a peptide linkage with thyroglobulin.
- **Release:**
  - Stimulation of thyroid gland by TSH (act by ↑ing cAMP) ➔ thyroglobulin is taken up by follicular cell by **endocytosis**.
  - **Lysosomes** secrete **proteases** which break peptide links ➔ release **free T_3 and T_4** ➔ T_3, T_4 diffuse through basal memb ➔ blood in capillaries.
  - **Iodotyrosines** (MIT and DIT) $\xrightarrow[\text{enz}]{\text{de iodinase}}$ iodine ➔ recycle in the gland ➔ formation of additional T_3 and T_4.



Release of T3&T4

- **Transport:** In the blood stream the hormones are bound to plasma proteins almost entirely.



- **Mechanism of action:**
  a) **Bind to specific nuclear receptors** (***T_3 has more affinity to the receptor than T_4***) ➔ hormone – receptors complex ➔ interact with DNA ➔ stimulating mRNA formation ➔ stimulating synthesis of specific proteins.
  b) ↑ size and number of **mitochondria**.
  c) ↑ **amino acids transport** across cell memb ➔ facilitate protein synthesis.
  d) ↑ **activity** and amount of memb **Na^+ - K^+ ATPase**.
  e) ↑ intracellular **enzymes**.

- **Function (Actions):**
  I. On metabolism:
  ❖ ***On general metabolism:***
    - Stimulating O_2 consumption, glucose uptake by cells.
    - ↑ heat production, and BMR.
    - 1 mg T4 ➔ ↑ heat production 1000 calories.

❖ ***On CHO metabolism:***

- **In physiological amount** ➔
  - Potentiate action of insulin.
  - Promote glycogenesis and glucose utilization.
- **In pharmacological amounts** ➔ hyperglycemia by:
  - Stimulating gluconeogenesis.
  - Potentiate glycogenolytic effect of epinephrine.
  - Promote intestinal absorption of glucose.

❖ ***On fat metabolism:***

- ↓ blood level of triglyceride, cholesterol and phospholipids.
- ↑ plasma free fatty acids and glycerol.

❖ ***Protein metabolism:***

- In physiological amount ➔ ↑ protein anabolism.
- In pharmacological amount ➔ ↑ protein catabolism.

❖ ***Vitamins and drugs:***

- ↑ synth of vit A from carotenes in liver.
- Stimulating utilization and clearance of vitamins.
- Stimulating clearance of drugs as digitalis.

II. On growth and development:

❖ ***Physical growth:***

- Has a permissive effect on GH & potentiate the effect of somatomedins.

- Development of teeth. - Closure of fontannels.

❖ ***Mental growth:***

- Growth, development & function of CNS during fetal life & 1st few years after birth.

- Myelination of nerve fibers & development of synapses.

❖ ***Sexual growth:***

- Essential for normal menstrual cycle & spermatogenesis (fertility).

- Stimulates milk secretion during lactation.

III. On body systems and organs:

❖ ***Cardiovascular system: (CVS)***

- ↑ heart rate.
- ↑ stroke volume.
- ↑ SBP.
- ↓ DBP due to VD of peripheral arterioles (as a result of accumulated metabolites).

❖ ***Respiratory system:***

- ↑ respiratory rate.
- ↑ depth of breathing.
- ↑ pulmonary ventilation.

❖ ***GIT:***

- ↑ appetite.
- ↑ GIT motility.
- ↑ glucose absorption from intestine.

❖ ***Gonads and other endocrine systems:***

- essential for proper sexual function.
- ↑ sex hormone – binding globulin.
- ↓ clearance of testosterone and estrogen.
- ↑ clearance of glucocorticoids by liver ➔ ↑ ACTH release from A. pit.

❖ ***Haemopoietic system:***

- stimulate erythropoietin production ➔ stimulating erythropoiesis.
- ↑ 2,3 DPG in RBC_S ➔ facilitate O_2 dissociation from Hb.

❖ ***Skeletal muscles:***

- Normal skeletal muscle function.
- Muscle weakness occur in:
  - Hypothyroidism.
  - Hyperthyroidism (due to ↑ catabolism of muscle proteins).

• Control of thyroid functions:

(1) T.S.H:

a. Actions:

i. Hyperplasia of gland cells.
ii. ↑ iodide uptake from blood.
iii. Stimulating synthesis & release of T3 & T4.

b. Control:

i. –ve feed back mech between thyroid Hs & TSH.
ii. ↑ T_3 or T_4 ➔ ↓ TSH by acting:
   1. Directly on thyrotrop cells of **A. pit** (**mainly**).
   2. On anterior **hypothalamus** (site of TRH release) (**to a lesser extent**).

(2) Thyroid stimulating immunoglobulins (long acting thyroid stimulator):

- Produced by **lymphocytes** in **Grave's disease**.
- **Autoimmune disease** ➔ abnormal activation of the thyroid gland.
- TSI act on thyroid as TSH but **not affected by blood T_3 or T_4 level** (**no –ve FB**).

(3) **Stress:** e.g. cold ➔ stimulating thyroid ➔ ↑ MR & heat production ➔ counteract the effect of low temp.

(4) **Age:** ↑ age ➔ ↓ thyroid activity.

(5) **Pregnancy:** thyroid activity increase in pregnancy because human chorionic Gn is similar to TSH.

(6) **Anti thyroid agents (Goitrogens)** ➔ interfere with T_3 and T_4 synthesis ➔ ↓ T_3 and T_4 ➔ ↑ TSH ➔ enlargement of thyroid gland (goiter). **e.g** thiocyanate (in cabbage) ➔ ↓ I^- uptake.

(7) **blood iodine level:**

a) I_2 decrease ➔ ↓ T3 and T4 ➔ ↑ T.SH ➔ Goiter

b) I_2 increase (Wolf Chaikoff effect)

i- ↓ organic binding of I_2 in gland

ii- ↓ proteolysis of thyroglobulin.

iii- Inhibiting TSH effect on the gland (by ↓ cAMP response to it).

Disorder of thyroid gland

(I) Hypofunction (Hypothyroidism):

- ***Causes:*** primary (thyroid defect) or secondary (defect in the pituitary gland).
- ***Manifestations:*** ***vary according to age:***

A) Cretinism: (hypothyroidism in infants).

- **Not recognized until 5-6 months after birth** as some thyroid H reach infant through **milk from his mother**.

• Manifestations:

1- **Retardation of physical, mental & sexual growth:** The cretin is dwarf.

2- **↓ BMR and O_2 consumption**.

Fig: cretinism. ***Note puffy eyelids, depressed nose, disproportionate dwarfism (A); umbilical hernia (B), swollen lips and protruded tongue*** **(C).**

3- <u>Skin</u> ➔

- **<u>Yellow</u>** due to carotenemia (failure of formation of vit A from carotin in liver).
- **<u>Thick</u>**.

4- <u>Scanty course hair</u> (due to ↓ vit A).

5- <u>Facial features</u>:

- Dull uninterested expression.
- Puffy eye lids.
- Thick lips.
- Swollen tongue (macroglossia).

6- <u>Protuberant abdomen</u> with umbilical hernia.

• **<u>Treatment:</u>**

- By giving thyroid H.
- Should be as **<u>early</u>** possible because **<u>mental retardation</u>**, once developed, is irreversible.

<u>B) Myxoedema:</u> (hypothyroidism in adults)

• **<u>Manifestations:</u>**

- **<u>Retardation of mental processes</u> e.g.** lack of concentration, slow thinking and speech, sleepy, long reflex time.
- **<u>↓ BMR and O_2 consumption</u> ➔**
  - Weight gain.
  - ↑ sensitivity to cold weather
- **<u>Increased level of cholesterol & triglycerides</u>**.
- **<u>Decrease HR and ABP</u>**.
- **<u>Skin</u> ➔**
  - ✓ **<u>Thick</u> ➔** due to protein deposition (myxoedematous tissue) subcutaneously.
  - ✓ ***<u>Pale</u>* ➔** *due to:*
    - Fe deficiency anemia.
    - Compression of cutaneous bv_s by deposited subcutaneous tissue.
  - ✓ **<u>Yellow</u> ➔** due to hypercarotenemia.
  - ✓ **<u>Cold</u> ➔** due to decrease BMR.
  - ✓ **<u>Dry scaly with brittle hair</u> ➔** due to ↓ vit A.
- **<u>Failure of sexual functions</u> ➔**

  ♂ ➔ impotence. ♀ ➔ oligomenorrhea.

(II) Hyperfunction (hyperthyroidism) (thyrotoxicosis):

• **Causes:** Excess thyroid H secretion resulting from:

1- Thyroid tumour.

2- Over stimulation of thyroid by TSH or TSI (Grave's disease).

• **Manifestations:**

(1) **Excess nervousness, irritability, insomnia & tremors** of outstretched hand.

(2) **↑ appetite** but there is **weight loss** due to **↑ catabolism of tissue protein & oxidation of stored fat**.

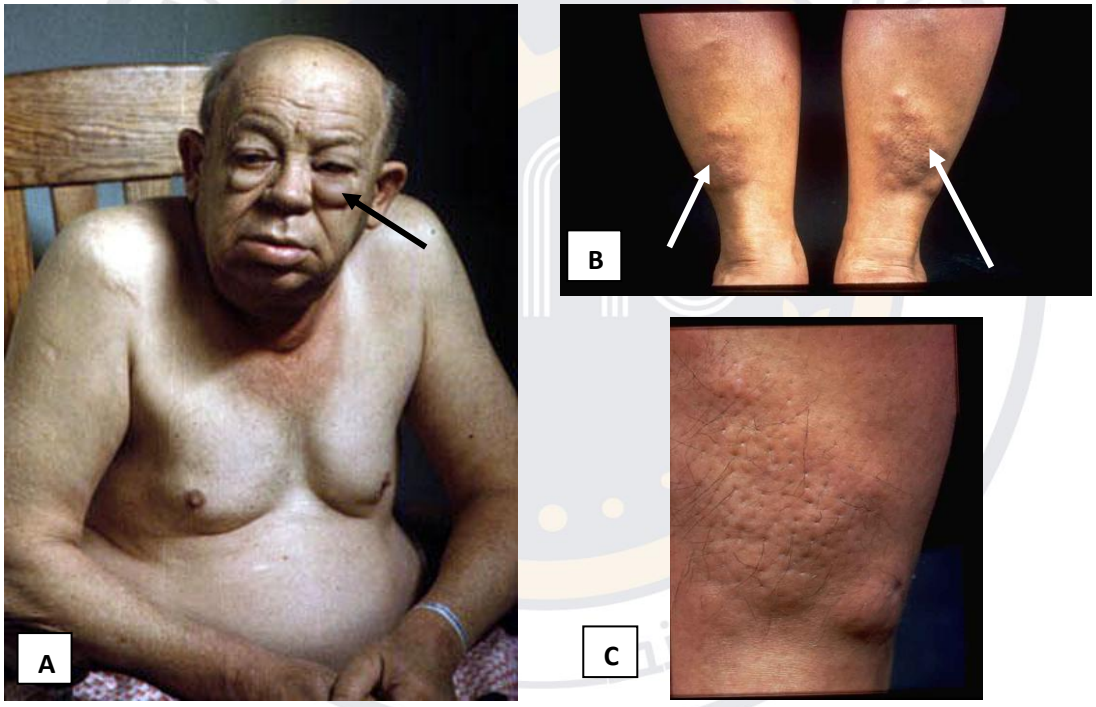


Fig: Myxoedema. ***Note puffy face, generalized fatigued appearance (A), peritibial myxoedema (B), and skin changes (C).***

(3) **↓ serum cholesterol.**

(4) **↑ BMR & O_2 consumption** ➔ patient is susceptible to heat but tolerates cold weather (body temp is not increased as extra heat is lost by VD & sweating).

(5) Skin ➔

- ✓ **Warm**.
- ✓ **Moist**.
- ✓ **Hair ➔** fine and silky.

(6) Ocular signs: ➔

a. **Characteristic staring look** with widened palpebral fissure due to upward retraction of upper eye lid.

b. **Lid lag phenomenon ➔** a delay in the downward movement of upp lid on following a falling object.

c. **Infrequent blinking**.

d. **Failure of convergence**.

♦ All the above signs are due to **sympathetic over stimulation**.

e. Exophthalmos:

- ➢ **Def:** Protrusion of one or both eye balls.
- ➢ **Due to:**
  - ✓ Accumulation of fat, water and inflammatory cells in the retro-orbital tissue and in the extraoccular ms.
  - ✓ Expothalmos producing factor (EPS) (a degradation product of TSH).

(7) C.V.S:

i. ↑ heart rate.
ii. ↑ SBP.
iii. DBP not increase due to peripheral VD.
iv. ↑ Pulse pressure.
v. Atrial arrhythmia (AF).

Fig: Hyperthyroidism. ***Note the staring look (A), the marked protrusion of the eyeball (exophthalmos) (B), and Lid lag phenomenon (C).***

(8) <u>Sexual disturbances</u> ➔

i. ♂ ➔ impotence.

ii. ♀ ➔:

1. polymenorrhea (more frequent menstruation).
2. menorrhagia (excess menst. bleeding).

Goiter

• ***Def:*** Enlargement of thyroid gland.

• Accompanied by: - Hypofunction. - Hyperfunction. - Normal function

• Causes:

1- **Goitrogens** (e.g. thiocyanate and thiocarbamides) ➔ block one or more of reactions involved in synthesis of thyroid hormones ➔ ↓ T_3 and T_4 ➔ ↑ TSH ➔ ↑ gland size.

2- **I_2** ↓ ➔ ↓ T_3 and T_4 ➔ ↑ TSH ➔ goiter (colloid goiter, as acini are distended with colloid).

3- **Physiological goiter** ➔ in: Adolescence & Pregnancy.

4- **Grave's disease** ➔ due to TSI which binds to TSH receptors on thyroid cells ➔ diffuse goiter.

5- **Nodular goiter:** irregular enlargement of thyroid with discrete nodules due to stress.

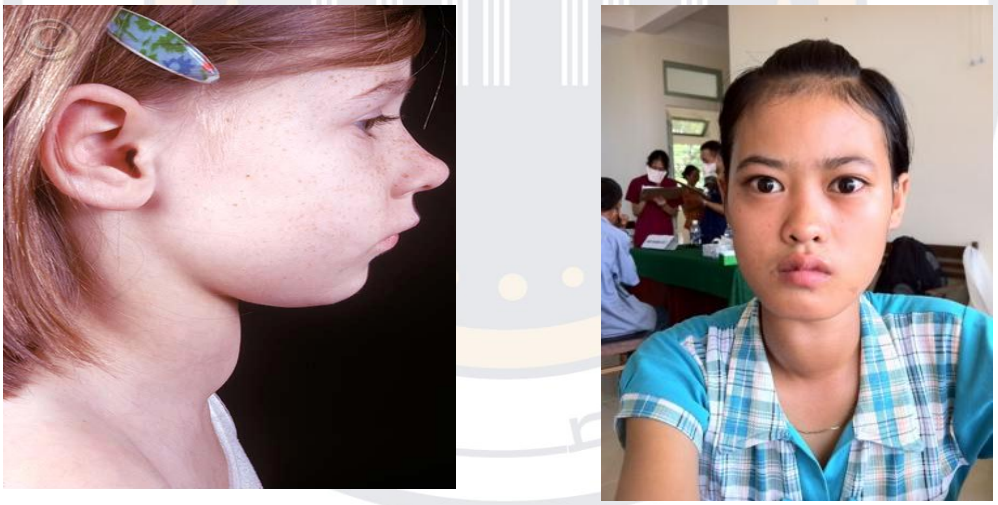


Fig: Goiter. ***Note the rounded bulges in the front part of the neck representing the enlarged thyroid gland.***

Ca^{2+} Metabolism

♦ Significance of Ca:

1- Blood clotting.
2- Muscle contraction.
3- Release of neurotransmitters.
4- Formation of bone and teeth and production of milk.
5- Mechanism of hormone secretion and mediator of hormonal effects.
6- Participate in numerous enzymatic reactions.

♦ Distribution of Ca in body:

Skeleton

- Contain **99%** of total body ca (**1 kg** in young adult)
- **After the 3rd decade of life**, bone resorption exceeds bone formation ➔ slow and progressive **bone loss** (♀>♂)

Plasma
Ca^{2+} = 9 – 11 mg%

Non diffusible (40%) ↓ bound to **plasma proteins** mainly **albumin**

Diffusible (60%)

- **Ionized** (**50%**)
- **Complexed** in non ionic form with citrate, & HCO_3 (**10%**)

♦ Requirements of Ca^{2+}:

- **400mg/day** for adults.
- **↑ needs** occur in childhood, pregnancy and lactation.

♦ Intestinal absorption:

- **Site:** from all parts of small intestine.
- **Mechanism:**
  i. ***Active transport:*** In duodenum.(Controlled by **vit D3 & PTH**).
  ii. ***Passive or facilitated diffusion:*** in jejunum & ileum.

❖ **Factors affecting absorption:**

Decrease absorption	Increase absorption
1- Decrease vit D3. 2- Renal failure. 3- Intestinal malabsorption. 4- Excess unabsorped fatty acids in intestine. 5- Administration of phytate, phosphates or oxalate. 6- Advancing age.	1- Parathormone. 2- Growth hormone. 3- Vit D3.

♦ **Urinary excretion of Ca^{2+}:**

80-400 mg/day.

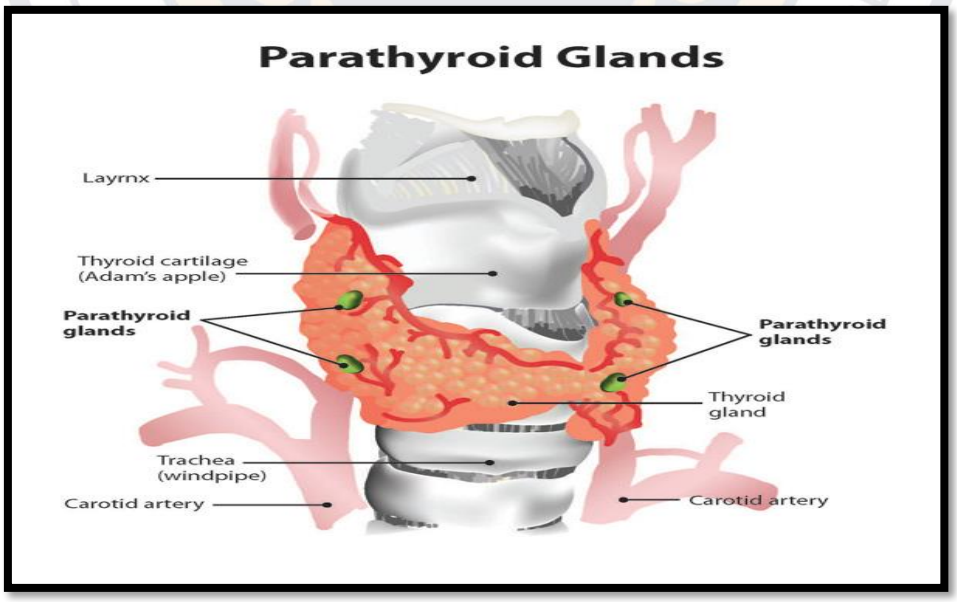


Fig: Parathyroid glands

Hormonal control of Ca metabolism

	Parathormone (essential for life)	Calcitonin	Vit. D
Nature	Polypeptide (84aa)	Polypeptide (32aa)	Steroid
Site of release	**Chief** cells of parathyroid glands (4 glands on posterior aspect of thyroid gland, 120 mg combined weight, 3-5mm diameter). **N.B.** Parathyroid glands contain **chief** cells & **Oxyphil** cells (little & represent inactive chief cells).	**Parafollicular or C** cells of thyroid gland.	• **Vit D_2:** (ergocalciferol) formed in plants from ergosterol. • **Vit D_3:** (cholecalciferol) formed by ultraviolet irradiation of 7- dehydro cholesterol present in skin **Vit D_3** is activated in liver & kidney to **1.25 DHCC**
Actions	↑ pl Ca^{2+} & ↓ pl $PO^{=}_4$ to maintain **solubility product constant**.	↓ pl Ca^{2+} & ↓ pl $PO^{=}_4$	↑ pl Ca^{2+} & ↑ pl $PO^{=}_4$
(1) Small intestine	• PTH indirectly stimulate Ca absorption from small intestine by ↑ formation of 1-25 DHCC in kidney. • ↑ Mg & PO_4 absorp	Calcitonin inhibits intestinal absorption of Ca and PO_4	↑ intestinal absorption of Ca & PO_4

(2) Kidney	• ↑ Ca & Mg reabsorption from renal tubules & ↑ $PO^{=}_4$ excretion.	• ↑ excretion of Ca^{+2} & $PO^{=}_4$ • inhibit renal α1 hydroxylase enzyme which activate vit D	Increase renal tubular reabsorption of Ca^{2+} and $PO^{=}_4$
(3) Bone	• ↑ **Ca permeability** of bone cells. • ↑ **number & activity of osteo-clast** ➔ ↑ bone resorption ➔ release of Ca to blood. • ↓ **activity of osteoblast**. • ↑ **activity of collagenase enzyme** of osteoclast ➔ breakdown of bone collagen.	•↓ **Ca permeability** of bone cells. •↓ **number & activity of osteo-clast** ➔ ↓ bone resorption ➔ ↓ mobilization of Ca from bone to bl. • ↑ **osteoblast activity** ➔↑ bone formation.	• In the presence of PTH, it increase Ca and PO_4 mobilization from bone. • **Paradoxically**, by increasing serum Ca^{2+} and $PO^{=}_4$, it stimulate calcium deposition in bone.
Mechanism of action	• ↑ intracellular cAMP • ↑ intracellular Ca^{2+}	↑ intracellular cAMP	Stimulating ribosomal protein synthesis.
Control of secretion	**(1) pl Ca^{2+}:** • ↓ pl Ca ➔ ↑ PTH. **(2) pl $PO^{=}_4$:** • ↑ pl $PO^{=}_4$ ➔ ↑ PTH. **(3) pl Mg^{2+}:** • ↓ pl Mg^{++} ➔ ↑ PTH.	**(1) pl Ca^{2+}:** • ↑ pl Ca ➔↑ calcitonin. **(2) GIT hormones:** (as gastrin, CCK, secretin…, **mainly gastrin**)	

Other Hormones That Affect Ca^{2+} Metabolism

(1) Estrogens and androgens	(2) glucocorticoids	(3) Thyroid hormones	(4) Growth hormone
• ***In adult*** ♀ ➔ **estrogen protect skeleton from osteoporosis by:** (1) ***Inhibiting PTH mediated bone resorption*** Osteoblasts (have estrogen receptors) ➔ release factors which inhibiting osteoclast resorption. (2) ***↓bone resorbing cytokines*** as IL-1 and 6 in bones. (3) ***↑ serum PTH,*** due to hypocalcemic effect of inhibition of bone resorption. It also **facilitate PTH action** on kidney ➔ ↑ $PO^{=}_4$ excretion, ↑ Ca absorb & vit D_3 activation.	• ***At physiological levels*** ➔ necessary for skeletal growth. • ***Chronic ↑*** ➔ (1) ↓ renal tubular Ca reabsorption. (2) ↓ intestinal ca absorption. (3) Stimulating PTH release due to low Ca level. (4) Inhibiting osteoblastic bone formation. (5) Inhibiting gonadal estrogen and androgen production.	• ***Important for*** the development and growth of skeleton in infants and childhood. • ***Hypothyroidism*** ➔ - Retarded bone growth. • ***Hyperthyroidism*** ➔ ↑ bone resorption.	• ***Stimulate bone growth*** by somatomedins (IGF-1). • ***↑ intestinal Ca absorption*** by Vit D – dependent mech. • ***↑ renal tubular PO_4 reabsorption.***

• Similarly, **androgens protect men from osteoporosis** as evidenced by excess bone loss in **hypogonadal conditions** as Klinefilter syndrome (47, XXY) & castration.			

Disorders of parathyroid gland

Hypoparathyroidism

• Causes: Accidental removal of parathyroid glands or damage to their blood supply during surgical operation on the thyroid.

• Characters:

- **Hypocalcemia** ➔ ↑ neuromuscular excitability due to ↑ neuronal membrane permeability to Na^+
- **Nerve Fibers:➔**
  - Hyperexcitable.
  - Spontaneously depolarized.
  - Initiate nerve impulses to skeletal muscles ➔ titanic cont.

♦ Tetany

• Def: A disease manifested by **↑ NM irritability due to ↓ pl Ca^{2+} conc**.

• Causes:

1) **Hypoparathyroidism**.
2) **Alkalemia**.
3) **Renal failure** due to phosphate retention.
4) **↓ Ca^{2+} absorption from small intestine due to**:
   a. ↓ Ca^{2+} intake.
   b. ↑ antacid intake (as in peptic ulcer) ➔ ↑ alkalinity of intestine ➔ Ca^{2+} precipitation ➔ ↓ absorption.
   c. Steatorrhea ➔ Ca^{2+} loss in stool.
   d. Vitamin D deficiency.

• Manifestations: Depend on the degree of lowering of plasma Ca^{2+} level.

Manifest Tetany	Latent Tetany
* **pl Ca^{2+}** ➔ below 7mg%.	* **pl Ca^{2+}** ➔ 7-9 mg%.
*** Manifestations:** ***1-Muscular spasm in hand and feet (carpopedal spasm).*** • **Hand** ➔ ❖ Flexion of wrist & metacarpo-phalangeal joints. ❖ Extension of interphalangeal joints. ❖ Adduction of thumb. • **Foot** ➔ ❖ Dorsiflexion of ankle. ❖ Planter flexion of toes. ***2-Generalized convulsions***. ***3-Laryngeal spasm*** ➔ difficult breathing.	*** Manifestations:** Manifest tetany does not develop and muscle spasm occurs only when the patient is exposed to stress. - **Patients may have:** ❖ Tingling. ❖ Sensation of heat and flushing (parathesia).

• Treatment:

(1) Intra venous **ca gluconate** stops immediately tetanic spasm.

(2) Ca level is maintained by: **Vit D & Oral ca**.

(3) **Acidifying salts** as NH_4Cl (ammonium chloride) ➔ ↑ Ca^{2+} ionization ➔ ↑ Ca absorption.

(4) **In hypoparathyroidism** ➔ PTH administration ➔ antihormone formation, which antagonize its action. So, **dihydrotachysterol (AT_{10})** (synthetic steroid) is used as it has similar effects as PTH but not produce anti-hormones.

Hyperparathyroidism

- Causes: Parathyroid tumour ➔ ↑ PTH ➔ hypercalcemia (**20mg%**).

- Manifestations:

(1) On the bone:

*** Bone resorption:** due to ↑ osteoclastic activity ➔ Ca mobilization from bone.

*** Bone ache & bone collapse** due to formation of fibrous masses & cysts in bone (**Ostitis fibrosa cystica**).

*** This may lead to** ↑ bone fragility & spontaneous fracture.

(2) On the kidney:

a) **↑ Ca in glomerular filtrate** ➔ precipitation of Ca compounds ➔ calculi formation ➔ renal failure.

b) **Polyurea due to**:

a. Excess excretion of Ca and PO_4 in urine ➔ osmotic diuresis.
b. Renal damage (from calculi).

(3) Hypotonia of muscles ➔ muscular weakness and sensation of tiredness.

(4) Vomiting, diarrhea, and intestinal pain.

(5) Cardiac irregularities, mental confusion, coma, and death.

- Treatment: Surgical removal of parathyroid tumour.

Pancreatic Hormones

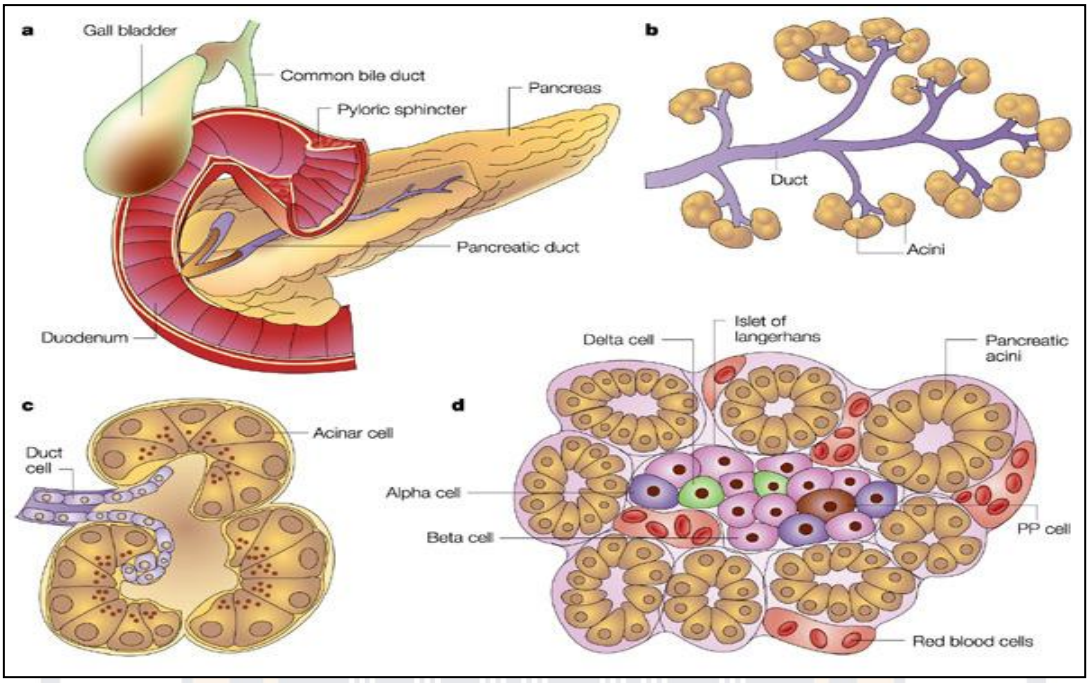


Fig.: Physiologic anatomy of the pancreas.

(I) Insulin:

- **Source:** **Beta cells** of islets of Langerhans of pancreas (60% of islet mass)
- **Nature:** Peptide hormone
- **Synthesis:**

  - **Preproinsulin** is first synthesized in the **ribosomes**

  - It is cleaved in **ER** to form **proinsulin**

  - Most of **proinsulin** is further cleaved in the **Golgi apparatus** to form **insulin** & **c-peptide** fragments before being packaged in the secretory **granules**.

  - C-peptide has **10% of biological activity of insulin**

- **Release:** by exocytosis

- **Functions:**

1-Effects on carbohydrate metabolism:

Lowering of blood glucose (the main function) by:

-**Stimulation of glycogenesis** in muscles & liver by activating glycogen synthetase enzyme

-**Inhibition of glycogenolysis** by inhibiting glycogen phosphorylase enzyme

-↑ **glucose uptake** by tissues by activating glucokinase enzyme (**except brain, renal tubules, intestinal mucosa, RBCs**)

-**Inhibition of gluconeogenesis** by decreasing hepatic uptake of amino acids

2-Effects on fat metabolism:

-**Stimulation of lipogenesis** in liver & adipose tissue by activating lipoprotein lipase enzyme

-**Inhibition of lipolysis** by inactivating hormone sensitive lipase enzyme

-↓ **ketogenesis** in the liver

3-Effects on protein metabolism: Protein anabolic effect by:

a- ↑ tissue uptake of amino acids
b- ↑ protein synthesis
c- ↓ protein catabolism
d- ↓ oxidation of amino acids

4-Effects on electrolytes:

-It ↑ uptake of K^+ (by stimulating Na^+-K^+ ATPase pump)

- It ↑ reabsorption of Na^+, K^+ & phosphate from renal tubules

- **Control of secretion:**

(A) Stimulators:

1- ***Hyperglycemia:*** glucose, mannose & fructose enter the beta cells independent of insulin & directly stimulate insulin secretion

N.B.

Plasma glucose	Insulin secretion
50mg %	No
150mg %	Half maximum
300-500mg %	Maximum

- When glucose is given **orally**, it induces **a greater insulin secretion** than intravenous glucose due to **release of GIT hormones** mainly **GIP**, CCK, gastrin & secretin (which potentiate insulin secretion).

- This GIT mechanism of insulinogenesis **reduces the early rise of glucose** that follows the ingestion and absorption of a carbohydrate meal.

2-***Amino acids:*** e.g. arginine, lysine, phenylalanine

3-***Fatty acids*** & ***ketone bodies***

4-***GIT hormones***: as GIP (**most important insulinogogue**), gastrin, secretin, CCK

5-**β *adrenergic stimulators***

6-***Acetylcholine*** & ***stimulation of right vagus nerve***

7-***Glucagon, GH, cortisol***

8-***Oral hypoglycemic drugs***: sulphonylureas

(B) Inhibitors:

1- ***α adrenergic stimulators***

2- ***β adrenergic blockers***

3- ***Somatostatin***

4- ***Alloxan & streptozocin*** which destroy beta cells

5- ***Long term stimulation of beta cells*** ➔ their exhaustion

6-***Exogenous insulin*** ↓ secretion of endogenous insulin by induced hypoglycemia

7- ***Drugs*** as diazoxide,thiazide, phenytoin

(II) Glucagon:

- **Source:** Alpha cells of islets of Langerhans (25% of islet mass)
- **Nature:** Polypeptide (29 a a)
- **Functions:**

1-Effects on carbohydrate metabolism: hyperglycemic effect which results from:

a-↑ hepatic **glycogenolysis** by stimulating glycogen phosphorylase enzyme

b-↑ **gluconeogenesis** in the liver by:

-Activating the necessary **enzyme**

-↑ **hepatic uptake of amino acids** especially alanine

2- Effects on fat metabolism:

-↑ **lipolysis** by activation of glucagon sensitive lipase in adipose tissue

- ↑ **plasma level of FFA & glycerol**:

Glycerol $\xrightarrow[\text{Gluconeogenesis}]{\text{Liver}}$ glucose

FFA $\xrightarrow{\text{Oxidation}}$ energy + KB (ketogenesis)

- ↓ **hepatic cholesterol** synthesis

3-Effects on protein metabolism: ↑ protein **catabolism** & ↓ protein **synthesis**

4-Others:

-↑ **Natriuresis** by inhibition of renal tubular Na^+ reabsorption

- **Stimulates myocardial contractility (+ve inotropic effect):** by activation of myocardial adenyl cyclase ➔ ↑ myocardial cAMP.

-Local CNS hormone for **regulation of appetite**

- **Control of secretion:**

(A) Stimulators:

1. Hypoglycemia
2. Glucogenic amino acids(alanine, serine, glycine)
3. GIT hormones (CCK, Gastrin)
4. Exercise
5. Infections
6. Cortisol, acetylcholine & β adrenergic stimulators
7. Low plasma level of fatty acids

(B) Inhibitors:

1. Hyperglycemia
2. Insulin, somatostatin &secretin
3. α adrenergic stimulators
4. Increased plasma level of fatty acids & ketone bodies

(III) Somatostatin:

- **Source:**

  1-Delta cells of islets of Langerhans of pancreas (10% of islet mass)

  2-GIT

  3-Hypothalamus

- **Nature:** Polypeptide
- **Functions:**

a-Effects on pancreas: inhibit secretion of insulin, glucagon & Panc polypeptide.

b-Effects on the GIT:

1-It inhibits the secretion of GIT hormones as gastrin, secretin, VIP, CCK

2-It decreases the motility of the stomach, duodenum, &gall bladder

3- It inhibits both secretion & absorption in the GIT

c-Effects on the anterior pituitary: inhibits secretion of GH & TSH

(IV) Pancreatic polypeptide:

- **Source:** F cells of islets of Langerhans of pancreas (5% of islet mass)
- **Functions:**

  1-Inhibits insulin & somatostatin secretion by direct pancreatic effect

  2-Slows the absorption of food in humans

Endocrinal regulation of blood glucose

a-Insulin: ↓ blood glucose (as before).

b-Glucagon: ↑ blood glucose (as before).

c-Adrenaline: ↑ blood glucose via glycogenolysis in liver & muscles (as before).

d-Glucocorticoids: ↑ blood glucose by:

* Stimulation of gluconeogenesis
* ↓ glucose uptake by tissues

e-Growth hormone: increase blood glucose by:

* ↓ glucose uptake by tissues
*Stimulating the release of glucagons

f-Thyroxine: ↑ blood glucose by:

* Increase glucose absorption from the intestine
* Increase glycogenolysis
* Increase glucose uptake by cells

Diabetes mellitus

- **Causes:** ↓ insulin secretion (**type I DM**) or ↓ sensitivity of tissues to it (**type II DM**)
- **Manifestations:**

1) **Hyperglycemia:** due to decreased glucose uptake by tissues, & increased hepatic glycogenolysis & gluconeogenesis
2) **Glucosuria:** occur when the plasma glucose concentration exceeds the renal threshold (180mg %)
3) **Polyuria** due to:

   a-Glucosuria ➔ omotic diuresis

   b-↑ osmotic pressure of blood ➔ drag water out of cells towards the blood➔ dehydration of tissue cells

4) Polydipsia: Excessive drinking of water due to intense thirst resulting from dehydration

5) Acidosis: Due to inhibition of carbohydrate metabolism ➔ body depends on fat metabolism to supply energy needs➔ accumulation of ketone bodies

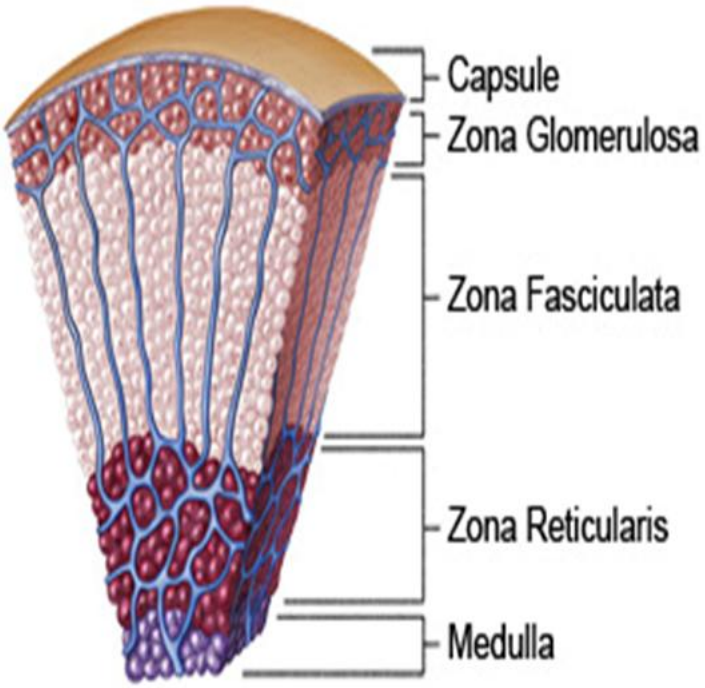
6) Loss of weight & asthenia: Due to mobilization of fat & proteins for the supply of energy

7) ↑ cholesterol, triglycerides, FFA & lipoproteins➔ atherosclerosis

Adrenal cortex

• Adrenal cortex **(essential for life)** constitutes the **outer 80 %** of adrenal gland.

• Histology and functions of adrenal cortex:



Zona glomerulosa	Zona fasiculata	Zona reticularis
- Constitute **15%** of adrenal cortex.	- Constitute **75%** of adrenal cortex.	- Constitute **10%** of adrenal cortex.
- Thin outer layer **under the capsule**.	- The **middle** and widest layer.	- The **deep** layer of the cortex.
- **Secretes:** mineralocorticoids as aldosterone.	- **Secretes:** glucocorticoids as cortisol and corti-costerone as well as small amount of adrenal androgens.	- **Secrets:** • Androgens as DHEA & Androstenedione. • Estrogen.

• Transport of adrenocortical hormones:

Hormone	Free	Bound	Half life
Cortisol	10%	90% bound: • 75% with globulin (transcortin) • 15% with albumin.	60-90 minutes
Aldosterone	40%	60% bound	20 minutes.

• Metabolism and Excretion of adrenocortical hormones:

1) Glucocorticoids: metabolized mainly in the **liver**.

- ✓ **Most of cortisol** is reduced ➔ dihydrocortisol ➔ tetrahydrocortisol, ➔ conjugated to glucuronic acid ➔ excreted in urine.
- ✓ **cortisol (10%)** ➔ liver ➔ 17-Ketosteroid ➔ excreted in the urine.

2) Aldosterone: **Most of aldosterone** ➔ liver ➔ tetrahydroaldosterone ➔ conjugates with glucuronic acid ➔ excreted in urine.

(I) Glucocorticoids

-About 95% of glucocorticoid activity is due to cortisol, a very little activity is produced by corticosterone.

✹ Physical effects of glucocorticoids:

(I) On metabolism:

a) On carbohydrate metabolism:

1- Stimulate gluconeogenesis (from amino acids mobilized from muscles).
2- Stimulate hepatic glycogenesis.
3- ↓ glucose utilization by cells.

b) On protein metabolism: ↓ protein synthesis & ↑ protein catabolism (in extrahepatic tissues) ➔ ↑ plasma amino acids ➔ amino acids transport to liver ➔ utilized for:

1- ↑ deamination of amino acids.
2- ↑ protein & plasma protein synthesis.
3- ↑ gluconeogenesis.

c) On fat metabolism: ↑ lipolysis ➔ mobilization of FFAs from adipose tissues ↑ plasma FFAs ➔ utilized for energy.

(II) On body systems and organs:

1- **Blood vessels (BVs):**
   - **a.** Essential for normal response of vascular smooth muscles to vasopressor effect of catecholamines ➔ maintenance of normal ABP.
   - **b.** Enhance catecholamine synthesis via activating epinephrine-forming enzyme.

2- **On blood cells and lymphoid tissues:**
   - **a.** ↓ **lymphocytes, monocytes, basophil & eosinophil**, because it stimulates migration of these cells from circulation to lymphoid tissues.
   - **b.** ↑ **RBCs, platelets & neutrophils because**:
     i. It stimulates haemopoiesis.
     ii. It inhibits migration of these cells from circulation.

3- **Gastric effects:**
   - **a.** ↑ gastric acid secretion.
   - **b.** Inhibit mucosal cell proliferation.

4- **Renal effects:**
   - **a.** ***Weak mineralocorticoid activity*** ➔ ↑ Na^+ reabsorption and K^+ secretion.
   - ***b. Cortisol effects on water excretion depends on water condition of the body:***

In case of dehydration	In case of hydration
Cortisol has an **antidiuretic effect** secondary to ↑ Na^+ reabsorption.	Cortisol has a **diuretic effect** caused by: • ↑ RBF & GFR. • Inhibition of ADH action on CDs.

(III) Anti allergic, Antistress, anti-inflammatory:

1-Anti allergic effect: Inhibits histamine release mast cells and basophils.

2-Anti-stress (resistance to stress):

a. ***Mobilization of:***
   i. FFAs ➔ to supply energy.
   ii. Amino acids ➔ for synthesis of other compounds as glucose.
b. ***Stabilization of lysosomal membrane*** ➔ cell protection.
c. ***Facilitation of action of catecholamines*** ➔ ↑ vascular reactivity ➔ maintain ABP.

3-Anti-inflammatory effect:

a. **Stabilizes lysosomal membrane** ➔ ↓ release of proteolytic enzymes which cause inflammation.
b. **↓ release of proteolytic enzymes** ➔ ↓ capillary permeability ➔ prevent plasma loss into tissues.
c. **↓ migration of WBCs** into inflamed areas.
d. **↓ phagocytosis** of damages cells.
e. **↓ T-cells and antibodies**.
f. **Inhibit fibroblast activity** ➔ inhibit collagen deposition.
g. **↓ release of IL-1 from WBCs** ➔ lowers fever.

✹ Control of glucocorticoids:

(1) Hypothalamic control:

- **CRH** is secreted by hypothalamus into the hypothalmo hypophyseal portal vein ➔ ant pit ➔ ACTH secretion.

- **ACTH:**

✓ ***Secreted by*** corticotrope cells of ant pit.

✓ ***Secreted in pulses:***

- ***More frequent*** in early morning.
- ***Less frequent*** in evening (circadian rhythm).

✓ ***Stimulate synthesis & secretion of glucocorticoids*****.** It has a minimal effect on mineralocorticoids.

- This hypothalamo-hypophyseal adrenocortical axis is ***stimulated by stress*** **e.g.** exercise, trauma, cold… etc.

(2)–ve feedback mechanism: exerted by cortisol on ant pit & hypoth.

* Circadian rhythm of ACTH secretion:

- **ACTH is secreted in irregular pulses** throughout the 24 hours.
- **These pulses are:**
  - ***More frequent*** early in morning.
  - ***Less frequent*** in the evening.
- Plasma cortisol ↑ & ↓ in response to these pulses. About **75%** of daily production of cortisol occurs between **4 and 10 am**.
- This circadian rhythm is related to **sleep hours** and is reversed if the sleeping hours are reversed.
- The **biological clock** responsible for the diurnal ACTH rhythm is located in **suprachiasmatic nuclei of hypothalamus.**

** Cushing syndrome "hyperadrenalism":*

- **Causes:**
  - Excessive secretion of glucocorticoids by adrenal tumour.
  - Excessive secretion of ACTH by pituitary tumour.
  - Excessive treatment with glucocorticoids for long time.
- **Manifestations:**

*i. **Exaggerated mineral corticoid effects:***

a) **Hypertension and edema** due to Na and water retention.

b) **hypokalemia** due to excessive loss of K^+ in urine.

c) **metabolic alkalosis** due to excessive loss of H^+ in urine.

*ii. **Increased protein breakdown: which results in:***

a) **Muscle wasting** and weakness.

b) **Osteoporosis:** bone become weak, fragile and easily fractured due to decreased protein content of bone matrix.

c) **Loss of collagenous tissues from:**

- ***Skin*** ➔ purple striate and delayed healing of wounds.
- ***Vascular wall*** ➔ Subcutaneous haemorrhages.

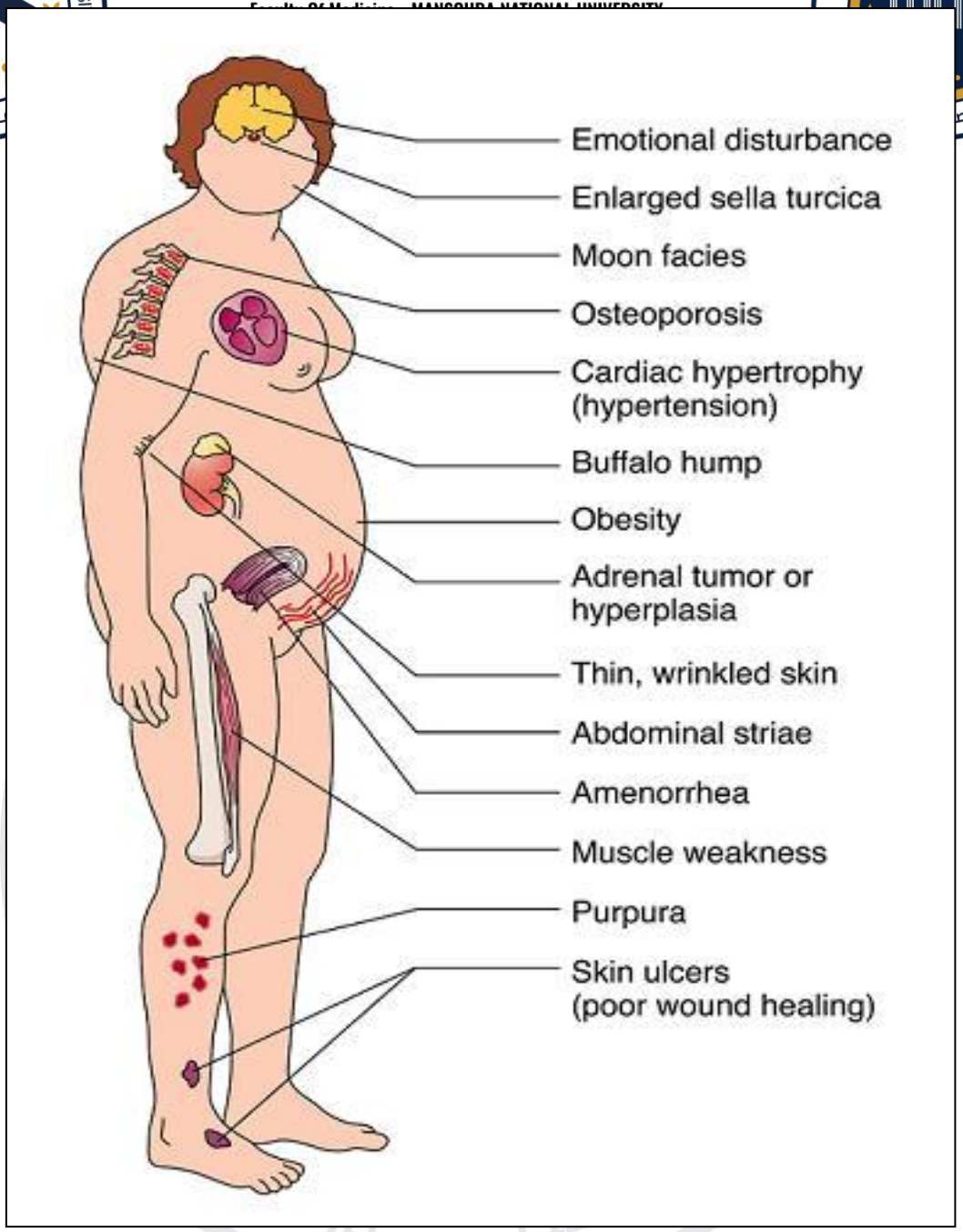


Fig. Manifestations of Cushing syndrome

iii. <u>Redistribution of fat: fat is mobilized from lower limbs which become thin and deposited in:</u>

1. **<u>Face</u>** which become:
    a. Rounded (moon face).
    b. Edematous (Na and H_2O retention).
    c. Red (polycythemia).

2. **subclavicular region, back of neck and interscapular region** (buffalo hump).
3. **trunk and abdomen** (trunkal obesity).

iv. ***Hyperglycemia (steroid diabetes) due to:***

- Excessive gluconeogenesis.
- Anti-insulin action of cortisol.

v. ***↑ BMR.***

vi. ***Peptic ulcer due to:***

1. ↑ gastric acid secretion.
2. ↓ resistance of gastric barrier.

vii. ***Polycythemia and decreased basophil, eosinophils and lymphocytes.***

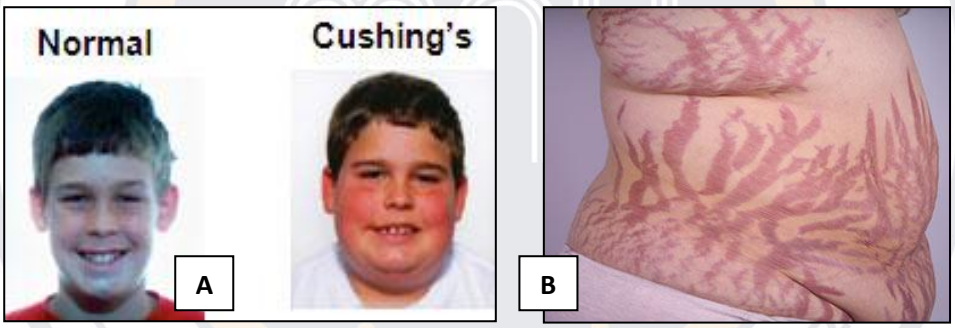


Fig.: Cushing syndrome. Note moon face, plethora (A), Abdominal stria and fatty abdomen (B).

(II) Mineral corticoids

• Effects of mineral corticoids:

(1) Renal effects:

- ***Active Na^+ reabsorption*** from DCT and CDs.
- ***K^+ secretion*** secondary to its effect on Na^+ reabsorption.
- ***H^+ secretion*** (in exchange with Na^+ reabsorption) especially in acidosis.

(2) Effects on other tissues: ↑ *Na^+ reabsorption from:*

i. Sweat.
ii. Saliva.
iii. Gastric juice.
iv. Milk.

- ***↑ Na^+ reabsorption and K^+ secretion in colon.***

• Regulation of aldosterone secretion: Aldosterone secretion is stimulated by:

1- **↑ activity of renin angiotensin system:** ↓ ECF volume ➔ ↑ renal sympathetic activity & ↓ renal arterial pressure ➔ increase renin secretion ➔ ↑ angiotensin II ➔ ↑ aldosterone secretion.
2- **Hyperkalemia (1%).**
3- **Hyponatremia (10%).**
4- **ACTH**.

• Primary hyperaldosteronism (Conn's syndrome):

- **Causes:** Excessive secretion of aldosterone due to adrenal hyperplasia or tumour.
- **Manifestations:**

1. **Hypokalemia:**
   a. ***Due to:*** excess secretion of K^+ in urine.
   b. ***Leads to:***
      i. **Muscle weakness and periodic paralysis** due to ↑ RMP.

ii. **Renal damage and polyurea** due to impaired renal concentration power (**hypokalemic nephropathy**).

iii. **ECG:**

1. Flat or inverted T wave.
2. Depressed ST segment.
3. Prolonged PR interval.

2. **Hypernatremia:**

a. ***Due to:*** ↑ Na^+ reabsorption from DCT and CDs.

b. ***Leads to:***

i. **Metabolic alkalosis** (due to excessive loss of H^+ in urine) ➔ tetany.

ii. **Mild hypertension** due to hypervolemia.

• Secondary aldosteronism:

- Causes: Excessive aldosterone secretion due to **excess secretion of renin due to:**

- Renal ischemia.
- Tumours.

- Characters:

1- Peripheral edema.
2- Hypertension.
3- Increased renin and angiotensin.
4- Hypokalemia.
5- Increased aldosterone.

(III) Adrenal androgens

- **Secreted from:** zona reticularis.

- **Include:**
  1. Dehydroepiandrosterone (DHEA).
  2. Androstenedione.
- **Controlled by:**
  1. ACTH.
  2. Pituitary adrenal androgen – stimulating hormone.
- **Functions:**
  1. **In male:** little effect.
  2. **In female:**
     a. Appearance of ***pubic and axillary hair***.
     b. Growth of ***clitoris***.
     c. ↑ Protein anabolism ➔ ***physical growth*** esp at puberty.
     d. Increased sebaceous gland secretion ➔ ***acne***.

- Adrenogenital syndrome:

- **Causes:** Androgen secreting **tumour** in adrenal cortex.
- **Manifestations:**

Age	Male	Female
In fetus	Enlarged external genital organs (**macrogenitosomia precox**)	Development of male type external genitalia (enlarged clitoris & big fused labila like scrotum) if androgen secretion ↑ before 12th week of pregnancy (**female pseudo-hermaphroditism**).
In children	**Precocious pseudopuberty** i.e appearance of male sex characters but without spermatogenesis.	**Virilism**.
In adults	Pass **unnoticed** except ↑ **musculinization** & ↑ **sexual activity**.	**Virilism**.

Virilism:

• **Def:** development of **male secondary sex characteristics in female** due to excessive secretion of adrenal androgens.

• **Manifestations:**

1- ***Hirsutism:***
   a. Male distribution of hair in face, axilla, pubis and all over the body.
   b. Recession of scalp hair.
2- ***Deeping of voice***.
3- ↑ ***muscle bulk and power***.

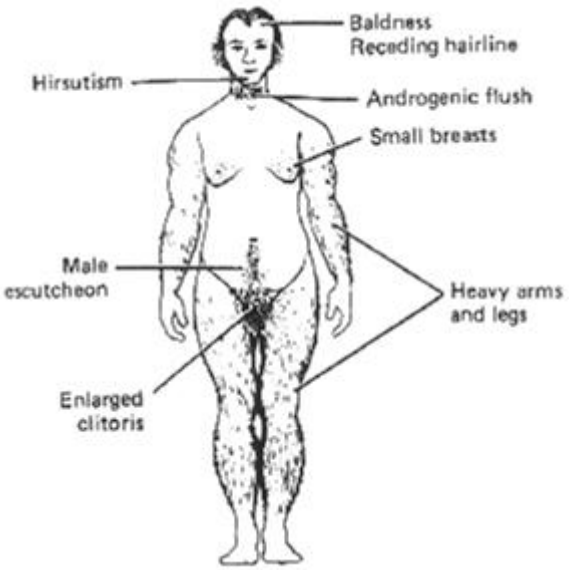


Fig: adrenogeital syndrome in a postpubertal woman.

4- ***Enlargement of clitoris***.
5- ***Atrophy of breast and external genital organs*** (***except clitoris***) due to suppression of estrogen action.
6- ***Amenorrhea***.
7- ***Psychological disturbance*** and homosexuality.

Addison's Disease (hypoadrenalism):

***Cause:** Hypofunction of the adrenal cortex caused by bilateral destruction of the glands by autoimmune disease, or T.B.

***Manifestations:** Are mainly due to deficiency of glucocorticoids and mineralocorticoids. **They include:**

1)Deficient mineralocorticoid activity which leads to:

a. **Hypotension** due to ↑ loss of Na^+ & H_2O in urine producing hypovolemia.
b. **Hyperkalemia** due to ↓ excretion of K^+ in urine ➔ muscle weakness & cardiac abnormalities.
c. **Metabolic acidosis** due to retention of H^+.

2) **Hypoglycemia** in between meals due to loss of gluconeogenic effect of cortisol.
3) **Muscle weakness** due to the combined effects of hypoglycemia, hyperkalemia & hypotension.
4) **Dark pigmentation** of skin and mucous membranes due to deposition of melanin pigment as a result of the MSH activity of ACTH.
5) **↓ BMR.**
6) **Moderate anemia** due to inhibited erythropoiesis.
7) **GIT troubles** including nausea, vomiting and diarrhea.

***Treatment:** replacement therapy with cortisol & aldosterone.

Adrenal medulla

- Represent **enlarged sympathetic ganglion**.
- ***Nerve supply:*** long sympathetic preganglionic cholinergic neurons.
- ***Histology:***

  Adrenal medulla consists of **chromaffin cells** which contain adrenaline and noradrenaline (stored in granules).

  - **Adrenaline:** 80%.
  - **Noradrenaline:** 20%.
- ***Synthesis:***

- Catecholamines are synthesized from **L-tyrosine**.

- The plasma **half-life** of epinephrine and norepinephrine is **2-3 minutes**.

- ***Metabolism:***

a) Neuronal uptake:

- Sympathetic nerve endings take up amines actively from the circulation➔

  * **nonenzymatic inactivation** by intraneuronal storage

  * **enzymatic inactivation** by monoamine oxidase (MAO) enzyme.

b) Extraneuronal uptake: by different tissues (as liver, kidney) where they are destroyed by COMT (catechol-O- methyl transferase).

N.B: vanillyl mandelic acid (VMA) is the major metabolic waste product for catecholamines found in urine

- ***Control of catecholamine secretion:***

  - by: **adrenaline secreting center (ASC)** in the medulla oblongata.
  - A.S.C ➔ impulses descend through reticulospinal tract (RST) ➔ LHCs in T_5-T_9 ➔ sympathetic preganglionic fibers through greater splanchnic nerve ➔ adrenal medulla.

- **Catecholamine secretion**:
  - **Low** ➔ in basal states.
  - **↓ further** ➔ at sleep.
- **ASC is stimulated by:**
  - ***Hypothalamus:*** **e.g.** pain, emotions, cold and hypoglycemia.
  - ***Baroreceptors in carotid sinus & Ao arch:*** ↓ ABP e.g haemorrhage ➔ release of ASC from baroreceptor inhibitory impulses ➔ ↑ catecholamine secretion ➔ ↑ ABP.
  - ***Peripheral chemoreceptors in carotid & aortic bodies*** as during hypoxia.
  - ***Volume receptors in right and left atria and in pulmonary vessels:*** in hypovolemia, ASC is released from inhibition of these receptors ➔ ↑ catecholamine secretion.

- ***Physiological effects of catecholamines:***

1-On heart: Catecholamine ↑ **all cardiac properties**:

- ↑ heart rate.
- ↑ force of myocardial contraction.
- ↑ cardiac metabolism and O_2 consumption.
- Coronary VD due to ↑ metabolites.

2-Vascular effect:

- **Vasoconstriction** in all organs except blood vessels of skeletal muscles and liver ➔ vasodilatation via β_2 receptors.

3-Respiratory effects:

- **Initially** ➔ **adrenaline apnea** occur **because:** adrenaline ➔ ↑ ABP ➔ stimulate arterial baroreceptors ➔ inhibit resp. center ➔ apnea.
- **Then** ➔ adrenaline ➔ stimulate resp. center ➔ ↑ **rate & depth of resp**.

4-Renal effects:

- ***VC of renal arterioles*** ➔ ↓ GFR.
- ***Stimulate Na^+ reabsorption***.
- ***Stimulate renin secretion*** from JGA ➔ stimulate renin – angiotensin – aldosterone system ➔ ↑ distal Na^+ reabsorption.

5-Effect on skeletal muscles: ↑ strength of skeletal muscles contraction & delay fatigue (**Orbelli phenomen**) **due to:**

- VD and increased blood flow to muscle.
- Stimulate metabolism and energy production.

6-Effects on skin:

- Cutaneous VC ➔ ***pallor***.
- Contraction of pilomotor muscle ➔ ***erection of hair***.

7-Effects on smooth muscles:

- Relaxation of smooth muscles of bronchi &bronchioles (B_2) ➔ ***bronchodilatation***.
- ***Relaxation of walls (β_2) and contraction of sphincters (α) in the GIT***.
- ***Relaxation of wall of urinary bladder (β_2) & contraction of internal urethral sphincter (α)***.
- ***Dilatation of pupil*** due to contraction of dilator pupillae muscle (β_2).

8-Nervous effects:

- ↑ ***excitability of CNS***.
- ***Shortens the response time***.
- ↑ ***alertness, awareness & mental activity*** by stimulating RAS.

9-Effect on blood clotting: Shortens clotting time due to:

- ↑ production of ***fibrinogen and prothrombin***.
- ***Activate clotting factor V***.

10-Effect on pancreatic islets:

- ↑ ***secretion of insulin and glucagon*** (via adrenergic mechanism) and ***inhibit their secretion*** (vie ***α*** adrenergic mechanism).

11-Effect on carbohydrate metabolism: ***hyperglycemia*** due to:

- Stimulation of ***glycogenolysis*** in liver and sk. ms.
- Stimulate ***glucagon*** secretion which ***amplify its hyperglycemic effect***.
- Stimulate ACTH secretion ➔ stimulate cortisol secretion ➔ ***gluconeogenesis.***
- ***Inhibit glucose uptake*** by:
  - ***Blockade of insulin secretion***.
  - ***Inhibition of glucose transporter*** proteins in cell membranes (skeletal and cardiac muscles and adipocytes).

12-Effect on fat metabolism:

- Stimulate ***lipolysis*** by activating triglyceride lipase.
- ***Mobilization of FFA*** from adipose tissue ➔ ***ketogenesis*** in liver.
- ***Cardiac muscle*** and ***renal cortex*** use ***FFA*** in preference to glucose whereas ***resting skeletal muscles*** use ***FFA*** as major source of energy.

- ***Pheochromocytoma:***

****Cause:*** Tumour of chromaffin cells.

****Manifestations:***

- Headache.
- Blurred vision due to papillary dilatation.
- Pale skin due to cutaneous vasoconstriction.
- Sweating.
- Palpitation due to tachycardia.
- Chest pain due to increased work of heart.

- Hypertension.
- Hyperglycemia and glucosuria.

**** Diagnosis:***

- By measuring **urinary catecholamines**.
- Normally ➔ **10 – 100 g/day**.
- Pheochromocytoma ➔ ↑ to **300 g/day**.

- ***Hyposecretion of adrenal medulla hormones:***

➢ **Occur during** T.B, malignant destruction of adrenal gland, adrenalectomy.
➢ **No manifestations**.
➢ **Catecholamine production from sympathetic nerves is satisfactory** as **ad. Med is not essential for life**.
➢ Adrenalectomized patient **do not require epinephrine replacement therapy**.

Physiology of male reproduction

* Physiological anatomy of male sex organs:

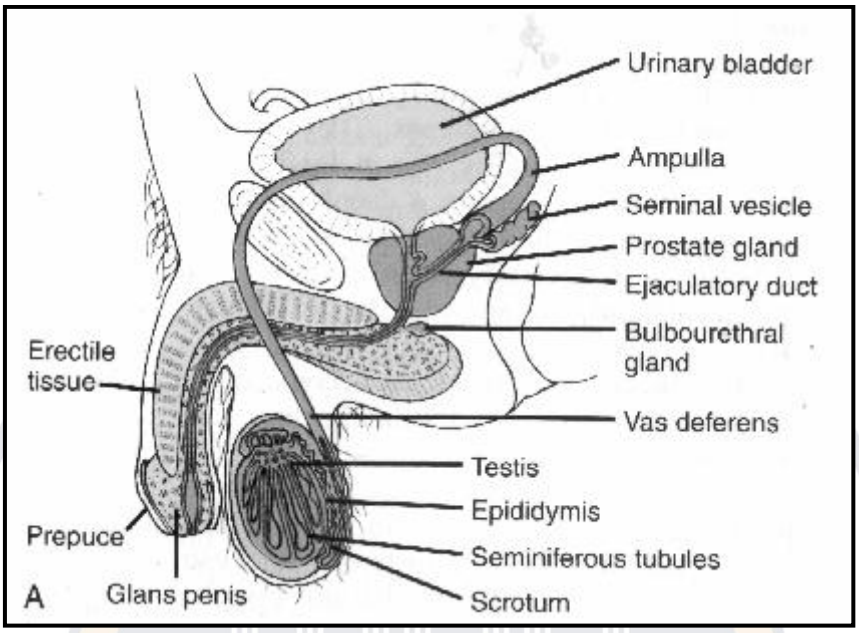


Fig.: Male reproductive system.

❖ **Primary sex organs: testes➔ functions:**

- **Spermatogenesis**.
- **Steroidogenesis** i.e synthesis and secretion of male sex hormones.

❖ **Secondary (accessory) sex organs:**

1) ***Epididymis:***

- **Single coiled tube**.
- **6 meters** long.
- **Receive** sperms from seminiferous tubules.
- **Functions:** sperms in epididymis become motile and acquire the power of fertilization.

2) ***Vas deferens:***

- **Long duct**.
- **Store sperms** in upper enlarged part (ampulla).
- **Transport sperms** to ejaculatory duct.

3) *Seminal vesicle:*

- A **coiled tubular** gland.
- It joins the **ampulla of vas** deferens to form the **ejaculatory duct**.
- The two ejaculatory ducts pass through the prostate and open into the **prostatic urethra**.

4) *Prostate:*

- It is a large gland which surrounds the prostatic urethra.

* Functional histology of testis:

❖ **Shape:** Ovoid.

❖ **Size:**

- ***Length :*** 4 – 5cm.
- ***Width :*** 2.5 – 3 cm.

❖ **Weight:** 10 -45 gm.

❖ **Structure:**

(I) Seminiferous tubules:

- **Number: 900** in each testis.
- **Account for: 80%** of testicular mass.
- **Cells lining:**

1-Spermatogenic (gametogenic) epithelium: responsible for spermatogenesis.

2-Sertoli cells:

☒ **Large pyramidal cells** lying on basal lamina.

☒ **Non motile**.

☒ **Non proliferating**.

☒ **Extend through** the entire thickness of germinal epithelium from the basement membrane to the lumen.

☒ *Function:*

- ✓ ***Supportive:*** they provide **mechanical support** for the growing gametes.
- ✓ ***Nutritive:*** they provide **nutrition** for the growing gametes due to their high glycogen content.
- ✓ ***Spermiogenesis:*** **removal of excess cytoplasm** from spermatids converting them to spermatozoa.
- ✓ ***Spermiation:*** **release of sperms from sertoli cells** to become free in the lumen of seminiferous tubules under the control of LH.
- ✓ ***Secretion*** of watery fluid rich in K^+ and HCO^-_3 into the tubular lumen to **pump immature sperms** into the epididymis where maturation occurs.
- ✓ ***Synthesis and secretion of:*** (under **F.S.H. effect**):
  - **Inhibin hormone:** inhibits F.S.H. secretion by ant. Pit.
  - **Estradiol**.
  - **Mullerian duct inhibiting factor:** causes regression of Mullerian duct system ➔ prevention of differentiation of female internal sex organs in male fetus.
  - **Androgen binding protein:** that carries testosterone into the seminiferous tubules to stimulate spermatogenesis.
- ✓ ***Blood – testis barrier:***
  - It is a **membrane formed by tight junctions** between the bases of sertoli cells.
  - ***Functions:***
    - ✪ It **prevents harmful substances in the blood** from entering the seminiferous tubules.
    - ✪ It keeps the germ cells **in the seminiferous tubules** because they are very **immunogenic** when introduced into the systemic circulation.

✓ ***H-Y antigen:***

- Formed at the **7th week** of gestation under control of **Y chromosome**.
- H-Y antigen binds to **H-Y receptors** in the primitive glands & induces gonadal cells to differentiate as testes.

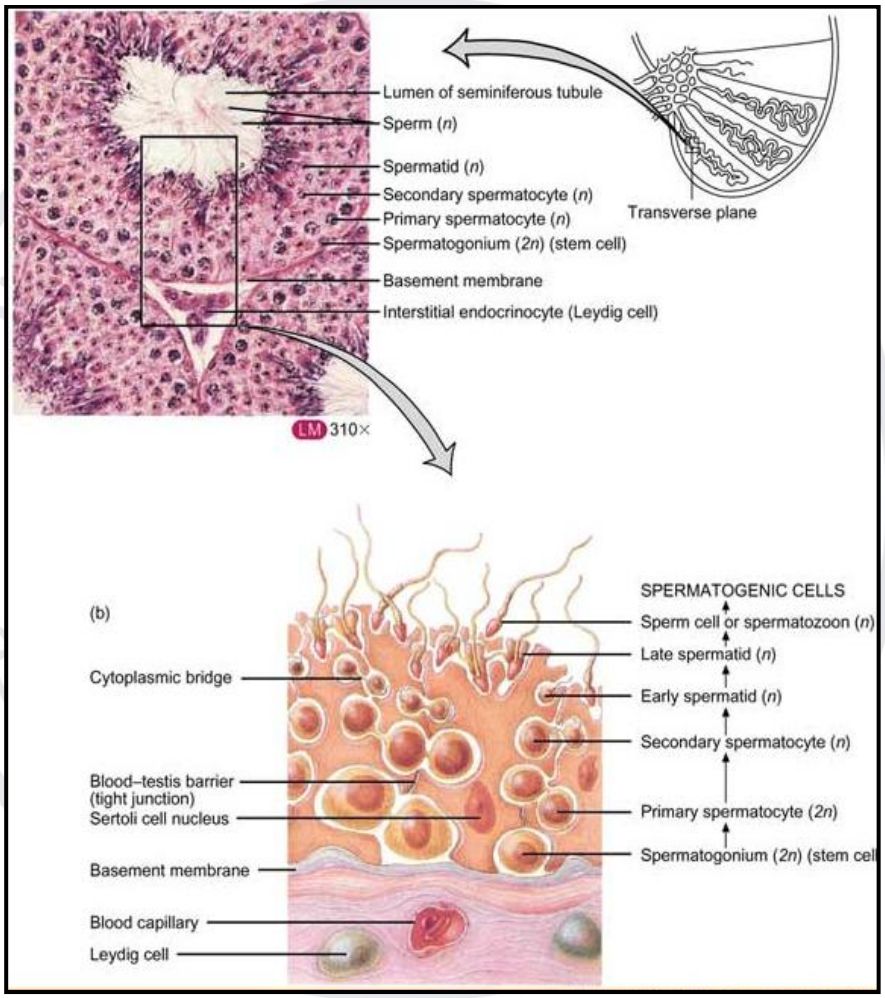


Fig.: A, cross section of a seminiferous tubule. B, stages of spermatogenesis

(II) Leydig cells (interstitial cells):

- **Site:** located between the seminiferous tubules.
- **Account for** 20% of testicular mass.
- **Appear at**: 7-9th week of pregnancy ➔ secrete androgens in fetal life under the influence of **human chorionic gonadotropin** (HCG).
- They are **extensive at birth**, but **disappear within the first 6 months** of postnatal life.
- **At puberty**, they reappear by differentiation of **fibroblast-like cells** of testis, and secrete androgens under the control of pituitary gonadotropin.

Spermatogenesis

- Def: It is the process of formation of spermatozoafrom spermatogonia in the testis.

- Site: in all seminiferous tubules.

- Age: it begins at age of 13 years and continue throughout life.

- It decreases markedly in old age.

- Steps:

- **Spermatogonia** $\xrightarrow{Mitosis}$ additional **stem cells** + **type A spermatogonia** .
- **Type A spermatogonia** become enlarged with large nucleus, granular, cytoplasm and thick cell membrane to form **primary spermatocytes**. (**diploid cells**).
- **Primary spermatocytes** $\xrightarrow{Miosis}$ two **secondary spermatocytes** (**haploid cells**).
- **Secondary spermatocytes** $\xrightarrow{Mitosis}$ **spermatids** (**haploid cells**).

spermiogenesis

- **Spermatids ⟶ spermatozoa**

- **Sperm:**

1-Head:

- Contains the **nucleus** with a **thin cytoplasm** and cell membrane.
- **Its anterior 2/3** is covered by a **thick cap** called the **acrosome** which contains the **hyaluronidase and proteolytic enzymes** that help **penetration of the ovum**.

2-Body:

- Contain mitochondria ➔ supply **ATP** for **flagellar movement of sperm**.

3-Tail (flagellum):

- Contains **contractile microtubules**.
- **To and fro movement of tail (flagellar movement)** provide motility for sperm.
- **Velocity:** 1-4 mm/min.

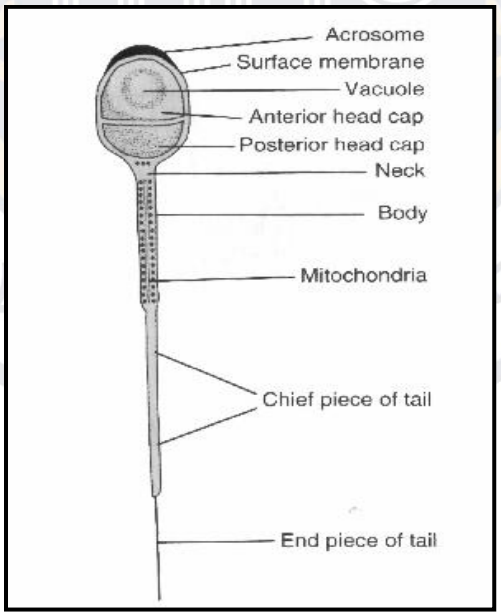


Fig.: Structure of the human spermatozoon.

- Duration of spermatogenesis:

- **74 days**.
- In addition to **12 – 21 days** for transport of sperms to ejaculatory duct.

- Maturation of sperms:

- **Site:** in epididymis.
- **Needs:** 18 hours to 10 days.

- Storage of sperms:

- In **vas deferens**.
- Stored for a **month** maintaining their fertility.
- They are kept in **an inactive state** by inhibitory substances in secretions of ducts.

- Factors Affecting Spermatogenesis:

(1) Hormonal control:

A. Hypothalamo-hypophyseal – testicular axis:

– **At puberty**, activation of hypothalamic LHRH pulse generators occurs ➔ pulsatile secretion of ant. pit gonadotropins (F.S.H and L.H).

– **Functions:**

a. F.S.H:

i. Maintains gametogenic functions of the testes.

ii. Stimulates growth and secretory functions of Sertoli cells.

b. L.H: Stimulates Leydig cells to secrete testosterone which is essential for spermatogenesis.

N.B:

* FSH is trophic to sertoli cells ➔ ↑ **inhibin** secretion ➔ which **by its turn inhibits FSH secretion** at the level of pituitary gland.

* LH is trophic to Leydig cells ➔ ↑ **testosterone** secretion ➔ which **by its turn inhibits LH secretion** at the level of pituitary gland & GnRH at the level of hypothalamus.

B. Testosterone:

- Secreted by **Leydig cells under the effect of LH.**
- **Essential for** growth and division of the germinal cells.
- **High concentration of testosterone in the lumen of seminiferous tubules is maintained by:**

i. The ***ability of hormones to penetrate*** the wall of the tubules.

ii. ***Androgen – binding protein***, which is synthesized by sertoli cells, carries the hormone into the tubular fluid.

iii. ***Counter current exchange:*** the blood in spermatic arteries runs parallel but in opposite direction to the blood in spermatic veins ➔ exchange of testosterone from the spermatic veins into spermatic arteries.

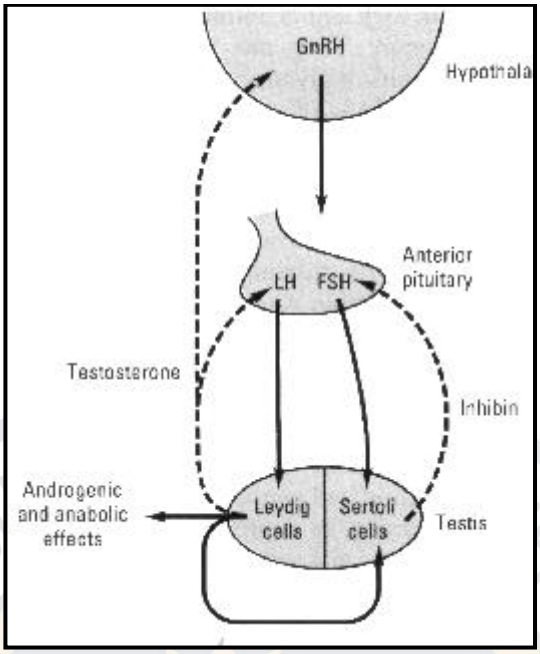


Fig.: Hypothalamic-hypophysial-testicular axis. Solid arrows indicate excitatory effects; dashed arrows indicate inhibitory effects.

C. Other hormones:

i. ***Inhibin:*** inhibit F.S.H secretion by a direct effect on the ant. Pit.

ii. ***Activin:*** stimulate F.S.H secretion.

iii. ***Growth hormone:*** stimulate early division of spermatogonia.

iv. ***Thyroid hormones:*** essential for spermatogenesis due to their metabolic functions.

(2) Temperature:

- ***Optimum temp*** for spermatogenesis is 35°C.
- ***This low temp is maintained by:***

i. The testes are present in the **scrotum outside the abdominal cavity**.

ii. The scrotal skin is:

- Thin.
- Rich in sweat glands.
- Contain little subcutaneous fat.

iii. Countercurrent system: heat exchange between spermatic arteries and veins.

iv. **The dartos muscle** acts as a buffer. It contracts in cold weather and relaxes in hot weather.

❖ ***Cryptorchidism:***

- **Def:** failure of descent of one or both testes from the abdomen into the scrotum at the time of birth of fetus.
- The testis remains in **abdominal cavity** or **original canal**.
- **Characters:**
  - **i.** Degeneration of **spermatogenic epithelium**.
  - **ii.** **Sertoli and leyding cells** are not affected.
  - **iii.** Undescended testes are liable to **malignant tumours**.
- **Treatment:**
  - i. Medical by Gonadotropins.
  - ii. Surgical.

(3) Diet:

- A **balanced diet** containing **proteins and vitamins** A, B, C and E is essential for spermatogenesis.
- **Complete starvation** inhibits spermatogenesis secondary to failure of gonadotropin secretion
- **Effects of vitamin deficiency**:

Deficiency Vit	Effects
Vit A	Keratinization and atrophy of spermatgenic epithelium
Vit B_{12} and folic acid	Inhibition of spermatogenesis (as these vitamines are essential for nucleic acid synthesis).
Vit C	Inhibition of spermatogenesis (as this vitamin is essential for testosterone synthesis).
Vit E	Irreversible tubular degeneration in animals.

(4) Extrinsic factors (that inhibit spermatogenesis):

a. ***Irradiation:*** destroy germinal epithelium.
b. ***Hypoxia and toxins*** (chemical and bacterial)
c. ***Infections*** e.g. mumps: destroy seminiferous tubules.
d. ***Excessive estrogen administration***: inhibit F.S.H secretion ➔ decrease testosterone level.

ENDOCRINAL FUNCTION OF TESTES

* Secretion and transport of androgens:

(1) Testosterone:

- Produced by **leydig cells** of testes.
- Adult male secreted **4-9 mg/day**.
- **Testosterone:**
  - **2%** unbound (free).
  - **98%** bound:
    - **68%** to albumin.
    - **30%** to □-globulin.

(2) Dihydrotestosterone:

- Testosterone $\xrightarrow{5\alpha \text{ reductase}}$ dihydrotestosterone (**twice the activity of testosterone**).
- **Dihydrotestosterone:**
  - **20%** synthesized in **testes**.
  - **80%** derived from **peripheral conversion** of testosterone in skin, liver, male reproductive tract, and male external genitalia.

* **Metabolism of testosterone:** Testosterone is converted in liver into 17-Ketosteroids ➔ excreted in the bile and urine.

* Physiological effects of testosterone:

(A) During fetal life:

1. **Differentiation and development of 2ry male sex organs:** testosterone (secreted by leydig cells of developing testes at 7-9th week of gestation) ➔
   - ❖ Stimulate differentiation of wolffian duct to internal genitalia in male (**paracrine action**).
   - ❖ Stimulate differentiation of external genitalia (**endocrine action**).
2. **Descent of the testes** from the abdominal cavity into the scrotum during the **last 2-3 months** of pregnancy.

(B) After puberty:

I. Sexual functions:

1. **Growth and enlargement of the testes (1ry) and 2ry sex organs.**
2. **Development of male sex characters**:

- ***Hair:***
  - ***General body hair*** ↑ especially at face, chest, axial and around anus.
  - ***Pubic hair*** is triangular with the apex toward the umbilicus.
  - Hair disappears from the ***anterior part of the scalp***.
- ***Voice:*** deep and low pitched due to:
  - Enlargement of larynx.
  - ↑ thickness of vocal cords.
- ***Skin:*** thick with excessive secretion of sebaceous glands ➔ acne.
- ***Body conformation:*** shoulders broaden and muscles enlarge.
- ***Behaviour changes:*** ↑ sexual desire & males become aggressive.

3.**Spermatogenesis:** testosterone is necessary for growth and division of germinal cells.

II. Metabolic effects:

1. **Protein anabolic effect:** which leads to:
   - ↑ **muscle bulk**.

- ↑ **bone growth** due to:
  i. Protein anabolic effect of testosterone.
  ii. Deposition of Ca^{+2} ions.

  Then, testosterone causes the epiphysis of the long bones to unit ➔ preventing overgrowth of long bones.
- ↑ **thickness of skin and vocal cords**.

2. ↑ **basal metabolic rate** (5-10%)
3. ↑ **RBCs count** (due to ↑ BMR rather than a direct effect).
4. **Effect on water and electrolytes**:
   a. Na^{+}, K^{+}, Ca^{2+}, PO^{-2}_{4}, SO^{-2}_{4} and water retention.
   b. ↑ the size of kidneys.

* Male hypogonadism:

- Causes:

(1) Primary: due to:

* Testicular disease.
* Congenital absence of testes.

(2) Secondary: due to failure of pituitary gonadotropin secretion as in pituitary or hypothalamic disease.

- Types:

(1) **Complete:** loss of both gametogenic and steroidogenic functions.

(2) **Partial**: loss of one function only

- Manifestation:

Prepubertal hypogonadism	Postpubertal hypogonadism
(A) SEXUAL	
(1) **Permanent sterility** due to absence of spermatogenesis. **(2)** **2ry sex organs** remain infantile. **(3)** **2ry sex characters** not develop ➔ • ***Fat & hair:*** feminine distribution. • ***Voice:*** high pitch. • ***Muscle:*** soft and weak. • ***Skin:*** soft and pale. (4) Loss of **sexual desire**.	**(1)** **Permanent sterility** due to absence of spermatogenesis. **(2)** Atrophy of **2ry sex organs** except penis & scrotum (maintained by small amount of adrenal androgens). **(3)** Slow regression of **2ry sex characters**. **(4)** Loss of **sexual desire**.
(B) METABOLIC	
(1) **Delayed union of epiphyses** ➔ over growth of long bones ➔ tall and span is greater than height. **(2)** **Low BMR**	**(1)** **Muscle wasting & osteoporosis** due to loss of anabolic effect of testosterone. **(2)** **Low BMR**.
(C) PSYCHOLOGICAL	
psychological disturbances due to: • Sexual inferiority. • Feminine appearance.	**Psychological disturbances:** the person becomes irritable, passive and depressed.

Physiology of female reproduction

* Anatomy of female sex organs:

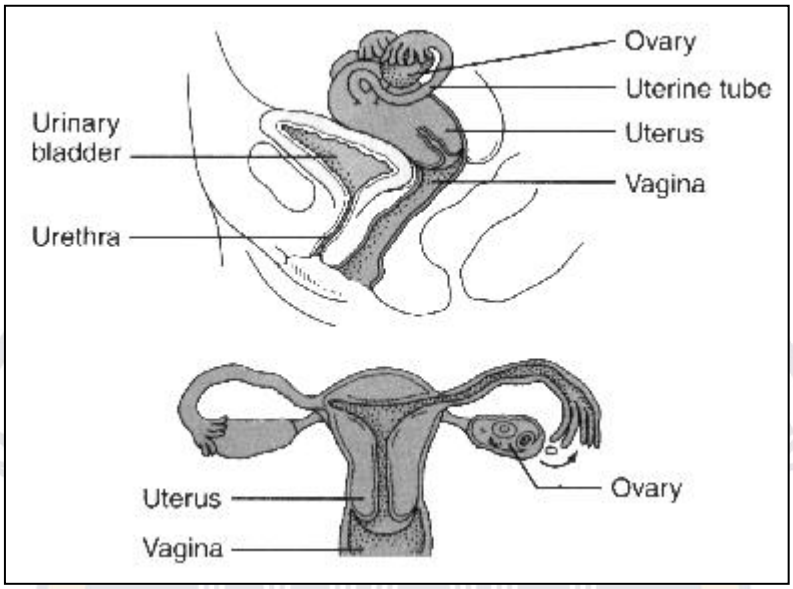


Fig.: The female reproductive system.

(1) Primary sex organs: ovaries functions:

- **Oogenesis**.
- **Steroidogenesis:** synthesis and secretion of the female sex hormones.

(2) Secondary sex organs:

They include: the vagina, uterus, two fallopian, tubes, external genitalia and the mammary glands.

FEMALE SEXUAL CYCLES

- The normal reproductive years of ♀, from puberty to menopause, are characterized **by monthly regular changes** in the rates of secretion of female hormones & corresponding physical changes in ovaries & other sexual organs.
- The cycles **stop** only during **pregnancy or disease**.
- The duration of the cycle averages **28 days** (**from 20 to 45 days**).

Ovarian cycle

Each ovarian cycle is composed of:

(I) Follicular (pre-ovulatory) phase:

- **At puberty**, the two ovaries contain **400.000 primordial follicles**.
- Each follicle is composed of **1ry oocyte surrounded by a single layer of flat granulose cells**.
- During each cycle, **20 primpordial follicles start to grow in the following sequence:**

(1) Formation of primary follicles:

a. ***Moderate enlargement*** of ovum occurs.

b. The ***single layer of flat follicular cells become cuboidal*** and divides to form several layers of granulose cells.

(2) Development of secondary follicles:

a. Antral follicle:

- **Granulose cells** proliferate rapidly ➔ more layers of cells.
- **Spindle cells** (from ovarian stroma) collect in several layers outside the granulose cells ➔ second mass of cells (**Theca**) **which is divided into:**

i. Theca interna:

- ***Highly vascular*** layer of epithelial cells.
- Secrete ***estrogen and progesterone***.

ii. Theca externa:

- ***Outer layer***.
- ***Less vascular*** connective tissue capsule.

- After few days, granulose cells secrete **follicular fluid** containing high conc of **estrogen**.
- Accumulation of this fluid ➔ appearance of **antrum** within the mass of granulose cells (**Antral follicle**).

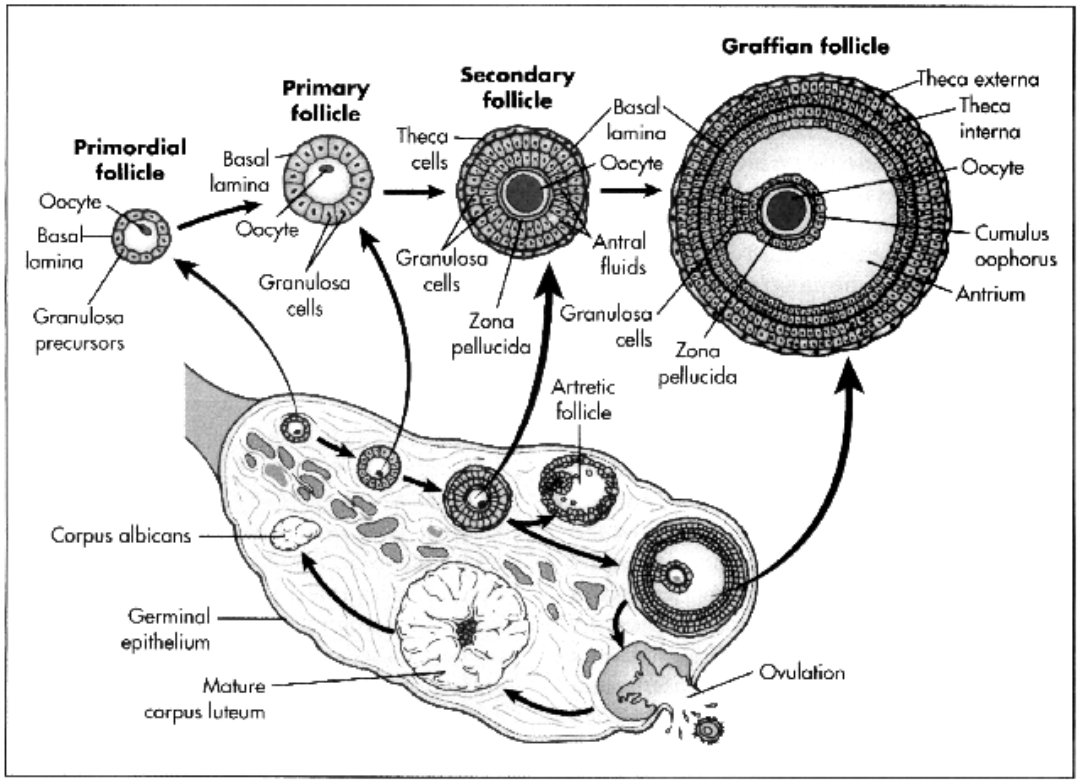


Fig: Phases of the ovulatory cycle.

b. Vesicular follicle:

- **Accelerated growth of antral follicle** ➔ larger follicles (**vesicular follicle**).
- **Causes of accelerated growth:**

i. ***Estrogen*** is secreted in the follicle➔ ↑ the number of FSH receptor in granulose cells ➔ ↑ sensitivity of granulose cells to ant pit FSH.

ii. ***FSH and estrogen***➔ ↑ LH receptors on granulosa cells ➔ ↑ in follicular secretion.

iii. ***Estrogen and LH*** ➔ proliferation of theca cells &↑ their secretion.

(3) Formation of mature follicle (Graafian follicle):

- ***After a weak of growth***, one of the follicles begins to outgrow all the others and the other growing follicles involute and become atretic.
- ***Cause:*** large amounts of estrogen secreted from the growing follicles act on hypothalamus ➔ inhibition of FSH secretion from ant pit ➔ prevention of

growth of less developed follicles. The outgrowing follicle continues to grow due to its high estrogen content.

- ***Layers of mature follicle (from inside outward):***

1. ***Ovum*** (***2ry oocyte***) surrounded by a thin membrane (***zona pellucida***).
2. Several layers of ***granulose cells*** surrounding ovum (***corona radiata***).
3. ***Antrum*** containing follicular fluid.
4. Several layers of ***granulose cells***.
5. ***Basal lamina***.
6. ***Theca interna***.
7. ***Theca extrena***.

(II) Ovulatory phase:

- ***Def:*** release of 2ry oocyte into the peritoneal cavity.
- ***Time of ovulation:*** 14 days before the onset of the next ovulatory cycle.
- ***Mechanism:***

1. ***Theca cells secrete estrogen*** ➔ reach its peak 48 hours before ovulation ➔ +ve feedback effect on ant pit ➔ ↑ LH secretion 6-10 folds (LH surge) and FSH secretion 2-3 folds ➔ rapid swelling of follicle.
2. ***Under the effect of LH*** ➔
   a. ***Release of proteolytic enzymes from theca externa lysosomes*** ➔ dissolution of follicular capsular wall ➔ weakening of the wall ➔
      - ✓ Further swelling of follicle.
      - ✓ Degeneration of a nipple like protrusion in the center of follicular capsule called **stigma**.
   b. ***Rapid growth of new vessels in follicular wall & prostaglandin secretion (cause VD)*** ➔ plasma transudation into the follicle ➔ more swelling.
3. ***Follicle swelling & degeneration of stigma*** ➔ rupture of follicle ➔ release of ovum.

- ***Diagnosis of ovulation:***

1. **Symptoms:**
   a. Pelvic **pain**.
   b. ↑ **vaginal discharge**.
   c. Midcycle **vaginal bleeding** due to sudden drop of estrogen.
2. **basal body temp:**
   a. At the day of ovulation, basal body temp ↑ **0.2-0.5°C** due to **thermogenic effect of progesterone** secreted by corpus luteum.
   b. The elevated temp remains till the **26th day of cycle**.

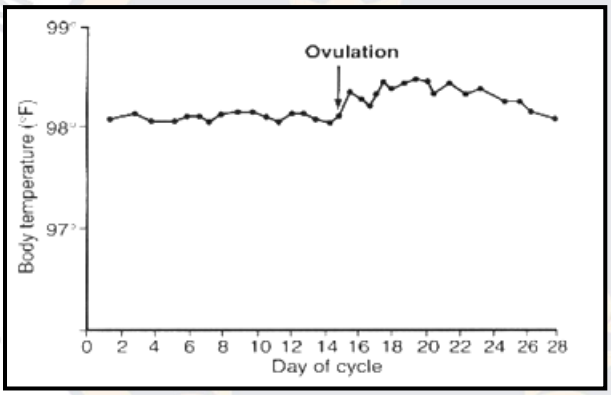


Fig.: Elevation in the body temperature shortly after ovulation.

3. **Detection of pregnandiole in urine.**
4. **Endometrial biopsy:** If ovulation occurs ➔ endometrium will be in secretory phase.
5. **Examination of cervical mucus:** Ferning and spinnbarkeit phenomena **disappear after ovulation**.
   a) ***Spinnbarkeit phenomenon:*** if a drop of mucus is placed between two slides, **long threads** of mucus will appear between them when they are separated.
   b) ***Ferning phenomenon:*** If a drop of mucus is spread on a slide and left to dry, crystals will be arranged in a **feather – like shape**.

(III) Luteal (Postovulatory) phase:

❖ **Formation of corpus luteum:**

- After ovulation, granulose and theca cells enlarge & become filled with lipid material that give them yellow appearance (**Lutin cells**).
- The total mass of cells is called **corpus luteum**.
- Luteinization depends mainly on **LH**.

❖ **Function of corpus luteum:** secretion of **progesterone and estrogen** under the control of out ant pit LH.

❖ **Fate of corpus luteum:**

If no fertilization occur	**If fertilization occurs**
↓	↓
C.L continue to function till 22th day of cycle	C.L continue to function till 12th week of gestation (under control of HCG)
↓	↓
Then degenerate and stop its function 2 days before the next cycle (**C.L of menstruation**)	Then its function is taken by placenta (**C.L of pregnancy**)

ENDOMETRIAL (MENSTRUAL) CYCLE

- **Def:** it is the structural and functional changes that occur in the endometrium every month from puberty to menopause.
- **Phases:**

1. **Menstrual phase:**

✓ **Duration:** 5 days (3-7 days) starting from the 1st day of menstruation.

✓ **Coincides with:** the beginning of the follicular phase of ovarian cycle.

✓ **Mechanism:**

a. C.L. degenerates 2 days before the onset of cycle ➔ sudden drop of estrogen and progesterone blood levels ➔ V.C of spiral arterioles supplying superficial endometrium.

b. VC + ↓ nutrients + loss of hormonal stimulation ➔ necrosis in endometrium especially bVs.

c. Later on, necrotic tissues released vasodilator substance ➔ rupture of necrotic walls of spiral arterioles ➔ bleeding between superficial and deep layers of endometrium ➔ separation of the superficial layer into the uterine cavity.

✓ **Composition of menstrual flow:**

– ***Menstrual flow*** ➔ 100ml.

– ***It contains:***

(1) Destroyed endometrial tissue.

(2) 35ml blood.

(3) 35ml serous fluid.

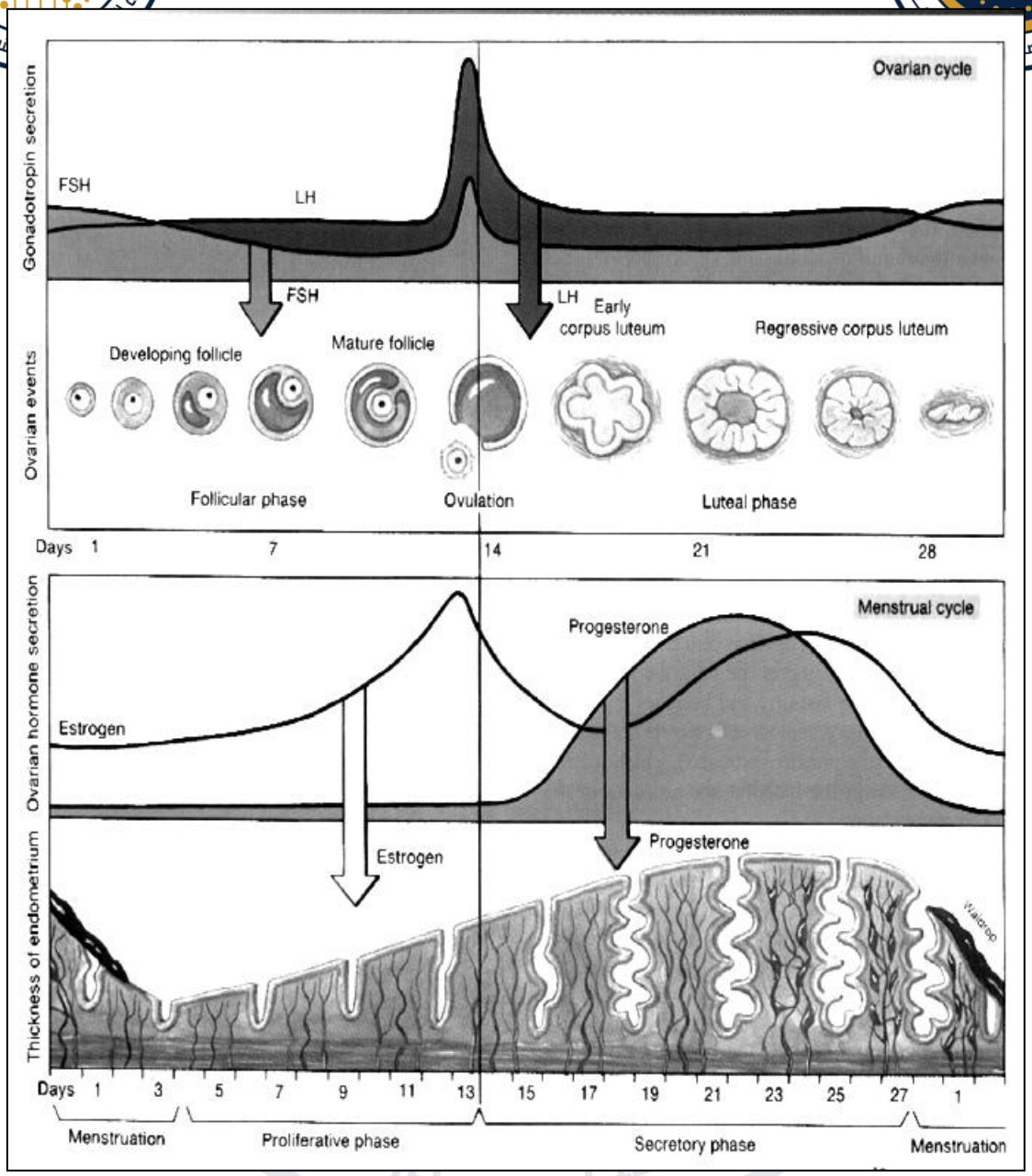
(4) Non fertilized ovum.

(2) Proliferative phase	(3) Secretory phase
1- **Regeneration of endometrium** under the effect of estrogen.	1-**Secretory changes in endometrium** under the effect of progesterone.
2- **duration:** 6th - 14th day of cycle.	2- **duration:** 14th - 28th day of cycle.
3- **Changes in endometrium:** - Regeneration of surface epithelium. - Elongation of uterine glands but without secretion. - Elongation of spiral arterioles. - Regeneration of endometrial stroma - Thickness: 2-3 mm	3- **changes in endometrium:** - Uterine glands become coiled and full of secretion. - Spiral arterioles become more tortuous and reach the surface of endometrium. - Stroma is filled with glycogen & lipids. Thickness: (4-8mm).

Hormonal changes during a female sexual cycle

	(1) Estrogen	(2) progesterone
a) In pre-ovulatory phase	**Secreted in large amounts** by growing ovarian follicles under the control of FSH	**Secreted in small amounts** by ovarian follicles.
b) two days before ovulation	Estrogen secretion by graafian follicle is **markedly increased**	
c) Post ovulatory phase	- Plasma estrogen is **initially low** due to rupture of graafian follicle. - **After formation of C.L, estrogen secretion ↑,** but it ↓ **two days before the end of cycle** due to C.L degeneration.	- **Progesterone secretion by C.L** ↑ till reaching the peak by the 22th day of the cycle. - **its secretion is markedly ↓** two days before the end of cycle due to degeneration of C.L.

	(3) F.S.H	(4) L.H
a) Pre ovulatory phase	**F.S.H secretion:** - **At beginning of the phase:** high due to low plasma estrogen. - **Then:** ↓ due to high plasma estrogen (-ve FB)	**L.H secretion is constant**
b) two days before ovulation	**FSH secretion ↑ by 2-3 folds** due to +ve FB effect of high plasma estrogen on ant pit	**LH secretion ↑ by 6-10 folds** due to +ve FB effect of high plasma estrogen on ant pit.
c) Post ovulatory phase	**FSH secretion is lowered** due to high estrogen level secreted by C.L.	**LH secretion is inhibited** due to high progesterone level secreted by C.L
Functions	1- **Early growth of ovarian follicles** during follicular phase of ovarian cycle. 2- **Maturation of graafian follicle** (with LH) 3- **Stimulate estrogen secretion** by granulose cells of ovarian follicles	1- **Estrogen secretion** from theca interna and granulose cells and ovarian follicles. 2- **Ovulation and C.L. formation** 3- **Estrogen and progesterone secretion** from C.L.


Ovarian cycle
Gonadotropin secretion
FSH
LH
FSH
LH
Early corpus luteum
Regressive corpus luteum
Developing follicle
Mature follicle
Ovarian events
Follicular phase
Ovulation
Luteal phase
Days 1
7
14
21
28
Menstrual cycle
Ovarian hormone secretion
Progesterone
Estrogen
Estrogen
Progesterone
Thickness of endometrium
Days 1 3 5 7 9 11 13 15 17 19 21 23 25 27 1
Menstruation
Proliferative phase
Secretory phase
Menstruation

Estrogens

- **Sources:**

(1) Ovaries:

a) **Theca interna** of ovarian follicles.

b) Lutin cells of **corpus luteum**.

c) **Granulose cells** of follicles **(remain in follicular fluid)**.

(2) Placenta.

(3) Adrenal cortices.

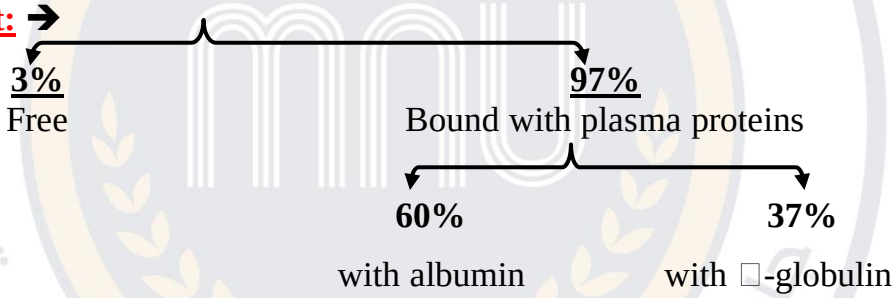
- **Types:**

(1) **-estradiol** (**most potent)** (12 times as estrone & 80 times as estriol).

(2) **Estrone:**

(3) Estriol:

- **Transport:** ➔



- **Metabolism:** The liver converts the potent **estradiol and estrone** into the least potent **estriol** & conjugates them to form **glucuronides & sulphates** which are excreted in the **urine mainly** and in the bile.

- **Effects:**

(1) Ovaries:

a) ***Stimulate growth of ovarian follicles*** during follicular phase of ovarian cycle.

b) ***Stimulate the generation of LH surge*** ➔ ovulation and C.L formation.

(2) Secondary sex organs:

a. *Uterus:*

i. **Endometrium:** regeneration during ***proliferative phase*** of endometrial cycle.

ii. **Myometrium:**

- ✓ ↑ uterine blood flow.
- ✓ ↑ amount of contractile proteins.
- ✓ ↑ excitability and contractility.
- ✓ ↑ sensitivity to oxytocin.

b. *Cervix:*

- ✓ ↑ cervical mucus secretion and ↓ its viscosity.
- ✓ Ferning and spinnbarkeit phenomena are present.

c. *Vagina:*

- ✓ Transformation of ***cuboidal epithelium*** in vagina of children to ***stratified epithelium*** (**more resistant to trauma and infection**).
- ✓ ↑ ***vascularity*** of vaginal wall .
- ✓ ***Deposition of glycogen*** in epithelial lining of vagina (glycogen ➔ lactic acid).

d. *Fallopian tubes:*

- ✓ Stimulate ***Motility*** of tube.
- ✓ ↑ ***number and activity of cilia***.

  This help ***transport of fertilized ovum*** into uterine cavity.

e. *Breasts:*

- ✓ ***Enlargement of breasts*** at puberty due to deposition of fat.
- ✓ ***Increased vascularity***.
- ✓ ***Growth of duct system and nipple***.
- ✓ ***Pigmentation of the areolas***.

(3) Secondary sex characters:

- ✓ ***Feminine deposition of fat*** in breasts, lower abdomen, buttoks, thigh, mons pubis and labia majora.
- ✓ ***↑ vascularity of skin*** which is soft and smooth.
- ✓ ***↑ libido***, and ***psychological make up*** of female.

(4) Metabolic effect:

- ✓ ***Protein anabolic effect*** on bones and sex organs.
- ✓ Stimulate ***bone growth*** due to proliferation of epiphyseal cartilage, followed by union of epiphyses.
- ✓ ***↓ plasma cholesterol***.
- ✓ ***Na^+, H_2O, Ca and PO_4 retention***.

(5) Endocrine glands:

- ✓ ↑ size of ***pituitary*** gland.
- ✓ Regulate secretion of ***pituitary gonadotropins***.
- ✓ ↑ synthesis of ***thyroxine binding globulin*** and ***transcortin***.
- ✓ ↑ secretion of ***angiotensinogen***.

Progestins

- **Source:**

1-Corpus luteum. 2-Placenta. 3-Adrenal cortex.

- **Types:**

(1) Progesterone. (2) 17-□-hydroxyprogesterone.

- **Transport:** ➔

2% free

98% Bound with plasma proteins

80% with albumin

18% with globulin

- **Metabolism:**

Progesterone ➔ pregnandiol ➔ conjugation with glucuronic acid ➔ excreted in urine.

- **Effects:**

(1) On sex organs:

a) Uterus:

- ***Secretory changes*** in endometrium.
- ***Anti-estrogenic effects on myometrial cells:***
  - * ↓ their excitability.
  - * ↓ their sensitivity to oxytocin.
  - * ↓ their spontaneous electric activity.
  - * ↑ their membrane potential.
- ***↓ the number of estrogen receptors*** in the endometrium.
- Conversion of ***β-estradiol to less active estrogens***.

b) Cervix:

- ↓ the secretion of ***cervical mucus*** which become viscid, alkaline & cellular.
- ***No fernin and spinnbarkeit phenomena***.

c) Vagina:

- Secretion of ***thick mucus***.
- ***Proliferation of epithelium***.
- ***Infiltration with leucocytes***.

d) Fallopian tubes:

- ***Secretory changes*** in tubal epithelium ➔ nutrition of fertilized ovum.

e) Breasts:

- Development of ***lobules and alveoli.***

(2) Thermogenic effect:

- It is responsible for the ***↑ body temp*** by 0.5°C after ovulation.

(3) Inhibition of ovulation:

- By inhibiting LH secretion.

(4) Natriuresis:

- By blocking aldosterone action on the kidney .

Abnormalities of ovarian functions

a) Hypogonadism:

- **Cause:**

***Primary: result from:**

- Poorly formed ovaries. - Lack of ovaries.
- Surgical removal of ovaries.
- Destruction of ovaries by disease.

***Secondary:** due to pituitary or hypothalamic disease.

- **Manifestations:**

Prepubertal hypogonadism	Postpubertal hypogonaidsm
1- ***Primary amenorrhea and sterility***.	1. ***Secondary amenorrhea & sterility***.
2- ***Secondary sex organs*** remain infantile.	2. ***Secondary sex organs*** regress.
3- ***Secondary sex characters*** not appear.	3. ***Secondary sex characters*** regress.
4- ***Tall patent*** due to delayed union of epiphyses of long bones, the **span exceeds the height.**	***4. osteoporosis and muscle wasting***
	5. ***Breasts atrophy*** & become pendulus.

b) Ovarian hypersecretion:

- **Causes:** ovarian tumour secreting excess estrogen.
- **Manifestations:**

Age	Manifestations
1- Before puberty.	Precocious puberty
2- After puberty	- polymenorrhea. - Menorrhagia.
3- After menopause	Irregular uterine bleeding.

Pregnancy

* Transport of sperms in female genital tract:

- **Ejaculatory volume:**
  - 3.5ml.
  - Each ml contains about 120 millions sperms.
  - 0.5 billion sperms are deposited in the vagina during sexual intercourse.
- **Only 1000-3000 sperms** reach the ampulla of fallopian tube where fertilization ampulla of fallopian tube where fertilization occurs.
- **The transport is facilitated by** increased contractility of uterus and fallopian tubes (by oxytocin and prostaglandins).

* Capacitation of sperms:

- **Means: increased capacity of sperms** to produce fertilization.
- **Requires: 1-10 hours**.
- **Mechanisms:**

(1) **Uterine and fallopian tube secretions** wash away inhibitory factors (secreted by male gentile duct epithelia) and cholesterol vesicles (from seminiferous tubules) that cover the acrosome of the sperm.

(2) **Membrane of sperm become more permeable to Ca^{+2}** ➔

- Increased activity and motion of flagellum.
- Release of enzymes from acrsome as the sperm penetrates the ovum.

*Transport of ovum:

- Ovulation is the **expulsion of ovum** into the peritoneal cavity.
- Ovum is picked up by the **fimbria to the ampulla of fallopian tube** where fertilization occurs.

* Fertilization:

1. Many sperms bind to **sperm receptors** in the zona pellucida.
2. **Acrosomal reaction:** breakdown of acrosome and release of hyalurnidase and proteolytic enzymes (as protease acrosin) ➔ penetration of pserms through zona pellucida.

3. **Polyspermy is prevented by**: fusion of one sperm to ovum ➔ decreased membrane potential of ovum ➔ structural changes in zona pelluicda ➔ protect against polyspermy.

*** Implantation:**

- Fertilized ovum reaches the uterus within **3-5 days**, during which it takes its nutrition from tubal secretion (stimulated by progesterone).
- Then it reaches the uterine cavity, it remains **3-5 days** before implantation **during which:**
  - ❖ A blastocyst develop and become surrounded by trophoblast.
  - ❖ It takes its nutrition from endometrial secretions.
- Implantation occurs **7 days after ovulation**.
- **Mechanism:** Trophoblastic cells secrete proteolytic enzymes which digest the endometrium ➔ ovum becomes gradually embedded in endometrium ➔ zygote takes its nutrition from decidua.

*** Formation of placenta:**

1. **At the time of implantation** the blastocyst consists of **two cellular masses:**
   a. Inner cell mass (**embryoblast**) will form the **embryo**.
   b. Outer rim of cells (**trophoblast**) forms the attachment to the endometrium and give rise to **fetal membranes**.
2. **Endometrium:** progesterone ➔ decidue (maternal portion of placenta)
3. **Trophoblast (foetal in origin) forms two cell layers:**
   a. Inner layer forms cytotrophoblast.
   b. Outer layer forms syncitiotrophblast.

*** Functions of placenta:**

1. **Respiration functions:**
   a. **O_2:** diffuses from maternal side of placenta (PO_2 = 50mmHg) to fetal blood (PO_2 = 30 mmHg).
   b. **CO_2:** diffuses from foetal blood (48mmHg) to maternal side of placenta (40-45 mmHg).
2. **Nutritive and metabolic functions:** Nutrients are transported from mother to fetus through placenta:
   a. *Carbohydrates*:
   - **Glucose** is transported by facilitated diffusion.
   - **Glycogen** is stored in placenta.
   - **Glucose** $\xrightarrow{\text{placenta}}$ fructose.

   b. Proteins:
   - **Amino acids** are actively transported into the fetus.
   - **Albumin** passes to fetus more than globulin.
   - Fetus **synthesizes proteins** from diffusible amino acids.

   c. Lipids:
   - **Fatty acids and ketone bodies** diffuse into the foetus.
   - Transport of **fat and fat soluble vitamins** through placenta is **low**.

   d. Minerals:
   - **Na^+, K^+, and Cl^-** diffuse from maternal to foetal blood.
   - **Ca and inorganic phosphate** are actively transported.
3. **Excretory function:** excretory products formed in fetus **e.g.** urea, uric acid and creatinine diffuse into maternal blood.

4. **Protective function:**
   - Placenta acts as a **barrier** against the transfer of harmful materials into the fetus.
   - However, **some drugs, viruses, and Rh agglutinins** cross the placenta and may cause foetal malformation.
   - **IgG and antitoxins** cross the placenta ➔ passive immunity to foetus.
5. **Endocrinal function:** placenta secretes:

a-Human chorionic gonadoropin (HCG).

b-Estrogens

c-Progesterone.

d- Human chorionic somatomammotropin (HCS) (= Human Placental Lactogen).

e-Relaxin.

f-Human chorionic thyrotropin.

(1) Relaxin:

- **Polypeptide** hormone.
- **Secreted by** C.L and placenta.
- **Plasma level:**
  - ↑ in the 1st trimester under the effect of HCG.
  - ↓ in the late days of pregnancy to allow delivery (***as it inhibits uterine contractions***).
- **Functions:**
  - Relaxation of pelvic ligaments and joints.
  - Softening of cervix at time of labor.
  - Inhibition of uterine contractions.

	(2) HCG	(3) Progesterone	(4) Estrogen	(5) HCS
Sources	**Syncytiotrophoblast** cells of placenta	• **1st 8 weeks**: C.L • **8-12 weeks**: C.L & placenta. • **After 12 weeks**: placenta.	• **1st 8 weeks**: C.L • **8-12 weeks**: C.L & placenta. • **After 12 weeks**: placenta.	**Placenta**
Nature	**Glycoprotein**	**Steroid**	**Steroid**	**Protein**
Plasma level	- **Start 8 days** after ovulation. - Reach the **peak** at 10-12 weeks of gestation. - ↓ **to lower level** at 16-20 weeks and remain constant till the end of pregnancy	- **Low** at the beginning of pregnancy. - ↑ **progressively** till the 7th month. - **Then, becomes constant** till the end of pregnancy.	- **Low** at the beginning of pregnancy. - ↑ **progressively** till the 7th month. - **Then, there is marked** ↑ in its level.	- **Starts at** 5th week of gestation. - ↑ **progressively** till end of pregnancy.
Functions	- **Maintain the function of C.L** which secrete estrogen & progesterone till 12th week of pregnancy - **Stimulate fetal testes** to secrete testosterone.	- Transformation of **endometrial cells into decidua**. - ↑ **secretion of uterus and fallopian tubes** for nutrition of early growing embryo.	- **Enlargement of uterus**. - **Enlargement of external genitalia**. - **Enlargement of breast** and growth of breast ducts. - **Relaxation** of pelvic joints and ligaments to ↑ the diameters of the pelvis	- **Weak lactogenic** effect. - **Weak anabolic** effect on protein metabolism. - **Stimulates lipolysis** ➔ release of FFA as a source of energy ➔ **sparing of glucose** ➔ high maternal blood glucose ➔ diffusion

	- **Trophic agent for fetal zone of adrenal cortex** which secretes DHEA. - **Intrinsic TSH activity**. - **Stimulates secretion of relaxin** from C.L & placenta.	- **Inhibit contraction of pregnant uterus** ➔ maintain pregnancy. - **On breast**: it stimulates growth of lobules & alveoli.	allowing descent of fetus during labor.	of glucose across placenta to the fetus.

Other hormonal changes during pregnancy

	(1) pituitary gland	(2) thyroid gland	(3) parathyroid gland	(4) Adrenal cortex
Size	Enlarge 50%	Enlarge 50%	Enlarge	
Secretion	• **ACTH, TSH and prolactin** secretion ↑. • **FSH and LH secretion ↓** due to inhibitory effect of estrogen and progesterone (from C.L and placenta)	• **thyroid hormone secretion ↑ due to:** (1) thyrotropic effect of HCG. (2) H.C. thyrotropin secreted by placenta.	**PTH secretion ↑** ➔ Ca^{2+} mobilization from mother bones➔ maintain normal Ca^{2+} concentration in mother ECF ➔ supply sufficient Ca^{2+} to fetus.	1- **Cortisol secretion ↑** ➔ mobilization of amino acids from the mother's tissues to fetus. 2- **Aldosterone secretion ↑** ➔ Na^{+} and water retention.

Parturition (Labor)

- **Duration of pregnancy:** **270** days from fertilization (or **284** days from the first day of the last menstrual cycle).
- **Def:** process by which a baby is born.
- **Mechanism:**

(I) Hormonal factors:

1. Ratio of estrogen to progesterone:

- **Progesterone inhibits uterine contractions during pregnancy** ➔ prevent expulsion of foetus.
- **Estrogen increase uterine contractions**.
- **Both are secreted** in progressively increasing amounts during pregnancy.
- **From 7th month onward**, estrogen secretion ↑ more than progesterone ➔ ↑ uterine contractions.

2. Oxytocin:

- **During early labor:** plasma **oxytocin is normal** but it causes uterine contraction due to marked ↑ in number of **oxytocin receptors** under the effect of estrogen.
- **Once labor starts:** uterine contractions ➔ dilatation of cervix ➔ afferent impulses arise and stimulate oxytocin secretion from posterior pituitary ➔ uterine contractions ➔ more cervical dilatation ➔ stimulate more oxytocin secretion. This **+ve FB circuit** ➔ expulsion of baby.
- **Oxytocin increases uterine contractions by:**
  i. **Direct action** on uterine smooth muscles.
  ii. Stimulating formation of **prostaglandins** in deciduas ➔ **enhance oxytocin-induced contractions.**

3. Relaxin:

- **Relaxes** pelvic joints.
- **Softens and dilates** the cervix.
- Its secretion ↓ in late days of pregnancy (***as it inhibits uterine contractions***).

4. Prostaglandins:

- Induce **uterine contractions**.
- **Secreted by** uterus and fetal membranes.
- Their formation is **stimulated by oxytocin and estrogens**.

(II)Mechanical factors;

1. **Stretch of cervix by baby's head** ➔ reflex contraction of body of uterus ➔ downward descent of head ➔ more stretch of cervix ands on.
2. **Cervical stretch** ➔ stimulate pituitary gland ➔ secrete oxytocin ➔ increase uterine contractility.

Breast development and lactation

(I) Development of breasts:

a. **During childhood:** Mammary glands are **rudimentary** consisting of few ducts lined by flat epithelial cells which are surrounded by small stroma.

b. **At puberty:** **estrogen, progesterone, GH, prolactin & cortisol** are necessary for mammary development.

Role of estrogen	Role of progesterone
1- **Enlargement of breast** due to fat deposition. 2- **Increased vascularity**. 3- **Growth of ducts and nipple**. **4- Pigmentation of areola.**	1- **Growth of lobules and secretory alveoli** which become lined by secretory cells.

c. **During pregnancy:** fully development of mammary glands occurs by the effect of**:**

a. High level of estrogen and progesterone.
b. Prolactin.
c. HCS.

(II) Milk secretion:

- ***Active process stimulated by:***

1- **Anterior pituitary hormones** as prolactin, TSH and ACTH. [TSH increases thyroid hormone releases and ACTH increases cortisol release]

2- **HCS**.

- ***Role of prolactin:***

1- During pregnancy:

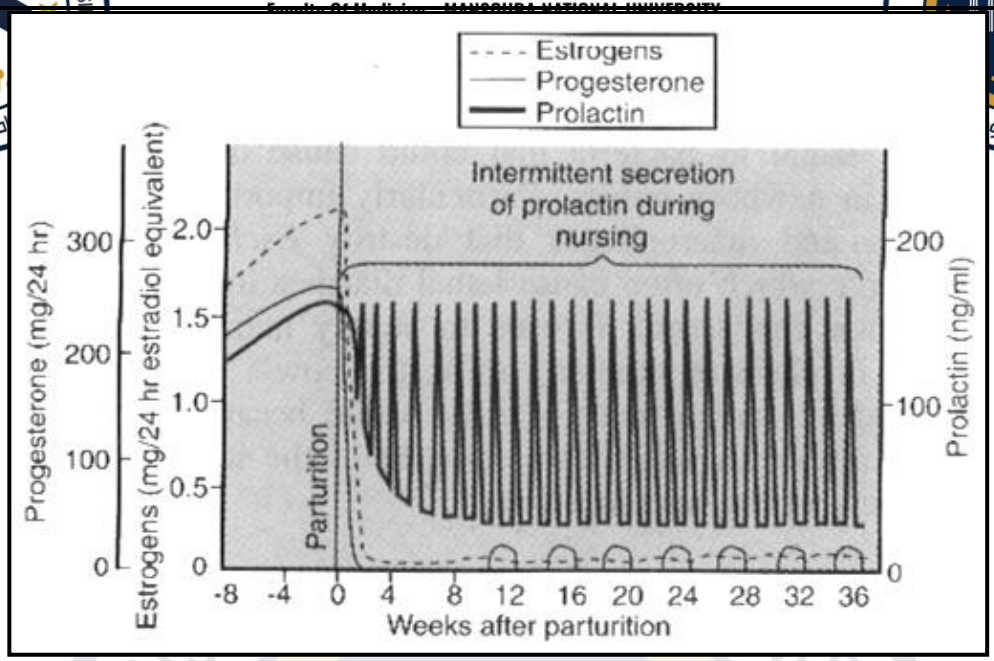
- ✓ **Secreted by** mother any pit.
- ✓ It s **blood level** rises steadily from the 5th week of pregnancy onward.
- ✓ High plasma estrogen stimulates prolactin secretion **but blocks its lactogenic action on mammary glands**.

2- After labor:

a) **Sudden loss of estrogen and progesterone** (from placenta) allows the lactogenic effect of prolactin.

b) **Following the birth of baby**, the basal level of prolactin secretion returns during the next few weeks to non pregnant level.

c) **However, each time the mother nurse her baby**, nerve impulses from nipples to hypothalamus ➔ 10 folds surge in prolactin secretion (last for one hour) ➔ act on breast to provide milk for **next nursing period**.



3- Milk ejection (let – down):

- Oxytocin ➔ **<u>contraction of myoepithelial cells</u>** surrounding alveoli and adults ➔ squeeze milk to the larger ducts then outward through nipples.

- **<u>Control of oxytocin secretion:</u>**
  i. **<u>Unconditional reflex (suckling reflex):</u>** ***<u>touching the nipple and areola during nursing</u>*** ➔ impulses stimulate hypothalamic nuclei mainly paraventricular nuclei ➔ impulses to post. pit ➔ releases of oxytocin.
  ii. **<u>Conditional reflex:</u>** the mother, on ***<u>seeing her baby, hearing his crying or thinking at him</u>***, can stimulate milk ejection due to releases of oxytcin.

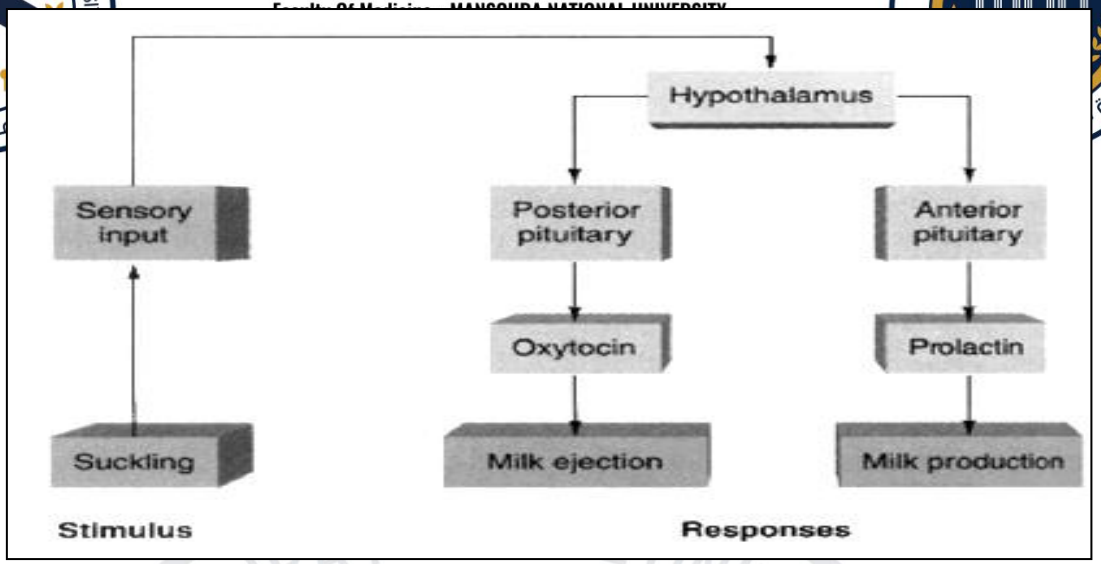


Fig.: Hormonal control of milk production and milk ejection.

FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

ANATOMY

Pancreas

☒ ***Site:*** lies across the upper part of the posterior abdominal wall behind the peritoneum of the lesser sac. It crosses from the concavity of the duodenum to the hilum of the spleen.

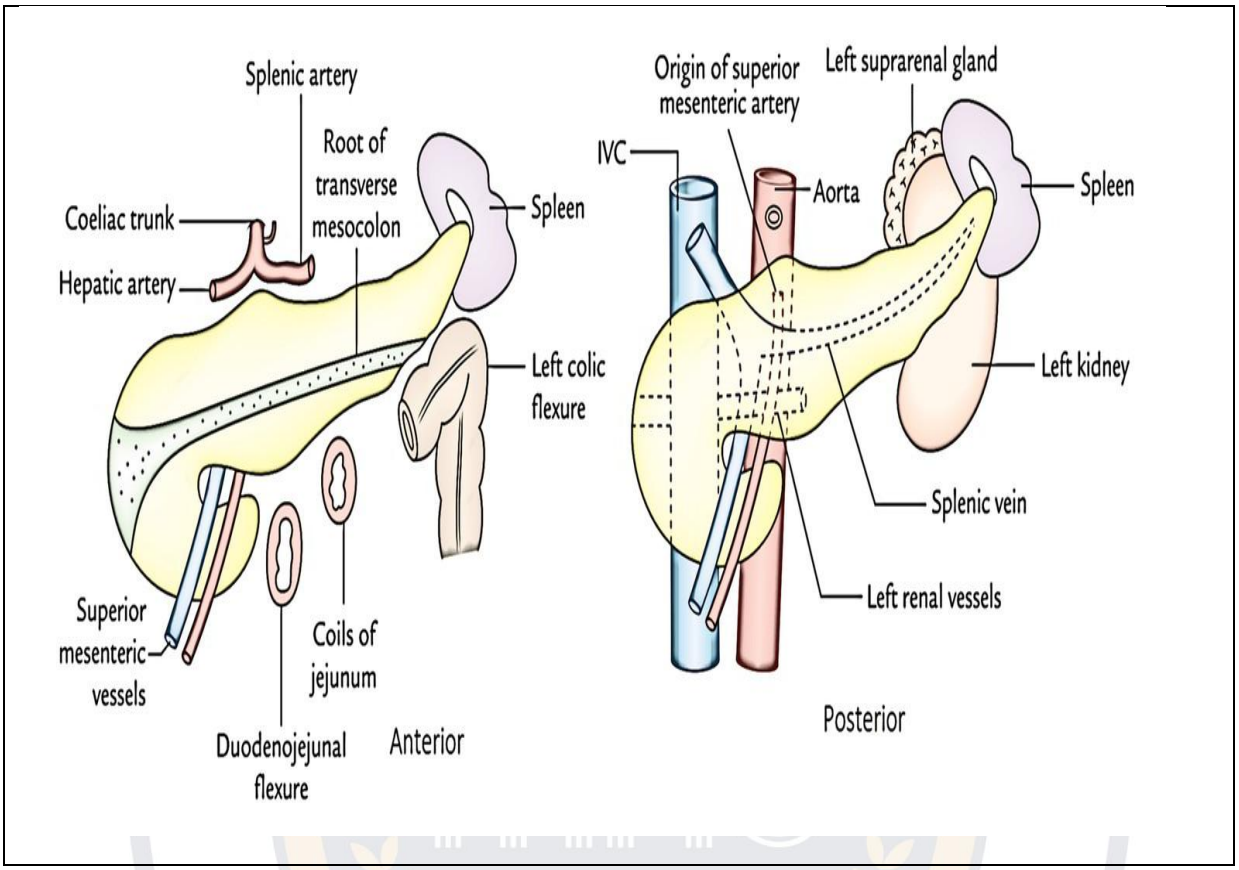
☒ ***Parts and Relations:*** it is divided into four parts:

Head of the Pancreas:

- Lies in the concavity of the duodenum, separated from it by groove containing the pancreaticoduodenal vessels.
- **Uncinate process**: projects upwards and to the left.
- ***Anterior relations:***
  1. The transverse colon.
  2. The coils of the jejunum
  3. The superior mesenteric vessels: in front of the uncinate process.
- ***Posterior relations:***
  1. The I.V.C.
  2. The common bile duct.
  3. The aorta: behind the uncinate process.

Neck of the Pancreas:

- ***Anterior relations:***
  1. The pylorus and the first part of the duodenum.
  2. The peritoneum of the lesser sac.
- ***Posteriorly:*** It is related to the **beginning of the portal vein** and the termination of the superior mesenteric and splenic veins.



Body of the Pancreas:

- It extends to the left behind the lesser sac.
- It is triangular in cross section. It has three surfaces and three borders.
- **3 Surfaces:**

1. ***The anterior surface:***
   - Is covered by the peritoneum of the lesser sac.
   - Is separated from the posterior surface of the stomach by the cavity of the lesser sac.
2. ***The inferior surface:***
   - Is covered by the peritoneum of the greater sac.
   - It is related to: The duodenojejunal flexure and left colic flexure.

3. The posterior surface:

- It is not covered by peritoneum, and it is related directly to:

The abdominal aorta.

The splenic vein: above the superior mesenteric artery.

The left renal vein: below the superior mesenteric artery.

- **3 Borders:**

A. ***The upper border:*** Related to the splenic artery.

B. The anterior border: Gives attachment to transverse mesocolon.

C. The posterior border: the same relations as posterior surface.

Tail of the Pancreas:

- Is thick and blunt.
- It lies between the two layers of the lienorenal ligament.
- It is related to the terminal parts of the splenic vessels.
- It comes into direct relation with visceral surface of spleen close to its hilum.

☒ Pancreatic ducts:

1. The main pancreatic duct:

- It passes through tail, body and lower part of head.
- In the lower part of the head of pancreas, the pancreatic duct joins the bile duct. The joining of these two structures forms the hepatopancreatic ampulla (ampulla of Vater), which enters the 2nd part of the duodenum at the major duodenal papilla.
- Surrounding the ampulla is the sphincter of ampulla (sphincter of Oddi), which is a collection of smooth muscle

2. The accessory pancreatic duct:

- It is small duct, which begins in the upper part of the head.
- It opens into the second part of the duodenum on the summit of the minor duodenal papilla, one inch above the major duodenal papilla.

Development of the pancreas

- **Development:** The pancreas develops from the duodenum by 2 buds:
  - ***Dorsal pancreatic bud:*** arises from the dorsal wall of the duodenum slightly above the hepatic bud. It extends dorsally and upwards in the mesoduodenum.
  - ***Ventral pancreatic bud:*** arises from the ventral wall of the duodenum in conjunction with the hepatic bud.
  - ***The ventral pancreas comes to lie below & behind the dorsal pancreas as a result of:***
    1. Differential growth of the duodenal wall.
    2. Axial rotation of the duodenum to right side.
  - ***Later the parenchyma as well as the duct systems of the two buds fuse together so that:***
    - ✓ ***The ventral bud*** forms the uncinate process & the inferior part of the head of the pancreas. The remaining part of pancreas is derived from ***the dorsal bud.***
    - ✓ ***The main pancreatic duct is formed by*** the distal part of the dorsal pancreatic duct & the whole ventral pancreatic duct.
    - ✓ The proximal part of the dorsal pancreatic duct is either obliterated or persists as ***the accessory pancreatic duct***.
    - ✓ In 10% of the cases the duct system fails to fuse.
  - ***The islets of Langerhans:*** develop from the parenchymatous tissue in the 3rd month, but they start insulin secretion during the 5th month.

- **Anomalies of the pancreas:**

1. ***Annular pancreas:***

- ✓ The ventral pancreatic bud consists of two components that normally fuse & rotate around the duodenum.
- ✓ In some cases, a portion of the ventral pancreas migrates along its normal route, but the other part migrates in the opposite direction.
- ✓ In this manner the duodenum is surrounded by pancreatic tissue.

2. ***Accessory pancreatic tissue:*** may be found in the wall of stomach or duodenum.

CRANIAL DURA MATER

☒ **Definition:** it is the outer layer of the brain meninges; it is dense & strong fibrous membrane surrounding the brain and spinal cord.

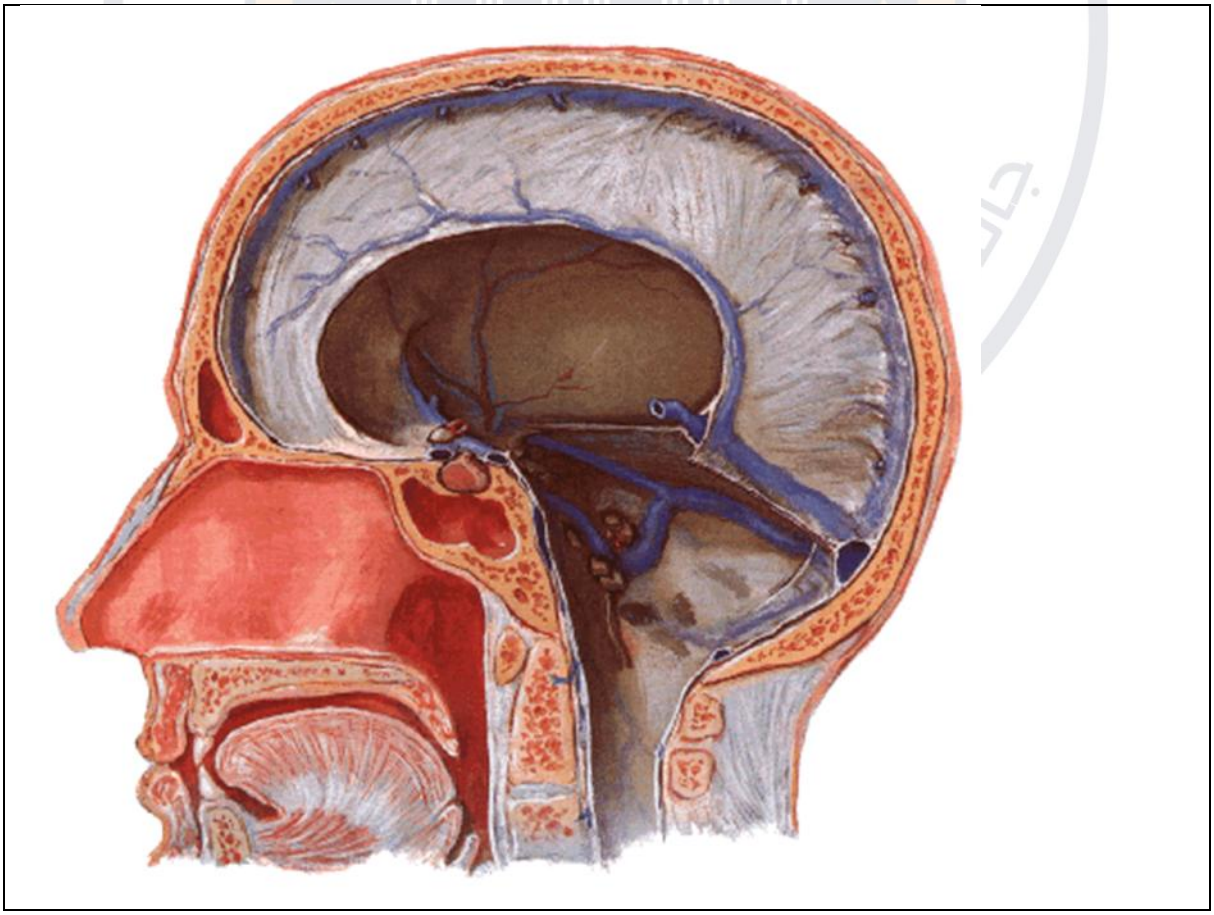
☒ **Formation**: is formed of 2 layers, outer endosteal layer and inner meningeal layer.

- The two layers are adherent to each other except in some areas where they separate to form the dural venous sinuses.
- The meningeal layer forms dural folds. These folds support the brain and prevent its displacement during movement of the head.

DURAL FOLDS

	1. Falx Cerebri	2. Tentorium Cerebelli
Definition	❖ Fold of the inner layer of the dura between the 2 cerebral hemispheres.	❖ Fold of the inner layer of the dura between cerebellum and cerebrum.
Site	❖ In the median longitudinal fissure between the 2cerebral hemispheres.	❖ Stretches horizontally across posterior cranial fossa separates cerebrum from cerebellum.
Shape	❖ Sickle-shaped fold, having an apex, base, two borders and two surfaces.	❖ Tent-shaped fold.
Attachment	☒ **Apex**: attached to frontal crest and cresta gali. ☒ **Base:** attached to the superior surface of the tentorium cerebelli. ☒ **Upper border:** convex and extends from the frontal crest to the internal occipital protuberance. ☒ **Lower border:** is concave, free and is related to the corpus callosum.	1) **Free anterior border:** ☒ U-shaped border that surrounds the midbrain (tentorial notch). ☒ Attached anteriorly to anterior clinoid process. 2) **Attached posterior border:** ☒ Attached to: a) Posterior clinoid process. b) Upper border of petrous bone.

		c) Margins of groove for the transverse sinus. **3) Superior surface:** ☒ Gives attachment to the falx cerebri in the median plane. **4) Inferior surface:** ☒ Gives attachment to falx cerebelli.
Sinus contents	**1. Superior sagittal sinus**: in the upper margin. **2. Inferior sagittal sinus:** in the posterior 2/3 of the lower margin. **3. Straight sinus:** at the junction of the falx cerebri with tentorium.	**1. The superior petrosal sinus:** in the attached margin. **2. The transverse sinus:** in the attached margin **3. The straight sinus:** at the junction of the falx cerebri with tentorium.



The point of decussation between the free and attached border of tentorium cerebelli determines the sites of three cranial nerves:

1. **Occulomotor nerve:** pierces the dura in front of the point of decussation.
2. **Trochlear nerve**: pierces the dura at the point of decussation.
3. **Trigeminal nerve:** pierces the dura behind the point of decussation.

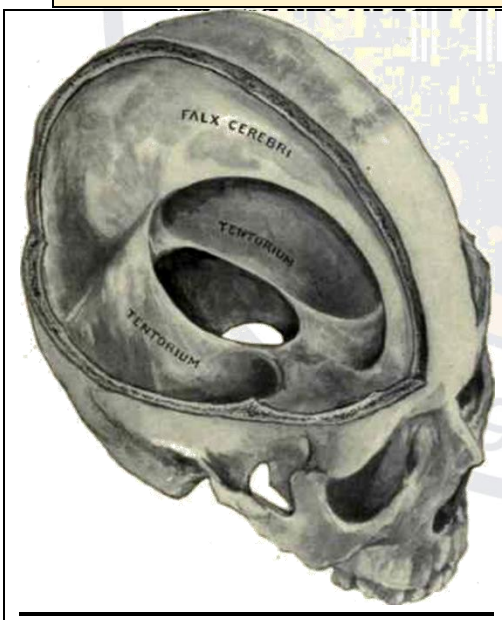
	3. Falx Cerebelli	**4. Diaphragma Sellae**
Definition	❖ Fold of the inner layer of the dura inside the posterior notch of cerebellum.	❖ Fold of the inner layer of the dura that covers the pituitary gland.
Shape	❖ Triangular.	❖ flat
Attachment	☒ **Apex**: attached to the posterior border of the foramen magnum. ☒ **Base:** attached to the inferior surface of the tentorium cerebelli. ☒ **Anterior border:** related to the internal occipital crest. ☒ **Posterior border:** free and related to the vermis of the cerebellum.	☒ **Anteriorly:** to the tuberculum sellae between the anterior clinoid processes. ☒ **Posteriorly:** to the dorsum sellae between the posterior clinoid processes. ☒ Transmits the infandibulum stalk of the pituitary gland through a central hole.
Sinus contents	❖ **Occipital sinus:** in its posterior border.	❖ **The intercavernous sinuses:** (anterior, middle and posterior) connecting the two cavernous sinuses.

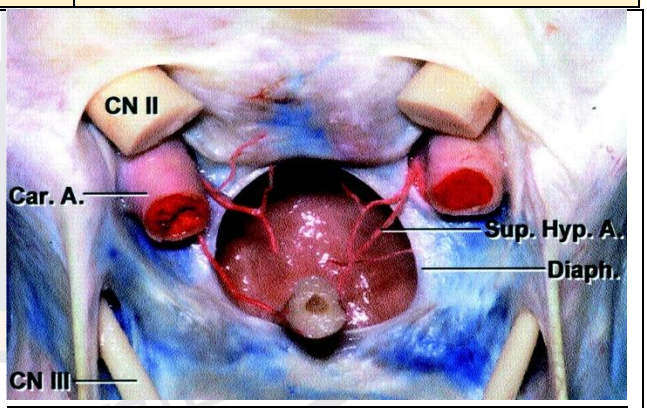
5. **Cavum trigeminal:** Fold of the inner layer of the dura, around the trigeminal ganglion, at the apex of petrous part of the temporal bone.

Dural Venous Sinuses

- **Definition:** Are venous channels located inside layers of the dura mater
- **Functions:**
  1. Drainage of the blood of the brain.
  2. Drainage of the C.S.F.
  3. Drainage of the emissary veins and diploic veins of the face and scalp.
- **Types:**

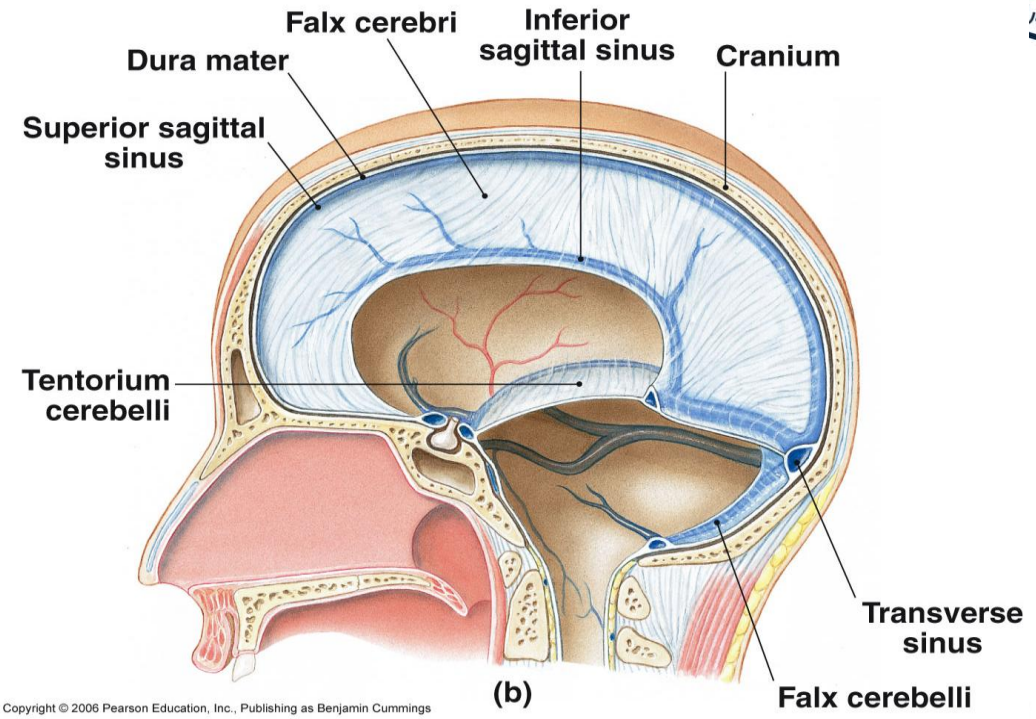
Single (unpaired) sinuses	Paired sinuses
1. Superior sagittal sinus. **2.** Inferior sagittal sinus. **3.** Straight sinus. **4.** Basilar plexus of sinuses. **5.** Intercavernous sinus. **6.** Occipital sinus.	**1.** Sphenoparietal sinus. **2.** Cavernous sinus. **3.** Superior petrosal sinus. **4.** Inferior petrosal sinus. **5.** Transverse sinus. **6.** Sigmoid sinus.





Single Sinuses

	Site	Termination
1. Superior sagittal sinus	❖ In the upper convex border of the falx cerebri	❖ Usually, turns to the right and continues as the **right transverse sinus.** ❖ Sometimes, unites with the straight sinus to form venous confluent, which gives right and left transverse sinuses. ❖ Receives superior cerebral, diploic, and emissary veins and CSF.
2. Inferior sagittal sinus	❖ in the posterior 2/3 of the lower free margin of the falx cerebri.	❖ By joining the great cerebral vein to form the straight sinus.
3. Straight sinus	❖ along the junction of the falx cerebri with the tentorium cerebelli	❖ Usually, turns to the left to form the left transverse sinus. ❖ Sometimes unites with superior sagittal sinus to form venous confluent, which gives right and left transverse sinuses
4. Occipital sinus	❖ posterior border of falx cerebelli	❖ In the sigmoid sinus.
5. Intercavernous sinus	**1.** Anterior: anterior margin of diaphragma sellae. **2.** Posterior: posterior margin of diaphragma sellae. **3.** Middle: below the pituitary gland. ❖ They Connect cavernous sinuses in both sides together.	
6. Basilar venous plexus	Connects the two inferior petrosal sinuses together.	



Paired sinuses

1. **Cavernous Sinus:**

☒ **Site:** Lies at the side of the pituitary fossa (sella turcica). It extends from the medial end of the superior orbital fissure to the apex of the petrous part of temporal bone.

☒ **Relations:** Related medially and inferiorly to pituitary gland and body of sphenoid

☒ **Contents:**

Structures at the floor	Structures at the lateral wall:
1. **The internal carotid artery:** runs forward surrounded with sympathetic plexus. 2. **The abducent nerve:** lies inferolateral to the artery.	from above downwards: 1. Occulomotor nerve. 2. Trochlear nerve. 3. Ophthalmic nerve. 4. Maxillary nerve.

☒ **Tributaries and communications:**

Anteriorly	1) ophthalmic vein: connecting it with anterior facial vein. 2) Central vein of the retina. 3) Sphenoparietal sinus.
Superiorly	cerebral veins.

Inferiorly	emissary veins connecting it with the pterygoid and pharyngeal plexus.
medially	The two sinuses communicate with each other through the 3 intercavernous sinuses
Posteriorly (termination)	divides into: a. Superior petrosal sinus: connecting it with the transverse sinus. b. Inferior petrosal sinus: connecting it with the internal jugular Vein.

	Site	**Termination**
2. <u>Sphenoparietal sinus.</u>	❖ along the free border of the lesser wing of sphenoid.	❖ Into the cavernous sinus.
3. <u>Superior petrosal sinus.</u>	❖ along the upper border of petrous part of the temporal bone	❖ At the junction of the transverse sinus and the sigmoid sinuses.
4. <u>Inferior petrosal sinus.</u>	❖ between the petrous temporal and occipital bones.	❖ Joins the upper part (bulb) of the internal jugular vein, below the skull.
5. <u>Transverse sinus.</u>	❖ Runs along the groove for transverse sinus in the occipital bone	❖ Continues as sigmoid sinus
6. <u>Sigmoid sinus.</u>	❖ Runs along the groove for sigmoid sinus	❖ Passes through the jugular foramen, to continues as **the internal jugular vein**

PITUITARY GLAND

☒ **Site:** Lies in hypophyseal fossa (sella turcica) below diaphragma sella.

☒ **Shape:** Oval in outline as seen from above.

☒ **Lobes:** It is composed of two lobes: anterior and posterior.

The anterior lobe (Adenohypophysis)	The posterior lobe (Neurohypophsis)
❖ Lies around the posterior lobe. ❖ Sends a process (**pars tuberalis**) upwards in front of the infundibulum. ❖ Its lower part is divided into: a) **Pars distalis** (in front of rudimentary cleft. b) **Pars intermedia** (at the back of the cleft).	❖ Small and lies at the back of the anterior lobe. ❖ Connected with the hypothalamus by the **infundibulum** (stalk). ❖ The stalk pierces the central part of diaphragma sella. ❖ Its lower end is called **pars nervosa.**

☒ Relations:

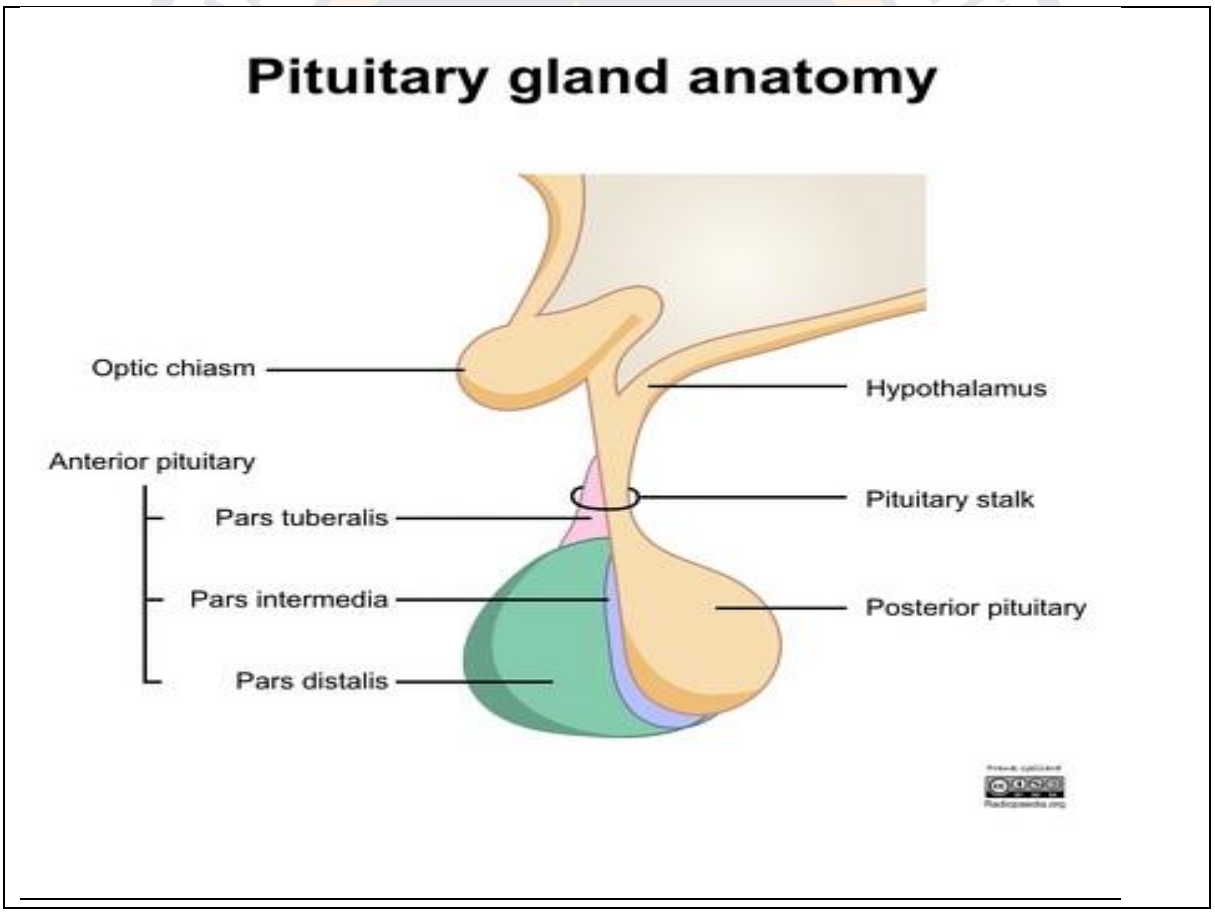
On each side	Cavernous sinus and its contents: a. Nerves: occulomotor, trochlear, abducent, ophthalmic and maxillary (in its lateral wall). b. Arteries: The internal carotid artery (in the floor).
Superiorly	**1.** diaphragma sella. **2.** Optic chiasma.
Inferiorly	**1.** Body of the sphenoid. **2.** Sphenoid air sinus. **3.** Separated from floor of hypophyseal fossa by dura and middle intercavernous sinus.
Anteriorly	**1.** tuberculum sellae, which separates it from the optic chiasma. **2.** Sphenoid air sinus.

Posteriorly	**1.** Dorsum sellae. **2.** Pons and basilar artery.

☒ **Arterial supply:** superior and inferior hypophyseal arteries (from the internal carotid artery).

☒ **Venous drainage:** cavernous and intercavernous sinuses.

☒ **Clinical note**: tumors of the pituitary gland tend to occlude the internal carotid artery and press abducent nerve before affecting the other cranial nerves in the sinus.



Development of the pituitary gland

- **Time:** at the middle of the 4th week.
- **Origin:** develops from two sources:

1. **The adenohypophysis:** develops as an up-growth pouch from the roof of the primitive mouth or the stomodeum as Rathke's pouch.
2. **The neurohypophysis:** develops as a down-growth diverticulum from the floor of the diencephalon (floor of third ventricle).

- **Development:**

The neurohypophysis: The neuroectodermal cells of the lower part of the diverticulum undergo proliferation and forms the posterior lobe of the pituitary gland (pars nervosa).

The upper part of the diverticulum remains as the infundibular recess of the 3rd ventricle.

The adenohypophysis:

A. This outgrowth develops a lumen to form a pouch known-as **Rathke's pouch**. This pouch comes in contact with the anterior aspect of the developing neurohypophysis.
B. The edges of the Rathke's pouch approximate each other and unite to form vesicle with lumen.
C. The pouch elongates and become constricted at its attachment to the oral epithelium.
D. The anterior wall of the Rathke's pouch proliferates and gives rise to the pars distalis.
E. A small upward extension from the anterior wall of Rathke's pouch grows around the stem of the neurohypophysis to form the pars tuberalis.

F. The posterior wall of the Rathke's pouch does not proliferate and gives rise to the thin, poorly defined pars intermedia.

G. The extensive proliferation of the anterior Wall of Rathke's pouch reduces its lumen to a narrow cleft (pituitary cleft).

- **Anomalies of the pituitary gland:**

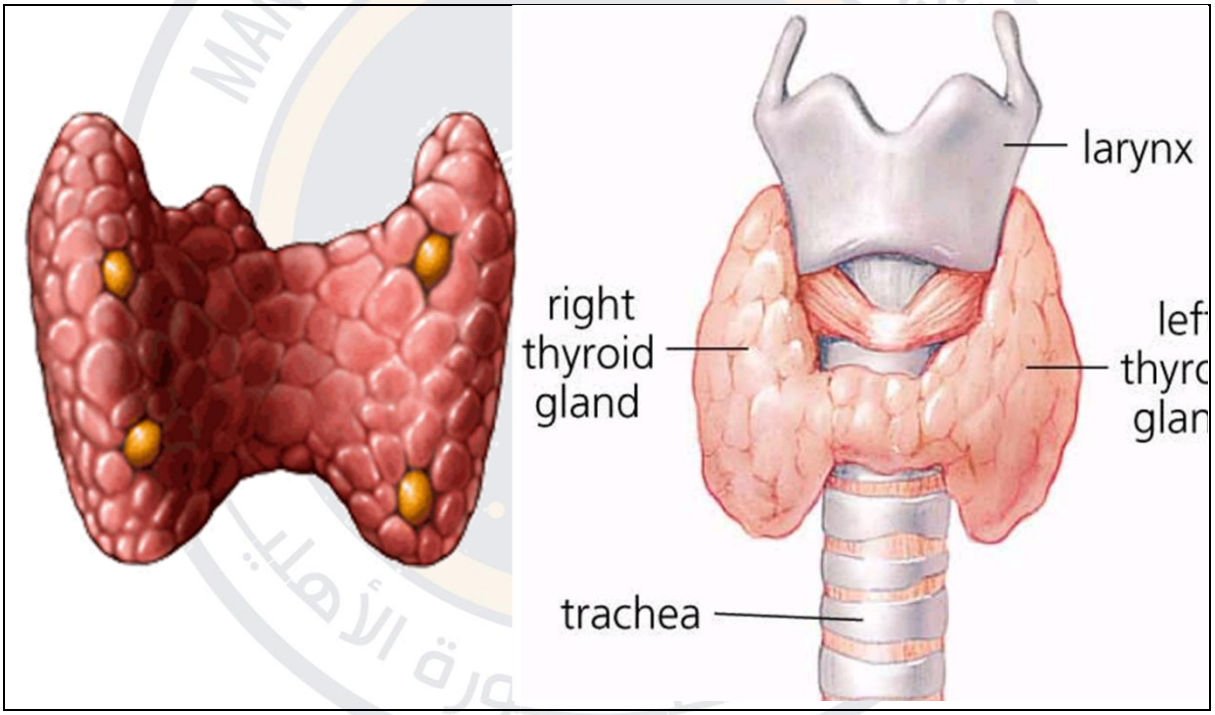
H.	**1. Pharyngeal pituitary gland:**	**2. Aplasia or hypoplasia of the pituitary gland:**
I. Cause	A remnant of the Rathke's pouch persists its connection with the roof of the oropharynx.	Failure or incomplete development of the anterior wall of the Rathke's pouch.
J. Feature	Accessory masses of the anterior lobe tissue develop outside the capsule of the pituitary gland, in the roof of the oropharynx.	The pituitary gland is ill-developed and hypofunction.

THE THYROID GLAND

- **Definition:** It is one of the endocrinal glands of the body responsible for production of the thyroxin hormone
- **Site:** In the lower part of the front of the neck opposite:
  - The lower three Cervical vertebrae and the first thoracic vertebra (behind).
  - From the middle of the thyroid cartilage to the fifth tracheal ring (in front).
- **Size:** variable, usually larger in female than in male.
- **Capsules :**
  1. True capsule: is the condensation of the connective tissue of the gland.
  2. False capsule: sheath of pretracheal fascia, which fixes the gland to the thyroid and cricoid cartilage.
- **Shape:** Butterfly in shape.
- **Subdivisions:**
  - Right lobe.
  - Left lobe.
  - Isthmus connecting the two lobes.
  - Pyramidal lobe.
- **Relations of the right and left lobes:** Each lobe is conical in shape and has:
  - Apex: reaches the oblique line of the thyroid cartilage.
  - Base: lies opposite the 5th or 6th tracheal ring.
  - 3 Surfaces: lateral, medial and posterior, each surface is related to:

Superficial (lateral) surface:	Medial surface:	Posterior surface:
1. Superior belly of omohyoid, at its upper part. 2. Sternomastoid, at its lower part.	Upper part: 1. Larynx (thyroid, cricoid cartilages and the cricothyroid muscle). 2. Pharynx (inferior constrictor muscle).	Carotid sheath (containing common carotid artery, internal jugular vein and vagus nerve in between).

3. Sternohyoid and Sternothyroid, at its middle part.	3. External laryngeal nerve (in between larynx & pharynx).	
	Lower part: 1. Trachea. 2. Esophagus. 3. Recurrent laryngeal nerve (in between trachea & esophagus).	



- 2 Borders:
  - **Anterior border:** thin border separates the medial surface from the lateral surface. Related to the anterior branch of the superior thyroid artery.
  - **Posterior border:** it is rounded border separates the posterior surface from the medial surface. It is related to:
    a. Parathyroid glands.
    b. Inferior thyroid artery.

c. Anastomotic branches between superior and inferior thyroid arteries.

❖ Relations of the Isthmus:

Surfaces	Borders
Anterior surface is covered by: ❑ Fascia and skin. ❑ Anterior jugular veins. ❑ Sternohyoid. ❑ Sternothyroid. **Posterior surface** related to: ❑ The second, third and fourth tracheal rings.	**Upper border:** is related to the anastomotic branches between the two superior thyroid arteries. **Lower border:** the inferior thyroid veins come out from this border.

❖ Relations of the pyramidal lobe:

- ❑ It is a small conical process that extends from the upper border of the isthmus.
- ❑ It connected to the hyoid bone by a fibromuscular band, the levator glandulae thyroidae.

❖ Nerves of Thyroid Gland.

- ❑ Sympathetic(vasomotor) nerves: derived from the superior, middle, and inferior cervical (sympathetic) ganglia.
- ❑ They reach the gland through the cardiac and superior and inferior thyroid periarterial plexuses that accompany the thyroid arteries.
- ❑ Endocrine secretion from the thyroid gland is hormonally regulated by the pituitary gland.

Blood supply of the thyroid gland:

1. Arterial supply

Artery	1) Superior thyroid artery:	2) Inferior thyroid artery
Origin:	❖ From the ECA.	❖ From the thyrocervical trunk from the 1st part of the subclavian artery.
Course:	❖ It descends downwards and forwards to the apex of the thyroid gland. ❖ accompanied by the external laryngeal nerve at its origin.	❖ It ascends upwards and medially behind the carotid sheath then downwards to the base of the gland. ❖ Accompanied by the recurrent laryngeal nerve at its termination.
Termination:	❖ divides into anterior and posterior branches along anterior and posterior borders of the gland.	❖ Anastomosis with the posterior branch of superior thyroid artery.
Branches:	**1.** Glandular branches: to the apex & upper 1/3 of the thyroid lobe and upper 1/2 of the isthmus. **2.** Superior laryngeal artery: pierces the thyrohyoid membrane. **3.** Infrahyoid artery. **4.** Artery to sternomastoid muscle. **5.** Artery to cricothyroid muscle.	**1.** Glandular branches: to the base & lower 2/3 of the thyroid lobe and lower 1/2 of the isthmus. **2.** Parathyroid glands **3.** Inferior laryngeal artery. **4.** Tracheal and esophageal branches. **5.** Ascending cervical artery: anterior to scalenus anterior.

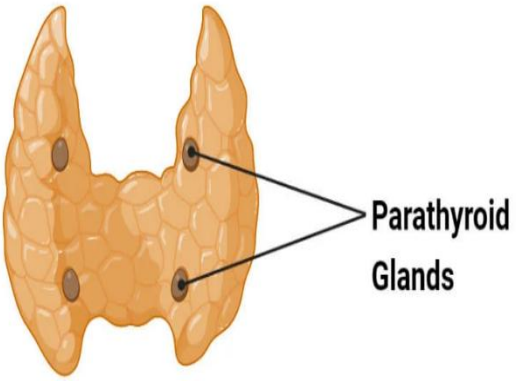
3) Thyroidea ima artery

- ❖ Single artery present in around 10% of people.
- ❖ Arises either from the brachiocephalic artery or the arch of the aorta.
- ❖ Ascends in front of the trachea to supply the isthmus.
- ❖ it is a potential source of bleeding when performing procedures in the midline of the neck inferior to the isthmus.

4) Accessory thyroid arteries: From the esophageal and tracheal branches.

2. Venous drainage

1) **Superior thyroid vein:**
   - ❖ Appears at the apex of the thyroid gland.
   - ❖ Ends in the internal jugular vein or common facial vein.
2) **Middle thyroid vein:**
   - ❖ Appears at the middle of the thyroid gland. Ends in the internal jugular vein.
3) **Inferior thyroid vein:**
   - ❖ Appears at the lower border of the isthmus.
   - ❖ Ends either in the corresponding brachiocephalic vein or unite together to end in the left brachiocephalic vein.



3. Lymph drainage

- ❖ Upper parts: upper and deep cervical lymph nodes.
- ❖ Lower parts: lower deep cervical lymph nodes.
- ❖ Isthmus: pretracheal lymph nodes.

THE PARATHYROID GLANDS

❖ **Number:** Most people have four parathyroid glands. Approximately 5% of people have more; some have only two glands.

❖ **Site:**

- lie outside to the thyroid true capsule and inside its sheath (false capsule)
- on the medial half of the posterior surface of each lobe of the thyroid gland.
- The superior parathyroid glands are usually at the level of the inferior border of the cricoid cartilage. The inferior parathyroid glands are usually near the inferior poles of the thyroid gland.

❖ **Blood supply:**

- Arterial supply: inferior thyroid arteries provide the primary source of blood supply
- Venous drainage: Parathyroid veins drain into the thyroid plexus of veins of the thyroid gland and trachea
- Lymph drainage: Deep cervical lymph nodes and paratracheal lymph nodes

THE SUPRARENAL (ADRENAL) GLANDS

- **Structure:** consists of an outer cortex and an inner medulla
- **position**: over the upper pole of the kidney one on each side of the midline.
- **Coverings**: enclosed together with the kidney in the renal fascia and perirenal fat, separated from the kidney by a septum of fibroareolar tissue.
- **Nerves:**
  - The medulla: supplied by preganglionic sympathetic fibres which end on the chromaffln cells of the medulla.
  - The cortex: under hormonal control of ACTH.

	Right suprarenal gland	Left suprarenal gland
Shape	pyramidal	semilunar
Anterior relations	➢ IVC. ➢ Bare area of the liver.	➢ lesser sac (stomach bed) ➢ stomach.
Posterior relations	➢ Right crus of diaphragm ➢ Right kidney.	➢ Left crus of diaphragm ➢ Left kidney.
Hilum	Directed upwards	Directed downwards
Suprarenal arteries	1. **Superior suprarenal artery:** from inferior phrenic artery. 2. **Middle suprarenal artery:** from abdominal aorta 3. **Inferior suprarenal artery:** from the renal artery.	
Suprarenal veins	ends in the inferior vena cava.	ends in the left renal vein.

Anatomy of the breast

Are specialized accessory glands of the skin that are capable of secreting milk and present in both sexes.

The breast consists of:

1. The mammary gland.
2. The superficial fascia in which the gland is embedded. The **Coopers ligaments** are connective tissues that supports the breast in bands and keeps it from sagging.
3. The overlying skin.

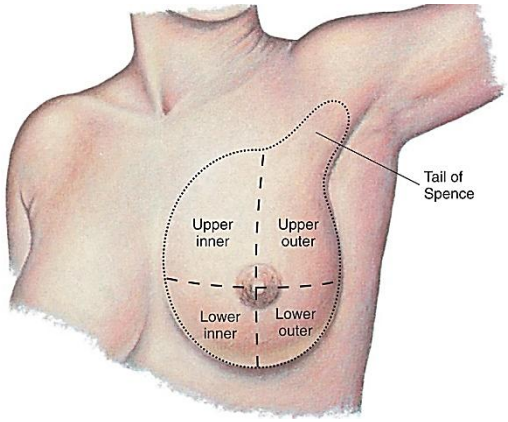
The Mammary Gland

☒ **Definition:** specialized glands of the skin that are capable of secreting milk. Present in both sexes. In the male and immature female, the mammary glands are rudimentary.

☒ **Shape:** hemispherical.

☒ **Site:**

- The glands extend from the 2nd rib to the 6th rib and from the lateral margin of the sternum to the midaxillary line.
- A small part, called the **axillary tail (Tail of Spence)**, extends upwards and laterally, pierces the deep fascia at the lower border of the pectoralis major and comes in contact with the axillary vessels. It contains a large amount of glandular tissue and is the site of 60 % of carcinomas of the breast.



The nipple

- **Definition:** Is a conical eminence that projects from the lower half of the breast.
- **Site:** Lies at the level of the 4th intercostal space.
- **Color:** It is pink in color in virgin and dark brown in the pregnant female.
- **Structure:**
  - ☒ It is traversed by the milk ducts (15-20).
  - ☒ It contains circular and longitudinal smooth muscle fibers for erection and retraction.

The areola

- **Definition**: A circular area of pigmented skin surrounds the nipple.
- **Structure:** It contains sebaceous glands called areolar gland (Montgomery Glands) which produces tubercles on the skin of the areola.

Blood supply of the breast

A. Arterial supply:

1. Perforating branches of the internal thoracic artery and the 2nd, 3rd,4th intercostal arteries.
2. Branches of axillary artery to the gland.
   a) Lateral thoracic artery
   b) Thoraco-acromial artery.

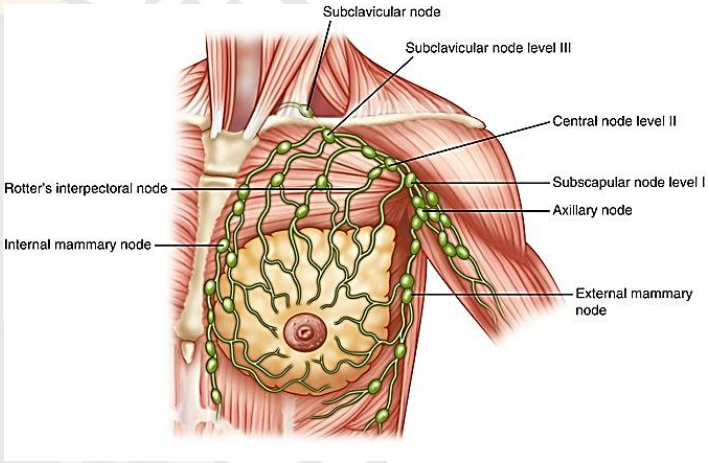
B. Venous drainage:

The veins accompany the arteries and drain into the axillary, internal thoracic and intercostal veins.

Nerve supply of the breast

A. **Sensory fibers:** from the anterior and lateral cutaneous branches of the intercostal nerves (3-6).
B. **Sympathetic fibers** from the thoracic sympathetic trunk.

Lymphatic drainage of the breast



A. **Lymphatics of the skin:**

1. From the lateral part of the breast: Pass to the pectoral group of lymph nodes.
2. From the medial part: Pass to the parasternal lymph nodes of same side and opposite side.
3. From the nipple and areola: Pass to the subareolar lymphatic plexus

B. **Lymphatics of the mammary gland:**

The lymph vessels of the gland form 2 plexuses:

1. <u>The superficial lymphatic plexus:</u> Lies beneath the areola. Receive lymph from nipple, areola and the central part of the gland.
2. <u>The deep lymphatic plexus</u>**:** Lies n the fascia covering the pectoralis major. Receive lymph from other parts of the breast.

C) Regional drainage:

1. **Lateral and central parts:**
   - Mainly into the pectoral group of lymph nodes in the axilla.
   - Few vessels may pass to the apical group of lymph nodes in the axilla.
2. **Upper part:** Drains into the apical group of lymph nodes in the axilla.
3. **Medial part:**
   - The vessels pass to the parasternal lymph nodes, which lie along the internal thoracic artery.
   - Few vessels pass to the posterior intercostal lymph nodes.
4. **Lower part: Piercing the abdominal wall to the:**
   - Rectus sheath.
   - Subdiaphragmatic and subperitoneal lymph nodes.

Development of the breast

- **Time: in the fourth week.**
- **Process:**

☒ 2 vertical ectodermal thickenings called the **mammary ridges (milk lines)**, appear on the trunk during embryonic life, and extend from the axilla to the inguinal region.

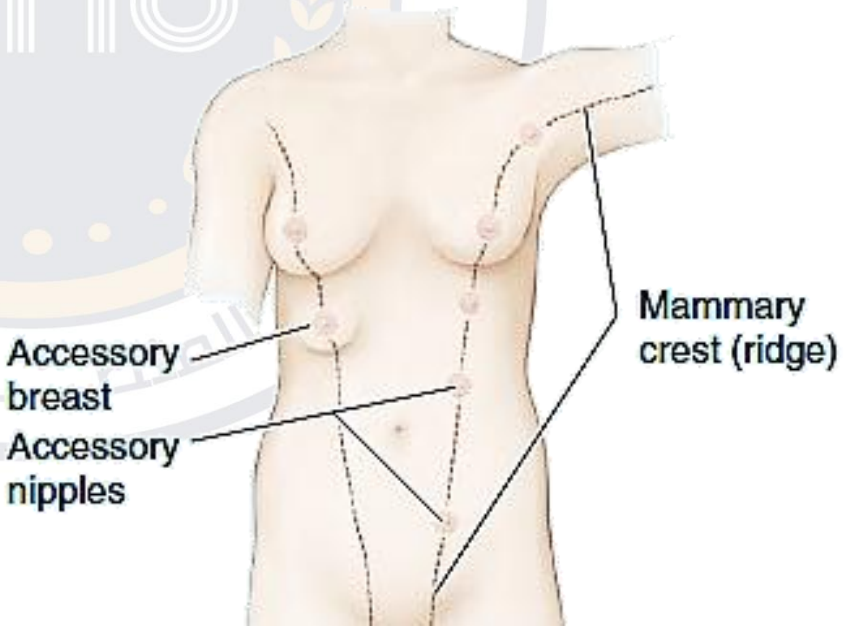
☒ These ridges disappear, except at the site of the breasts.

☒ **In the 7th week** the remained part of the mammary ridge produces a well-defined **primary bud** of the mammary gland. This bud grows down into the underlying dermis and fat in which the duct to branch.

☒ **In the 10th week**, the primary bud begins to branch, forming **secondary buds, which** lengthen and branch, and finally the resulting ducts canalize.

☒ **At birth,** the mammary glands consist of 15 to 25 **lactiferous ducts**, which open onto a small superficial depression called the **mammary pit**.

☒ Proliferation of the underlying mesoderm converts this pit to an **everted nipple** within a few weeks after birth. Occasionally the nipple remains depressed (**inverted nipple**).



☒ The skin surrounding the nipple proliferates to form the **areola**.

- ☒ **At puberty,** in the female, the breasts grow and the ducts bud and form lobules, **but true secretory alveoli do not develop until pregnancy.**
- ☒ **At menopause**, the glandular tissue involutes.

Anomalies of the breast

1. **Polythelia:** more supernumerary nipples.
2. **Polymastia:** supernumerary breasts form along the line of the mammary ridges. The most common location is just below the normal breast. Supernumerary nipples are about as common in males as in females.
3. **Ectopic nipple(s): Extra nipple** forms off the line of the mammary ridge as a consequence of migration of mammary tissue. Supernumerary breasts are often discovered at puberty or during pregnancy, when they enlarge or even lactate in response to stimulatory hormones.

- **The bony pelvis is formed of 2 hip bones and sacrum.**

Anterior relations of sacrum

A. Muscles:

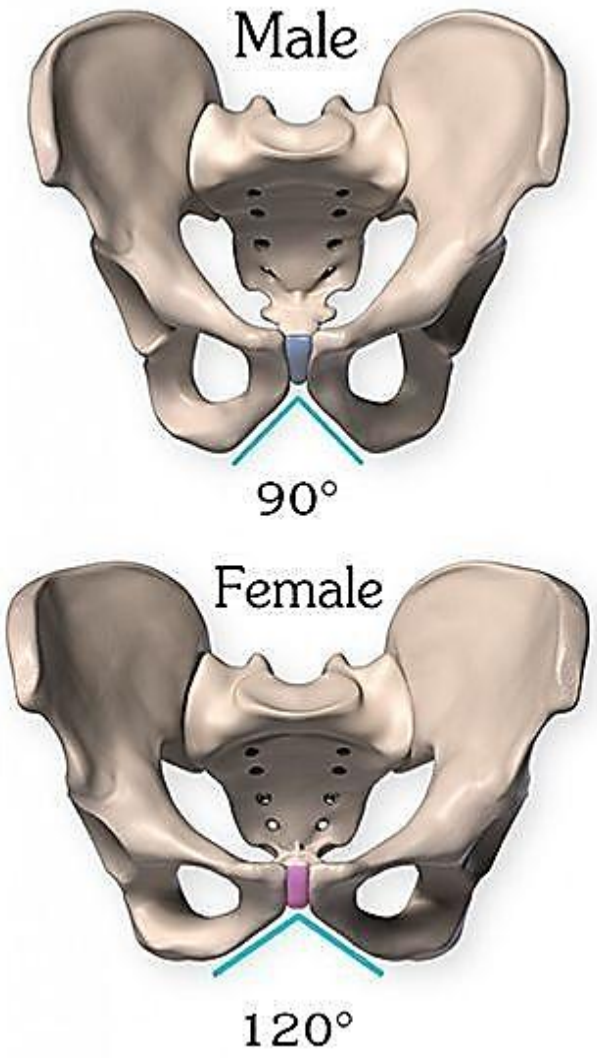
- ☒ **Iliacus:** ala of sacrum.
- ☒ **Piriformis:** anterior surface of second, third and fourth sacral pieces.
- ☒ **Coccygeus:** anterior surface of fifth sacral vertebra.

B. Vessels:

- ☒ **Median sacral artery:** runs in the median plane behind the rectum.
- ☒ **Lateral sacral arteries:** enter through the anterior sacral foramina.
- ☒ **iliolumbar artery:** on the ala.

C. Nerves:

- ☒ **Two sympathetic trunks:** end in the ganglion impar.
- ☒ **Ventral rami of sacral nerves:** appear through the anterior sacral foramina.
- ☒ **Lumbosacral trunk and obturator nerve:** on the ala of sacrum.



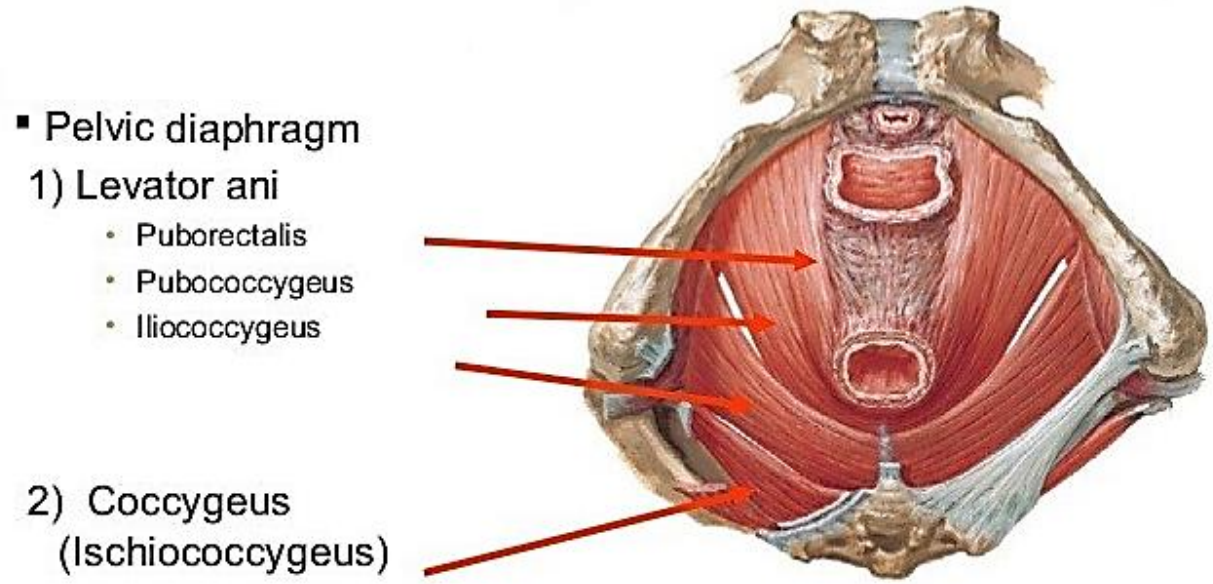
D. Viscera: Rectum opposite lower three segments of the sacrum.

The sacral canal

- The sacral canal corresponding to the vertebral canal of vertebral column.
- **Contents:**
  1. **Arachnoid and dural matter:** ends at S2.
  2. **Filum terminale:** it is the continuation of pia mater and it appear from the sacral hiatus to be attached to the coccyx.
  3. **Sacral and coccygeal nerves:** they form the cauda equina.
  4. Branches of lateral sacral and median sacral arteries.
  5. Fat and cerebrospinal fluid.
- **The sacral canal end with the sacral hiatus.**
- **Structures passing through sacral hiatus:**
  1. Filum terminate.
  2. Fifth sacral nerve.
  3. Coccygeal nerve.

The pelvic diaphragm

- Pelvic diaphragm is the pelvic floor that supports the viscera. It consists of 2 muscles: the levator ani and coccygeus muscles.



Coccygeus

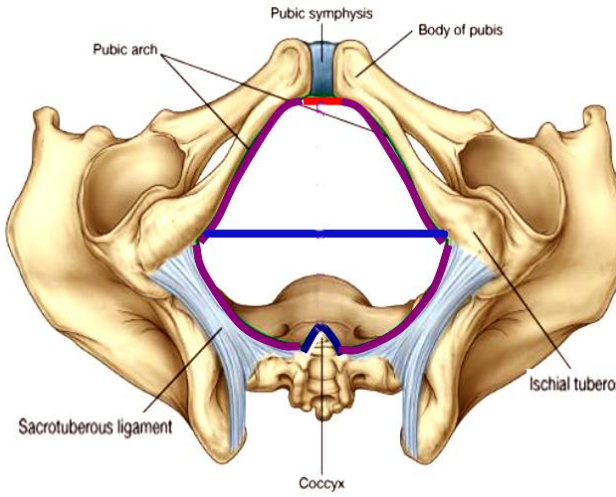
- **Origin:** from the tip of the ischial spine.
- **Insertion:** into the last piece of the sacrum and first piece of coccyx.
- **Nerve supply:** from the lower sacral nerves.
- **Action:** no action in man.

Levator ani

- **Origin:** Posterior surface of the pubis, white line, which is a part of obturator fascia covering the obturator internus muscle and ischial spine.
- **Insertion:**
  - ☒ **The anterior fibers** (from the pubis) meet in the perineal body.
  - ☒ **The middle fibers** (from the white line) curve around the anal canal.
  - ☒ **The posterior fibers** (from the ischial spine) meet in the anococcygeal body attached to the coccyx.
- **Nerve supply:** is supplied from both surfaces:
  - ☒ **Pelvic surface:** lower sacral and coccygeal nerves.
  - ☒ **Perineal surface:** inferior rectal nerve, branch of pudendal nerve.
- **Action:**
  1. Supports the pelvic viscera.
  2. Increase the intra-abdominal pressure in forced expiration.
  3. Puborectalis acts as a sphincter for the anal canal.
  4. Pubovaginalis acts as a sphincter for the vagina.
- **The levator ani is pierced by:**
  - ☒ In male:
    1. Prostate and the fibers surrounding it are known as **levator prostate.**
    2. Rectum and the fibers surrounding it are known as **puborectalis**.
  - ☒ **In female:**
    1. Urethra: and the fibers surrounding it are known as **pubourethralis.**
    2. Vagina: and the surrounding fibers known as **pubovaginalis.**
    3. Rectum: and the fibers surround it is called **puborectalis.**

The Perineum

- **Def:** The lower part of pelvic cavity below the pelvic diaphragm
- **Site:** inferior to pelvic diaphragm between the thighs
- **Shape:** diamond-shaped when seen from below
- **Boundaries: (Same as boundaries of pelvic outlet):**
  - ☒ **Anterior**: lower border of symphysis pubis.
  - ☒ **Posterior**: coccyx.
  - ☒ **Laterally**: Ischiopubic rami, Ischial tuberosity & Sacrotuberous ligament.
  - ☒ **Roof (ceiling)**: pelvic diaphragm (levator ani & coccygeus).



- **Divisions:** by a line between 2 ischial tuberosities into:
  - ☒ **Urogenital triangle**: (anterior): contain 2 perineal pouches & external genitalia.
  - ☒ **Anal triangle:** (posterior): contain anal canal & ischiorectal fossa.

The anal triangle

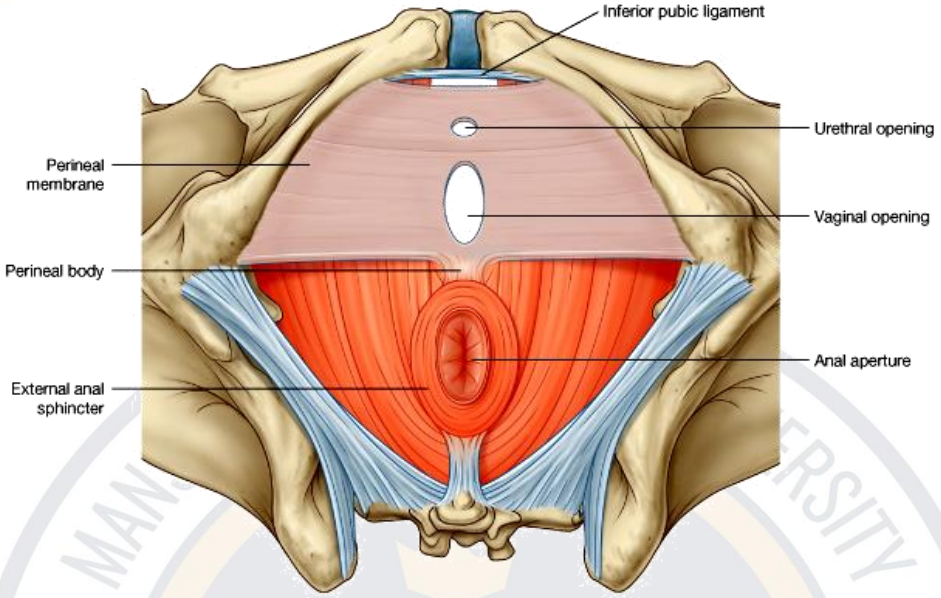
- **Boundaries:**
  - ☒ **Anteriorly:** imaginary line between the 2 ischial tuberosities.
  - ☒ **Posteriorly:** coccyx.
  - ☒ **On each side:** sacrotuberous ligament.
  - ☒ **Roof:** levator ani and coccygeus.
- **Contents:**
  1. Anal canal
  2. External anal sphincter
  3. Ischio-rectal fossa

The perineal membrane

- It is a triangular sheet of fibrous tissue stretches across the pubic arch.
- The middle of its posterior surface is attached to the perineal body.
- These are 2 fascial spaces in relation with each of the superior and inferior surfaces of the perineal membrane in the urogenital triangle.
- The 2 facial spaces are named superficial and deep perineal pouches.
- In relation with the superior surface: the pelvic fascia attaches to all its sides forming a completely closed space. This space is called the **deep perineal pouch**.
- In relation with the inferior surface: the membranous fascia of the anterior abdominal attaches to the sides and posterior border, but not to its apex, forming an incompletely closed space called the **superficial perineal pouch.**
- **Structures piercing the perineal membrane:**

In male	In female
1. Urethra 2. Artery of bulb of penis (clitoris) 3. Internal pudendal artery termination 4. Dorsal nerve of penis (clitoris)	
5. Bulbo-urethral ducts	5. Vagina

- **Therefore, the structures passing out of the pelvis should pass through:**
  1. Deep pouch
  2. Perineal membrane
  3. Superficial pouch.



The superficial fascia of perineum

- **Like that of the inferior anterior abdominal wall consists of:**

1. **Superficial fatty layer**. In male: it is replaced by dartos muscle in the scrotum.
2. **Deep membranous layer** (**Cool's fascia**): attaches posteriorly to the posterior border of perineal membrane forming the superficial perineal pouch (which is opened anteriorly**).**

The pelvic fascia

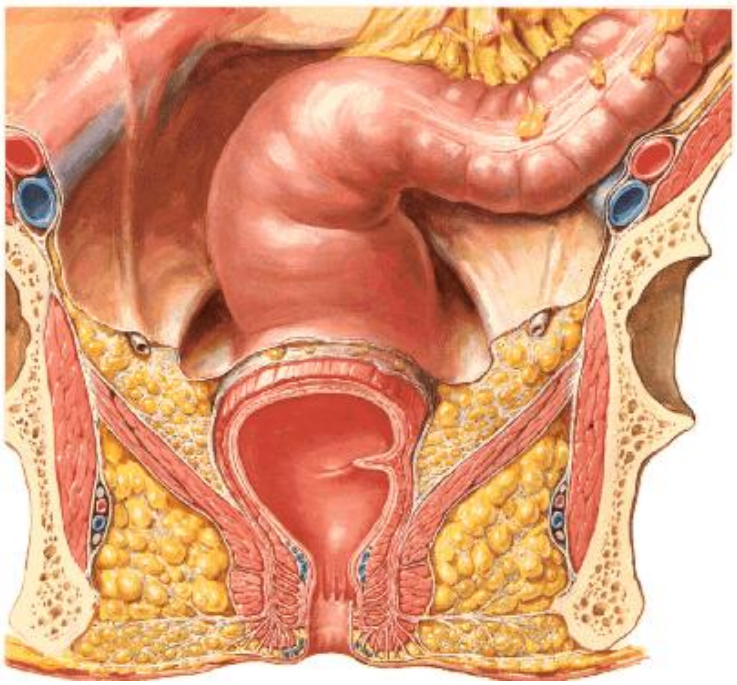
- Lies above perineal membrane.
- Attach to all side of the perineal membrane forming a completely closed space called deep perineal pouch.

The perineal body

- **Definition:** fibromuscular mass at midline of perineum
- **Site:**
  - In males: between anal canal and bulb of penis.
  - In females: between anal canal and lower part of vagina.
- **Muscles attached to it:**
  - On each side: transverse perineal muscles
  - Posterior: external anal sphincter (superficial and deep parts).
  - Anterior: bulbospongiosus.
  - Superior: levator ani.
- **Function of perineal body:**
  - Important support to pelvic organs especially in females.
  - Its damage during labour may result in prolapse of uterus & other pelvic organs.

The Ischio-rectal fossa

- **Definition:** Wedge shaped space (gutters) on each side of anal canal
- **Shape:** conical in shape lies in both sides of the anal canal.
- **Function:** it gives space of the anal canal to dilate during the process of defecation.
- **Boundaries:**
  - **Apex**: formed of origin of levator ani from obturator fascia.
  - **Base**: formed of skin and fascia.
  - **Medial wall**: consists of levator ani and external anal sphincter.
  - **Lateral wall**: consists of obturator internus and obturator fascia.
- **Contents:**
  1. Pad of fat.
  2. Inferior rectal vessels and nerves.
  3. Pudendal canal containing:
     a. Pudendal nerve.
     b. Internal pudendal vessels.



The pudendal (Alcock's) canal

- **Formed** by splitting of obturator fascia and lies in lateral wall of ischiorectal fossa.
- **Content:**
  1. Pudendal nerve
  2. Internal pudendal vessels.

Superficial perineal pouch

Boundaries:

- **Superior** (roof): perineal membrane.
- **Inferior** (floor): Cool's fascia.
- **On either side:** fusion of the roof with the floor.
- **Posteriorly**: fusion of fusion of the roof with the floor.
- **Anteriorly**: opened.

Contents:

In female	In male
1. Root of clitoris	1. Root of penis
2. Greater vestibular glands	2. Duct of bulbourethral gland
3. Bulbospongiosus muscle. 4. Ischiocavernosus muscle. 5. Superficial transverse perineal muscle. 6. Posterior scrotal (labial) nerve & vessels	

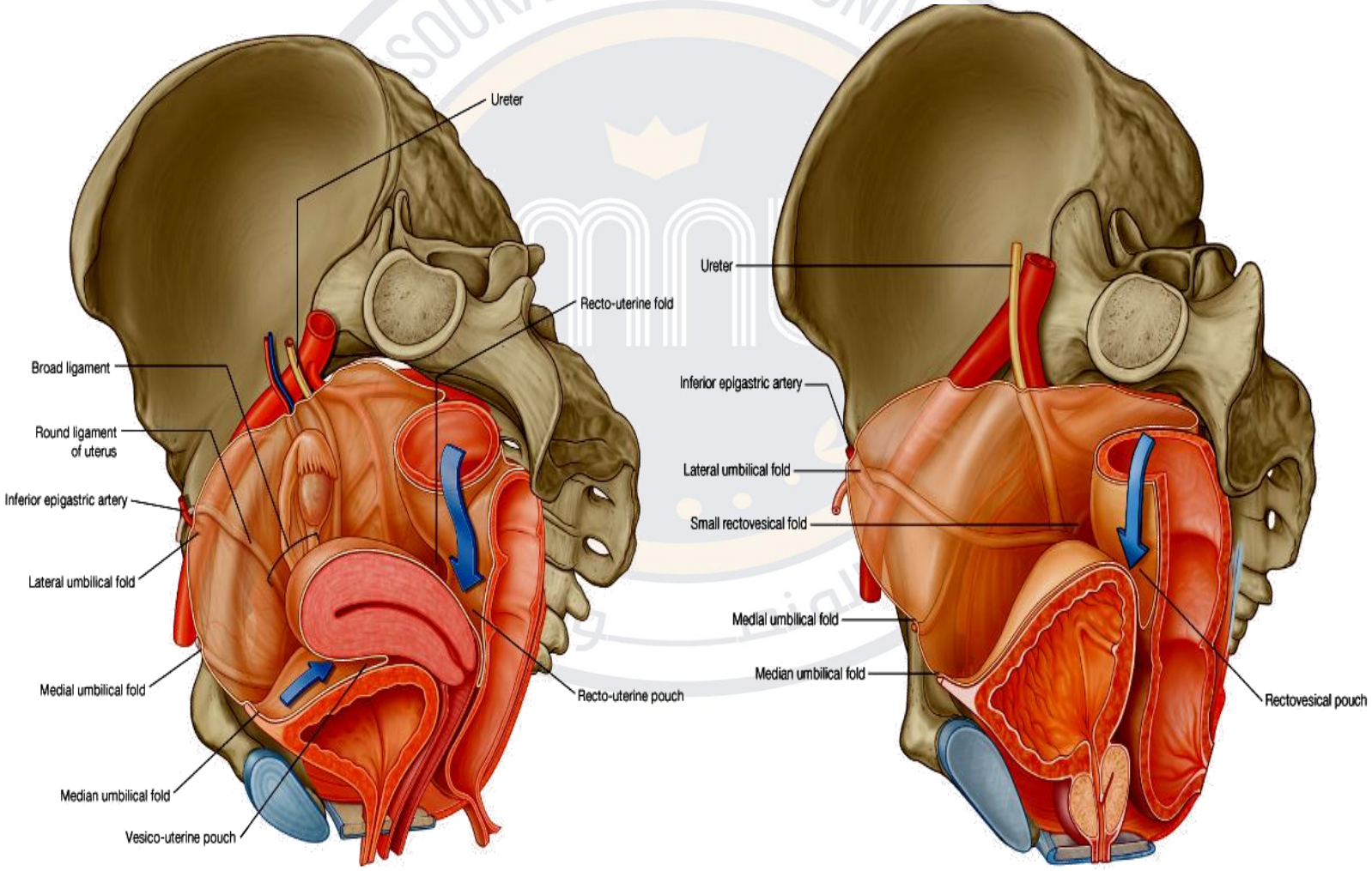
Deep perineal pouch

- **Boundaries:**
  - ☒ **Superior** (roof): Pelvic fascia.
  - ☒ **Inferior** (floor): perineal membrane.
  - ☒ **On either side**: fusion of the roof with the floor.
  - ☒ **Anteriorly**: fusion of the roof with the floor.
  - ☒ **Posteriorly**: fusion of the roof with the floor.
- **It is a completely closed space.**
- **Contents:**

In female	In male
1. Urethra: anterior	1. Urethra: membranous part
2. Vagina: posterior	2. bulbourethral glands
3. External urethral sphincter: around the urethra 4. Deep transverse perineal muscle 5. Internal pudendal vessels 6. Dorsal nerve of clitoris (penis)	

Arrangement of the pelvic viscera

- **The pelvic cavity contains:**
  1. The sigmoid colon and rectum (posteriorly).
  2. The urinary bladder (and prostate in males) (anteriorly).
  3. The uterus with its broad ligaments (in females) (having an intermediate position).



The pelvic peritoneum

- **In the males:**
  - ☒ The peritoneum lining the anterior abdominal wall is reflected to cover the upper surface of the bladder. From the bladder, the peritoneum is reflected backwards on to the front of the rectum to form the rectovesical pouch.
  - ☒ n each side of the rectum the peritoneum forms a shallow depression called the **pararectal fossae**. Similarly, on each side of the urinary bladder it forms the **paravesical fossae**.
- **In females:**
  - ☒ The peritoneum lining the anterior abdominal wall is reflected to cover the upper surface of the bladder. From the bladder, the peritoneum is reflected backward on to the front of the uterus to form the **uterovesical pouch**.
  - ☒ The peritoneum is then reflected on the rectum to form the **recto-uterine pouch (Douglas pouch).**
  - ☒ The peritoneum then covers the following surfaces of the uterus and vagina:
    1. Anterior surface of the body of uterus.
    2. Fundus of uterus.
    3. Posterior surface of the body of uterus.
    4. Posterior surface of the cervix.
    5. 5-The upper part of the posterior wall of the vagina.

The internal iliac artery

- **Origin:** as one of the two terminal branches of the common iliac artery at the level of sacroiliac joint.
- **Termination:** at the upper margin of the greater sciatic foramen by dividing into anterior and posterior divisions.
- **Relations:**

☒ **Anterior:**

- Ureter.
- Ovary and lateral end of uterine tube (in female).

☒ **Posterior:**

- Internal iliac vein.
- Lumbosacral trunk.
- Sacroiliac joint.

☒ **Lateral:**

- External iliac vein.
- Obturator nerve.

☒ **Medial:**

- Coils of ileum (on the right side).
- Sigmoid colon (on the left side).

- **Branches of internal iliac artery:**

Posterior division	Anterior division	
Parietal	**Parietal**	**Visceral**
1. Iliolumbar. 2. Lateral sacral. 3. Superior gluteal.	1. Obturator. 2. Internal pudendal. 3. Inferior gluteal.	1. Umbilical ⟶ superior vesical. 2. Middle rectal. 3. Inferior vesical in male or vaginal in male. 4. Uterine (only in female).

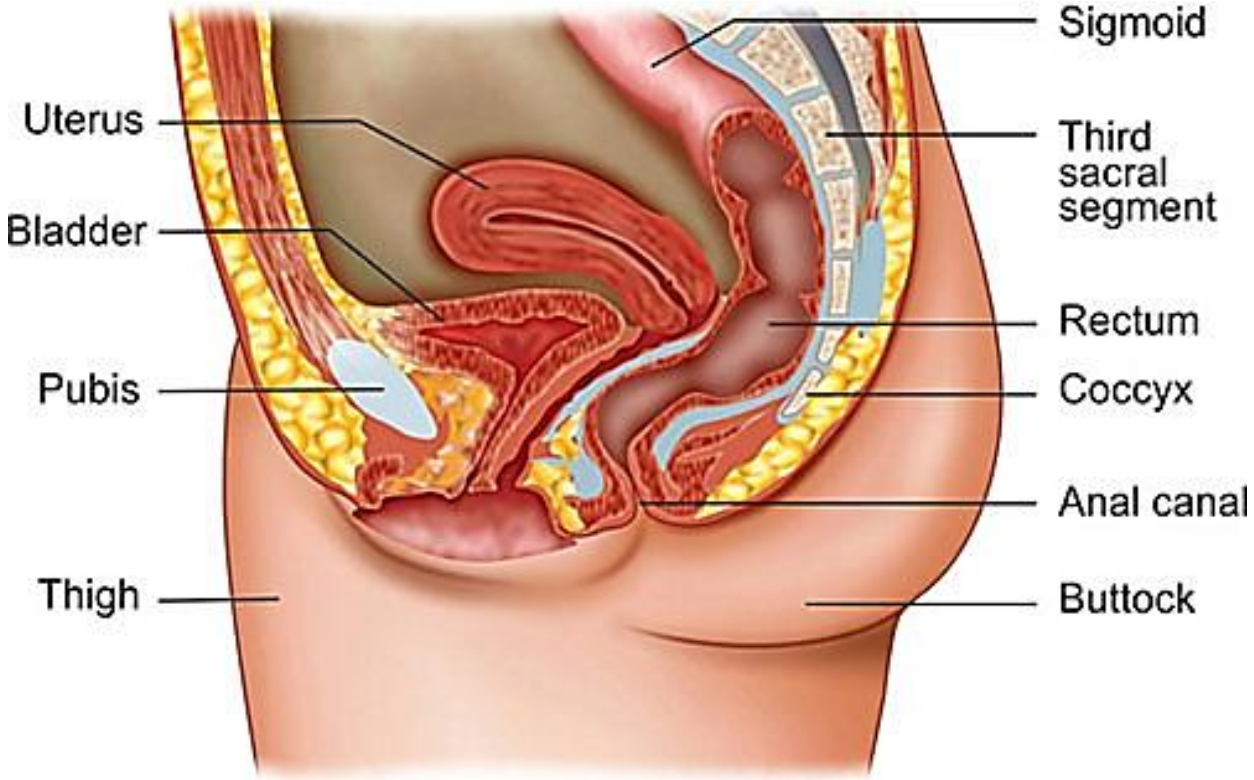
Pudendal nerve

- **Origin:** It is a one of the two terminal branches of the sacral plexus.
- **Course:** it crosses the back of sacrospinous ligament to lesser sciatic foramen to enters the pudendal canal to end at the deep perineal pouch.
- **Branches:**
  1. Inferior rectal nerve: to levator ani and external anal sphincter.
  2. Perineal nerve: to the skin of scrotum or labia majora.
  3. Dorsal nerve of penis.

Internal pudendal artery

- **Origin:** It is a one of the two, terminal branches of anterior division of the internal iliac artery.
- **Course:** accompany the pudendal nerve.
- **Branches:**

In female	In male
1. Inferior rectal artery	1. Inferior rectal artery
2. 2 labial arteries	2. 2 scrotal arteries.
3. Artery of the bulb of clitoris	3. Artery of the bulb of penis
4. Deep and dorsal arteries of clitoris	4. Deep and dorsal arteries of penis


Sigmoid
Uterus
Third sacral segment
Bladder
Rectum
Pubis
Coccyx
Anal canal
Thigh
Buttock

The rectum

- **Beginning:** in front of the third piece of sacrum (S3).
- **Termination:** It ends 1 inch below and in front of coccyx to form anal canal.
- **Length:** it is five inches long.
- **The rectum differs from the large intestine in that it:**
  - **A.** Has no taenia coli.
  - **B.** Has no appendices epiploicae.
  - **C.** Site of Porto-systemic anastomosis.
- **Flexures:**
  - ☒ Lateral curvatures (3): upper and lower ones are directed to the right, and the middle is directed to the left.
  - ☒ Perineal curvature: at the junction of rectum and anal canal.
  - ☒ Sacral curvature: follow the anteroposterior curvature of sacrum.
- **Peritoneal covering:**
  - ☒ Upper third: front and sides
  - ☒ Middle third: front only.
  - ☒ Lower third: no peritoneal covering.
- **Relations:**

A. Posteriorly: are the same in both male and female.

- ☒ Bones: lower three pieces of sacrum and coccyx.
- ☒ Vessels: median sacral and superior rectal.
- ☒ Nerves: sympathetic trunk, lower sacral and coccygeal nerves.
- ☒ Muscles: piriformis, coccygeus and levator ani.

B. Anteriorly: differs both in male than in female:

- In males: rectovesical pouch- base of urinary bladder- seminal vesicle vas deferens- prostate.
- In females: rectovaginal pouch- vagina.

C. On each side:

- Pararectal fossa,
- superior rectal vessels,
- Pelvic diaphragm (coccygeus and levator ani).

Blood supply of the rectum:

A. Arteries:

- Superior rectal: from the inferior mesenteric artery. Supplies the upper third.
- Middle rectal: from the internal iliac artery. Supplies the middle third.
- Inferior rectal: from internal pudendal: Supplies the lower third.

B. Veins:

- Veins of the rectum form plexus of veins from which 3 veins accompany the arteries.

Lymphatic drainage of the rectum:

- Upper part: paraaortic lymph nodes.
- Lower part: inguinal lymph nodes.

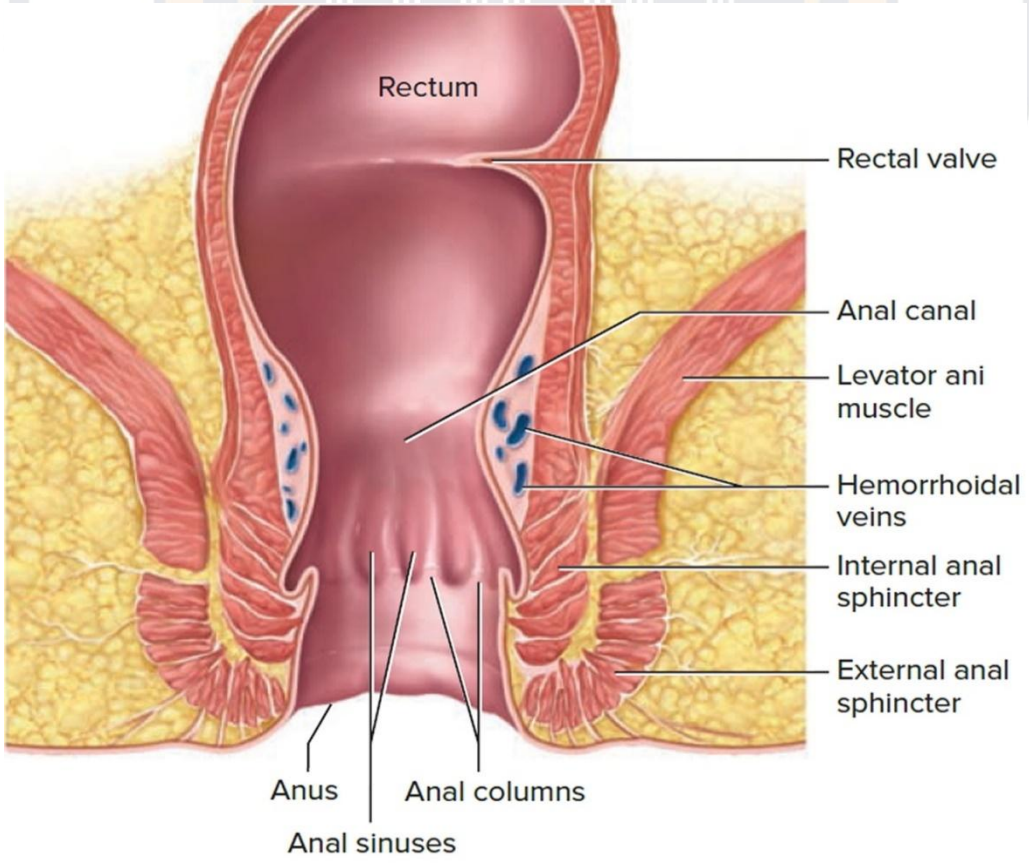
The anal canal

- **Definition:** It is the terminal part of the large intestine.
- **Length:** one and a half inches.
- **Beginning:** It begins at the end of the rectum; one inch blow the tip of the coccyx**.**
- **Course:** it passes downwards and backwards to open at the anus.
- **Relations: (No peritoneal coverings at all).**
  - ☒ Anteriorly: related to perineal body.
  - ☒ Posteriorly: anococcygeal body and tip of coccyx.
  - ☒ On each side: levator ani and ischiorectal fossa.
- **The anal sphincters:**

Internal anal Sphincter	External anal sphincter
1. Smooth muscle fibers. 2. Surrounds upper two-thirds of anal canal. 3. Controlled by automatism. 4. Supplied by sympathetic and parasympathetic. 5. Has only one part.	1. Striated muscle fibers. 2. Surrounds lower two-thirds of anal canal. 3. Controlled by well. 4. Supplied by somatic nerve fibers from: A. Fourth sacral nerve. B. Inferior rectal nerve. 5. Has 3 parts: subcutaneous, superficial & deep.

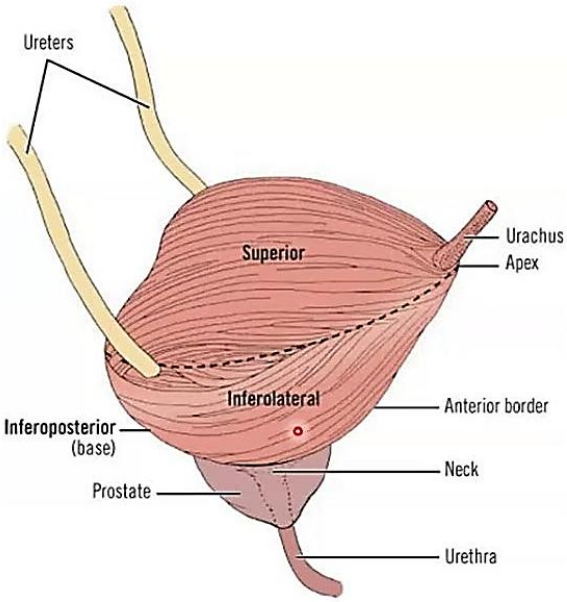
- **The anal mucosa:**
  - ☒ The pectinate (dentate line) separates the upper endodermal 2/3 from the lower ectodermal 1/3.
  - ☒ It is marked by the anal valves (**transverse** folds of mucosa)

The upper 2/3	The lower 1/3
☒ Endodermal ☒ Covered with columnar epithelium mucosa. ☒ Insensitive like intestinal mucosa. ☒ Has 6-10 longitudinal (vertical) mucosal folds the **anal columns (of Morgagni).** ☒ At the bottom of these columns are anal **sinuses or crypts**, into which open the **anal glands and anal papillae**.	☒ Ectodermal in origin ☒ Covered with pigmented skin. ☒ Sensitive like skin.



The urinary bladder

- **Site:** behind the symphysis pubis. When it is distended it enters the abdomen.
- **Shape:** the empty urinary bladder is in the form of three-sided pyramid.
- **It has four angles:**
  A. Anterior angle (called apex of the bladder)
  B. Inferior angle (called neck of the bladder)
  C. Two posterosuperior angles
- **It has four surfaces:**
  A. Inferoposterior surface called base.
  B. Two inferolateral surfaces.
  C. Superior surface. **All surfaces are triangular in shape**.



- **Relations:**

☒ **Apex**: Lies behind the symphysis pubis. It is continuous to the umbilicus with median umbilical ligament.

☒ **Neck**:

- In male: it rests on the prostate and is continuous with the prostatic urethra.
- In female: it is continuous with the urethra.

☒ **Posterosuperior angles:** receive the ureteric orifices.

☒ **Base: related to:**

- In male: to the rectum from which it is separated by:
  A. Rectovesical pouch.
  B. Seminal vesicles.
  C. Ampulla of vas deferens.

- In female: it is related to:
    A. Cervix of uterus.
    B. Anterior wall of vagina.

☒ **Superior surface**: is the only surface, which is covered with peritoneum. It is related to:

- In male: it is related to pelvic colon and loops of ileum.
- In female: it is related to pelvic colon and loops of ileum and uterus.

☒ **Inferolateral surfaces:** are related to the fat of retropubic space which separates it from obturator internus and levator ani.

Blood supply of the bladder:

☒ **Arterial supply:**

1. Superior vesical arteries: from umbilical artery from internal iliac artery.
2. Inferior vesical arteries (vaginal in female) from internal iliac artery.
3. Other nearby arteries:
    A. Obturator artery.
    B. Inferior gluteal artery.
    C. Uterine artery.

☒ **Venous drainage:** through vesical venous plexus from which veins accompany the arteries.

The urethra

- **Site:** it is a duct, which begins at the neck of the bladder and ends by opening into the outside.

Male urethra

- **Length:** It is a long duct, about 8 inches (20 cm) long.
- **Course:** It takes an S-shaped course. It can be divided into three parts: prostatic, membranous, and spongy.
  - ☒ **Prostatic** part: It is about 1.5 inches long. It traverses the prostate mucous Its membrane presents:
    a. Urethral crest.
    b. Seminal colliculus.
    c. Prostatic sinus.
    d. Prostatic utricle:
  - ☒ **Membranous urethra:** It is about 0.5 inch long (1.5 cm).It is surrounded with urethral sphincter and bulbourethral gland.
  - ☒ **Spongy (penile) urethra:**
    - It is about 6 inches long (15 cm).
    - It traverses the penis.
    - It receives the duct of the bulbourethral gland.

Female urethra

- It is a short, only 1.5 inches (4 cm) long.
- It extends from the neck of the bladder to the outside.

Male reproductive tract

A. Primary Sex Organ: Testis

B. Accessory Sex Organs

a) Duct system:

1. Epididymis.
2. Vas deferens.
3. Ejaculatory duct.
4. Urethra.

b) Genital glands

1. Prostate.
2. Seminal vesicle.
3. Bulbourethral gland.

c) External geneitalia

1. Penis.
2. Scrotum.

I. The testis

- **Definition:** It is the male primary sex organ.
- **Function:** production of:
  a. Spermatozoa (exocrine function).
  b. Testosterone hormone (endocrine function).
- **Location:** in the scrotum suspended by spermatic cord.
- **Coverings:** each testis has the following coverings:

☒ **3 Capsules:**

a. Tunica vasculosa: it is the inner-most. It consists of a vascular plexus and loose connective tissue.
b. Tunica albuginea: fibrous layer, which thickened posteriorly to form mediastinum testis.
c. Tunica vaginalis: serous layer, which has visceral & parietal layers.

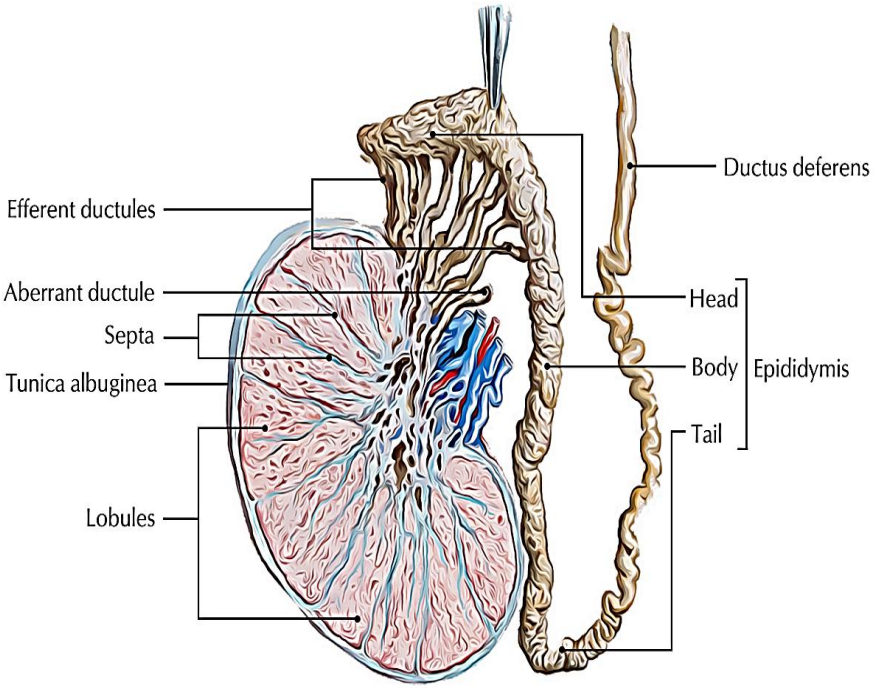
☒ **3 Coats:** derived from anterior abdominal wall:

a. Internal spermatic fascia: derived from the fascia transversalis.
b. Cremasteric muscle and fascia: derived from the internal oblique muscle.
c. External spermatic fascia: derived from the external spermatic aponeurosis.

☒ **Arrangement of the coverings of the testis (From outside inwards):**

1. Skin of the scrotum.
2. Dartos muscle.
3. Colle's fascia.
4. External spermatic fascia.
5. Cremasteric muscle & fascia.
6. Internal spermatic fascia.
7. Tunica vaginalis: 2 layers (parietal & visceral layers).
8. Tunica albuginea (fibrous capsule).
9. Tunica vasculosa.

- **Blood supply of the testis:**
  - ☒ **Arterial supply:** testicular artery: it is a branch from abdominal aorta at the level of the 2nd lumbar vertebra.
  - ☒ **Venous drainage:** pampiniform plexus of veins which end in a testicular vein that terminates in:
    - The right side into the inferior vena cava.
    - The left side into the left renal vein.
- **The lymph drainage:** lumbar or paraaortic lymph nodes at the level of the first lumbar vertebra.



The spermatic cord

- **Definition:** The spermatic cord is a collection of structures that pass through the inguinal canal to and from the testis.
- **Coverings:** it is covered with 3 concentric layers of fascia derived from the layers of the anterior abdominal wall.
- **Structures of the spermatic cord:**
    1. Vas (ductus) deferens
    2. Testicular artery
    3. Testicular vein (pampiniform plexus)
    4. Testicular nerve (autonomic)
    5. Testicular lymph vessels
    6. Remains of processus vaginalis

II. Genital ducts

- **They act as passages and storage for the sperms.**
- **They include:**
  - A. Tubuli recti.
  - B. Rete testis.
  - C. Efferent ductules.
  - D. Duct of epididymis
  - E. Vas deferens
  - F. Ejaculatory ducts
  - G. Urethra

A. The Epididymis

- **Definition:** It is a highly coiled tube (6 meters)
- **Shape:** forms a comma-shaped structure in relation to the posterior part of testis.
- **It is formed of:**
  - **A.** Head: the upper part that forms a cap around the upper pole of the testis.
  - **B.** Body: the middle part behind the testis.
  - **C.** Tail: the lower part which is continuous with the vas deferens.

B. The Vas deferens

- **Definition:** It is a cord like structure (45 cm) with thick muscular wall.
- **Shape:**
  - ☒ **It begins in** the scrotum as a continuation of the tail of the epididymis behind the testis.
  - ☒ It ascends in the spermatic cord to enter the inguinal canal
  - ☒ At the deep inguinal ring, it hooks around the lateral side of the inferior epigastric artery to enter the pelvis.
  - ☒ Then, it **passes on the side wall of pelvis crossing the following from above down**:
    A. External iliac vessels.
    B. Umbilical artery.
    C. Obturator nerve & vessels.
  - ☒ Then, it passes medially crossing over the ureter and descends behind the base of urinary bladder medial to seminal vesicle where it forms the ampulla of vas.
  - ☒ **It ends by joining the duct of seminal vesicle to form ejaculatory duct.**

C. The ejaculatory duct

- Formed by union of the ampulla of the vas deferens with the duct of the seminal vesicle.
- It opens in the prostatic urethra.

D. The urethra

- It is a common passageway for urine and semen

III. The accessory glands

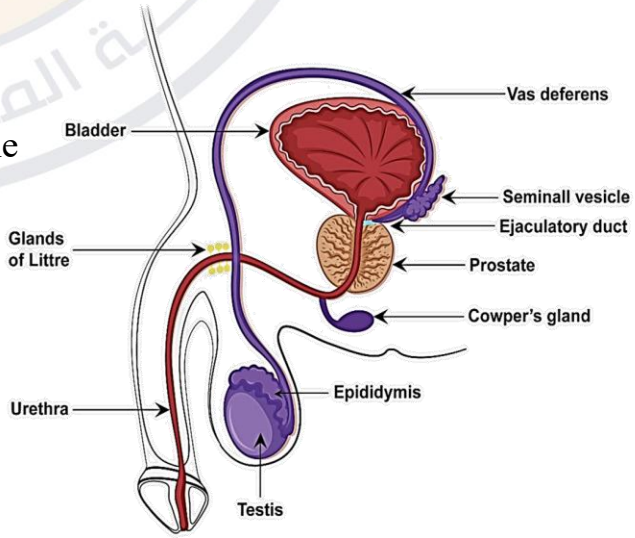
- **They include:**
  - **A.** Seminal vesicle
  - **B.** Prostate
  - **C.** Bulbourethral (Cowper's) glands

A. The seminal vesicles

- 2 sacculated glands (5 cm long).
- Lying behind the urinary bladder, lateral to the ampulla of vas & anterior to the rectum.
- Its duct joins the vas deferens to form ejaculatory duct.

B. The prostate gland

- **Size**: Single gland (2x3x4 cm)
- **Site**: lies below the neck of urinary bladder behind the lower border of symphysis pubis surrounding the upper part of the urethra (prostatic urethra).
- **Shape: <u>inverted pyramid</u>** with:
  - ☒ **Apex**: directed downwards.
  - ☒ **Base**: directed upwards to surround the neck of the urinary bladder. It **is pierced by the urethra.**
  - ☒ **Posterior surface:** related to ampulla of the rectum. It is **pierced by 2 ejaculatory ducts.**
  - ☒ **Anterior surface:** lies behind the lower border of the symphysis pubis.



☒ The urethra & 2 ejaculatory ducts traverse the prostate**: dividing it into 5 lobes:**

- **Median lobe:**
  - It lies between the urethra and the 2 ejaculatory ducts.
  - It projects inside the urinary bladder forming “uvula vesicae” just behind the internal urethral meatus.
  - It contains much glandular tissue (**common site of enlargement and adenomas**).
- **Anterior lobe.**
- **Posterior lobe.**
- **Right lobe.**
- **Left lobe.**

C. The bulbourethral (Cowper’s) glands:

- They are small gland that lie on either side of membranous urethra.
- They open into penile urethra.

IV. Male external genitalia

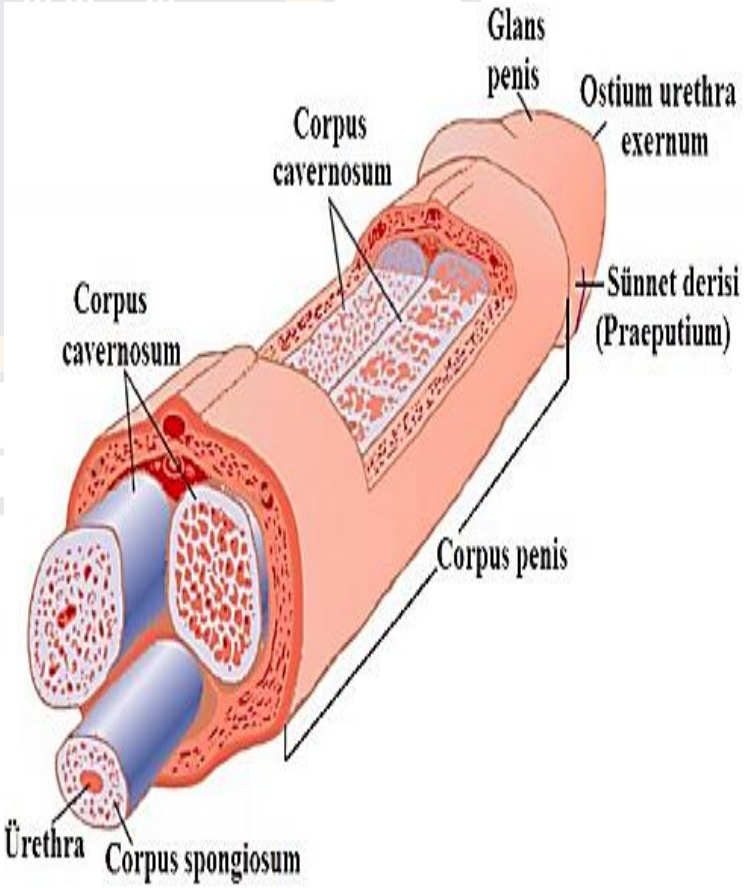
A. The penis

- **Definition:** Is the copulatory organ in man that passes urine & semen. It is a highly vascular cylindrical organ
- **Structure:** It consists of:
  1. Root: that attach penis to perineum.
  2. A body (shaft).
  3. Glans penis: enlarged end of the body.
- **The prepuce (foreskin):** partially covers glans and surrounds external urethral meatus (may be removed in circumcision)
- **The internal structure of the penis:**

  It consists of 3 masses of erectile tissue:

  A. Two corpora cavernosa.

  B. One corpus spongiosum: is traversed by the urethra & its posterior end expand to form the bulb of the penis.



B. The scrotum

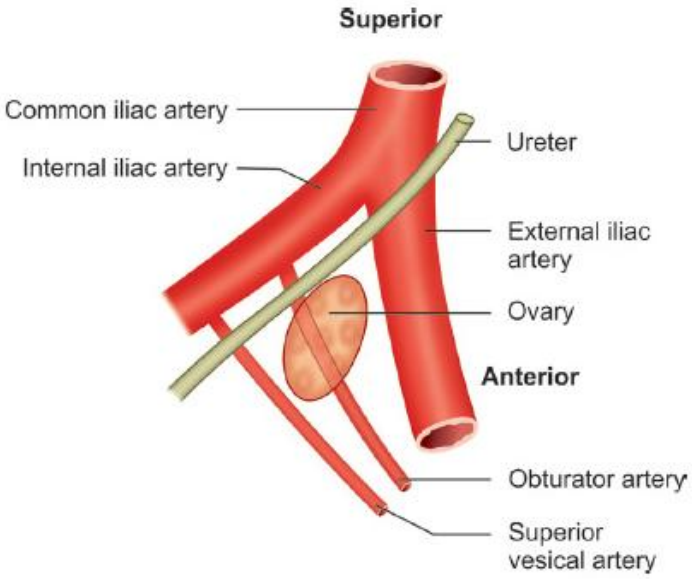
- **Definition:** It is a sac of dark & wrinkled skin.
- **Shape:** it is divided by a septum into right & left compartments, each of which enclose:
  1. A testis.
  2. The epididymis.
  3. The lower end of the spermatic cord.
- **The wall of the scrotum has the following layers:**
  - ☒ Skin; dartos muscle; Colles' fascia; external spermatic fascia; cremasteric muscle &fascia; internal spermatic fascia& tunica vaginalis.
  - ☒ The dartos muscle is innervated by sympathetic nerve &contraction of dartos muscle wrinkles the scrotum & reducing heat loss.
- **Lymph drainage:**
  - ☒ Structures of the scrotal wall structures is into the **superficial inguinal** lymph nodes.

Female reproductive tract

- **The female reproductive system is formed of:**
  - ☒ **Primary sex organ:** ovaries.
  - ☒ **Genital ducts:** uterine tubes, uterus & vagina.
  - ☒ **Accessory glands**: Greater vestibular (Bartholin's).
  - ☒ **External genitalia:** The vulva.

I. The ovary

- **Site:** The position of the ovary is variable but commonly lie against the lateral wall of the true pelvis in a depression called the ovarian fossa.
- **The ovarian fossa is bounded by:**
  - ☒ External iliac vessels above.
  - ☒ Internal iliac vessels behind.
- **Size:** 1 x 2 x 3 cm.
- **Shape: almond-shaped** having two ends, two surfaces and two borders



  - ☒ **2 ends:**
    - **Uterine end:** attached to the **uterus** by ovarian ligament
    - **Tubal end:** related to the fimbria of the uterine tube
  - ☒ **2 surfaces:**
    - **Lateral:** related to the lateral pelvic wall & obturator nerve and vessels.
    - **Medial:** related to fimbriated end of Fallopian tube.

☒ **2 borders:**

- **Anterior border:** gives attachment to the mesovarium.
- **Posterior border**: directed backwards.

Relations: completely covered by peritoneum and attached to the broad ligament by mesovarium. It has:

A. Peritoneal ligaments:

1. **Suspensory** ligament; between the tubal end of the ovary to side wall of the pelvis.
2. **Mesovarium**: between the anterior border of the ovary to the upper layer of the broad ligament.

B. Non-peritoneal ligaments

Ovarian ligament: from the uterine end of the ovary to the lateral angle of the uterus

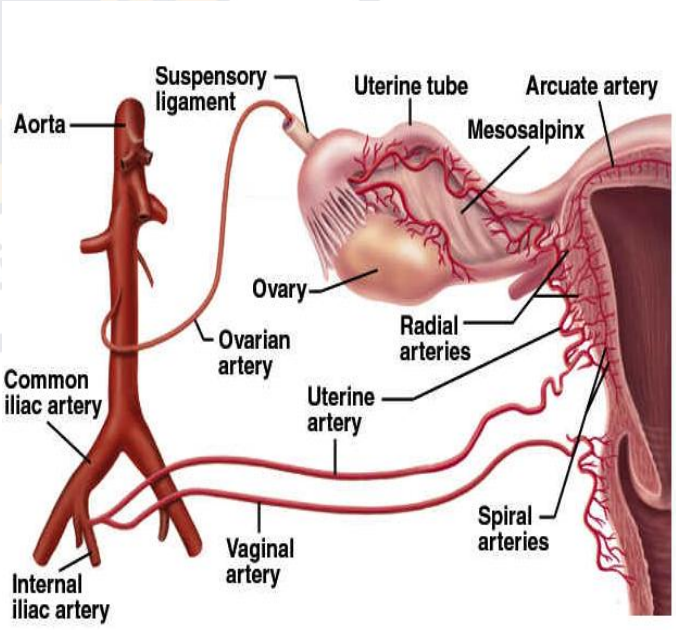
Blood supply of the ovary:

☒ **Arterial supply:**

- Ovarian artery from abdominal aorta
- Uterine artery from internal iliac artery.

☒ **Venous drainage:** venous plexus end in ovarian vein. It terminates:

- The right one ends in the inferior vena cava.
- The left ends in left renal vein.



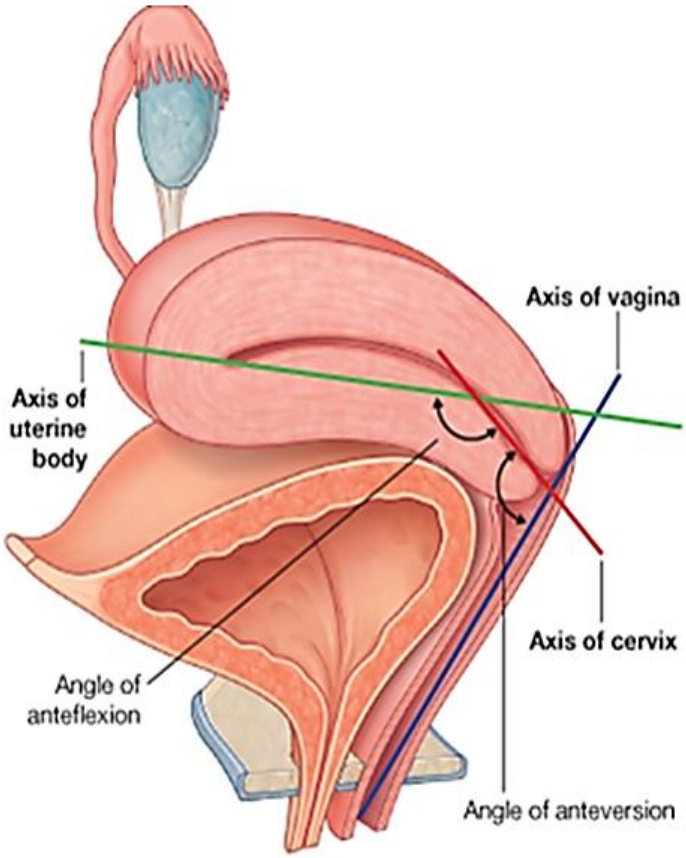
Lymph drainage: Lymphatic vessels end in the **paraaortic lymph nodes.**

Function: production of ova and female sex hormones.

II. The uterine tubes

- **Site**: in the medial 4/5 of the upper free border of the broad ligament. It extends from the superior angle of the uterus to the ovary on the side wall of the pelvis.
- **Length:** 10 cm.
- **Course**
  - ☒ It runs laterally & backwards from the uterus to the side wall of the pelvis.
  - ☒ Then, it curves backwards piercing the upper layer of the broad ligament to end on the medial surface of the ovary.
- **Parts: (from medial to lateral)**
  - ☒ **Intramural (uterine) part:**
    - It is the shortest (1 cm) and narrowest part.
    - It passes through the wall of the supereoateral angle of the uterus to open into the uterine cavity.
  - ☒ **Isthmus:** It is 2 cm in length, rounded, narrow and thick-walled.
  - ☒ **Ampulla:**
    - It is the longest (5 cm), thin-walled, tortuous and widest part.
    - It is the site of fertilization.
  - ☒ **Infundibulum (fimbriated end):**
    - It is 2cm in length and funnel-shaped.
    - It opens into the peritoneal cavity near the ovary.
    - Its margins carry fimbria which spread over the medial surface of the ovary.
    - The largest fimbria is called the ovarian fimbria which is attached to the upper end of the ovary.

- **Blood supply of the uterine tube:**
  - ☒ **Arterial supply**
    - **Medial 2/3:** by the uterine artery.
    - **lateral 1/3 :** by the ovarian artery.
  - ☒ **Venous drainage:** By veins accompanying the arteries into the uterine and ovarian veins.
- **Lymph drainage:**
  - Most of the tubal lymphatics pass to the **paraaortic lymph nodes**.
  - Lymphatics of the isthmus pass to the **superficial inguinal lymph nodes**.
- **Function**
  - It receives the ova from the ovary.
  - It provides site for fertilization of the ova.
  - It provides nourishment to the fertilized ova.



III. The uterus

- **Site:** in the true pelvis in between urinary bladder and rectum.
- **Size:** 1x2x3 inches.
- **Shape:** Pear shaped.
- **Parts:**
  - ☒ **Fundus:** is the upper rounded end of the uterus
  - ☒ **Body:**
    - It is triangular in outline
    - It has two surfaces: anterior (vesical) and posterior (intestinal).
  - ☒ **Cervix:**
    - It is cylindrical tube 1x1 inch. It is subdivided into two parts: vaginal and supravaginal portions.
    - The cervical canal is fusiform lies between the internal and external os.
- **Position: the normal uterus lies in:**
  - ☒ **Anteversion**: the **right** angle between long axis of the **vagina** and long axis of the uterus.
  - ☒ **Anteflexion**: the **obtuse** angle between the long axis of the body of the uterus and long axis of the **cervix.**
  - ☒ Abnormal uterine position may be **retroverted and/or retroflexed.**
- **Peritoneal relations of the uterus:**
  - ☒ **Fundus:** completely covered with peritoneum.
  - ☒ **Body:** covered anteriorly and posteriorly with peritoneum. The two layers meet at the lateral border as the broad ligament.
  - ☒ **Cervix:** the supravaginal portion:
    - **Posteriorly,** is covered with the peritoneum.
    - **Anteriorly:** it is not covered with the peritoneum.

Ligaments of the uterus

I. Peritoneal ligaments:

1. Broad ligament:

- ☒ It is a double layer of peritoneum (upper & lower), extends between the lateral margin of the uterus to the side wall of the pelvis.
- ☒ The upper layer is related to the coils of small intestine and invaginated by the ovary and forms the mesovarium.
- ☒ It has four borders. Its anterior free border encloses the uterine tube.
- ☒ **Parts of the broad ligament:**
  1. **Mesosalpinx:** the part between Fallopian tube & mesovarium & and round ligament of ovary.
  2. **Suspensory ligament of ovary:** the part lateral to the ovary.
  3. **Mesometrium:** the remaining medial lower part on the side of the uterus.
- ☒ **Contents of the broad Ligament:**
  1. **2 Uterine tubes**: in the medial 4/5 of the upper free border.
  2. **2 Ureters** at root of the ligament.
  3. **2 Ligaments:** round ligament of ovary & round ligament of the uterus.
  4. **2 Arteries:** uterine (along the medial border) and ovarian (in the suspensory ligament).
  5. **2 Embryological remnants:** (Epoophoron & Paroophoron).
  6. **Sympathetic nerve plexus**.
  7. **Connective tissue (parametrium)** & lymphatics & lymph nodes.

2. Anterior ligament: (uterovesical):

extends from the front of the cervix to the urinary bladder.

3. **Posterior ligament (rectovaginal):** extends from the posterior surface of the cervix and posterior fornix to the rectum.

II. Non peritoneal (fibromuscular) ligaments:

1. **Round ligament of the uterus:** extends from the superolateral angel of the body of the uterus to the labium majus.
2. **Ovarian ligament:** from the uterine end of the ovary to the upper lateral angle of the uterus.
3. **Mackenrodt's ligaments (transverse ligament of the cervix):** extends from the sides of the cervix and lateral fornices to the side wall of the pelvis. **It is the main support of the uterus.**
4. **Uterosacral ligaments:** extend from the back of the cervix to the front of the sacrum.

IV. The vagina

- **Site:** it is fibro-muscular tube between the cervix and vestibule. It lies between urinary bladder and urethra (anteriorly) and rectum and perineal body (posteriorly).
- **Direction:** it is directed up & backwards forming a right angle with the uterus (normally).
- **Parts:** It has anterior and posterior walls and two lateral borders.
- **The lateral borders** related to the ureter, uterine and vaginal arteries.
- **Fornices of the vagina:**
  - **Definition:** they are the vaginal cavity around vaginal portion of the cervix.
  - **Number: 4: anterior, posterior and two laterals.**
  - **The posterior fornix is the deepest one.**
- **Blood supply of the vagina:**
  - **Arterial supply: 4 arteries a**nastomose in front & behind the vagina to form anterior & posterior **azygos arteries. They are:**
    1. Uterine artery.
    2. Vaginal artery.
    3. Middle rectal artery.
    4. Internal pudendal artery.
  - **Venous drainage:** the vaginal veins form plexuses that drains into **internal iliac vein.**
- **Lymphatic drainage:**
  - Upper 1/3 ➔ external iliac lymph nodes.
  - Middle 1/3 ➔ internal iliac lymph nodes.
  - Lower 1/3 ➔ superficial inguinal lymph nodes.

V. Female external genitalia

- **The vulva** is the global term that describes all of the structures that make the female external genitalia.
- The components of the vulva are **the mons pubis, labia majora, labia minora, clitoris, vestibular bulbs, vulva vestibule, Bartholin's glands, Skene's glands, urethra, and vaginal opening.**

Development of genital system

- **The study of the development of the genital system includes:**
  A. The development of the gonads (testis and ovary).
  B. The development of the duct system.
  C. The development of the external genitalia.

I. Development of the gonads

- **Time:** 4th week**.**
- **Origin:** the gonads (the testis and ovaries) develop from three sources:
  1. The mesothelium lining the posterior abdominal wall.
  2. The underlying mesoderm.
  3. The primordial germ cells.
- **The stages of the development of the gonads:**

I. The indifferent stage: there is no difference in both sexes.

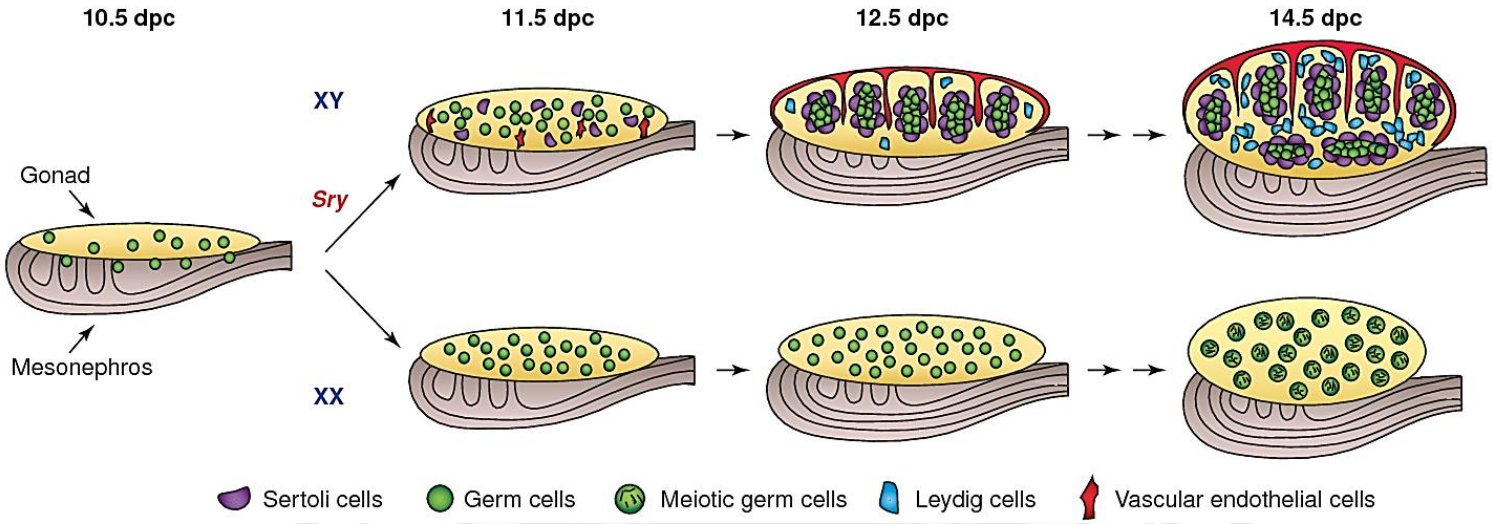
- ☒ A longitudinal ridge called the **genital ridge** appears on the posterior abdominal wall, on each side of the midline between the mesonephros and the dorsal mesentery.
- ☒ In the 6th week, the primitive sex cells (**endodermal cells of the yolk sac** near the origin of the allantois) migrate along the dorsal mesentery of the hindgut and invade the genital ridge.
- ☒ These primitive germ cells have an **inductive influence** on the development of the gonad into ovary or testis.
- ☒ The epithelial cells (under the inductive effect of the germ cells), invade the underlying mesoderm. They form a number of **irregular cords** (the **primitive sex**

cords) which gradually surround the invading primitive germ cells. These sex cords are connected to the surface epithelium.

☒ The indifferent gonad consists of an **outer cortex and an inner medulla.**

- **In female:** the cortex differentiates into an ovary and the medulla regresses.
- **In male:** the medulla differentiates into a testis and the cortex regresses.

II. The different stage:



A. Development of the male gonad (testis):

☒ The primitive sex cords continue to proliferate and form a series of anastomosing cords (the testis cords).

☒ By the end of the 7th week, the testis cords lose contact with the surface epithelium, and are separated from it by a dense fibrous capsule (tunica albuginea).

☒ During the 4th month, the testis cords elongate and become **horseshoe**-shape and then differentiates into three types of tubules:

- **The seminiferous tubules**: Its wall is lined by 2 types of cells:
  1. Sertoli celts: supporting cells derived from the epithelium of the testis.
  2. Spermatogonia: derived from the primitive germ cells.

- **The tubuli recti**: occupy the part close to the mediastinum testis.
- **The rete testis**; occupy the mediastinum testis.

☒ The interstitial cells of leydig: develop from the mesoderm between the seminiferous tubules.

B. Development of the female gonad (ovary):

☒ The primary sex cords **degenerate.**

☒ Secondary sex cords are formed and extend from the epithelium into the underlying mesoderm.

☒ The secondary sex cords increase in size and the primitive germ cells are incorporated into them, forming primary follicles.

☒ Active mitosis of oogonia occurs during fetal life producing thousands of primary follicles.

Descent of the testis

- **Definition:** The process of migration of the testis from its original position (high lumbar region) to reach the genital swelling (scrotum).
- **Factors help in descent of the testis:**
  - **A. Main factors:**
    1. **Gubernaculum ligaments**: is a fibromuscular band connects the testis to the scrotum.
    2. **Processus vaginalis:** is a diverticulum from the peritoneum in front of gubernaculum.
    3. **Male sex hormone (testosterone) and gonadotrophin hormone**: testosterone stimulate the muscles of gubernaculum to contract. It reaches a peak during the 2nd month. This explains why testis does not descent before 2nd month.
  - **B. Subsidiary factors:**
    1. **Increase intra-abdominal pressure due to:**
       A. Increase size of liver and viscera.
       B. Reduction of the physiological umbilical hernia.
    2. **Enlargement of the testis and atrophy of mesonephric kidney**: allow caudal descent.
    3. **Atrophy of the paramesonephric duct** enables the testis to move trans-abdominally to the deep inguinal ring.
- **Process of the descent of the testis:**
  - **A. Internal descent:**
    - ☒ The descent of the testis from its high position to the deep inguinal ring.
    - ☒ The gubmiaculum contract under the effect of the testosterone and pull the testis downward to reach the iliac fossa then the deep inguinal ring.

B. External descent:

- ☒ The descent of the testis from the deep inguinal ring to the scrotum.
- ☒ The testis traverses the inguinal canal at the **7th month**, reaches the superficial inguinal ring at the **8th month** and reaches the scrotum at the **9th month**.

Result of descent of testis:

A. As a result of the passage of the testis through the anterior abdominal wall it takes 3 covering:

- ☒ The external spermatic fascia: from the external oblique muscle.
- ☒ Cremasteric muscle \and fascia: from the internal oblique muscle.
- ☒ The internal spermatic fascia; from die fascia transversals.

B. As a result of the descent of testis, it pulls the blood supply and lymphatic drainage. This explains:

- ☒ The origin of testicular artery from abdominal aorta.
- ☒ Lymphatic drainage of testis into the para-aortic lymph node.

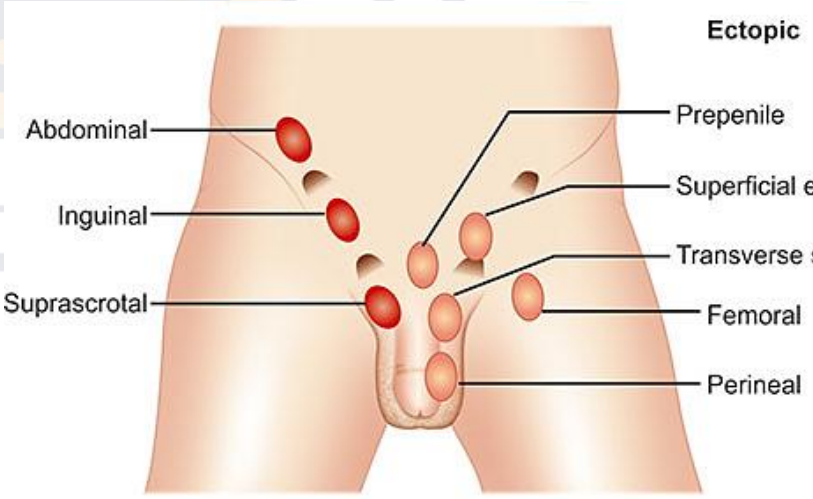
Fate of gubernaculum and processus vaginalis:

- ☒ **Gubernaculum:** degenerates and is replaced by fibrous tissue at the bottom of the scrotum.
- ☒ **Processus Vaginalis:** loose its connection with the peritoneal cavity and forms the visceral layer and parietal layers of tunica vaginalis.

N.B. the gubernaculum in female forms the ligament of the ovary and the round ligament of the uterus.

Anomalies of the testis

1. **Absence of the testis:**
   - ☒ **Cause:** Failure of formation or migration of the primordial germ cells.
   - ☒ **Features:** absent one or both testes.
2. **Anomalies of descent:**
   - **A. Undescended testis (cryptorchism):**
     - ☒ **Cause**: Improper development of gubernaculum.
     - ☒ **Features**: The testis fails to reach the scrotum. The testis may remain at the following sites:
       - On the posterior abdominal wall.
       - In the iliac fossa.
       - Within the inguinal canal.
       - At the superficial inguinal ring.
   - **B. Maldescended testis (ectopic testis):**
     - ☒ **Cause:** Abnormal attachment of the gubernaculum.
     - ☒ **Features:** The testis present in abnormal locations:
       - In the medial side of thigh.
       - On the dorsal surface of the penis.
       - On the opposite side of the scrotum.



3. **Persistent process vaginalis:**
   - ☒ **Cause:** the tunica vaginalis remains connected to the peritoneal cavity.
   - ☒ **Features:** Congenital inguinal hernia and/or congenital hydrocele.

II. Development of the genital ducts

- **Both male and female embryos have two pairs of genital ducts:**
  1. **The mesonephric (Wolffian) ducts:** forms duct system of the male reproductive system.
  2. **The paramesonephric (mullerian) ducts:** forms duct system of the female reproductive system.

The male genital duct (fate of mesonephric tubules and duct)

I. Mesonephric tubules:

1. Superior aberrant tubules (lose its connection with the mesonephric duct).
2. Vasa efferentia (middle mesonephric tubules connected to rete testis).
3. Inferior aberrant tubules (lose its connection with the rete testis but remains connected to the mesonephric duct).
4. Paraepididymis (the most caudal. they lose its connection with both the rete testis and mesonephric duct).

II. Mesonephric duct:

1. Appendix epididymis: most cephalic part of the tube.
2. Head of the epididymis: The cranial part of mesonephric duct connected with the vasa efferentia.
3. Body and tail of the epididymis: The caudal part to the head of the epididymis become convoluted.
4. The ductus deferens: caudal to the epididymis.
5. Ureteric buds: formed from the caudal part of the mesonephric duct.
6. The seminal vesicle: formed as a diverticulum from the caudal part of the mesonephric duct.

7. The ejaculatory duct: formed from the most caudal part between the seminal vesicle and urethra.
8. The part of mesonephric duct caudal to the ureteric bud becomes:
   a) The trigone of the urinary bladder.
   b) The posterior wall of prostatic urethra.
   c) The capsule of the prostate.

The female genital duct (paramesonephric ducts)

- The paramesonephric ducts appear as longitudinal invagination (groove) on the lateral aspects of the mesonephric ridge.
- The edges of these invagination approach each other and fuse to form the paramesonephric ducts.
- The cranial end of these ducts open into the peritoneal cavity and develops fimbriae.
- The paramesonephric ducts pass caudally lateral to the mesonephric ducts.
- At the pelvic region of the embryo, the paramesonephric ducts cross ventral to the mesonephric ducts.
- The paramesonephric ducts approach each other in the median plane and fuse to form the uterovaginal canal which projects into the dorsal wall of the urogenital sinus and produce an elevation called the Mullerian tubercle.
- **The fate of paramesonephric ducts in females:**
  1. The cranial vertical part: forms the uterine tube.
  2. The intermediate horizontal part: forms the fundus and most of the body of the uterus.
  3. The caudal vertical part fuse together and form the uterovaginal canal which gives rise to the cervix and the vagina.

Development of the uterine tubes:

1. Epithelium: from the cranial vertical parts of the paramesonephric duct. It's cranial end open into the peritoneal cavity and surrounded by fimbriae.
2. Stroma and smooth muscles: from the surrounding mesoderm.

Development of the uterus:

1. Epithelium: from the intermediate horizontal part of the paramesonephric duct.
2. Stroma and smooth muscles: from the surrounding mesoderm.

Development of the vagina

1. The upper one-third of the vagina: from the caudal part of the paramesonephric ducts.
2. The lower two-thirds of the vagina: from the pelvic part of the urogenital sinus. It forms solid plate (the vaginal plate).
3. The central cells of this plate break down, forming the lumen of the vagina.
4. The lumen of the vagina remains separated from that of the urogenital sinus by a thin tissue plate, known as the **hymen.**

NB Fate of the paramesonephric duct in males: The paramesonephric duct degenerates and disappears except at its two ends: The cranial end persists as **the appendix, of the testis**. The caudal end of the two tubes persist as the **prostatic utricle.**

NB Fate of the mesonephric tubules and duct in female: The mesonephric tubules degenerate and forms the **Epoophoron and Paroophoron** which are contained in the broad ligament of the uterus. The mesonephric tubules forms the ureteric bud (which joins the metanephric kidney) and part of the urinary bladder and urethra. The remaining part degenerates and join the lateral walls of the cervix and vagina, forming the **Gartner's duct.**

Anomalies of the uterus and the vagina

1. Uterus didelphys:

- ☒ **Cause:** Complete failure of fusion of the two paramesonephric ducts.
- ☒ **Feature:** double uterus, double cervix and double vagina.

2. Uterus bicornis bicollis:

- ☒ **Causes:** Failure of the intermediate parts of the two paramesonephric ducts to fuse.
- ☒ **Features:** Double uterus, double cervix and single vagina.

3. Bicornuate uterus:

- ☒ **Cause:** incomplete canalization of the superior part of the paramesonephric ducts.
- ☒ **Features:** Duplication involves only the superior part of the body of the uterus.

4. Bipartite uterus:

- ☒ **Cause:** Incomplete canalization of the intermediate part of the of the paramesonephric ducts.
- ☒ **Features: There is a septum dividing the uterine cavity into two cavities.**

5. Arcuate uterus:

- ☒ **Cause**: Incomplete fusion of the intermediate part of the paramesonephric ducts.
- ☒ **Features: The fundus of the uterus is depressed in its middle part.**

6. Bicornuate uterus with a rudimentary horn:

- ☒ **Cause:** Failure of one paramesonephric duct to complete its development and fuse with the other duct.
- ☒ **Feature**: One vagina and cervix and the uterus have two horns; one develop and the other rudimentary.

7. Unicornuate uterus:

- ☒ **Cause:** One paramesonephric duct fails to develop.
- ☒ **Feature**: One uterine tube, one horn of the uterus.

8. Absence of the vagina and uterus:

- ☒ **Cause**: Failure of the development of both paramesonephric ducts.
- ☒ **Features**: Absence of vagina, uterus and uterine tube.

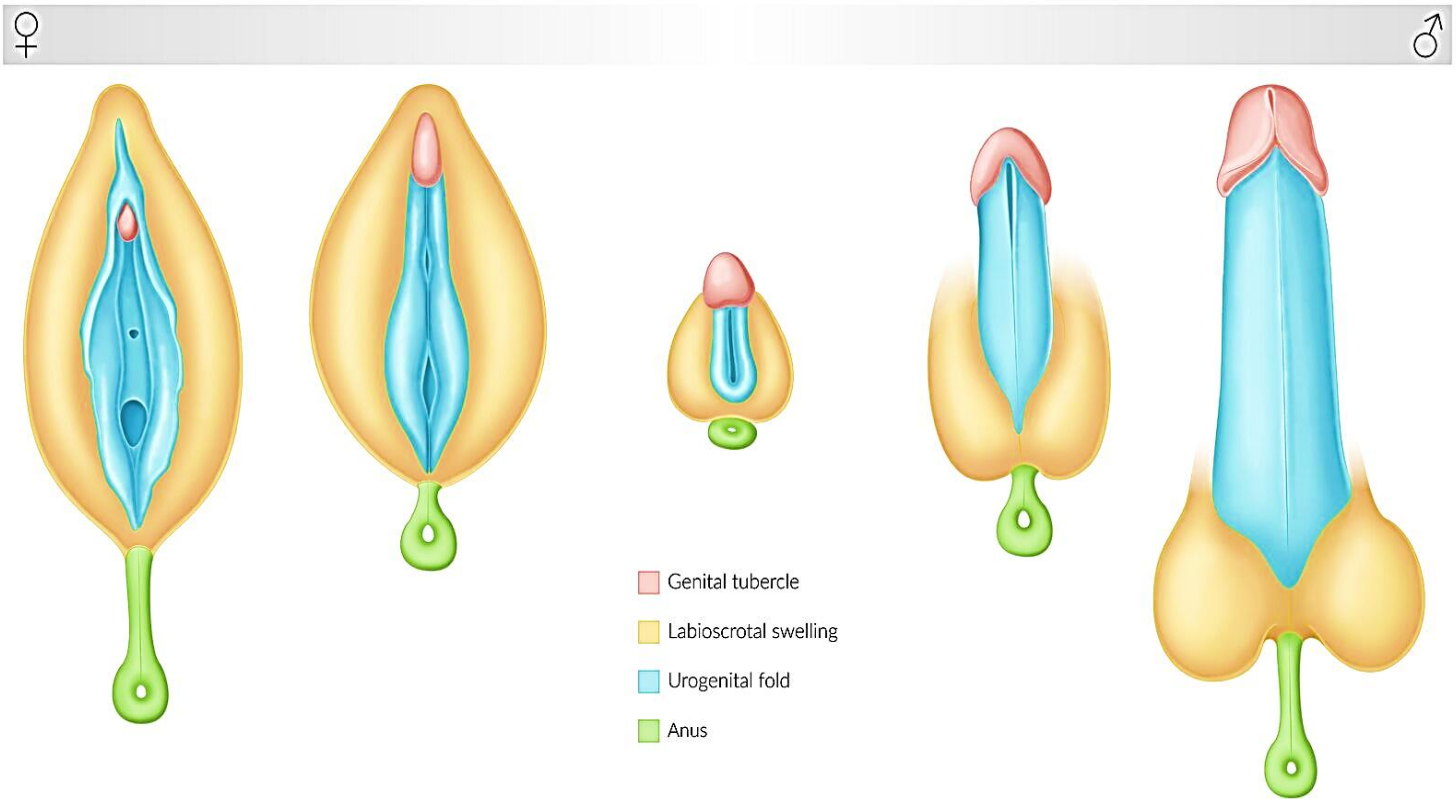
9. Vaginal atresia:

- ☒ **Cause:** Failure of canalization of the vagina.
- ☒ **Feature**: A transverse vaginal septum obliterate the vaginal lumen.

10. Imperforate hymen:

- ☒ **Cause:** Failure of degeneration of the central part of the hymen.
- ☒ **Features**: in adult, this condition represented by delay menstrual cycles.

11. Infantile or rudimentary uterus: underdevelopment of the fused intermediate part of the paramesonephric ducts. The adult uterus is small than normal.



III. Development of the external genital organs

A. The indifferent stage:

Up to the 7th week of development, the external genitalia are similar in both sexes. They consist of:

1. Genital tubercle: mesodermal in origin.
2. Genital folds: are ectodermal in origin.
3. Labioscrotal swellings: mesodermal in origin.

B. The different stage

☒ Female external genital organs:

- Induced by the ovarian hormones.
- **Steps:**
  1. Growth of genital tubercle and it becomes the clitoris.
  2. The urogenital folds do not fuse and form the labia minora.
  3. The labioscrotal swellings don't fuse and form the labia majora.

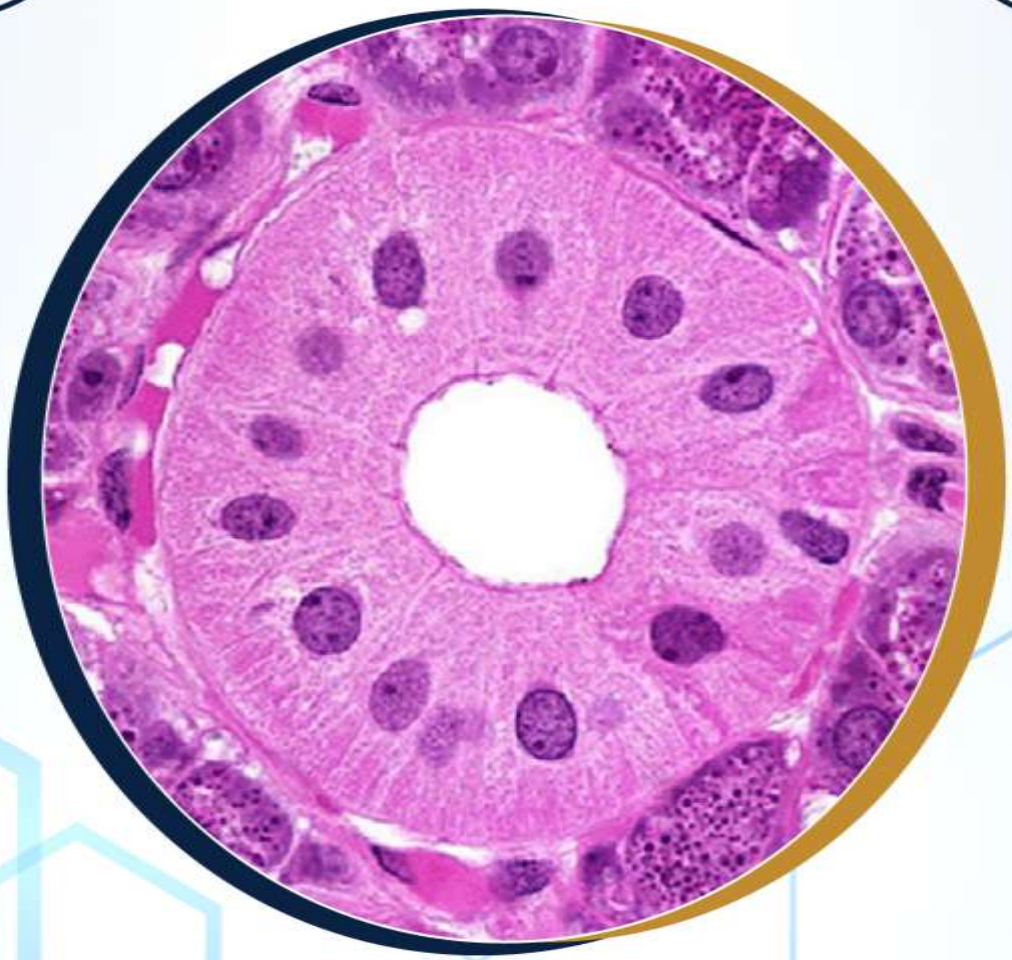
☒ Male external genital organs:

- Induced by testosterone produced by the fetal testes.
- **Steps**:
  1. Growth of genital tubercle and it becomes the penis.
  2. The urogenital folds fuse and form the spongy urethra.
  3. The labioscrotal swellings fuse and form the scrotum.

Anomalies of the external genitalia

1. **True hermaphroditism:**
   - ☒ **Cause:** unknown
   - ☒ **Features:** The phenotype may be male or female, but the external genitalia are ambiguous
2. **Female pseudohermaphroditism:**
   - ☒ **Cause**: Exposure of the female fetus to androgens.
   - ☒ **Features**: The phenotype is female with masculinization of the external genitalia (**c**litoral hypertrophy & partial fusion of the labia majora).
3. **Male pseudohermaphroditism.:**
   - ☒ **Cause**: Exposure of the male fetus to estrogen
   - ☒ **Features** The phenotype is male with virilization of the external geneitalia.
4. **Androgen insensitivity syndrome:**
   - ☒ **Cause**: Resistance of the tissues to the action of testosterone.
   - ☒ **Features:**
     - The phenotype is male, but the external genitalia are female.
     - The vagina end blindly, the uterus and uterine tube are absent.
     - At puberty, there is normal development of breast, but menstruation does not occur.
5. **Agenesis of external genitalia:**
   - ☒ **Cause**: failure of genital tubercle to develop.
   - ☒ **Feature**: Absence of penis or clitoris. The urethra opens into the perineum near the anus.
6. **Micropenis:** abnormal small penis.

FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY



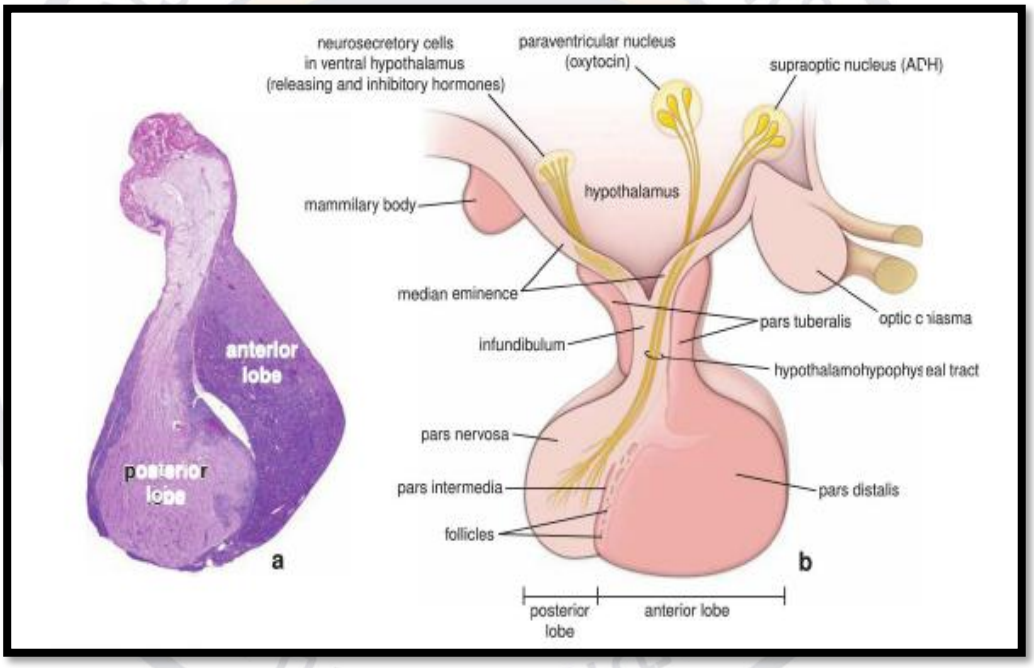
HISTOLOGY

THE ENDOCRINE SYSTEM

- The endocrine glands are ductless glands secreting hormones.
- Endocrine glands are: the pituitary, the suprarenal, the thyroid, the parathyroid, the sex glands, the pineal body and the islets of Langerhans.

THE PITUITARY GLAND

- It is the master control gland of most endocrine glands.
- It is located in a bony depression (sella turcica) and attached to the base of the brain by the pituitary stalk.



The gland is made up of two lobes:

1. **Anterior lobe**

- It is highly vascular and stains brightly acidophilic.
- It consists of:

A. Pars distalis.

B. Pars tuberalis.

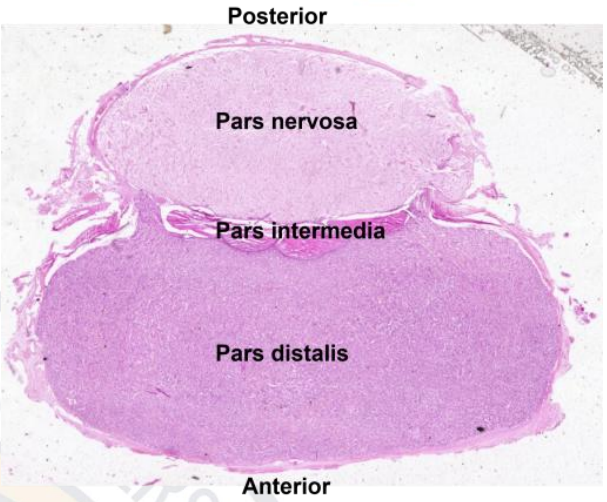
C. Pars intermedia.

D.

2. Posterior lobe

- It is whitish in colour and stains pale.
- It consists of:

- Infundibular process (pars nervosa).
- Infundibular stalk (pituitary stalk).



HISTOLOGICAL STRUCTURE:

A. Pars Distalis

- It consists of stroma and parenchyma

1. The stroma:

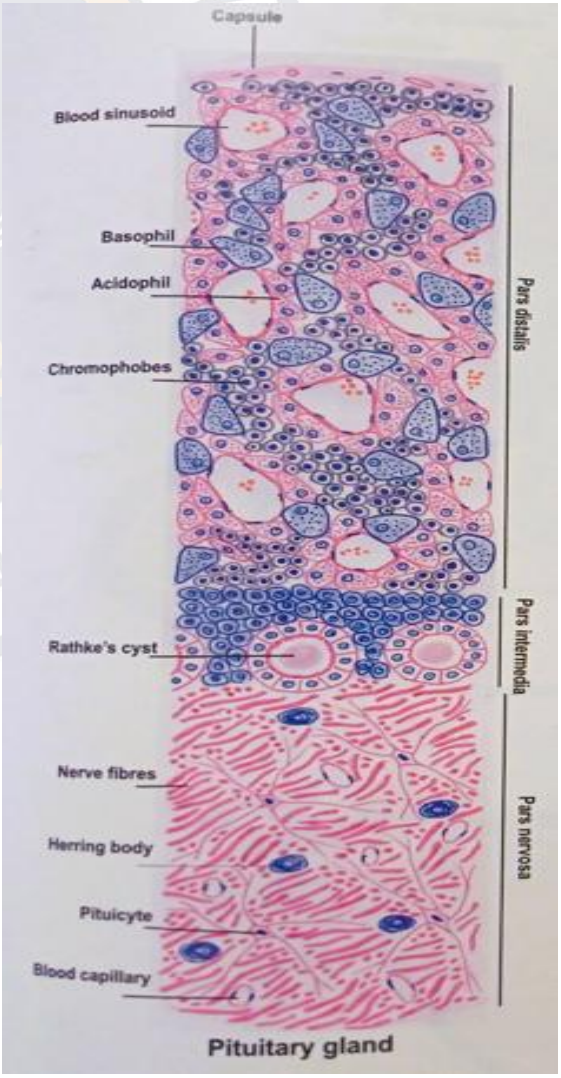
A- Dense fibrous capsule.

B- Trabeculae extending from the capsule.

C- Reticular fibres surround the cords of cells.

2. The parenchyma:

- Irregular anastomosing cords or clumps of cells. They are surrounded with extensive system of fenestrated sinusoidal capillaries.



Cells of pars distalis:

They are classified on the basis of their affinity or lack of affinity for dyes of routine staining into:

A. Chromophilic (48%) which are differentiated into:
1-Acidophilic cells (37%).
2-Basophilic cells (11%).

B. Chromophobic (52%) they are smaller in size and are lightly stained.

A. Chromophilic cells:

i) Acidophilic cells (acidophils or alpha cells)

- They are numerous, appear large in size and stain well with eosin.
- They are larger in size than chromophobes but smaller than basophils.
- Their granules are protein in nature.
- **With EM:** they reveal a well-developed Golgi, small mitochondria, rER and electron dense granules.

According to the size of their granules and the hormone which they secrete, they are classified into:

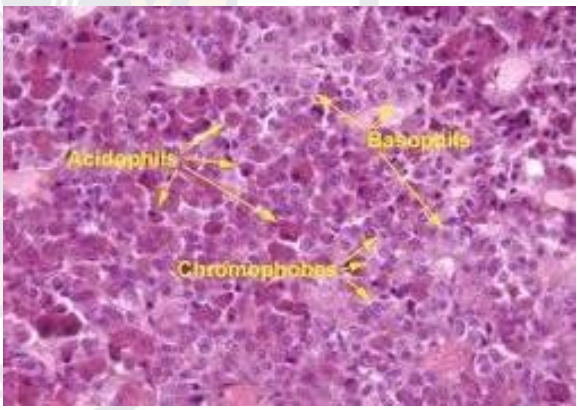
1. **Somatotrophs:**
   - They are rounded cells with rounded nuclei.
   - They are stained with orange G (may be called orangophils).
   - They occur in groups along the blood sinusoidal capillaries.
   - They secrete the **growth hormone (somatotropin)** which has a role in the growth of long bones.

   Tumours of somatotrophs:

   - Before puberty → gigantism.
   - After puberty → acromegaly.

   Impaired function of somatotrophs:

   → dwarfism.



2. **Mammotrophs (prolactin cells)= Lactotroph cells:**
   - They have fusiform shape.
   - Their granules are stained with azocarmine (carminophils).
   - They are distributed singly in the interior of the cell cords.
   - They secrete **prolactin**, which initiates and promotes milk secretion.

ii) Basophilic cells (basophils or β cells):

- They are larger than acidophils.
- They stain poorly with H & E.
- They stain well with PAS as their granules are glycoprotein in nature.

Somatotrophs	Mammotrophs (prolactin cells)= Lactotroph cells
• They are rounded cells with rounded nuclei.	• They have fusiform shape.
• They are stained with orange G (may be called orangophils).	• Their granules are stained with azocarmine (carminophils).
• They occur in groups along the blood sinusoidal capillaries.	• They are distributed singly in the interior of the cell cords.
• They secrete the **growth hormone (somatotropin)** which has a role in the growth of long bones.	• They secrete **prolactin**, which initiates and promotes milk secretion.

The basophilic cells are classified into three types:

1. **Thyrotrophs:**
   - They are polygonal in shape.
   - They secrete thyrotrophic hormone (thyroid stimulating hormone) TSH which controls the functions of thyroid gland.

Thyroidectomy → hypertrophy of thyrotrophs.

Thyroxine administration → atrophy of thyrotrophs.

2. **Corticotrophs:**
   - They are the commonest type of basophils.
   - They are oval or round in shape.
   - They synthesise a pro-hormone, with cleavage, It produces:
     a. ACTH which control the function of suprarenal cortex.
     b. Melanocyte stimulating hormone and endorphin.

Adrenalectomy → the corticotrophs increase in number and size and the cells contain more granules.

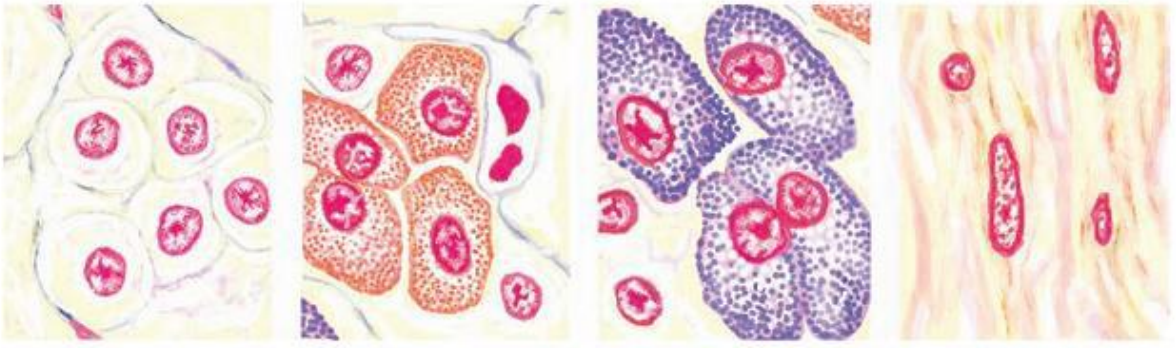
Prolonged administration of cortisol → the cells decrease in size.

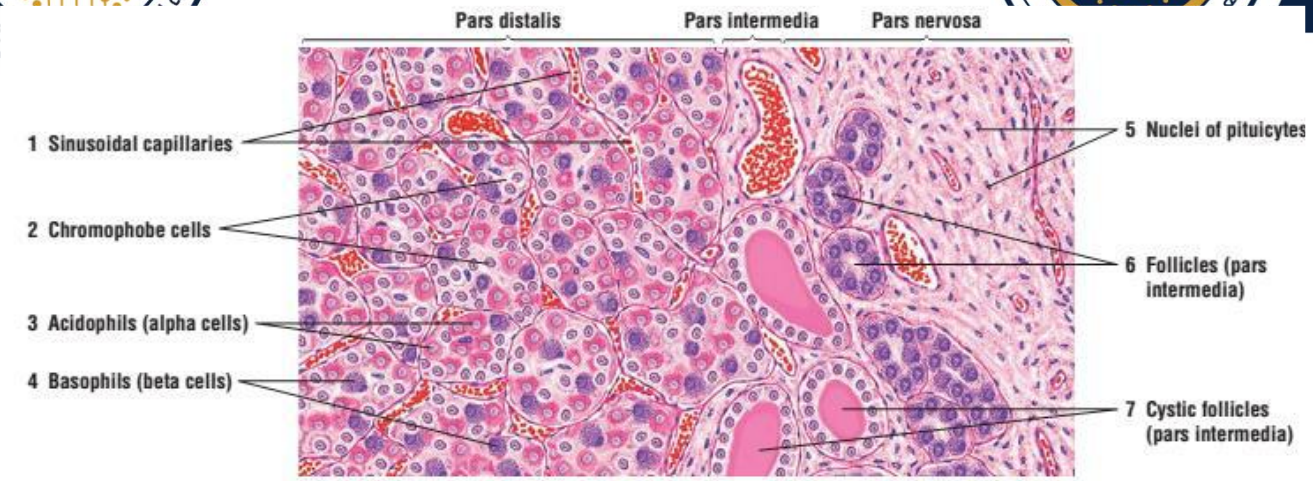
3. Gonadotrophs or (FSH-LH cells)

- They are rounded cells.
- They are of two types:
  a. Cells secrete **follicle stimulating hormone (FSH)** which stimulates follicle development in the ovary and spermatogenesis in male.
  b. Cells secrete **luteinizing hormone (LH)** or **Interstitial cell stimulating hormone (ICSH)**.

B- Chromophobic Cells:

- They lack affinity to stains.
- They present in groups.
- They are smaller in size than chromophils.
- They are devoid of specific granules.
- They are considered to be a reserve population of relatively undifferentiated cells capable of differentiation into either acidophils or basophils.





Pars Nervosa

It consists of:

1. **Pituicytes:**
   - They are irregularly branched cells which form a three-dimensional network around the axons.
   - They contain lipochrome pigments and lipid droplets.
   - They act as neuroglia cells.
2. **Nerve fibres:**
   - They are unmyelinated axons of neurosecretory neurons in the hypothalamus (the paraventricular and supra-optic nuclei).
   - The axon endings contain neurosecretory granules and are associated with fenestrated capillaries.
3. **Herring bodies:**
   - They are irregular masses of basophilic hyaline material formed of accumulation of neurosecretion in the terminal bulbs of the nerve fibres.
4. **Fenestrated capillaries.**
5. **Neuroglia cells.**
6. **Reticular fibres:** around the capillaries.

Function of Pars nervosa:

- It is the reservoir for the neurosecretion, which is formed by hypothalamic neurons in the supraoptic and paraventricular nuclei of the hypothalamus.
- The secretory granules descend along the axons of the pituitary stalk and accumulate in the terminal bulbs nearby the fenestrated capillaries as Herring bodies.
- The secretory granules are absorbed to the circulation.

The secretion is fractionated into:

1. **Oxytocin** which causes:
   - Contraction of the smooth muscles of the uterus and facilitates childbirth.
   - Contraction of the myoepithelial cells around the alveoli of the mammary gland leading to ejection of milk during nursing.
2. **Vasopressin or antidiuretic hormone which causes:**
   - Antidiuretic effect by acting on the collecting tubules of the kidney → increased reabsorption of water.
   - In large amount, it causes contraction of smooth muscles of blood vessels → ↑ blood pressure.
   - Destruction of the pituitary stalk or pars nervosa → diabetes insipidus.

THE THYROID GLAND

- It is the only endocrine gland whose secretory product is stored in great quantity and occurs extra-cellularly.

Structure:

The thyroid gland consists of stroma and parenchyma.

I- The stroma:

1- The gland is covered by two **capsules**

2- Fine fibrous **septa** extend from the capsule and divide the gland into incomplete lobules.

3- **Reticular fibres**.

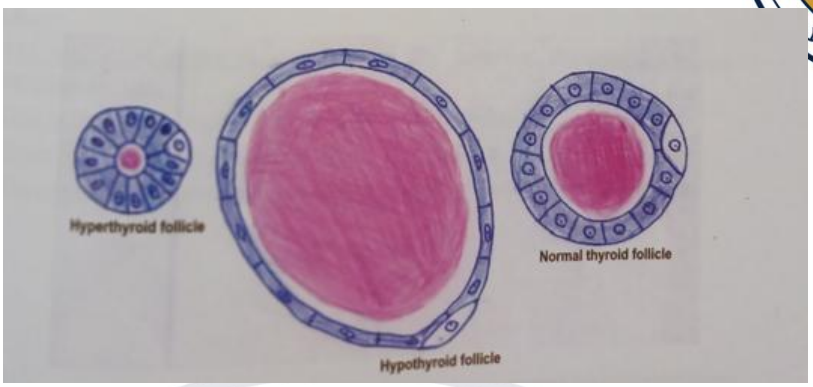
II- The parenchyma:

It consists of thyroid follicles and interfollicular cells.

1. **The thyroid follicles**:

- They are the structural and functional unit of the gland.
- They may be round or oval in shape.
- Normally, they are lined with low cuboidal epithelium.
- The follicles contain colloid (a gelatinous substance) in their lumen. The morphologic appearance of the follicles varies according to the region of the gland and its functional activity (In the same gland larger follicles full of colloid and have low cuboidal epithelium are found beside smaller follicles which are lined with columnar cells).

- The gland is considered **hypoactive** when the majority of the follicles are lined with squamous cells and **hyperactive** when the majority of the follicles are lined with columnar cells.

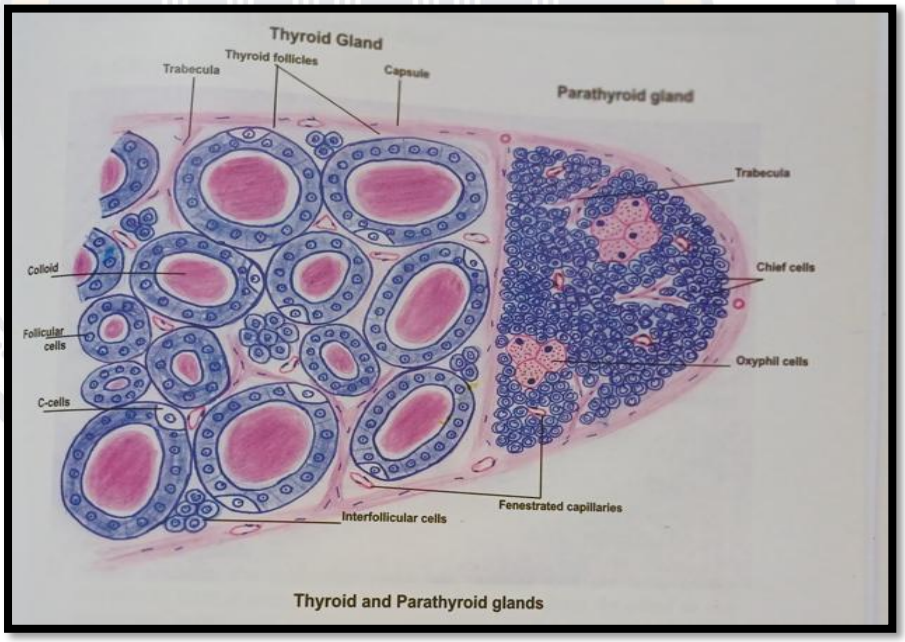


The colloid:

- Is a homogenous acidophilic material formed of thyroglobulin (a glycoprotein containing various iodinated amino acids; T4 & T3).
- It stains intensely with PAS and is eosinophilic with H & E.

- **The cells lining the follicles are of two types:**

a. Follicular cells. b. Parafollicular cells.



A-The follicular cells

- They constitute the majority of the cells lining the thyroid follicle (98%).
- With LM they are cubical secretory cells with basophilic cytoplasm and central rounded nucleus.
- **Function:** They synthesize and release the thyroid hormone.

B- The para-follicular cells (C cells or light cells or clear cells):

- They form the minority of the cells lining the follicles (2% of the cells).
- They are larger and paler than the follicular cells.
- They are rounded or oval in shape.
- They do not bound to the lumen of the follicle and is enclosed between the follicular cells and the basement membrane surrounding the follicle.
- **Function:** They secrete calcitonin; a hormone which lowers the blood calcium level by inhibiting bone resorption.

2-Inter-follicular cells

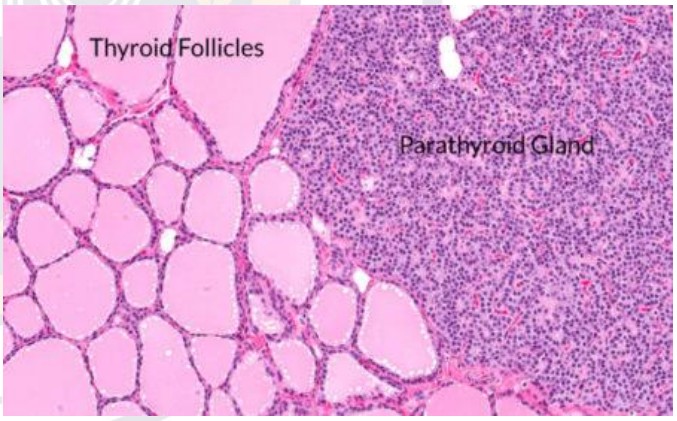
- They are masses of cells present in-between the follicles.
- They represent tangentially cut follicles (consist of follicular and para-follicular cells).

THE PARATHYROID GLANDS

- They are four small masses present on the posterior aspect of the thyroid gland.

Structure:

It consists of stroma and parenchyma.



I. Stroma:

1- Connective tissue capsule.
2- Delicate connective tissue septa divide the gland into poorly defined lobules.
3- Reticular fibres.

II. The parenchyma:

- It consists of anastomosing cords of cells separated by blood capillaries.
- Two types of cells are present in the gland of adults: **chief cells** and **oxyphil cells**.

A- Chief cells (principal cells)

- They are the most numerous cells in the gland.
- They are smaller in size than oxyphil cells.
- They are polygonal in shape.

- The nuclei are vesicular and rounded.
- They have pale cytoplasm because they contain large amount of glycogen and lipid.
- **Function:** They secrete parathormone (parathyroid hormone) when calcium level drops below normal.

- Removal of parathyroid glands or hypo function → tetany and death due to diminished calcium level in blood.
- Hyper function of parathyroid → Ca level increases, P. level decreases and calcium deposits in several organs e.g.: kidney, arteries etc. The bone matrix is decalcified and the bone fractures easily (osteitis fibrosa cystica).

B- Oxyphil cell:

- They are few in number.
- They are polygonal and larger in size than the chief cells.
- They have small densely stained nuclei.
- They have numerous acidophilic granules which are mitochondria.
- **Function:** They may be involved in secreting calcitonin.

THE SUPRARENAL GLANDS

- They are paired glands, lying over the superior margin of the kidney.
- The gland consists of stroma and parenchyma.

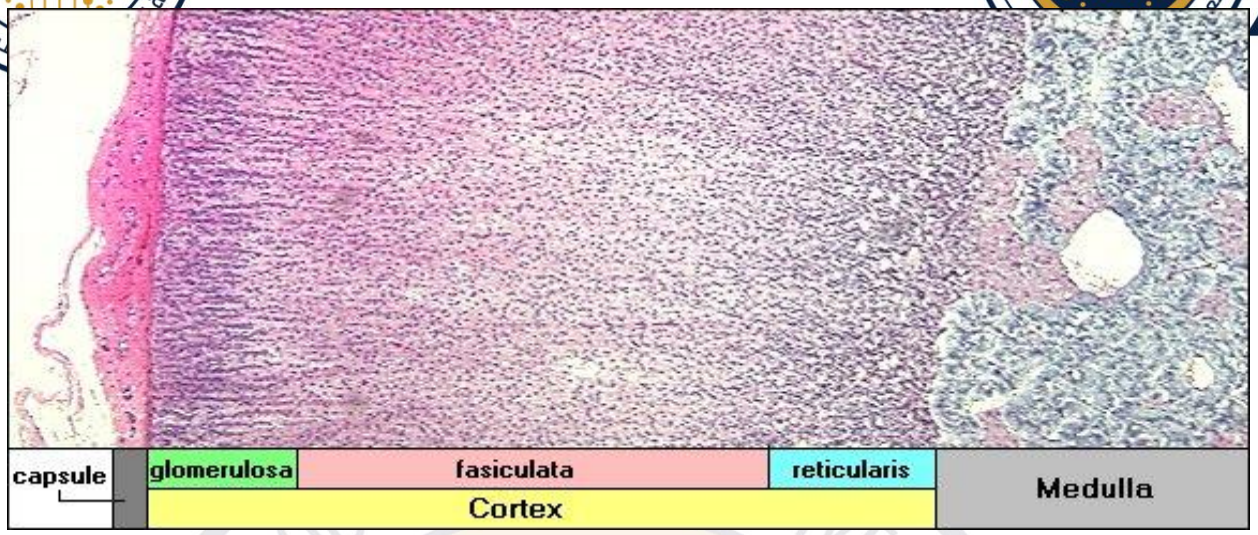
I. The Stroma:

1- Capsule

2- Trabeculae

3- Reticular fibres

II- The parenchyma: is divided into **cortex** and **medulla**.



The Suprarenal Cortex

- It is thick and yellowish in colour due to high content of lipid.
- It is essential for life.
- It is divided into three zones:

a. Zona glomerulosa:

- It is a relatively narrow zone under the capsule. The cells are arranged into round and oval groups (glomeruli) without a central cavity.
- The cells are columnar and have spherical deeply stained nuclei and few lipid droplets.
- A rich network of capillaries surrounds the glomeruli.

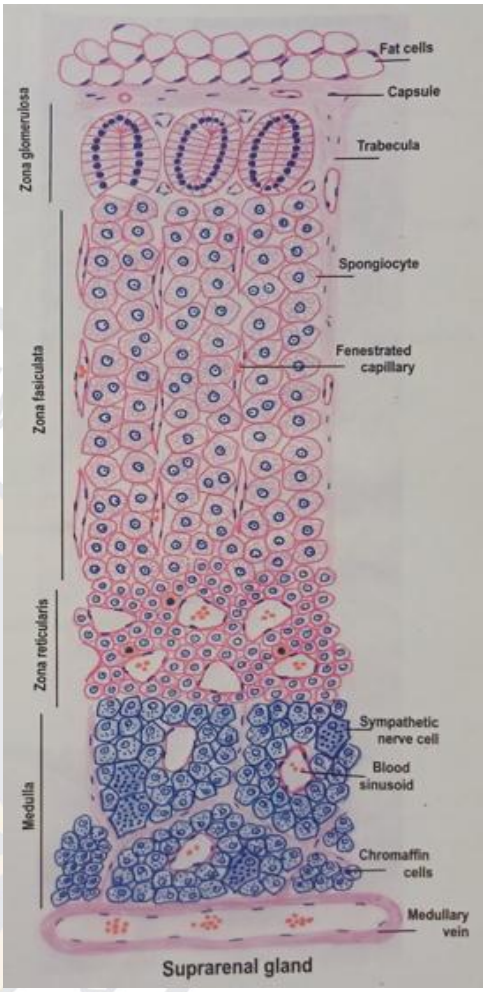
Function: The cells secrete mineralo-corticoid (aldosterone) which causes sodium retention by enhancing sodium reabsorption from the distal convoluted tubules of the kidney.

b. **Zona Fasciculata**:

- It is the broadest zone, composed of straight parallel cords of cells coursing in a radial direction toward the medulla.
- The cords are usually one or two cells in width, and they are surrounded by a longitudinally oriented network of fenestrated sinusoidal capillaries.
- The cells are polyhedral, with large vesicular nuclei, binucleated cells are frequently seen.

- Their cytoplasm is vacuolated (due to dissolved lipid droplets) and has a spongy appearance; therefore the cells are called **spongiocytes**.

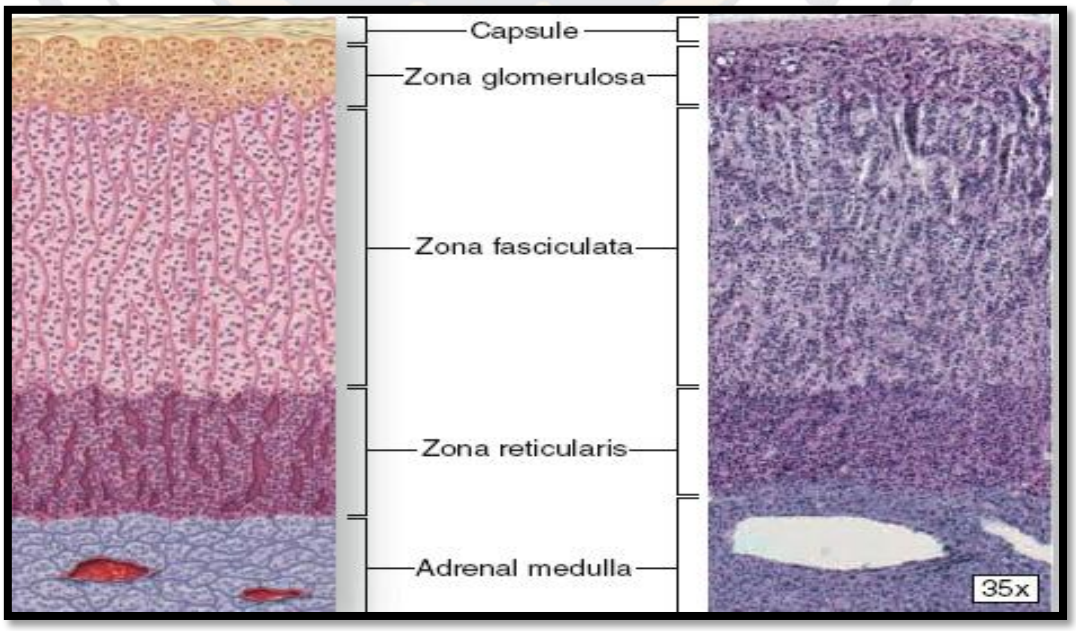
Function: The cells secrete gluco-corticoids (Cortisol and hydro-cortisone).



c. **Zona reticularis**:

- It is a relatively thin zone as zona glomerulosa.
- It is composed of branching and anastomosing cords of cell which are separated by fenestrated blood sinusoidal capillaries.
- The cells are small, polyhedral with few lipid droplets.
- Some cells are darker (**dark cells**) as they contain lipofuscin pigment. They are present toward the inner part of zona reticularis.

Function: The cells secrete sex hormones and small amounts of gluco-corticoids.



The Suprarenal Medulla

- In the fresh state, it has a pink colour.
- It is not essential for life.

Structure: It consists of a stroma and parenchyma.

I. The stroma: is a highly vascular connective tissue.

II. The parenchyma: is formed of:

1- Chromaffin cells.
2- Few scattered sympathetic ganglion cells.
3- Few lymphocytes around blood vessels.

Chromaffin cells:

- They are the secretory cells in the medulla.
- They are arranged in groups around the blood vessels or in anastomosing cords.
- The cells are oval or polygonal in shape, with eccentric nucleus.
- The cytoplasm is basophilic containing fine granules of adrenaline and nor-adrenaline.

Identification of the medulla from the cortex:

- **Chromaffin reaction**: fresh specimens of the suprarenal gland + potassium dichromate → the cells of the medulla revealed brown granules. (Positive chromaffin reaction).

Function of chromaffin cells:

Under stress conditions they secrete adrenaline and noradrenaline directly into the blood causing a rapid generalized sympathetic effect to meet emergency situations.

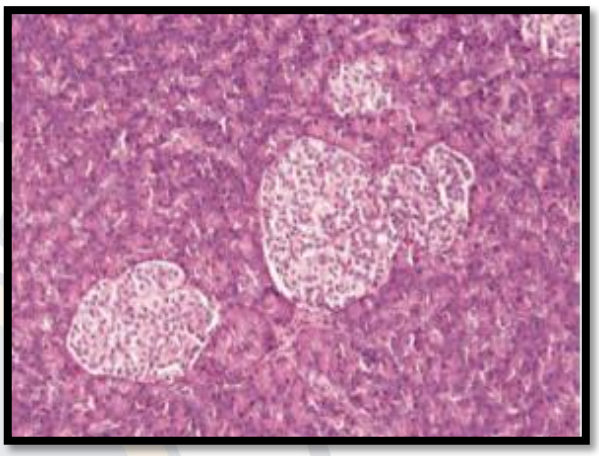
- Destruction of the suprarenal gland → Addison's disease.
- Hyperfunction of the suprarenal gland → Cushing syndrome.
- Tumours of the superarenal medulla are called pheochromocytoma.

The endocrine part of pancreas (Islets of Langerhans)

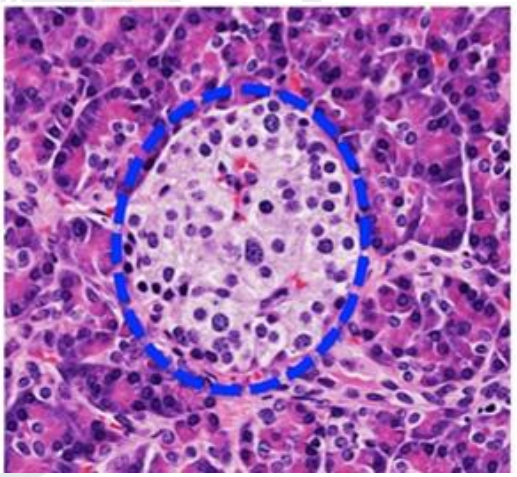
Definition: non capsulated masses of endocrine cells scattered in the pancreatic lobules especially at the tail region.

Number: about ¼ - ¾ million (in human).

Structure:



1. They are formed of anastomosing cords of epithelial cells separated by labyrinthine network of fenestrated blood capillaries.
2. They are separated from the exocrine acini by a layer of reticular connective tissue.
3. In H. & E. stained sections they appear as lighter non capsulated areas surrounded by darker acini. The endocrine cells can not be differentiated from each other.
4. Differentiation of the islet cells depends on:
   a. Specific stains.
   b. E/M features.
   c. Immunohistochemical techniques.

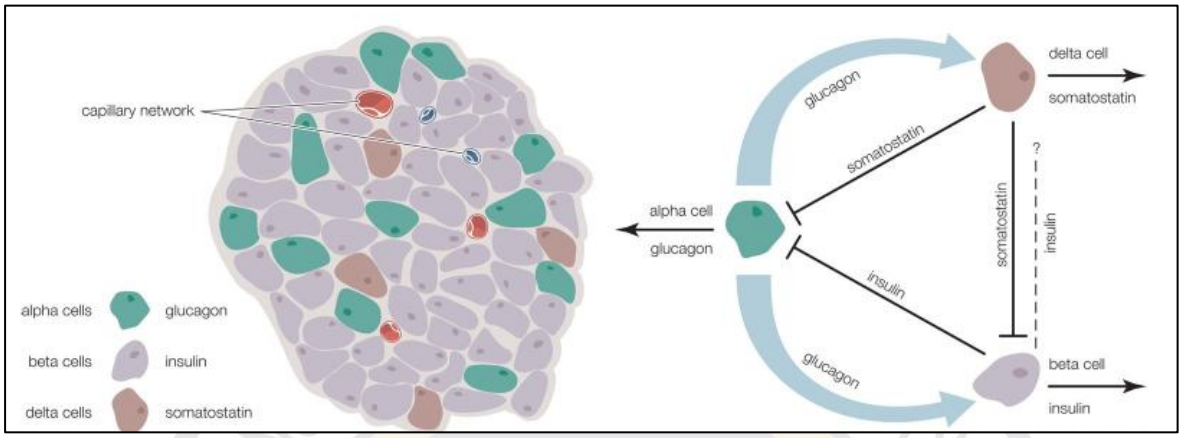


5. The endocrine cells forming the islets of Langerhans are:
   A (α) cells →glucagon.
   B (β) cells →insulin.
   D (δ) cells →somatostatin.
   F (PP) cells →pancreatic polypeptide.
6. Ganglion cells (sympathetic neurons) scatter between the endocrine cells to regulate their functions.

A (α) cells

- Nearly oval in shape.
- Present at the periphery of the islets.
- Represent about 20% of cells.

- Can be stained by immunohistochemical technique using a primary antibody against glucagon hormone.
- **Function:** secretion of glucagon which elevates the glucose level in blood.



B (β) cells

- Nearly oval in shape.
- Present mainly in the center of the islets.
- Represent about 60-75% of cells.
- Can be stained by immunohistochemical technique using a primary antibody against insulin hormone.
- **Function:** secretion of insulin which lowers the glucose level in blood

D (δ) cells

- Oval in shape.
- Variable in size and granular content.
- Scattered between α cells in the periphery of the islets.
- Represent about 2% of cells.
- **Function**: secretion of somatostatin which suppresses the function of both A and B cells and also inhibits the release of growth hormone.

F or (PP) cells

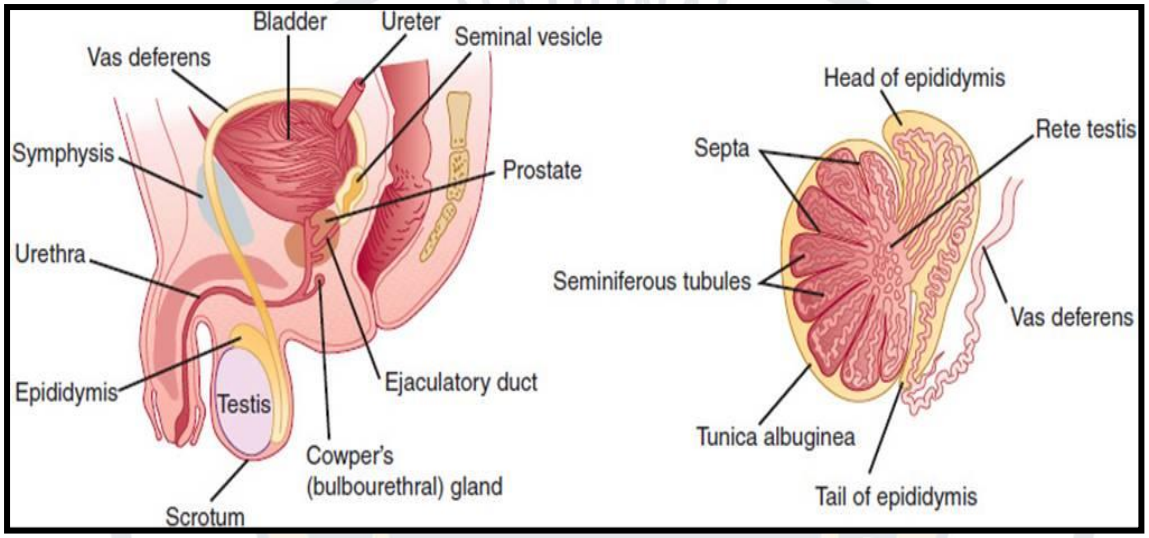
- Small oval cells , represent about 2%
- Secrete pancreatic polypeptide hormone involved in carbohydrates and protein metabolism.

The male genital system

The male genital system includes:

1- Primary sex organs (testis).

2- Accessory sex organs.



The accessory sex organs include:

A. Excretory tubules of the testis:

1. Intratesticul:	2. Extratesticular:
- Tubuli recti - Rete testis	- Vasa efferentia - Epididymis - Vas deferens - Ejaculatory duct - Urethra

B. Glands:

- ☒ **Seminal vesicle.**
- ☒ **Prostate.**
- ☒ **Cowper's gland.**
- ☒ **Glands of Littre.**

C. Copulatory organ: penis.

THE PRIMARY SEX ORGAN THE TESTIS

Characters:

☒ It is the primary sex organ of the male genital system.

☒ It is a compound tubular mixed exocrine (seminiferous tubules) and endocrine gland (Interstitial cells of Leydig).

Covering:

1. Scrotum:

☒ It is formed (from outside) of:

- A pouch of thin skin with no hypodermis.
- A thin layer of smooth muscle fibers (Dartos muscle).
- A lining layer of flat cells which is the parietal layer of the tunica vaginalis.

2. Tunica vaginalis:

☒ It is a pouch of peritoneum which covers the testis.

☒ Its inner visceral layer forms the outer covering of the testis.

☒ Its outer parietal layer lines the scrotum.

Stroma of the Testis:

1. Tunica albuginea:

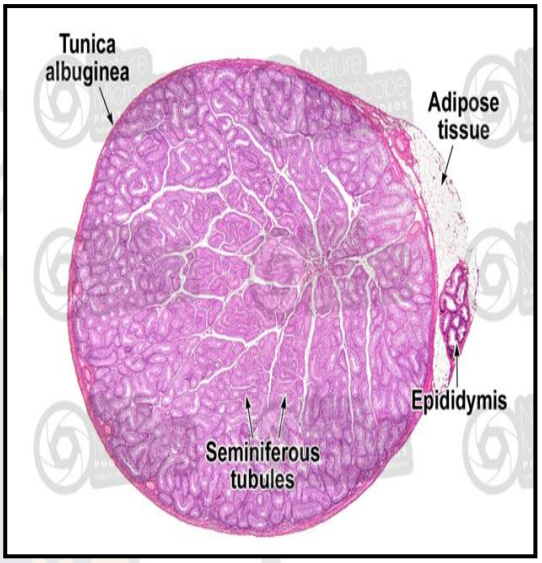
☒ It is a thick layer of white collagenous fibers.

2. Tunica vasculosa:

☒ It is formed of loose C.T. rich in blood vessels.

3. Trabeculae:

☒ These are incomplete septa which divide the testis into 250 compartments of testicular lobules. Each testicular lobule contains 1-4 convoluted seminiferous tubules.



4. Reticular tissue:

☒ It is a network of reticular fibers.

☒ It supports parenchyma and forms the background of lobules.

Parenchyma of the testis:

The parenchyma of the testis is formed of:

☒ Exocrine parenchyma (seminiferous tubules).

☒ Endocrine parenchyma (Interstitial cells of Leydig).

(1) Seminiferous tubules

Characters:

☒ It is the exocrine portion of the testis that produces spermatozoa.

☒ It is a highly tortuous compound tubular gland.

☒ It has a clear basement membrane which is surrounded by loose C.T containing blood vessels, smooth muscles fibers.

Lining cells:

☒ spermatogenic cells.

☒ Supporting Sertoli cells.

A. Spermatogenic cells

- ☒ These are the main cells which line the seminiferous tubule.
- ☒ They undergo the process of spermatogenesis which results in the production of mature spermatozoa.
- ☒ These cells are arranged in rows.
- ☒ The process of spermatogenesis occurs in 2 main steps:
  1. **Spermatocytogenesis** (spermatids production from the spermatogenic cells).
  2. **Spermiogenesis**: (morphological changes which occur in the spermatid to be changed into spermatozoa).

.

Spermatocytogenesis

☒ **Definition:**

It is a process by which **spermatids** are produced from the spermatogenic cells.

☒ **Duration:** 64 days

☒ **Stages:**

1-Proliferation:

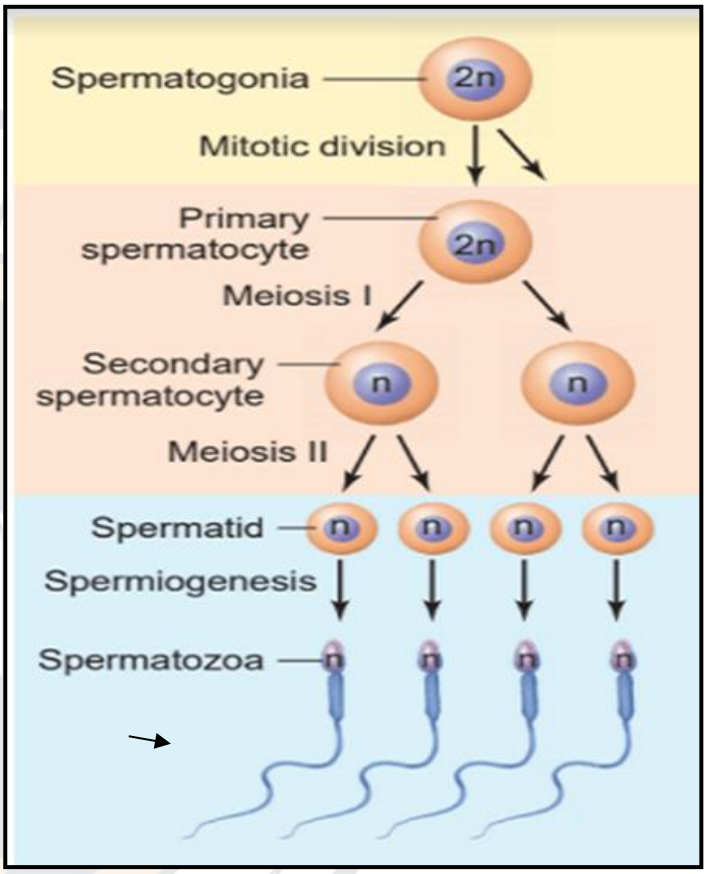
- Proliferation of spermatogonia by mitosis

2-Growth:

- spermatogonia grow ⟶ primary spermatocytes.

3-Maturation: (2 meiotic divisions)

- 1st meiotic division of primary spermatocytes ⟶ secondary spermatocytes.
- 2nd meiotic division of secondary spermatocytes ⟶ spermatids.



☒ **Steps:**

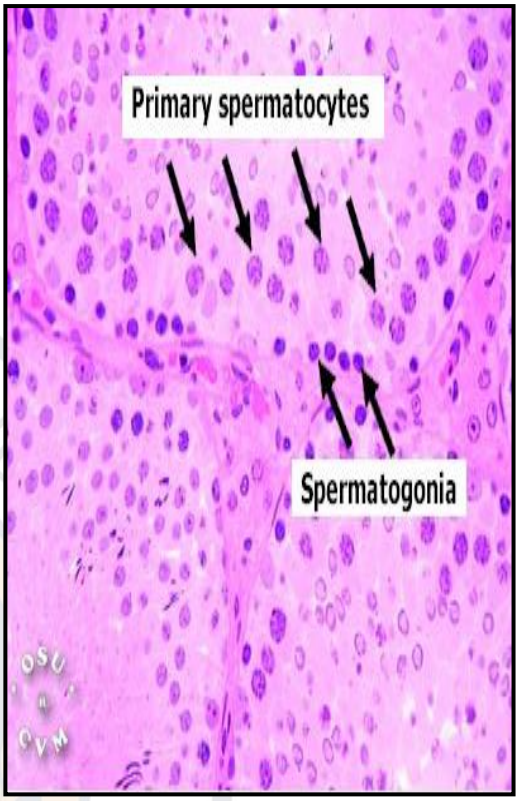
A. Spermatogonia:

- **Site:** they form 1-2 layers on the basement membrane.
- **Shape:** rounded
- **Nuclei:** rounded

B. Primary spermatocytes:

- **Site:** they form 2-3 layers inner to the spermatogonia**.**
- **Shape:** rounded**.**

- **Size:** the largest cells.
- **Nuclei:**
  - Large, central, rounded.
  - Contain 46 d- chromosomes.
- **Changes:**
  - They enter the first meiosis at puberty to form secondary spermatocytes with half number of chromosomes (23 chromosomes) and separation of X and Y chromosomes.



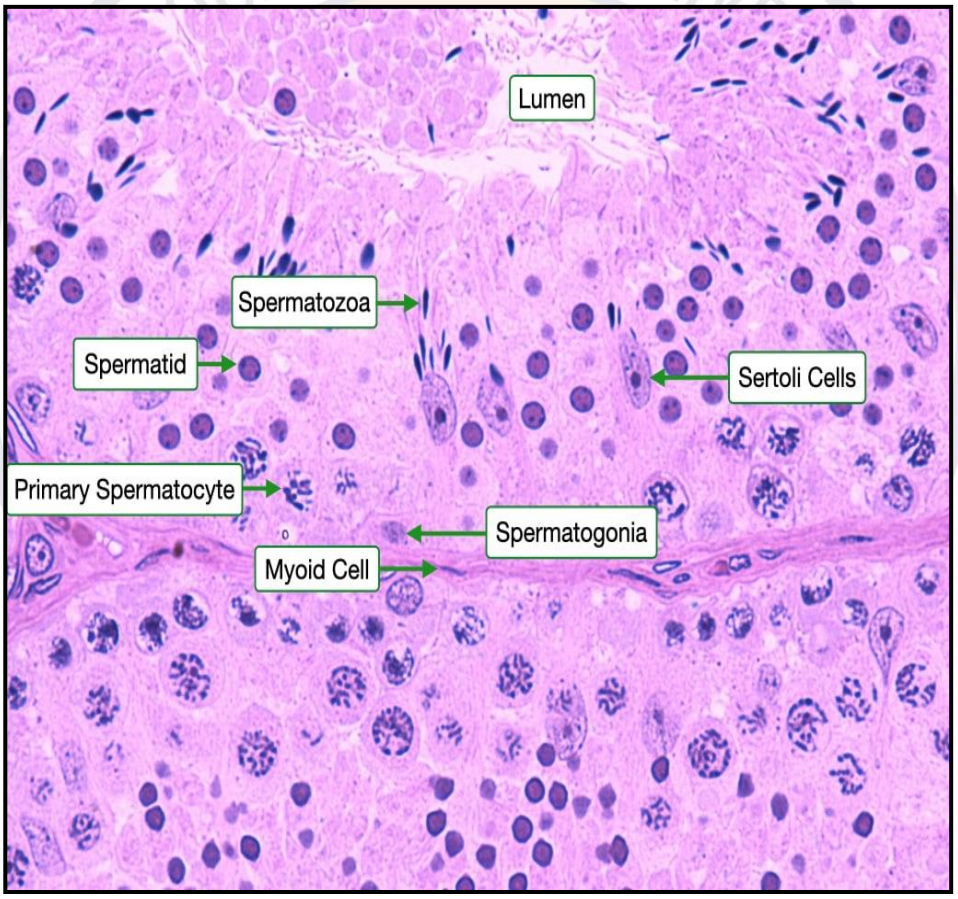
C. Secondary spermatocytes:

- **Site:** they are difficult to be seen as they rapidly change into spermatids
- **Shape:** rounded.
- **Size:** smaller than primary spermatocytes
- **Nuclei:**
  - Small, central, rounded.
  - Contain 23 d-chromosomes and some cells have X chromosomes and others have Y chromosomes.
- **Changes:**
  - They rapidly form spermatids.

D. Spermatids:

- **Site:**
  - At the inner parts of the tubules.
  - They are attached to the apex of Sertoli cells.
- **Shape:** rounded then changed into elongated.
- **Size:** very small (9 µm).

- **Nuclei:**
  - Small, deeply stained.
  - Contain 23 S. chromosomes.
- **Changes:**
  - undergo spermiogenesis and change into spermatozoa.



Spermiogenesis

☒ Definition:

- It is the morphological changes which occur in the spermatid to be changed into spermatozoa.
- It occurs without cell division.
- It includes different changes in nucleus, Golgi apparatus, mitochondria, centrioles and cytoplasm.

☒ Changes:

A. The nucleus:

- It is found at one pole of the cell.
- It becomes more condensed, elongated and flattened.

B. Golgi apparatus:

- It becomes closely associated with nucleus.
- It is changed into membranous vesicle called a***crosomal vesicle***.
- This vesicle encloses the anterior 2/3 of the nucleus to form the ***head cap***.
- A dark granular mass appear in the vesicle which is called ***acrosome*.**
- The head cap and acrosome are called ***acrosomic system***.
- This system contains hyaluronidase enzyme which help the spermatozoa to penetrate the ovum.

C. The centrioles

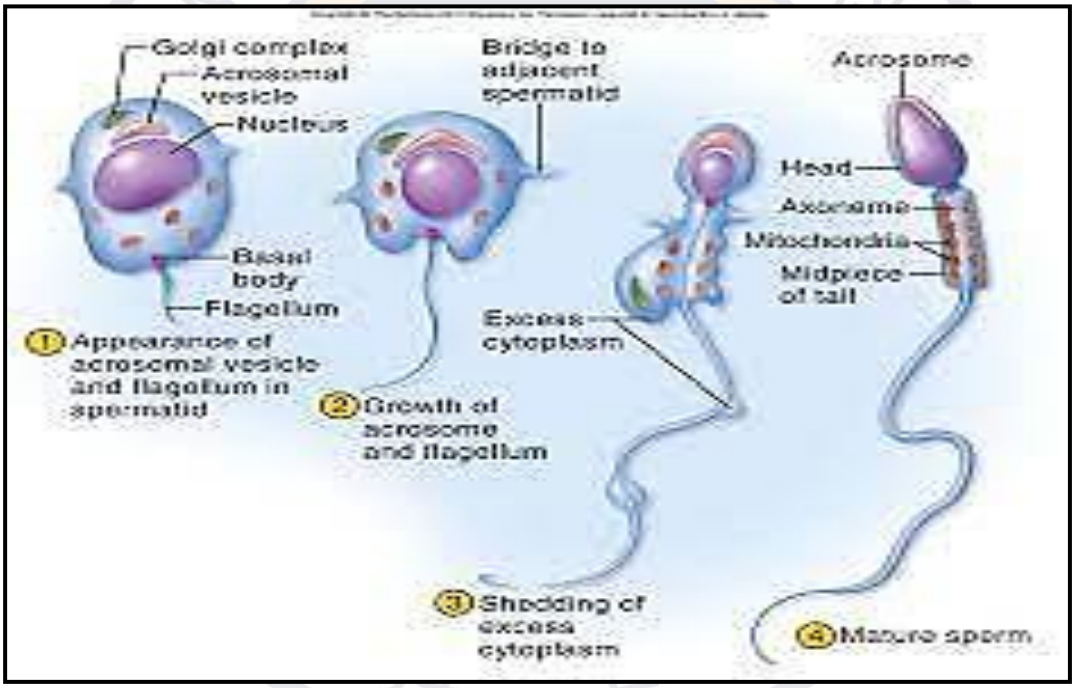
- The 2 centrioles migrate to the caudal pole of the nucleus.
- One of them becomes attached to the nucleus.
- The other is elongated to form the flagellum which is structurally similar to cilium.

D. Mitochondria:

- They are arranged as a sheath around the proximal part of the flagellum to form the middle piece of the spermatozoa.
- They provide energy for the motility of the spermatozoa.

E. Cytoplasm:

- It is reduced in amount (part of the cytoplasm is phagocytosed by Sertoli cells)

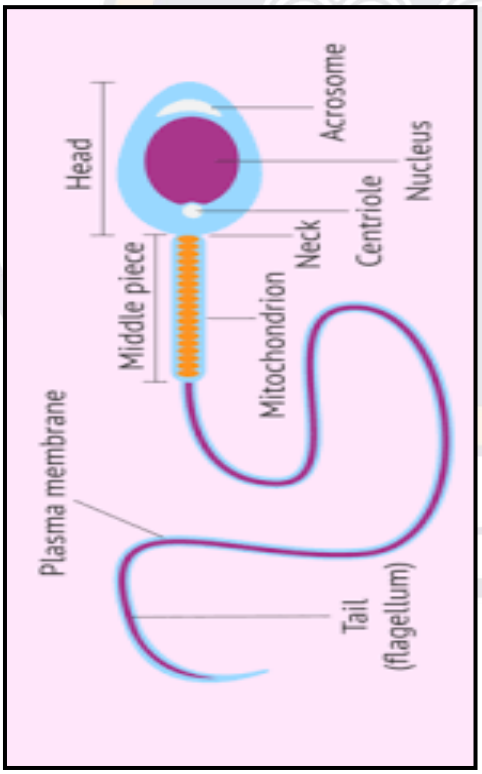


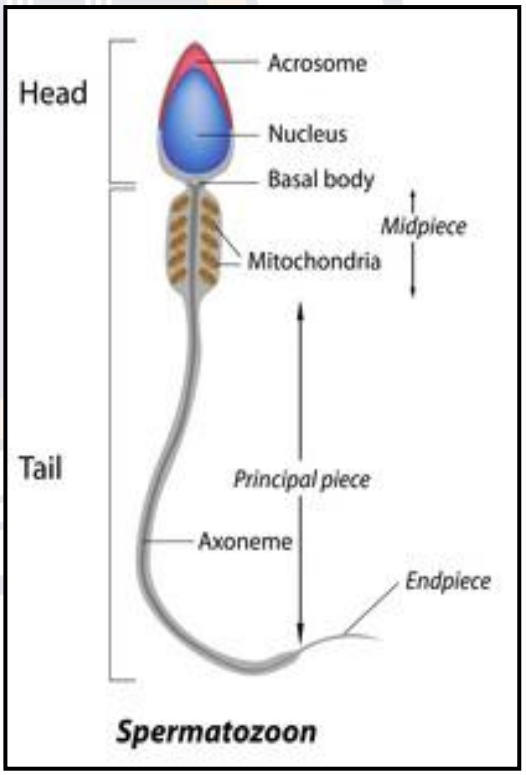
F. Mature spermatozoa:

- The mature spermatozoon is formed of:

1. **The head:**
   - Shape: pyriform.
   - Length: 5 µm.
   - Contents:
     1. The condensed nucleus.
     2. Acrosomic system covering the anterior 2/3.

2. **The neck:** It is a constriction behind the head which contains the 2 centrioles.
3. **Middle piece:**
   - Length: 5 µm.
   - Contents: It is formed of the flagellum
   - surrounded by the mitochondrial sheath.
4. **The tail:**
   - Length: 50 µm.
   - Contents: it is formed of principal and end piece.
   - It is highly motile.

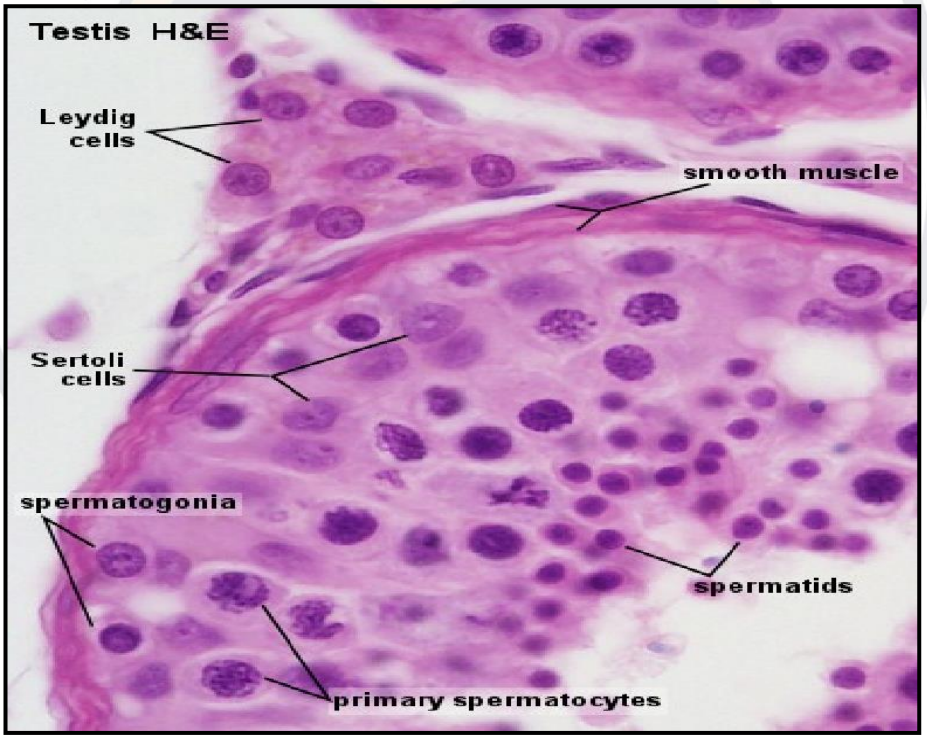




B. Sertoli cells

☒ **LM:**

- **Shape**: Tall irregular columnar cells
- **Site**: insinuated between spermatogenic cells and extend from the basal lamina to the lumen.
- **nucleus**: ovoid, near the base, pale stained with dispersed chromatin and 1-2 prominent nucleoli.
- **cytoplasm**: pale stained and contains lipochrome pigment and lipid droplets.



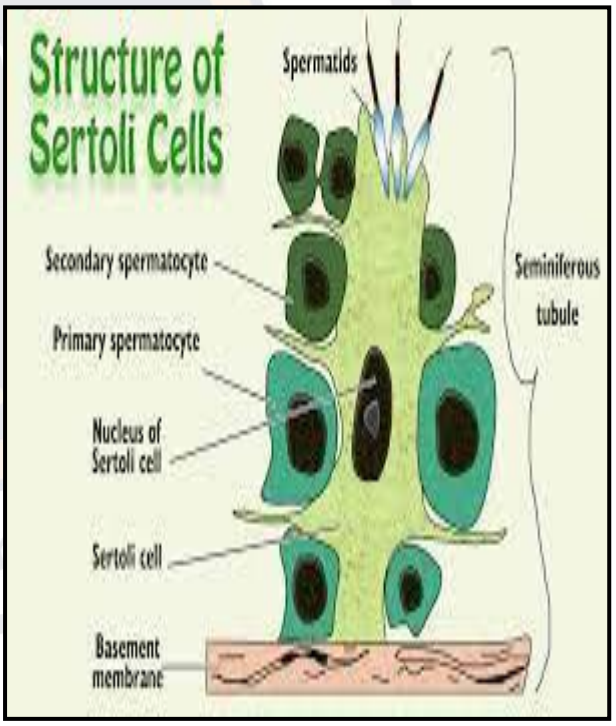
☒ **EM:**

- They are joined to each other by tight junction which act as blood testis is barrier.
- The nuclear membrane shows a characteristic longitudinal groove.
- The nucleolus is associated with chromatin on both sides ⟶ triplet structure.

- The cytoplasm have:
  - Numerous mitochondria, numerous SER, and Golgi apparatus.
  - Lipid and glycogen granules.
  - Cytoskeleton (actin and microtubule).
  - Digestive system (1ry, 2ry lysosomes and lipochrome pigment)

☒ **Function of Sertoli Cells:**

- Phagocytose degenerated germ cells.
- Make a blood testis barrier which protect
- the developing sperm from any injurious agent.
- Nourish spermatogenic cells.
- Prevent autoimmune disease.



The Blood -Testis Barrier

☒ Definition:

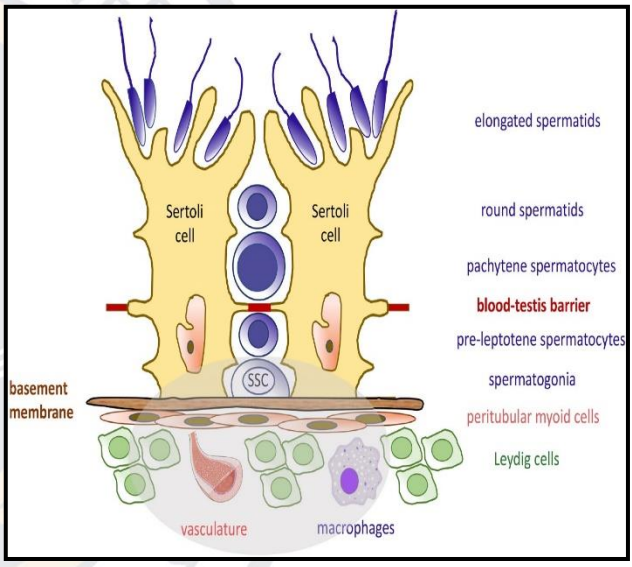
- It is a continuous membrane formed by the continuous tight junctions between the lateral borders of Sertoli cells near their bases to control the selective passage of substances to the cells of the tubules.

☒ Structure:

- The junction divides the seminiferous tubule into two compartments:

1-Inner Compartment:

- Towards the lumen of the seminiferous tubule.
- It includes:
  - Primary, secondary spermatocytes, spermatid and sperm.
  - They are isolated from direct exchange with tissue fluid which is present outside the seminiferous tubule.



2-Outer Compartment:

- Towards the basement membrane.
- It includes spermatogonia.
- It permits free exchange of nutrients and waste products between interstitial vasculature and the more primitive spermatogenic cells.

☒ **Function:**

- Select the passage of nutrients, hormones, proper fluid needed for differentiation and growth of spermatogenic cells.
- Isolate and protect the spermatocyte from the damaging substances in the blood outside the tubules.
- Decrease the entry of antisperm immunoglobulin which may damage the sperm.
- Prevent the back passage of the antigen of the sperm to the blood, thus prevent the autoimmune reaction which cause death to sperm.
- Maintain high concentration of K, Na, and ABP in the inner compartment which help proper spermatogenesis.

(2) Interstitial Cells of Leydig

Site:

Found singly or more commonly in clumps in the stroma between seminiferous tubules.

LM:

☒ **Nucleus:**

- Pale rounded

☒ **Cytoplasm:**

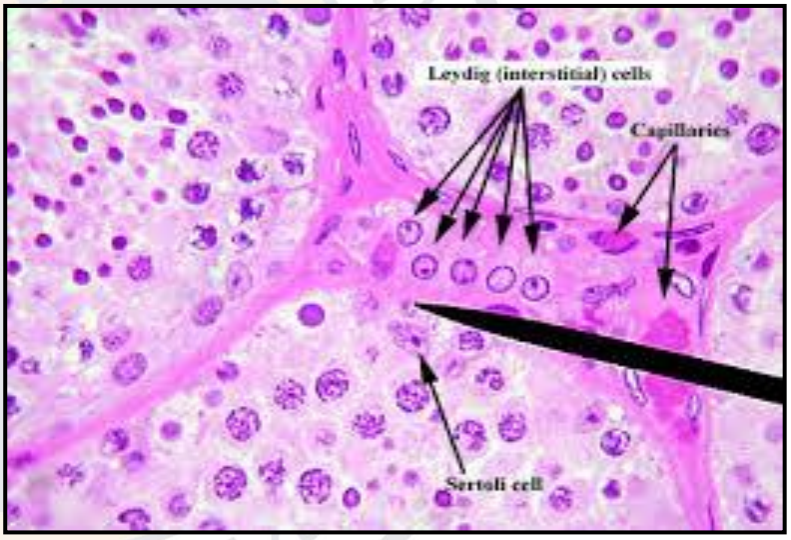
- Pale stained, acidophilic due to dissolved lipid droplets.

EM:

☒ ↑↑ sER, mitochondria

☒ Lipochrome pigment.

☒ Peroxisomes-Lysosomes.



Function:

☒ They secrete testosterone.

The excretory tubules of the testis

A. Intra testicular:

1-Tubuli recti:

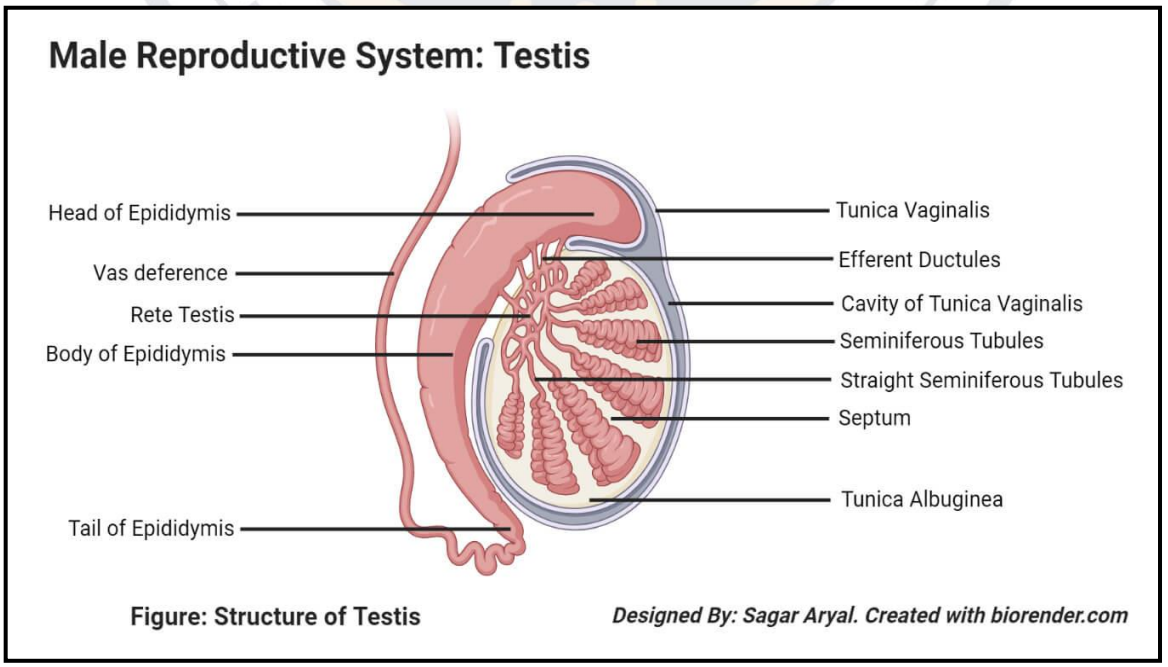
- These are short straight tubules which receive the sperms from the seminiferous tubule.
- They are lined with tall columnar Sertoli like cells and supported by a thin C.T. sheath.

2- Rete testis:

- These are narrow tubules which branch and anastomosis to form a reticulum. They are lined with low cubical epithelium which rest on a prominent basal lamina and covered by lamina propria of vascular C.T.

B. Extra testicular

1. Vasa Efferentia.
2. Epididymis.
3. Vas deferens.
4. Ejaculatory duct
5. Urethra.



1. Vasa Efferentia (ductui efferentes)

Definition:

- ☒ They are small tubules attached with each other by vascular C.T.
- ☒ They become convoluted to form the head of the epididymis.

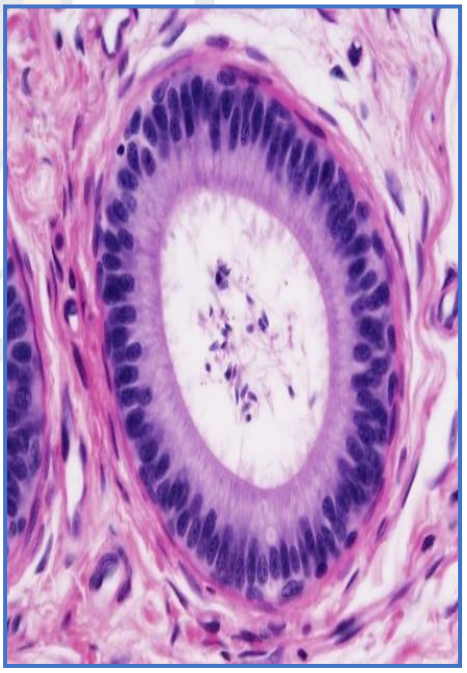
Lining: (festooned epithelium)

- ☒ High columnar ciliated (for the movement of non-motile sperm) alternating with low columnar non-ciliated (for absorption of some testicular fluid).
- ☒ Rest on basement membrane.
- ☒ Surrounded by C.T. (elastic fibers + smooth muscle fibers).

2. Epididymis

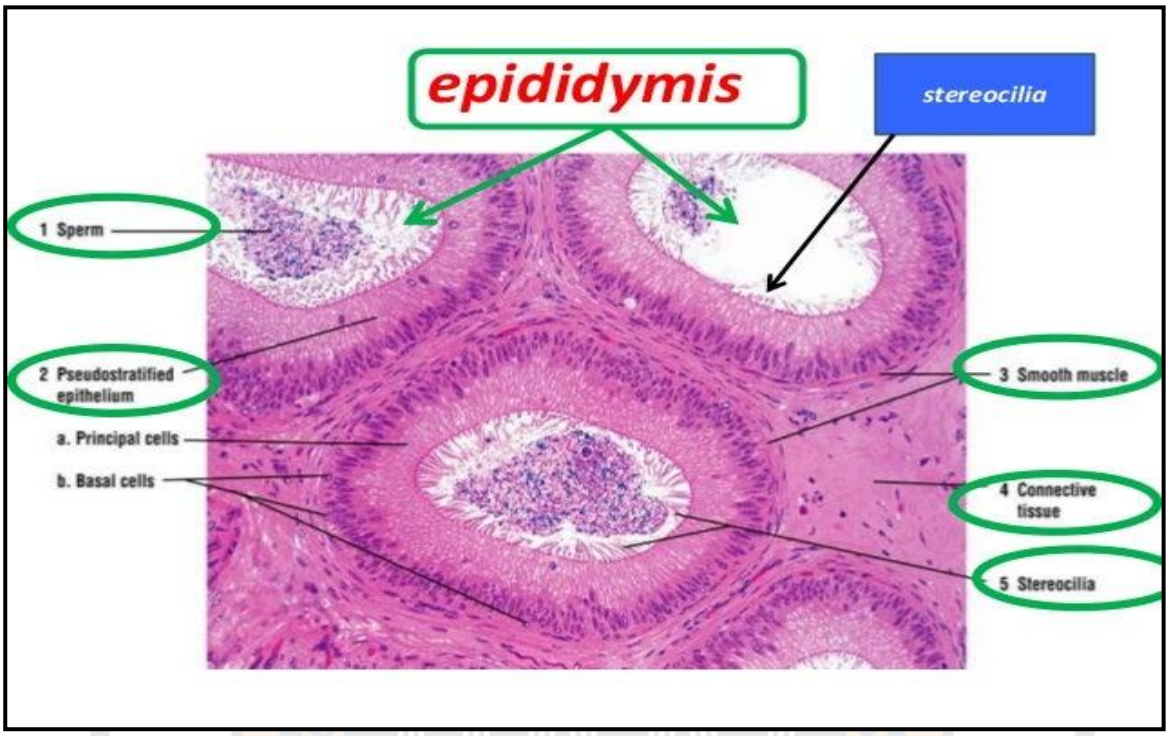
Definition:

- ☒ Long, highly tortuous tubule (6 meters).



Lining epithelium:

- ☒ It is lined with pseudo stratified columnar ciliated epithelium.
- ☒ The cilia is stereo cilia (contain tonofilament only).
- ☒ It is considered as long microvilli to:
- ☒ Facilitate the process of transportation of the secretion from the cell to lumen and facilitate the process of absorption of cytoplasmic fragments from the process of spermiogenesis.
- ☒ Outside the basement membrane there is a vascular layer of C.T. and smooth muscle fibers.



Capacitation:

- ☒ It is a series of biochemical changes which occur in the sperm to have the full capacity of fertilization.
- ☒ Begin in the lumen of epididymis.
- ☒ Complete in the uterus and fallopian tube.

Function of epididymis:

- ☒ Secretion of glycerol-phospho-choline and glycoprotein necessary for spermatozoa maturation.
- ☒ Phagocytosis of residual bodies.
- ☒ Storage of spermatozoa.
- ☒ The muscle fibers in the tail are thick. It depends on sympathetic stimulation to vigorously discharge the sperm into the ducts deferens, in response to the ejaculatory reflex.

3. Vas Deferens

Structure:

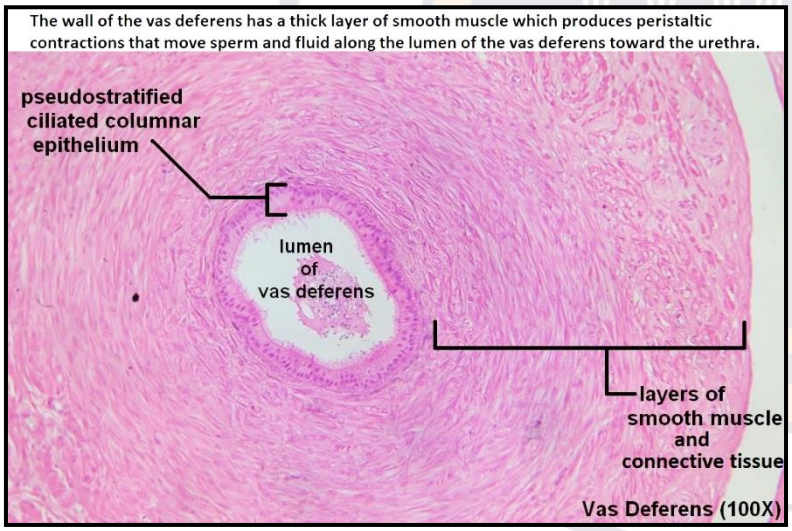
☒ **Mucosa:**

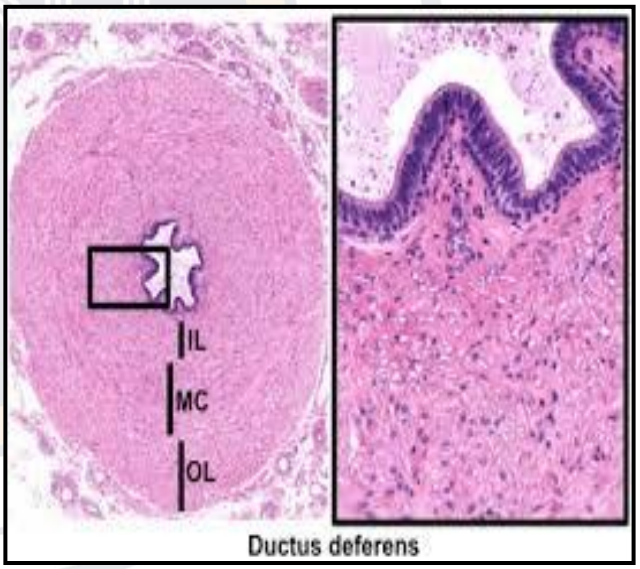
- Epithelium: Pseudostratified columnar with stereo cilia.
- corium: loose connective tissue blood vessels, nerves, lymphatic and elastic fibers.

☒ **Musculosa:**

- Both contain inner longitudinal, thick middle circular and outer longitudinal layers of smooth muscle fibers.

☒ **Adeventia:** loose connective tissue





4. Ejaculatory Duct

Formation:

☒ Ampulla of vas deferens and seminal vesicles.

☒ It penetrates the prostate and open into prostatic urethra.

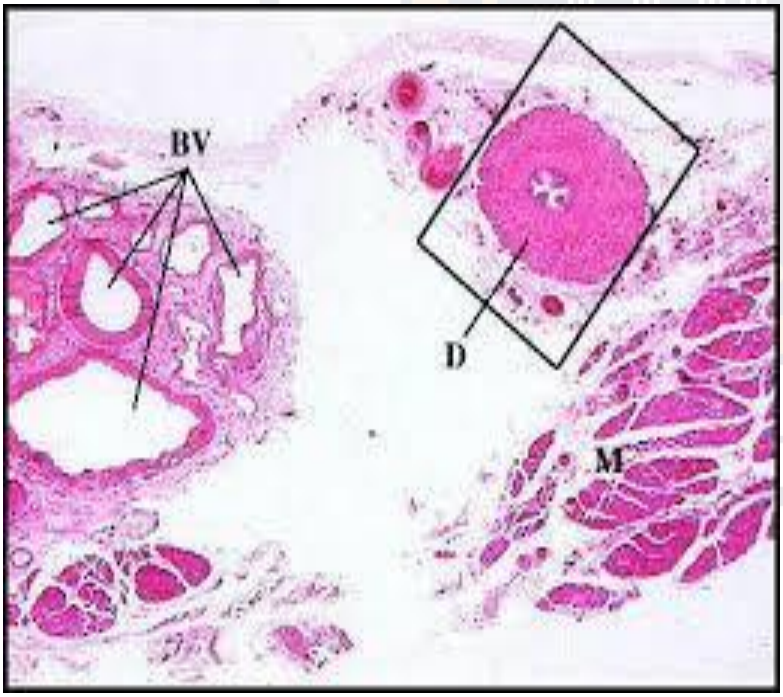
Lining:

☒ Simple columnar **or**

☒ Pseudostratified columnar epithelium.

SPERMATIC CORD

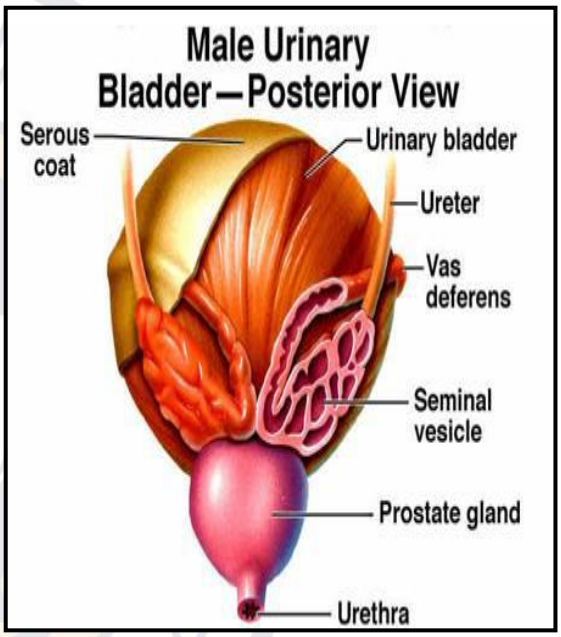
- It arises from the scrotum and enters the inguinal canal.
- **Contents:**
  - ☒ Vas deferens.
  - ☒ Pampiniform plexus of veins.
  - ☒ Cremasteric striated muscle.
  - ☒ Testicular artery and vein.
  - ☒ Nerve fibers.



ACCESSORY GENITAL GLANDS

1.The Seminal Vesicles

- These are paired highly tortuous tubular glands that lie posterior to the prostate.
- **Structure:**



1- Mucosa:

- ☒ Folded.
- ☒ Wide lumen
- ☒ Epithelium:
  - Branched and anastomosing.
  - Tall columnar or pseudostratified columnar.
- ☒ Corium:
  - C.T. containing elastic fibers and smooth muscle fibers.

2- Musculosa:

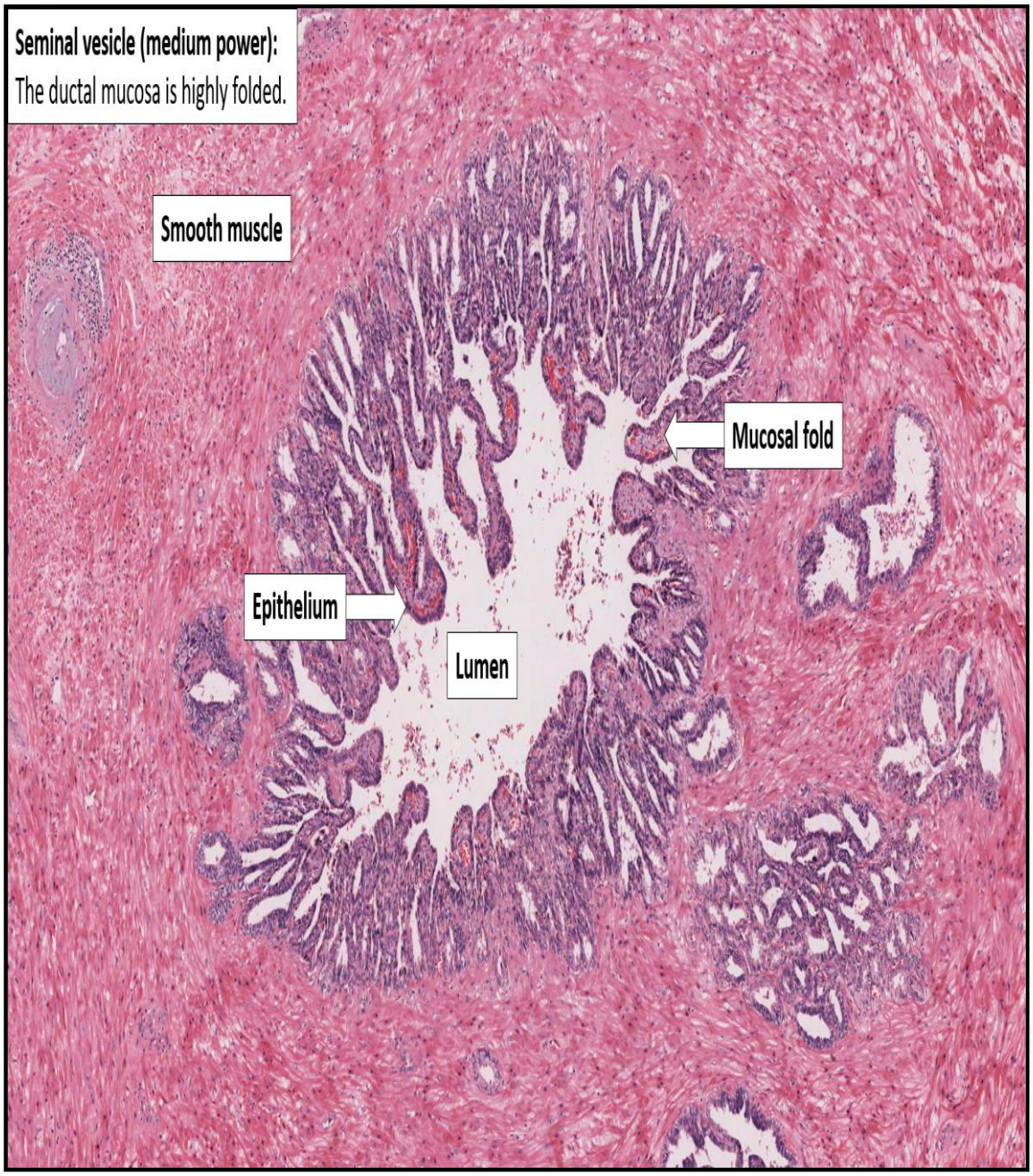
- Inner circular.
- Outer longitudinal

3- Adventitia:

- Loose C.T. containing blood vessels.

- **Function:**

- ☒ Nourishment of the sperm.
- ☒ Secrete viscid yellowish fluid rich in:
  - Fructose.
  - Ascorbic acid.
  - Prostaglandin.
  - Protein


Seminal vesicle (medium power):
The ductal mucosa is highly folded.
Smooth muscle
Mucosal fold
Epithelium
Lumen

The Seminal Fluid (Semen)

- **Definition:**

  It is the fluid secretion of the accessory sex glands (prostate, seminal vesicles and epididymis).

- **Contents:**

  - ☒ Fat.
  - ☒ Sperms.
  - ☒ Few epithelial cells.
  - ☒ Pigment granules.
  - ☒ Spermatogenic cells.
  - ☒ Prostatic concretion.
  - ☒ Crystals of spermin phosphate.

- **Volume:** 2-5 c.c.
- **Reaction:** alkaline.
- **Count:**
  - ☒ 60-100 million sperms / cc.
  - ☒ If < 20million → sterility.
- **Abnormal forms:**
  - ☒ less than 10%.
  - ☒ If > 25% → sterility
- **Motility and Viability:**
  - ☒ 75% → motile
  - ☒ Live for 2-3 days in proper vaginal media.

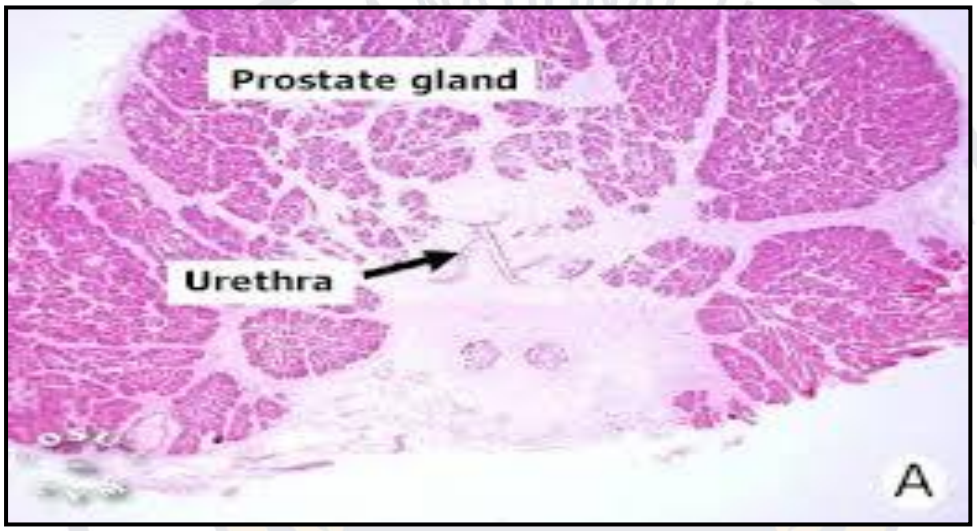
2.Prostate Gland

Type:

It is exocrine compound tubulo-alveolar gland.

Site:

It surrounds the first part of the male urethra which is a V-shaped urethra.



Structure:

A. Stroma

☒ Capsule:

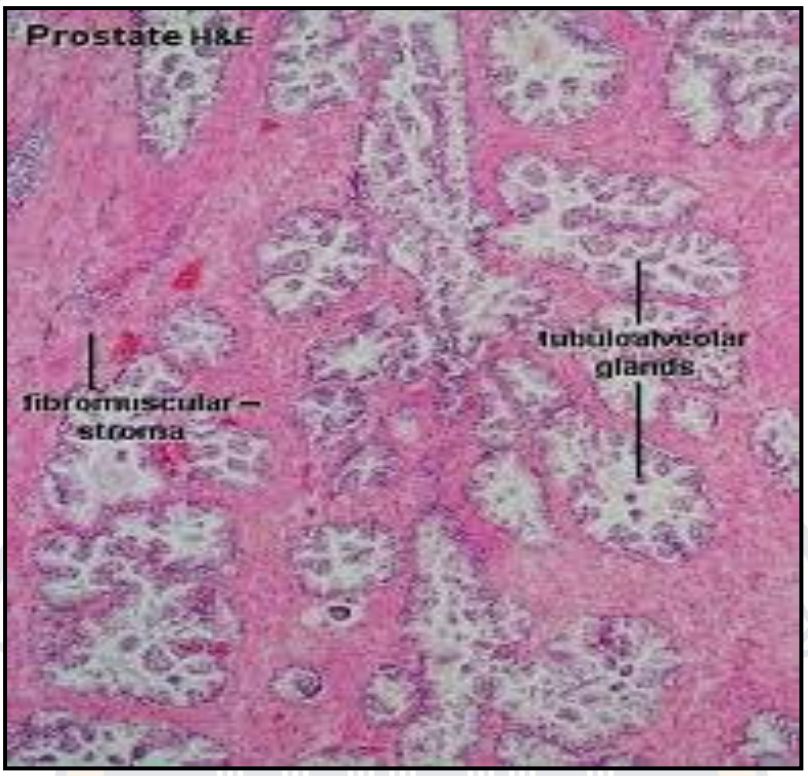
- It is formed of thick fibroelastic tissue rich in smooth muscle fibers and blood vessels.

☒ Trabeculae:

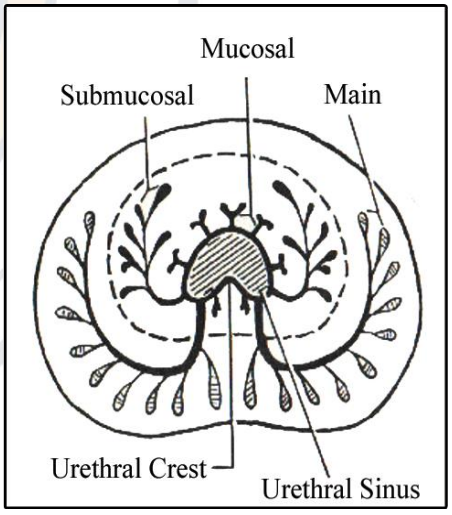
- These are thick C.T. septa arising from the capsule.
- They divide the gland into lobules.
- They are rich in smooth muscle fibers which condense around the urethra to form the internal urethral sphincter.

☒ Reticular Fibers:

- It is a network of reticular fibers.
- It supports parenchyma.



B. Parenchyma



☒ The ejaculatory duct divides the gland into 3 lobes.

☒ Each lobe is subdivided into lobules.

☒ Each lobules contains 3 types of acini which are:

1. Mucosal acini:

- The smallest type.
- Lie in periurethral tissue.
- Open by small ducts in the prostatic urethra.
- In old age, they enlarge → obstruction (prostatic adenoma).

2. Submucosal acini:

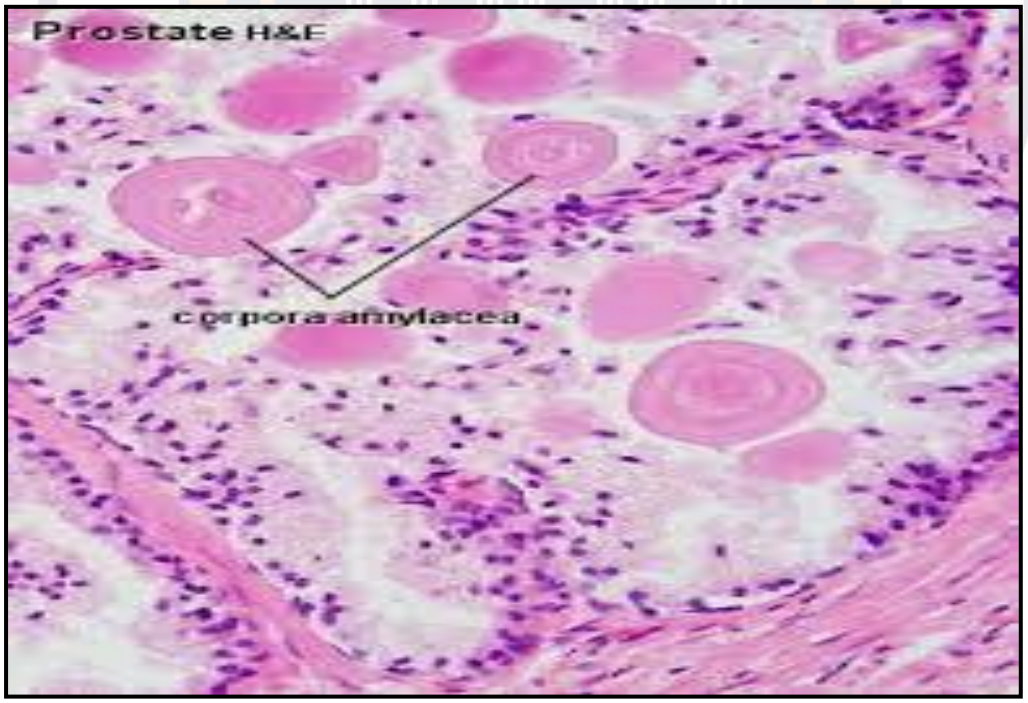
- They lie outer to the mucosal acini
- They are larger in size than the mucosal acini.

- Some prostatic acini are lined with pseudo stratified columnar epithelium, others are lined columnar or even cubical cells depending on the activity of the gland.
- In old age, the prostatic secretion may be dried and clacified in the lumen of the acini to form prostatic concretion called **corpora amylacea.**

Prostatic Secretion:

☒ They secrete milky alkaline, rich in Fructose, acid phosphatase and citric acid which:

- Neutralize the acidity of the vagina.
- Nourish the sperm.



3.The Bulbo-Urethral Gland (Cowper's Gland)

- These are paired small tubulo-alveolar glands.
- They are present under the membranous urethra and the first part of the penile urethra.
- Their ducts open into the penile urethra.They are lined with columnar, cubical or flat cells.
- **Structure:**

A. Stroma:

☒ Each gland has a limited C.T. capsule with septa that divide the gland into irregular lobules.

B. Parenchyma:

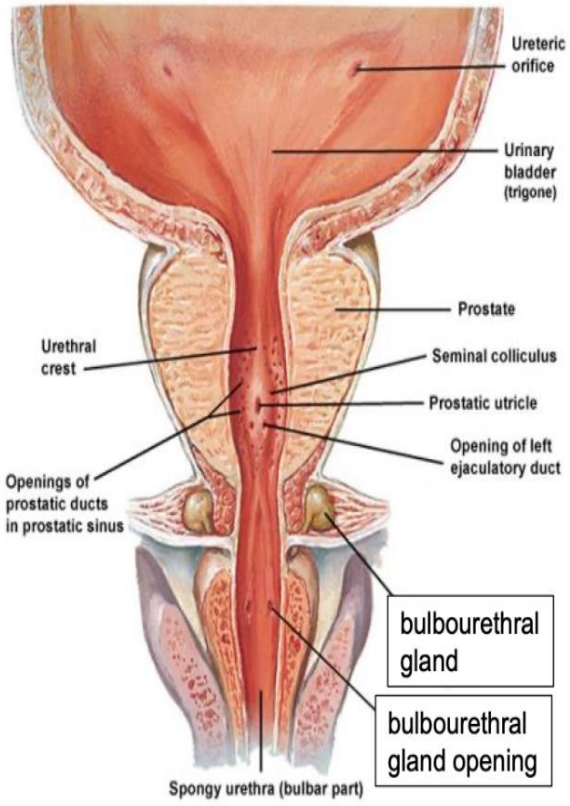
☒ The acini are lined with simple cubical, columnar or squamous epithelium.

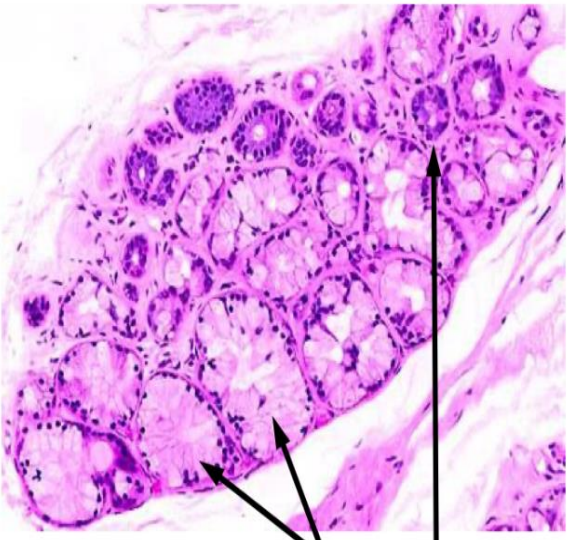
- **Function:**

☒ Under erotic stimulation, they secrete a clear viscid (mucous) fluid into the penile part of urethra ⟶ lubricant to urethra.

Bulbourethral Glands (of Cowper)

Secrete Alkaline Mucus





Mucous secretory units & ducts

-secretes clear mucus fluid
-active upon sexual stimulation
-lubricates urethra and neutralizes residual urine

4.Glands of Littre

- These are simple branched tubular glands.
- **Types:**

A. Extra mucosal:

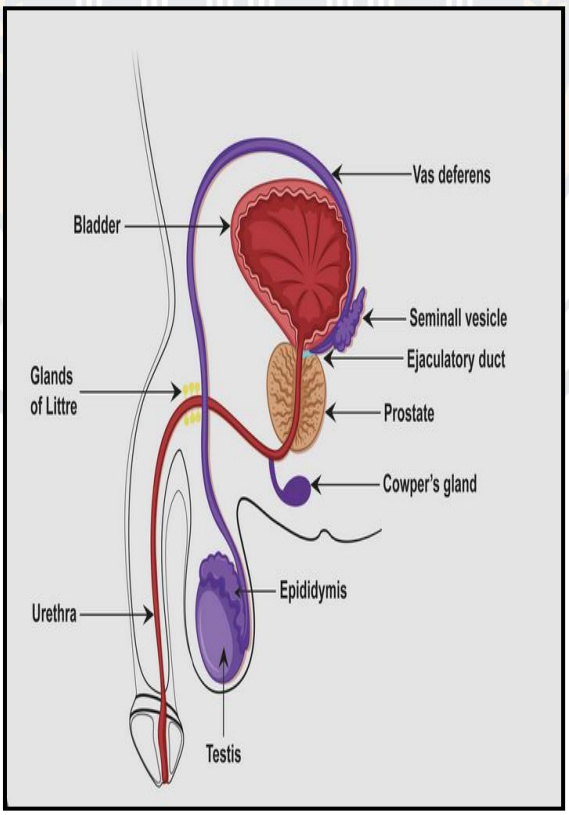
- ☒ Outside the epithelium.
- ☒ Open by short ducts.

B. Intra mucosal:

- ☒ In C.T. of penis close to the epithelium.
- ☒ The 2 types open into penile urethra.

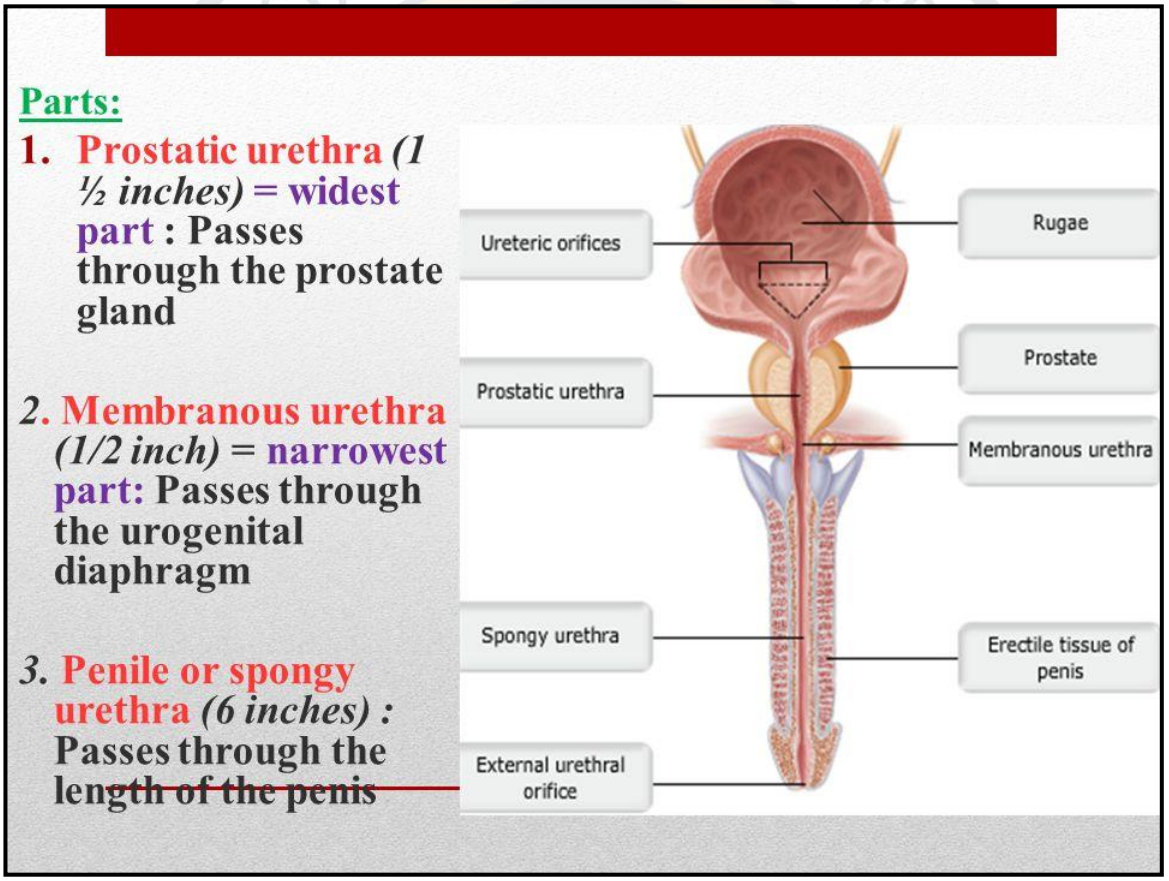
- **Function:**

They secrete mucous secretion for lubrication of the urethra



The Male Urethra

- The male urethra is long (20cm) twisted tube, that conducts urine from bladder (and seminal fluid from male genitalia) to the outside of the body.
- Many glands open in the course of the urethra. As prostatic gland, glands of Littre and bulbo-urethral gland.



- **The male urethra has three parts:**

A. Prostatic:

☒ Arise from the neck of the bladder and passes through the prostate.

☒ It has a V- shaped in cross section.

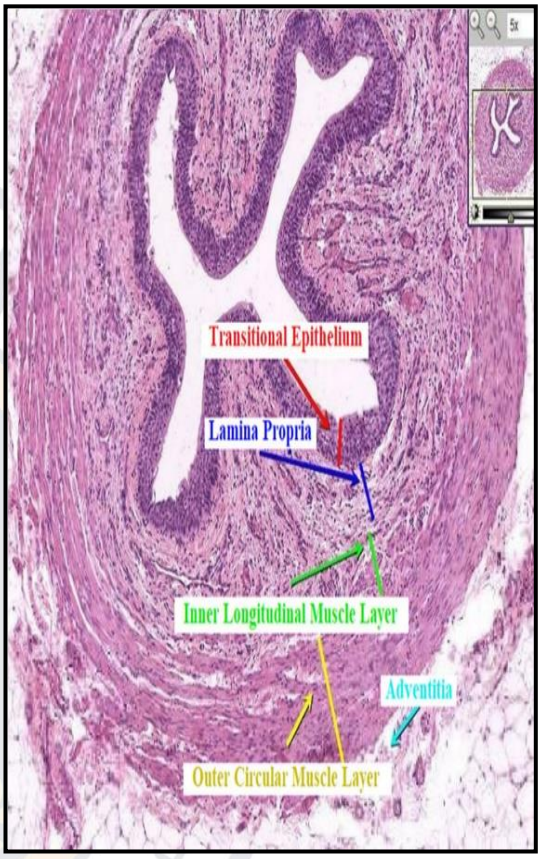
☒ The ejaculatory duct and prostatic duct open into it.

☒ **Epithelium:** It is lined with:

- Transitional epithelium.
- Pseudostratified columnar → distally.

☒ **It is surrounded by:**

- Outer circular layer of smooth muscle fibers which condense to form **(internal Sphincter of urinary bladder)**
- Inner longitudinal smooth muscle fibers.



B. Membranous:

☒ It is very short (1cm).

☒ It lies within the urogenital diaphragm.

☒ It is lined with stratified columnar epithelium.

☒ **It is surrounded by:**

- Striated muscle which form the **external Sphincter of urinary bladder.**
- Cowper's glands are present outside its wall.

C. Penile Urethra:

☒ It is the longest part.

☒ Within the penis.

☒ Its proximal part is dilated to form the bulb of urethra.

☒ Its distal part is dilated to form the fossa navicularis.

☒ **It is lined with:**

- Stratified columnar epithelium → proximally
- Stratified squamous → distally.

☒ **It is surrounded** by vascular C.T., smooth muscle fibers and glands of Littre.

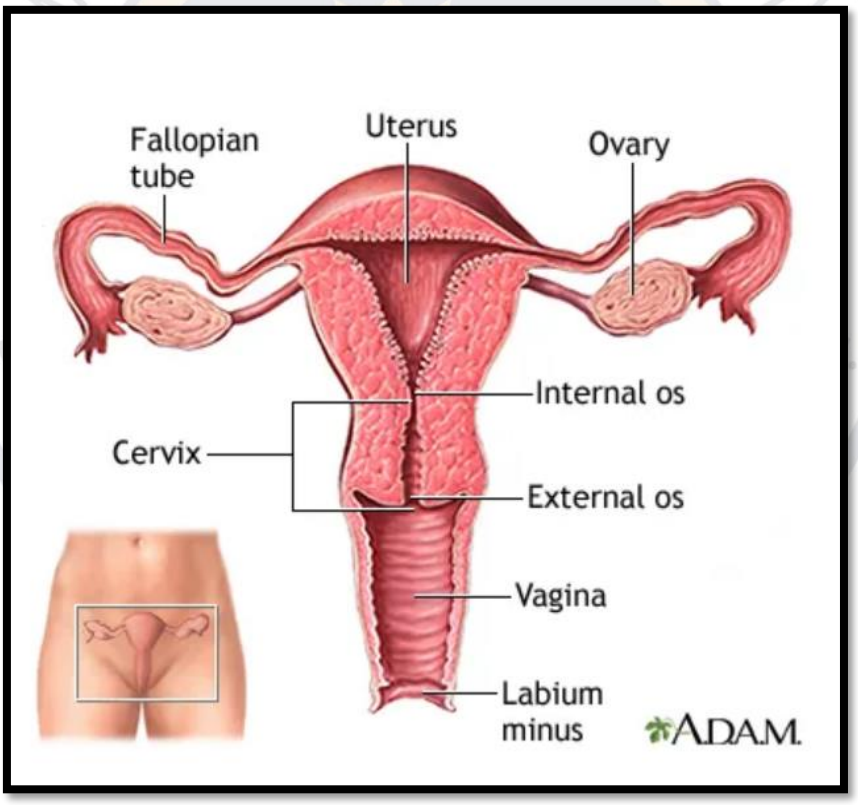
The female genital system

- **This system includes:**

(A) **<u>Primary sex organ</u>**: (the ovaries)

(B) **<u>Secondary sex organs</u>**:

1. Fallopian tubes.
2. Uterus.
3. Vagina.
4. External genitalia.
5. Mammary glands.



THE OVARY

- The ovary is a flattened almond-shaped body.
- **Histological structure:**

A. Stroma: Tunica albuginea:

- ☒ A whitish capsule.
- ☒ Formed of dense collagenous C.T.

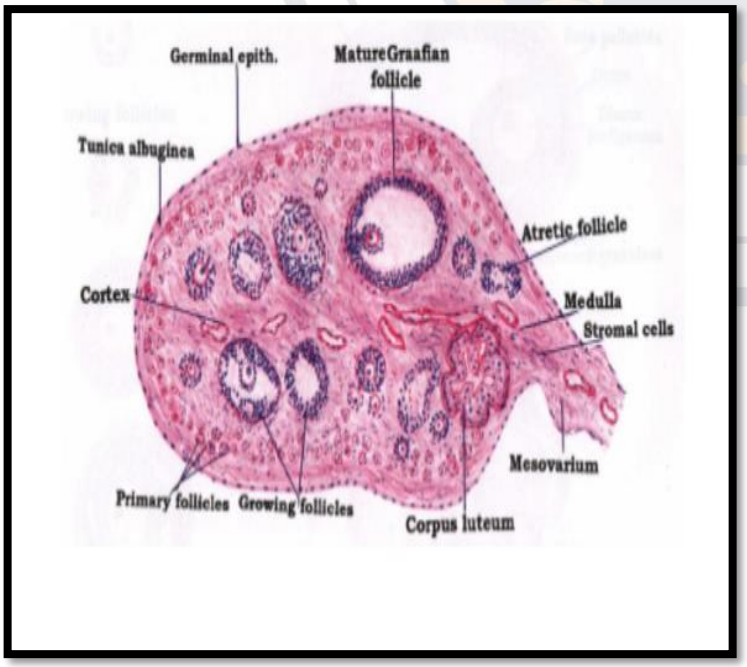
B. Stroma cells:

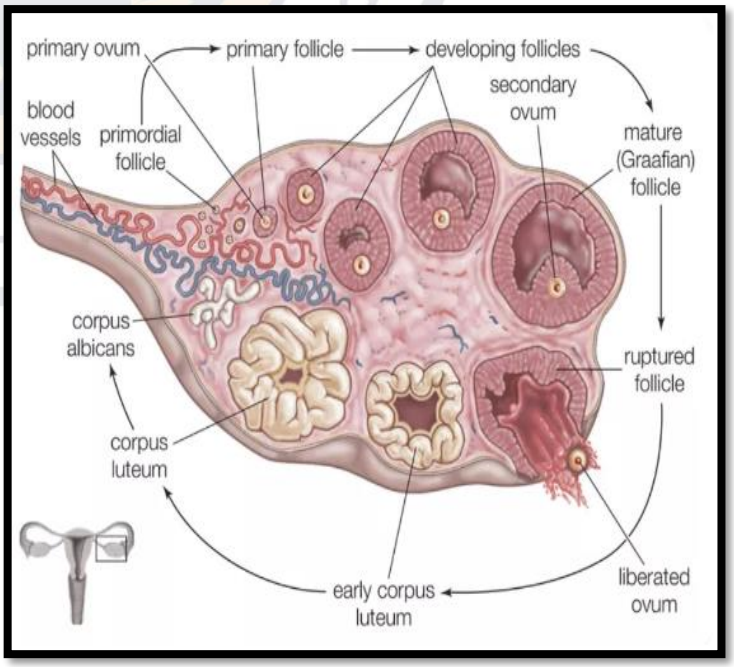
- ☒ These are fusiform cells with oval nuclei.

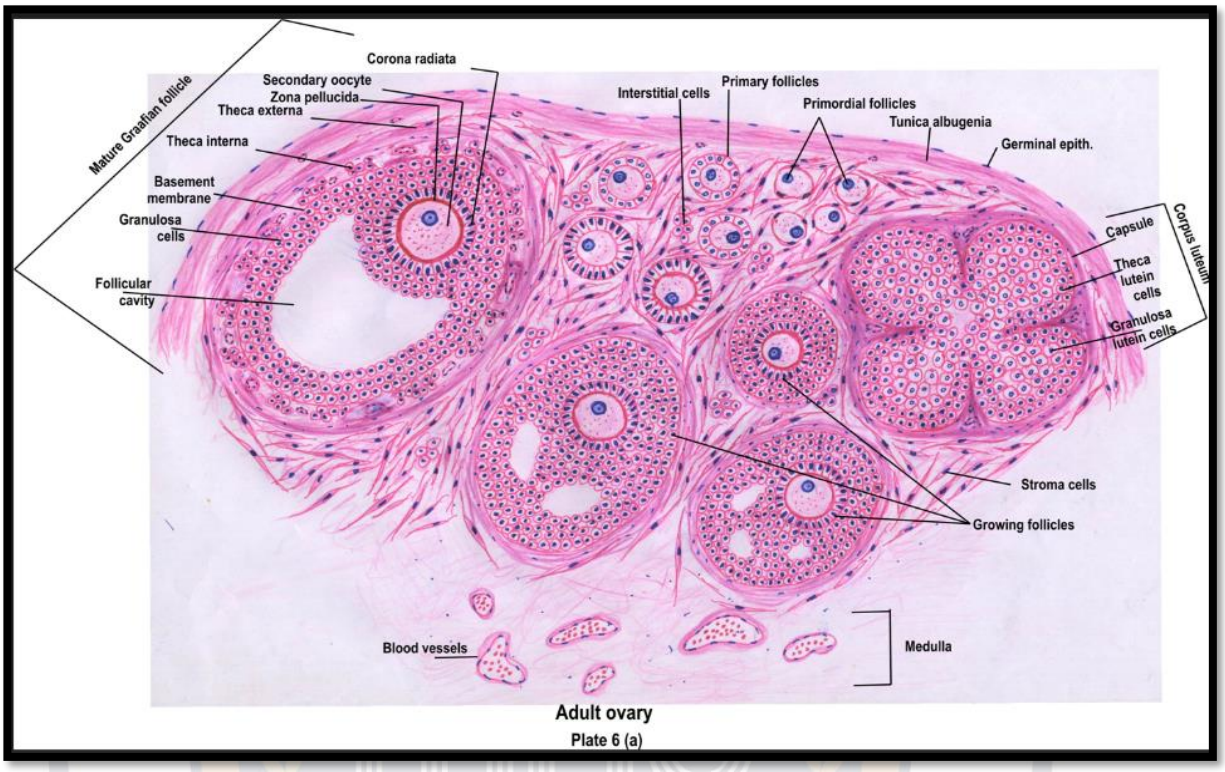
C. Reticular connective tissue: In between the follicles.

D. Parenchyma:

- ☒ Covering epihelium.
- ☒ Cortex.
- ☒ Medulla.







Adult ovary
Plate 6 (a)

Covering (Germinal) Epithelium

- ☒ The ovary is not covered with peritoneum.
- ☒ It is covered by a single layer of epithelial cells.
- ☒ This epithelium was called germinal because it was supposed to be the origin of oocyte but now, it is proved that it is not germinal as oocyte arises from the primordial germ cells.
- ☒ In adult, it is simple squamous epithelium.
- ☒ In young girls, it is simple cubical epithelium.

The Cortex

- ☒ The cortex of the ovary consists of:
  - **A. Ovarian follicles.**
  - **B. Interstitial gland.**

A. Ovarian Follicles

1. Primordial Follicles

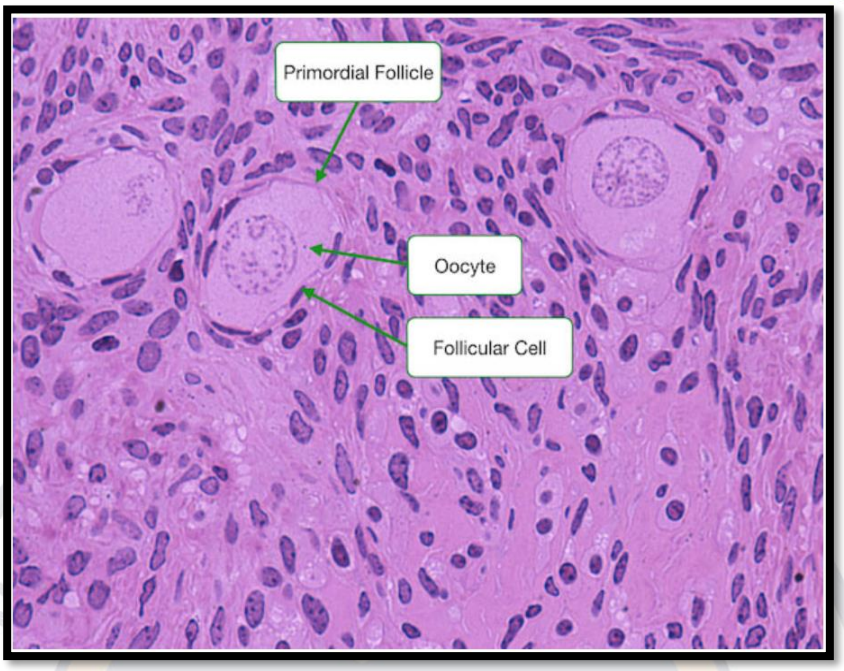
- **Number**: numerous and in groups.
- **Site**: under the tunica albuginea.
- **Size**: small.
- **Structure**:

☒ **Primary oocyte:**

- **Origin**:
  - From primordial germ cells of the yolk sac.
  - These cells migrate to the ovaries and form the oogonia which enlarge in size to form primary oocytes.
- **Size**: 30 µm.
- **Nucleus**:
  - Large vesicular, rounded and eccentric.
  - Contains 46 d-chromosomes.
- **Cytoplasm**:
  - Pale acidophilic.
  - Contains few yolk granules.
- **EM**: contains the usual organoids.

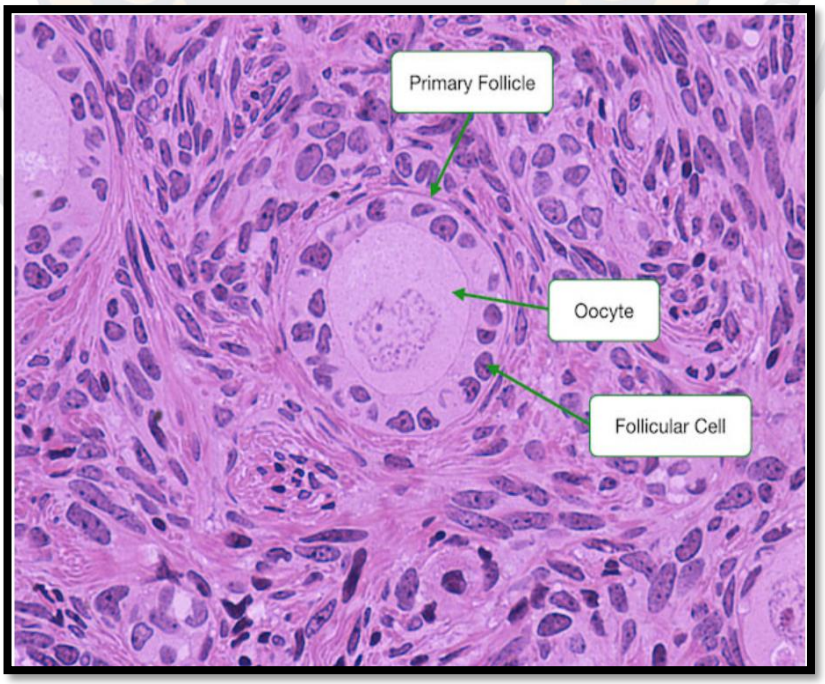
☒ **Follicular cells:**

- These are flat cells, which form a single layer around the primary oocyte.



2. Primary Follicles

- They are similar to the primordial follicles but:
- Primary oocytes are larger in size.
- Follicular cells become cubical, then columnar.



3. Growing Follicles

- **Site**: deep in the cortex.
- **Size**: double its size.
- **Structure**:

☒ **Primary oocyte:** As described above but:

- It doubles its size (60 µm).
- Its cytoplasm contains more yolk granules.
- It becomes surrounded by an acidophilic membrane called (**Zona pellucida**).
- **By EM** its cell membrane produces microvilli into the zona pellucida.

☒ **Zona pellucida:**

- It is an acidophilic membrane around the oocyte.
- It is glycoprotein in nature (stained with PAS).
- Produced by both the oocyte and follicular cells.
- The oocyte sends microvilli into it.
- Also the follicular cells send processes through it to provide the oocytes with nourishment.

☒ **Follicular cells:**

- In response to FSH, the follicular cells proliferate to form many layers.
- In response to LH, they begin to secrete follicular fluid, which accumulate in multiple spaces.
- These spaces join to form a single large cavity.
- This cavity pushes the oocyte to one side and divides the follicular cells into 2 groups:

a. **Cumulus oophorus:**

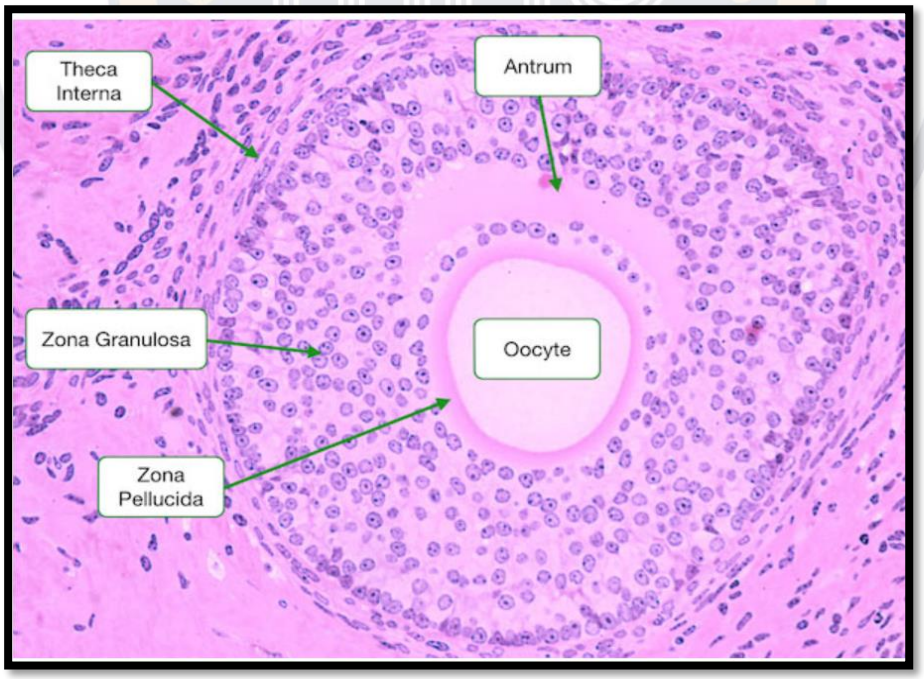
- These groups of cells surround the oocyte.
- They connect oocyte to one side of the follicle.

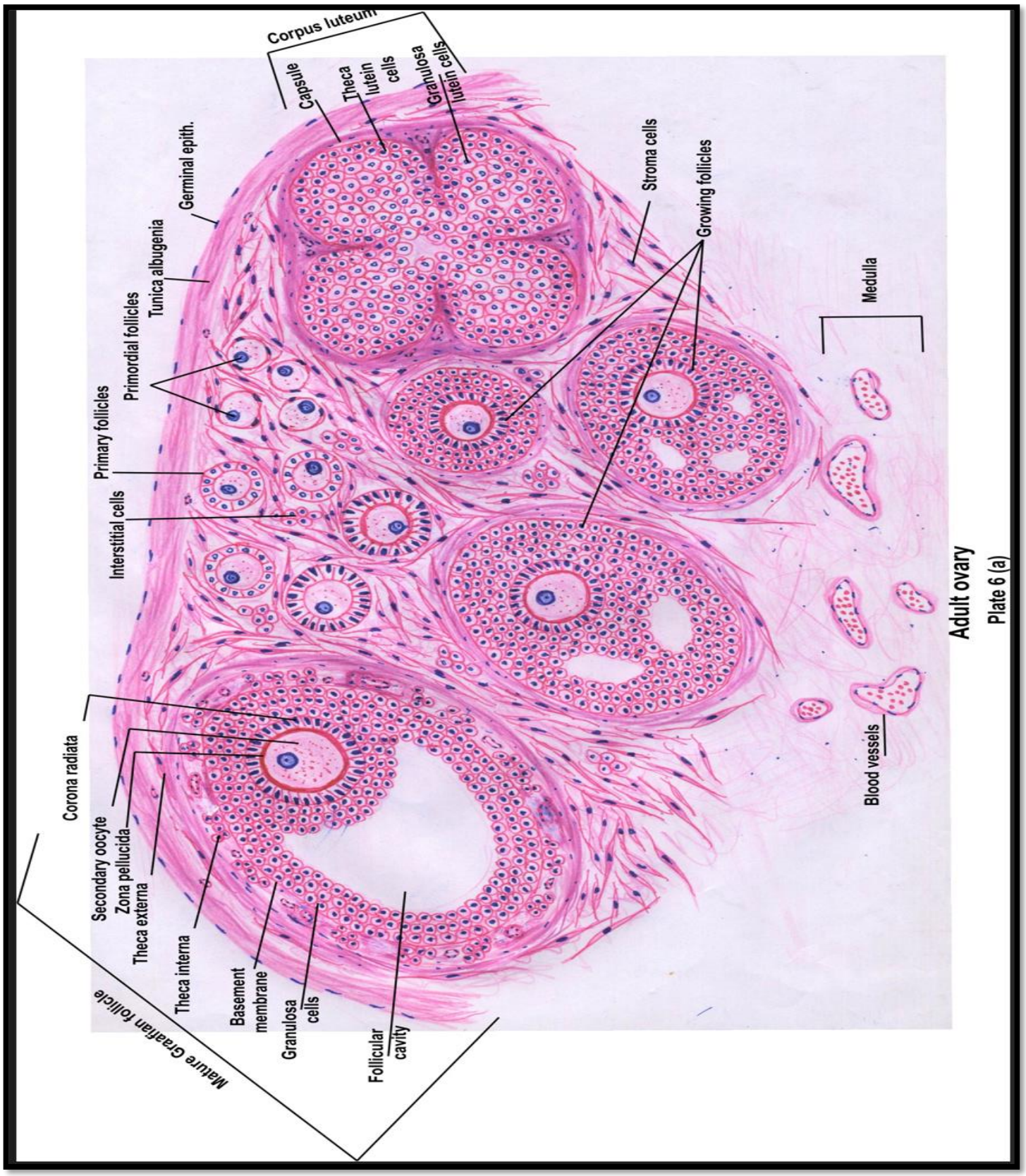
b. Granulosa cells:

- These groups of cells line the cavity.
- They are polygonal in shape.
- They have pale acidophilic cytoplasm.
- They have central rounded nuclei.
- They secrete estrogen hormone.

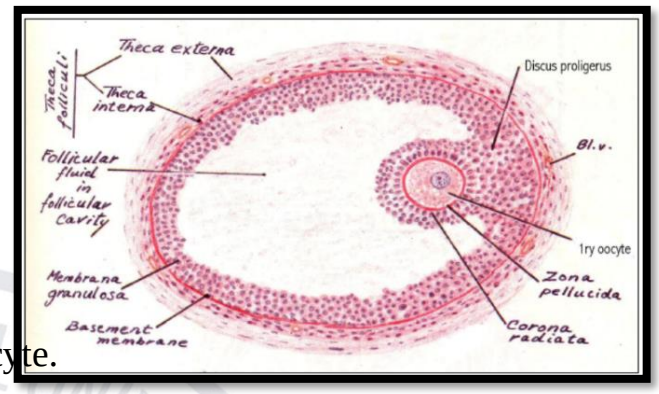
☒ Theca folliculi:

- As a result of growth of the follicles, the stroma cells become condensed around them to form a capsule called theca folliculi.
- The theca later differentiate into theca externa and theca interna (see mature graafian follicle).




Corpus luteum
Capsule
Theca lutein cells
Granulosa lutein cells
Germinal epith.
Tunica albugenia
Primordial follicles
Primary follicles
Interstitial cells
Stroma cells
Growing follicles
Medulla
Blood vessels
Adult ovary
Plate 6 (a)
Corona radiata
Secondary oocyte
Zona pellucida
Theca externa
Theca interna
Basement membrane
Granulosa cells
Follicular cavity
Mature Graafian follicle

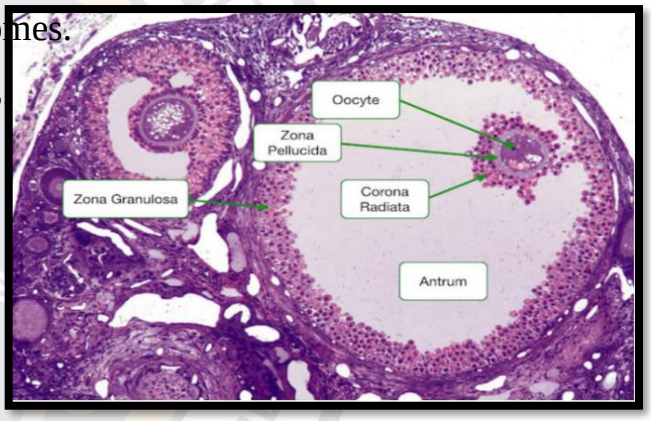
4. Mature Graafian Follicles



- **Site:** bulging on the surface of the ovary.
- **Size:** 1 cm.
- **Number:** one every 28 days.
- **Structure:**

☒ **Secondary oocyte:**

- **Origin:** first meiosis of primary oocyte.
- Similar to primary oocyte but:
  - **Size:** 120 µm.
  - **Nucleus**: contains 23 d-chromosomes.
  - **Cytoplasm**: full of yolk granules



☒ **Zona pellucida: described before.**

☒ **Follicular cells:**

- **Granulosa cells:** see before.
- **Cumulus oophorus:** see before.
- **Corona radiata:**
  - It is a layer of columnar cells surrounding the zona pellucida.
  - They send processes into the zona pellucida to give nutrition to the oocyte.
  - **Theca folliculi:** See before.
- It is differentiated into:

a. Theca interna (vasculosa):

- It is cellular, vascular and secrets estrogen.

b. Theca externa (fibrosa):

- It is fibrous and less vascular.

- **Fate of mature graafian follicle:**

☒ When the follicular fluid is markedly increased, the follicle ruptures and releases its secondary oocyte on the surface of the ovary (ovulation).

Ovulation

- **Definition:**
  - ☒ It is the rupture of a mature graafian follicle and discharge of the secondary oocyte into the peritoneal cavity.
  - ☒ It occurs once every 28 days.
- **Mechanism:**
  - ☒ At the middle of menstrual cycle, the LH reaches its peak and stimulates the follicular cells to increase the intrafollicular fluid causing rupture of the follicle.
  - ☒ The oocyte is released and the remaining part of the follicle forms the corpus luteum.

Corpus Luteum

- **Definition:**
  - ☒ It is a temporary endocrine structure secreting progesterone and some estrogen.
- **Formation:**
  - ☒ Rupture of the mature follicle and release of the oocyte (ovulation) causes a sudden drop of the intra-follicular pressure.
  - ☒ The wall of the follicle becomes folded and the aperture on its surface closes to form the corpus luteum.
  - ☒ The follicular fluid becomes mixed with blood.
- **Structure:**

1- Granulosa lutein cells: These are the zona granulosa of follicular cells.

- ☒ **Shape:** large polyhedral cells.
- ☒ **Nucleus:** central, rounded and vesicular.
- ☒ **Cytoplasm:** pale acidophilic.
- ☒ **EM:** rich in sER, mitochondria & lipid droplets.
- ☒ **Function:** secrete progesterone hormone.

2- Theca Lutein cells:

☒ These are the theca interna cells.

☒ They are similar to granulosa lutein cells but:

- Smaller in size.
- Have darkly stained nuclei.
- Secrete estrogen.

3- Fibrous capsule:

☒ It is the remaining part of the **theca externa** surrounding the corpus luteum.

Types of corpus luteum:

1- <u>Corpus luteum of menstruation:</u>

☒ If fertilization does not occur, the corpus luteum is maintained for 10-12 days under effect of **LH**.

☒ After this period, it starts to involute, its cells degenerate and stop secreting progesterone.

☒ Sudden drop of progesterone causes menstruation

☒ The corpus luteum then, changes into a white scar called “corpus albicans”.

2- <u>Corpus luteum of pregnancy:</u>

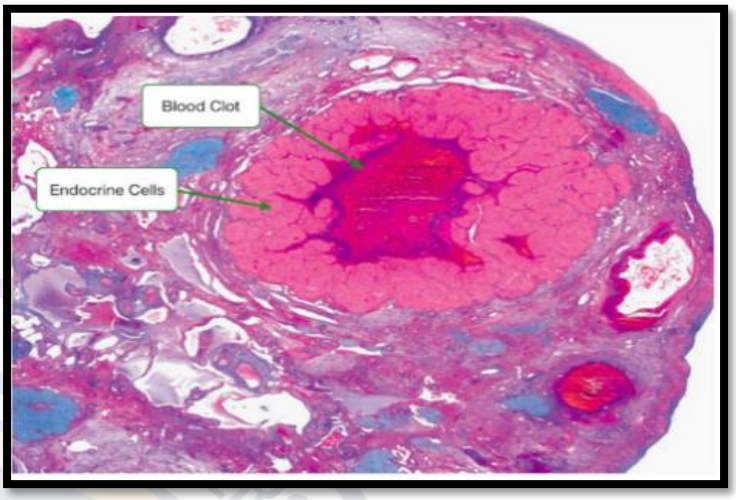
☒ If fertilization occurs, the corpus luteum continues to enlarge to about 5 cm under effect of HCG.

☒ It’s secretion of progesterone maintains pregnancy till the 3rd month when its function is taken by the placenta.

☒ After labour it involutes into “corpus albicans”.

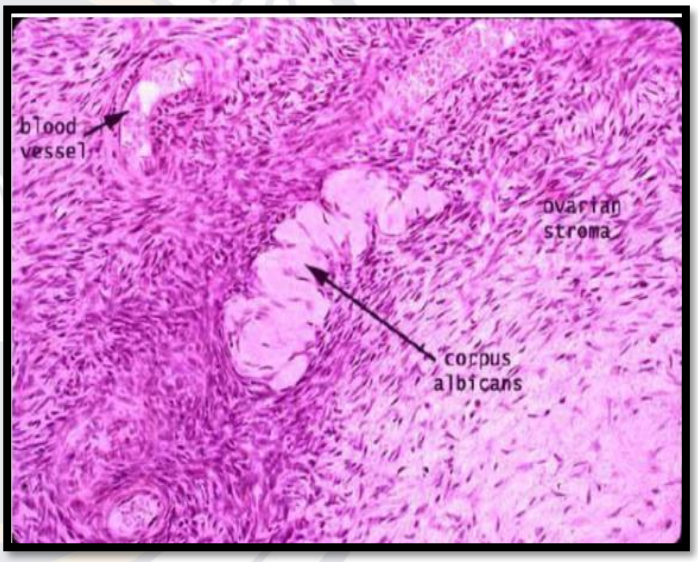
3- Corpus haemorrhagicum:

- ☒ The cavity of this type contains blood clot.
- ☒ It appears as a red spot on the surface of the ovary.
- ☒ It is useful in pregnancy test.



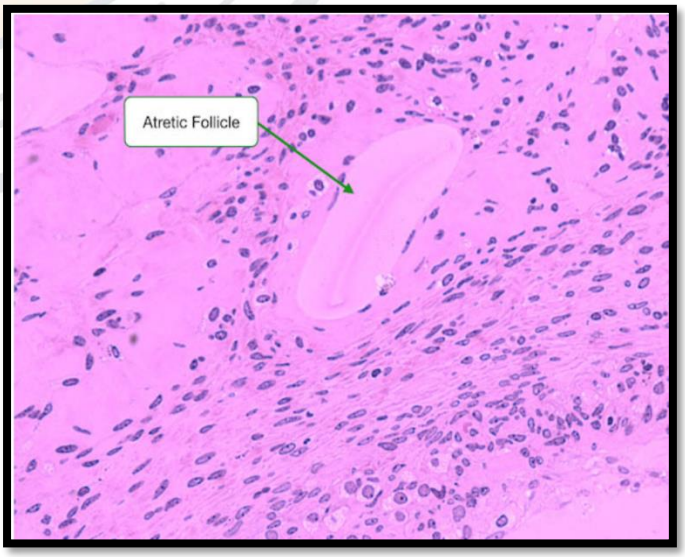
4- Corpus albicans:

- ☒ It is the involuted corpus luteum.
- ☒ It appears as a scar of dense collagenous tissue.



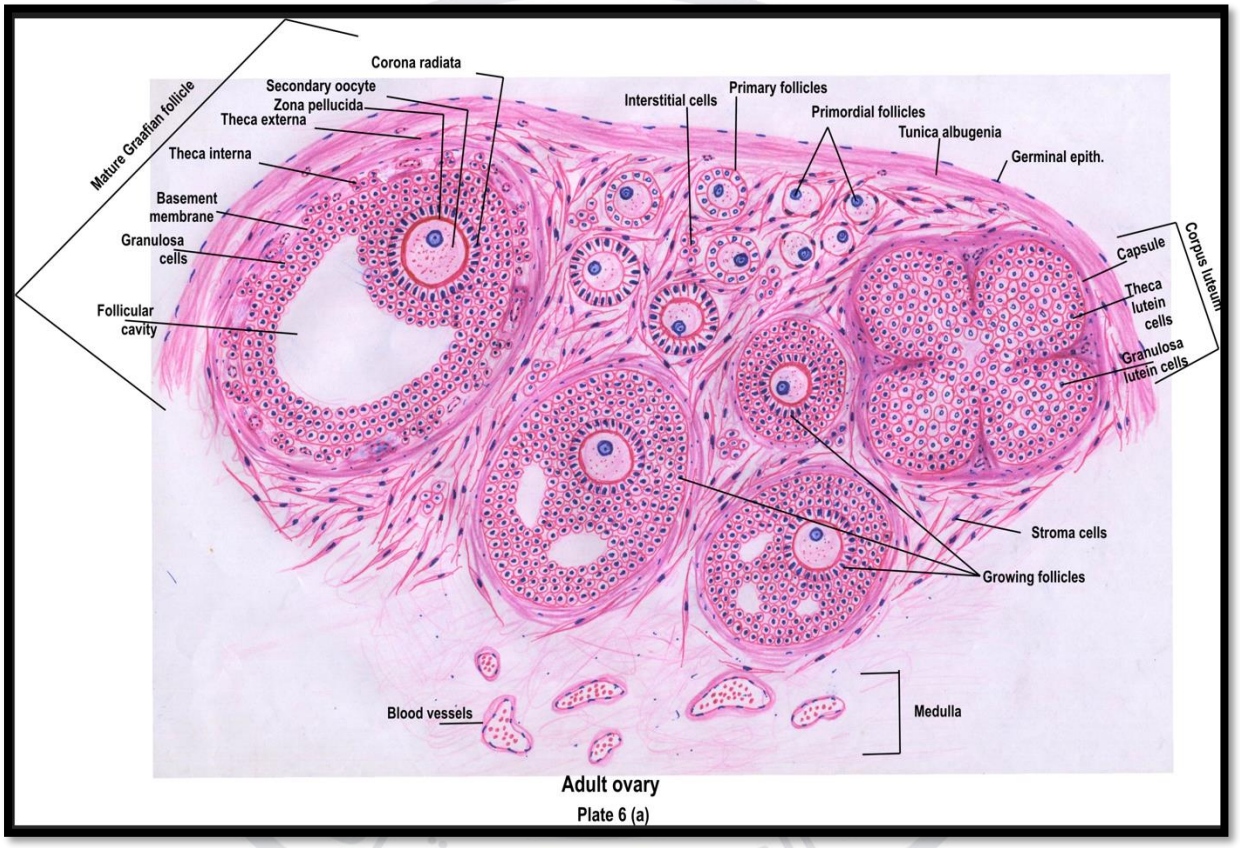
5- Corpus atreticum (atretic follicle):

- ☒ Only one of the growing follicles reaches maturity and ruptures every 28 days.
- ☒ The remaining follicles degenerate and are replaced by a fibrous C.T (atretic follicles).
- ☒ Some cells of theca interna will form the interstitial glands of the ovary.



B. The Medulla

- It consists of highly vascular loose connective tissue.
- It contains blood vessels, nerves and lymphatics.
- It also contains elastic fibres and few sm. m. fibres



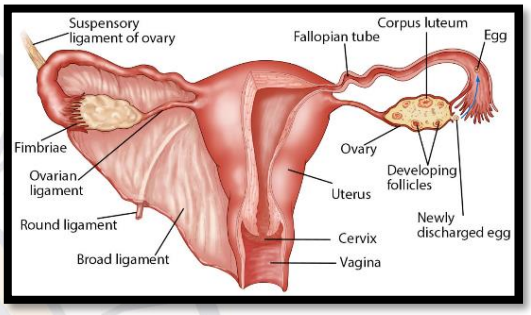
Adult ovary
Plate 6 (a)

C. Interstitial Glands of the ovary

- These are some cells of the theca interna of the atretic follicle.
- They are present in groups in the stroma.
- These are polygonal cells with central rounded nuclei and contain lipid droplets.
- They secrete estrogen.

THE FALLOPIAN TUBE
(Oviduct or Uterine Tube)

- **Definition:**
  - ☒ It is a highly mobile tube extending between the ovary and uterus.
- **Length:** about 12 cm.
- **Histological structure:**



A. Mucosa:

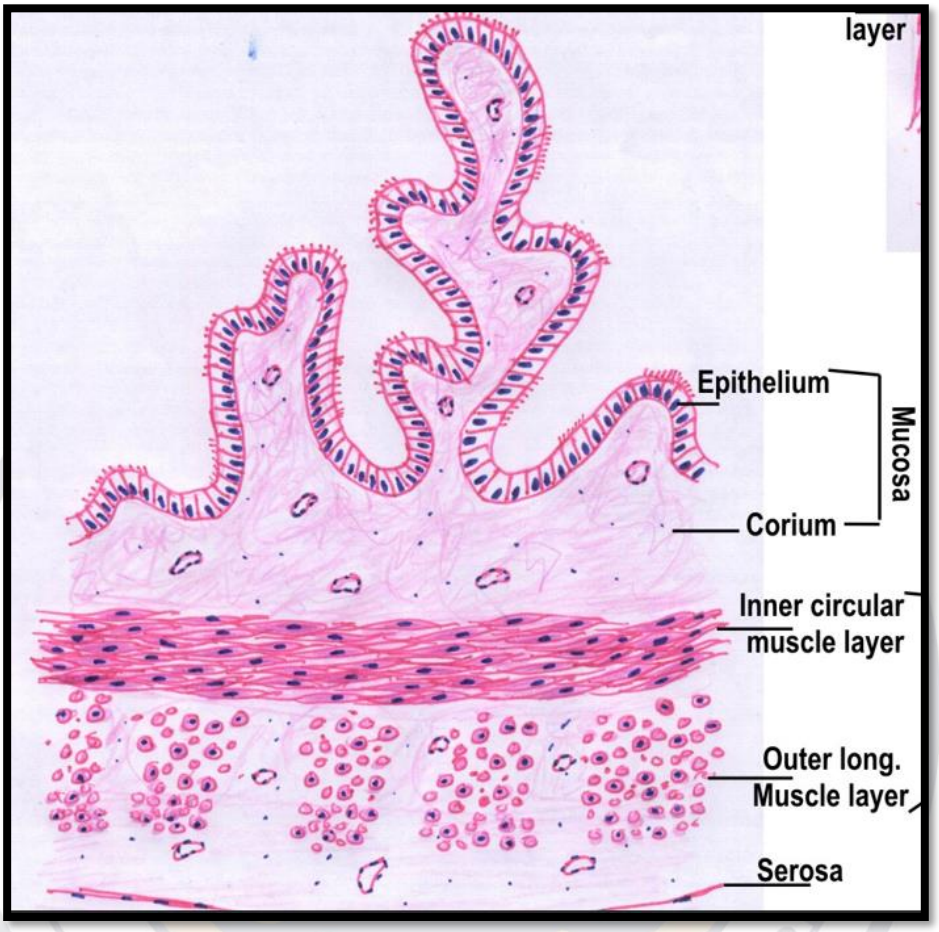
- ☒ It is highly folded, branching and anastmosing.
- ☒ **Epithelium:**
  - Simple columnar partially secretory and partially ciliated.
  - The cilia move the ovum toward the uterus.
  - The secretory cell secretes nutrients to the ovum.
- ☒ **Corium:**
  - Loose connective tissue rich in blood vessels.
- ☒ **N.B.:** cyclic changes occur in the mucosa of the tube during the secretory phase of the menstrual cycle.

B. Muscle layer:

- ☒ It consists of inner circular and outer longitudinal layers of smooth muscle fibres.

C. Serosa:

- ☒ It consists of a layer of loose C.T. covered with a layer of simple squamous mesothelial cells.


layer
Epithelium
Mucosa
Corium
Inner circular
muscle layer
Outer long.
Muscle layer
Serosa

THE UTERUS

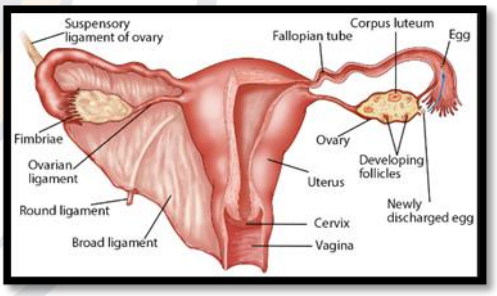
Anatomy:

- ☒ It is pear-shaped with thick wall and flat lumen.
- ☒ It is formed of a larger body, and smaller cervix.
- ☒ Its upper dome shaped part is called the fundus.

Histological structure:

A. Endometrium (mucosa): It is smooth with no folds.

1. **Epithelium:**
   - ☒ Simple columnar partly ciliated and partly secretory.
   - ☒ Interrupted by the openings of uterine glands.
2. **Corium: (endometrial stroma):** Formed of reticular network which contains:
   - ☒ Blood vessels.
   - ☒ Decidual (branched) cells.
   - ☒ Leucocytes and phagocytic cells.
   - ☒ Uterine glands which are:
     - Simple branched tubulo-alveolar.
     - Lined with columnar secretory cells.



<u>The endometrium is divided into two zones:</u>

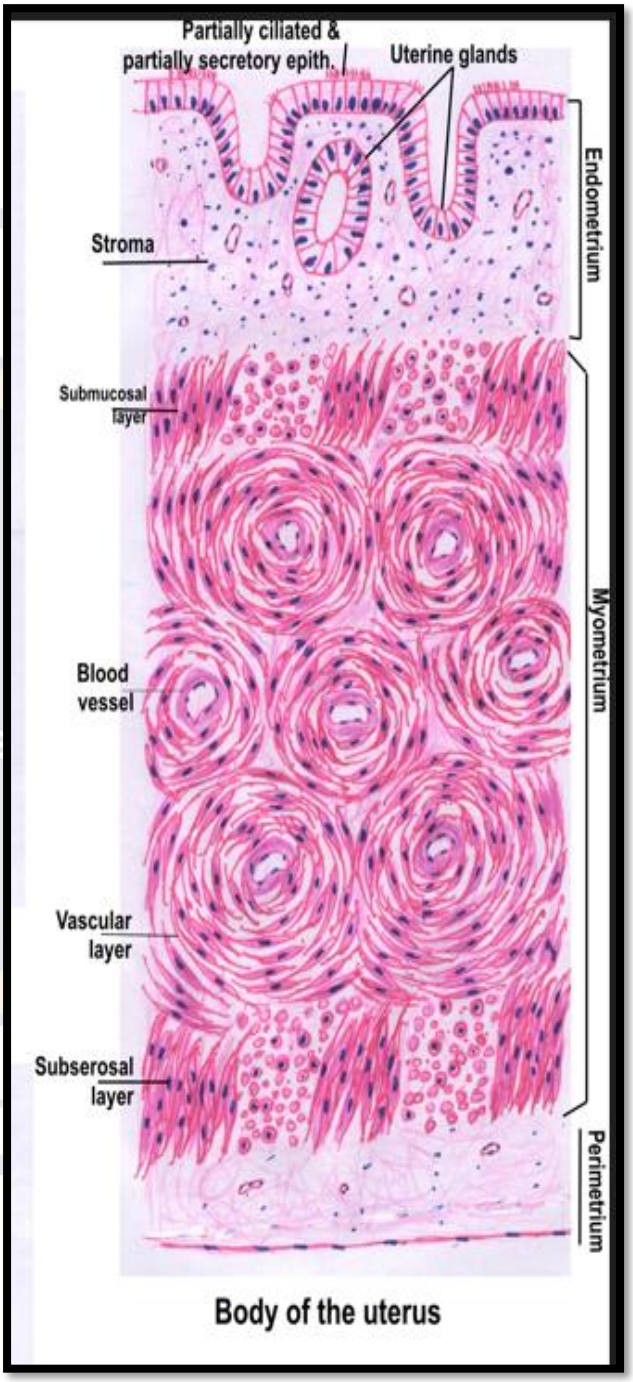
1. **Superficial functioning zone:**
   - It is shed off during menstruation.
   - It contains spiral arteries and the top of uterine glands.
2. **Deep (basal) zones:**
   - It is responsible for regeneration of the endometrium.
   - It contains straight arteries and the bottom of the glands.

B. Myometrium (musculosa): It is formed of three layers of sm. m. fibres:

1. **Submucosal (inner) layer:**
   - ☒ Thin layer of oblique and longitudinal fibres.
2. **Vascular (middle) layer:**
   - ☒ Thick layer of fibers arranged in spiral manner around blood vessels to give "8" shape.
3. **Supravascular (outer) layer:**
   - ☒ Thin layer of oblique and longitudinal fibers.
   - ☒ During pregnancy the smooth muscle fibres increase in size and number.
   - ☒ After delivery, the uterus is reduced in size to be involuted after 72 hours.

C. Perimetrium (serosa):

- ☒ Loose C.T containing blood vessels.
- ☒ Covered with simple squamous mesothelial layer.



The Uterine Cervix

- It is the lower segment of the uterus.
- Its lumen (the cervical canal) is narrow.
- It has a vaginal and supravaginal parts.
- Its wall consists of two layers:

A. Mucosa: It shows two longitudinal folds (anterior & posterior) and many transverse rugae.

1. **Epithelium:**
   - ☒ Simple columnar secretory at the internal os.
   - ☒ Stratified squamous at the external os.
2. **Corium:**
   - ☒ Connective tissue containing branched tubulo-alveolar mucous secreting glands.

B. The substance of the cervix:

1. Dense fibrous tissue.
2. Few muscle fibres (15%).
3. Rare elastic fibers.
   - ☒ During labour, the cervix becomes lax due to secretion of relaxin hormone by the ovary which leads to increase in the intercellular fluid and softening of the tissue of the cervix.

THE PLACENTA

It is a disc-shaped structure which is formed of:

A. Foetal part:

- ☒ The trophoblasts, which cover the chorion, proliferate to form finger-like processes called chorionic villi.
- ☒ These villi extend from the chorion to erode the endometrial stroma.
- ☒ They branch and anastomose freely causing rupture of the congested vessels thus, they become separated by inter-villous spaces containing maternal blood.
- ☒ Each chorionic villus consists of:

1. **A central core:** Mesenchymal tissue containing foetal blood.
2. **Epithelial covering (2 layers of trophoblast):**
   - **i. Cyto-trophoblast :**
     - It is the inner pale layer.
     - Cubical cells with clear boundaries.
   - **ii. Syncytio-trophoblast:**
     - It is the outer dark layer.
     - Have indistinct boundaries.
     - Show microvilli covered with fibrinoid coat.
     - After the fourth month of pregnancy, the cyto-trophoblast disappears.

B. Maternal part:

- ☒ This is the decidua basalis which is the part of the endometrium surrounding the villi.
- ☒ Its stroma cells show marked decidual reaction.

The placental barrier:

☒ It is the barrier between foetal and maternal blood.

☒ It consists of:

- Endothelium of foetal capillaries
- Basement membrane of foetal capillaries.
- Mesenchymal connective tissue.
- Thick basement membrane.
- The syncytio-trophoblast.

Functions of the placenta:

☒ The placental barrier provides the foetus with nourishment and oxygen from the maternal blood.

☒ Secretion of placental hormones:

i. Chorionic gonadotrophin.
ii. Somatomammotrophin (growth and prolactin).
iii. Chorionic thyrotrophin (TSH).

☒ The fibrinoid coat acts as immune barrier which prevent contact between the foetus and maternal lymphocytes thus prevent rejection of the foetus.

THE VAGINA

The wall of the vagina consists of:

1. **Mucosa:** It shows transverse ridges or rugae.

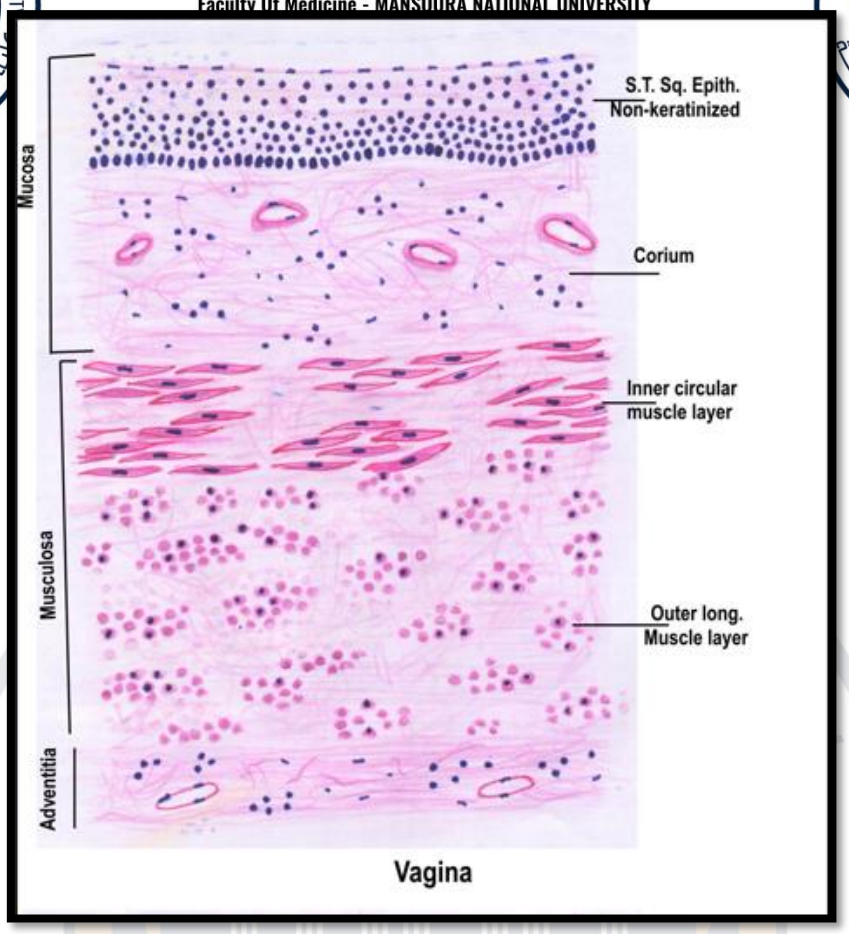
☒ Epithelium:

- Stratified squamous non-keratinized.
- Rich in glycogen giving nutrition to sperms.
- When glycogen is fermented, it forms lactic acid which prevents the harmful bacteria to penetrate the vagina.

☒ Corium:

- It is dense C.T. rich in elastic fibers.
- It contains blood vessels and lymphocytes.
- Has no glands.

2. **Musculosa:**
   - Thin inner circular smooth muscle fibers.
   - Thick outer longitudinal smooth muscle fibers.
3. **Adventitia:**
   - It is dense fibrous C.T. rich in blood vessels, nerves and lymphatics.



Vaginal Smear

☒ It is smear taken from vagina, cervix and endometrium.

☒ It can detect the following:

1. **Ovulation time:**
   - The epithelium tends to be keratinized.
   - The cells are acidophilic with dark nuclei.
2. **Estrogen deficiency:** epithelium shows atrophy.
3. **Efficiency of estrogen therapy:** The epithelium is thick and keratinized.
4. **Early diagnosis of cancer.**

EXTERNAL GENITALIA

1- Labia majora:

- They are folds of adipose C.T. + smooth muscle fibers + elastic fibers.
- It is covered with pigmented hairy skin.

2- Labia minora:

- They are thin folds of non fatty C.T & blood vessels.
- It is covered with pigmented & non hairy skin.

3- Clitoris:

- It consists of 2 erectile bodies (correspond to penis).
- It is rich in sensory nerves.

4- The hymen:

- It is thin fold of mucous membrane rich in blood vessels.
- Covered in both sides by stratified squamous epithelium.
- It partially covers the vaginal opening in virgin.

5- Bartholin gland:

- They are mucous secreting gland.
- They open into the inner surface of labia minora.

6- Female urethra:

- It is a muscular tube 2-6 cm.
- Lined with transitional epithelium near the bladder, change in pseudostratified columnar then stratified squamous at its opening.
- Surrounded by inner longitudinal and outer circular smooth muscle fibers
- At external orifice, striated muscles form external sphincter.

THE MAMMARY GLANDS

Type:

These are a pair of compound alveolar glands.

Structure:

I. The Resting Mammary Gland

(In the adult non pregnant female)

A. Covering skin:

☒ The gland is covered with thin skin which shows:

1. **The areola:**
   - A central pink area of skin.
   - It becomes permanently pigmented during pregnancy.
   - Glands of Montgomery are modified sweat glands under the areola.
2. **The nipple:**
   - An elevation in the centre of the areola.
   - It consists of dense connective tissue and smooth muscle fibres.
   - It contains a number of lactiferous ducts.

B. Stroma:

1. **Inter-lobar septa:**
   - Thick fibrous C.T called “susppensory ligaments of cooper”.
   - They divide the gland into 15-20 lobes.
2. **Inter-lobular septa:** Divide the lobes into lobules.
3. **Adipose connective tissue:** In both inter-lobular and inter-lobar septa.
4. **Loose connective tissue:** It contains fibroblasts, lymphocytes, plasma cells and macrophages.

C. Parenchyma:

☒ The resting mammary gland consists of duct system only with no secretory units.

1. **Intra-lobular ducts:**
   - Found inside the lobule.
   - Lined with two layers of cubical cells.
2. **Lactiferous ducts:**
   - They result from union of intra-lobular ducts.
   - They become dilated to form lactiferous sinus just before their opening on the summit of the nipple.
   - Their proximal parts are lined with stratified columnar epithelium.
   - The lactiferous sinuses and terminal parts are lined with stratified squamous epithelium.

II. The Mammary Gland at Pregnancy

A. Covering skin.

B. Stroma:

- See before.
- The intra-lobular C.T. is reduced in amount.

C. Parenchyma:

1. **Duct system:**
   - See before.
   - Proliferates with new branches.
2. **Alveoli:**
   - They begin to appear at the 6th month.
   - They are lined with columnar epithelium.
   - They are surrounded by myoepithelial cells.

- In later months, special secretion "colostrum" appears in the alveoli which are rich in protein.

Hormones causing enlargement of breast at pregnancy:

- Ovarian hormonal: estrogen and progesterone.
- Placental hormones: (somatomammotrophin and progesterone).
- Anterior pituitary: (growth hormone and prolactin).
- Suprarenal: (glucocorticoids).

III. Lactating Mammary Gland

☒ **Type:**

- It is a compound alveolar gland.
- It is apocrine as the apical part of the cells is lost during secretion.

☒ **Structure:**

A. Covering skin.

B. Stroma: See before.

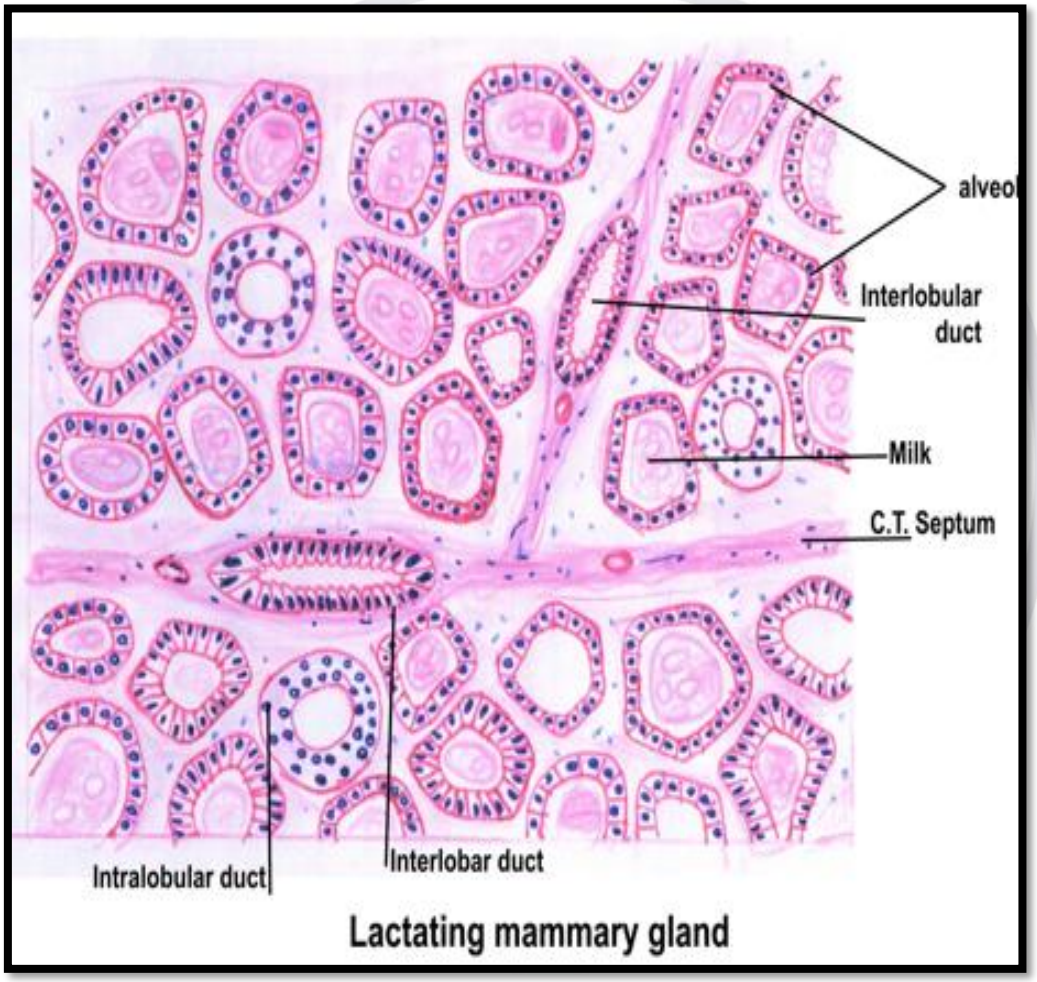
- The intra-lobular C.T is reduced and the septa are thin as the lobules are packed with alveoli & ducts.

C. Parenchyma:

1. **Duct system: (see before).**
2. **The alveoli:**
   - Some are lined with columnar & others by cubical cells.
   - They are surrounded by myoepithelial cells.
   - Some are distended with milk & others are empty.
   - Milk secretion appears vacuolated due to dissolved fat droplets.

Hormones involved in lactation:

1. Prolactin secreted by mammotrophs, stimulates the alveolar cells to form milk.
2. Oxytocin → contraction of myoepithelial cells → squeezes the alveoli → ejects milk (ejection reflex).



FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

PATHOLOGY

Pituitary , Adrenal and Pancreas

Pitutary gland

"Master endochrine gland."

Parts:

1 **.Adenohypothesis** (Anterior pitutary).

2. **Neurohypithesis** (Posterior pitutary).

❖ Disorders of the anterior pituitary

1-Hyperpitutary syndromes:

Caused by:

-Hyperplasia ,

-Functioning adenomas of anterior pituitary is the most cause, may produce Prolactin, Growth Hormone, and ACTH

-Carcinoma (rare).

2-Hypopituitarism

(1)Congenital anomalies (agenesis-Aplasia-hypoplasia).

(2)Sheehan's syndrome which is Post-partum Pituitary Necrosis; Coagulative necrosis, followed by fibrosis.

(3) Destruction of the pituitary by a pituitary adenoma, surgery, radiation or trauma ,metastatic tumors.

❖ Tumors of the anterior pituitary

Pituitary Adenoma

NE: Adenomas appear as a lobulated mass covered by a thin, attenuated shiny capsule.

ME:

Tumors have a uniform in appearance with fibrovascular stroma; cells classified as acidophilic, basophilic or chromophobic based on content of hormone secretory cells.

●Crooke hyaline change is characterized by large cells with a glassy hyaline appearance (due to accumulation of keratin filaments).

Craniopharyngioma

They are benign epithelial neoplasm of sellar region, arise from epithelial remnants of Rathke's Pouch.

Age: children and young adults.

NE:

Craniopharyngiomas are calcified yellow (due to cholesterol crystal deposits).

Cross-sections reveal multiple cystic areas containing oily fluid.

ME:

-May appear well circumscribed

-Cords, lobules, nodular whorls and trabeculae of well differentiated squamous epithelium bordered by palisading columnar epithelium

-Peripheral cells surround looser plumper cells called stellate reticulum

-Nodules of plump, anucleate squamous cells (ghost cells) and wet keratin

Diseases of supra-renal gland

Cortical hyperfunction: due to Hyperplasia, adenoma or carcinoma of the adrenal cortex.

Effects:

1 .Conn's disease:aldosterone hypersecretion.

2 .Cushing syndrome:glucocorticoides hypersecretion

3. Adrenogenital syndrome:androgen hypersecretion.

Cortical hypofunction

A.Acute adrenal insufficiency leads to shock and death

-Waterhouse-Friederichsen Syndrome: Acute Hypofunction occurs in association with overwhelming bacteremia (usually Meningiococcus).

B. Chronic adrenal insufficiency leads to Addison's disease

Causes:

1-Idiopathic Atrophy (60-75%)

2 -An autoimmune disease

3-Tuberculosis

4-Amyloidosis

5-Metastatic Carcinoma [lung]

❖ Tumors of suprarenal gland

Primary

Cortex	**Medulla**
*Cortical Adenoma	Ganglioneuroma*
*Cortical carcinoma	Pheochromocytoma*
	*Neuroblastoma

Secondary

*lung

*breast

*melanomas

- **Ganglioneuroma**

Benign tumor composed of ganglion cells and nerve fibers (schwanian stroma)

Neuroblastoma

Highly malignant tumor of children under the age of 4 years.

N/E:

Large, soft mass with yellow areas of necrosis and red areas of hemorrhage.

M/E:

The tumor consists of small blue malignant round cells with dark nuclei "neuroblasts" arranged in sheets or in rosettes.

- **Pheochromocytoma**

Paraganglioma of the adrenal medulla composed of chromaffin cells that produce catecholamines.

ME:- Nested, trabecular or solid arrangement.

-Cells: large, polygonal, uniform or extensively vacuolated.

-Cytoplasm: abundant fine, granular red-purple cytoplasm.

Diseases of Endocrine Pancreas

Diabetes Mellitus (DM)

A group of metabolic disorders characterized by hyperglycemia caused by defects in insulin secretion, insulin action, or both.

DM causes secondary damage in multiple organ systems, especially the blood vessels, kidneys, eyes, and nerves.

Clinically:

A.Classic triad of symptoms: Polyuria +polydipsia +polyphagia

B. Elevated plasma glucose level confirmed by :

-Fasting plasma glucose >126 mg/dL.

-Random plasma glucose ≥ 200 mg/dL (in a patient with classic clinical signs or in repeated measures).

-Glycated hemoglobin (HbA1C) level ≥6.5%.

Types

I.Type 1 DM:

Etiopathogenesis:

-Autoimmune disease due to production of autoantibodies against ß cell antigens.

ß cell destruction.

-Absolute insulin deficiency .

-Associated with:Specific class I, MHC genes (HLA-DR 3,4).

-Environmental factors: as mumps, rubella, and coxsackie B virus infections.

II Type 2 DM:

Etiopathogenesis:

1.Insulin resistance* (failure of target tissues to respond normally to insulin) associated with obesity or metabolic syndrome.

2. Beta cell dysfunction*: B cells compensate for insulin resistance by hypersecretion, followed by ß cell failure, and diabetes.

Complications

Mechanism :

Formation of advanced glycation end products (AGEs)* that bind to receptors (RAGE)* on inflammatory, endothelial and vascular smooth muscle cells leads to:

•Release of cytokines, growth factors, reactive oxygen species.

•Inflammation.

•Deposition of basement membrane material, extracellular matrix.

•Neovascularization, increased vascular permeability.

Trapping of low-density lipoprotein (LDL) within AGE-modified large-vessel walls > accelerated atherosclerosis.

Complications

1. Diabetic Macrovascular Disease (Macroangiopathy)

2 .Diabetic Microangiopathy:

.a. Diabetic nephropathy.

.b. Ocular complications .

.c. Diabetic neuropathy.

3 .Increased liability to infections.

4 .Impaired wound healing.

5 .Diabetic foot

6. Diabetic coma.

<u>1 .Diabetic Macrovascular Disease (Macroangiopathy)</u>

Its hallmark is accelerated atherosclerosis (greater severity and earlier age at onset).

•Affect the aorta and large- and medium-sized arteries.

Outcomes:

-Myocardial infarction (coronary atherosclerosis), is the most common cause of death in diabetics.

-Cerebral ischemia and infarction.

-Peripheral vascular diseases: intermittent claudications and gangrene of the lower extremities.

-Renal artery atherosclerosis.

2. Diabetic Microangiopathy

Its hallmark is diffuse thickening of basement membranes.

Affects:

Capillaries of the skin, skeletal muscle, retina, renal glomeruli, and renal medulla.

•Non-vascular structures: renal tubules, Bowman capsule, nerves.

Outcomes development of :

.a. Diabetic nephropathy.

.b. Diabetic retinopathy and ocular complications .

.c. Diabetic neuropathy.

Diabetic Nephropathy

•Renal failure is the second cause of death in diabetics.

Categories:

1.Glomerular lesions:

-Thickening of glomerular capillary basement membranes

-Nodular glomerulosclerosis (Kimmelstiel-Wilson lesion)

2 .Thickening of tubular basement membran

3.Renal vascular lesions: atherosclerosis and hyaline arteriolosclerosis.

4 .Pyelonephritis more severe than non-diabetics.

5. Necrotizing papillitis (acute papillary necrosis): special pattern of acute pyelonephritis more frequent in diabetics than in non-diabetics.).

Occular complications of DM

1.Cataract

2.Glucoma

3.Non proliferative retinopathy: edema, hemorrhage, exudate, aneurysms and thickening of retinal papillae.

4. Proliferative retinopathy: Neovascularization and fibrosis, vitreous hemorrhages (more risk of blindness and retinal detachment).

Outcomes: Visual impairment, retinal detachment, total blindness.

Diabetic Neuropathy

•Due to microangiopathy +direct axonal damage.

Includes:

1 .Peripheral, symmetric neuropathy: of the lower extremities (mainly sensory than motor function).

2 .Autonomic neuropathy: disturbances in bowel and bladder function.

3. Mononeuropathy: footdrop or wristdrop or isolated cranial nerve palsies.

Other complications

A. Increased liability to infections: due to hyperglycemia + defects in leukocyte functions and cytokine production.

•Skin, respiratory and urinary tract infections .

•Tuberculosis, fungal infections and AIDS.

B. Impaired wound healing (sensory loss, poor circulation and immune response, infection).

C. Diabetic foot: ulceration, infection, gangrene due to *neuropathy *poor circulation and increased liability to infection

D. Diabetic coma:

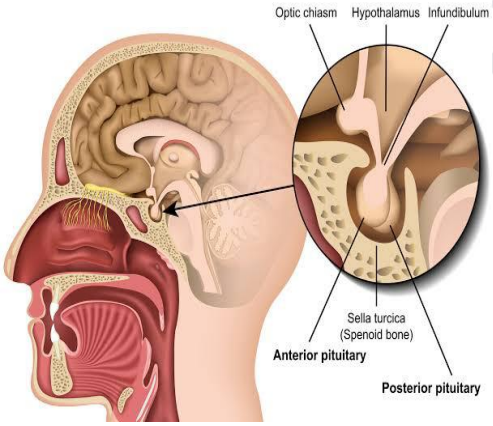
•Diabetic ketoacidosis (common in type 1DM).

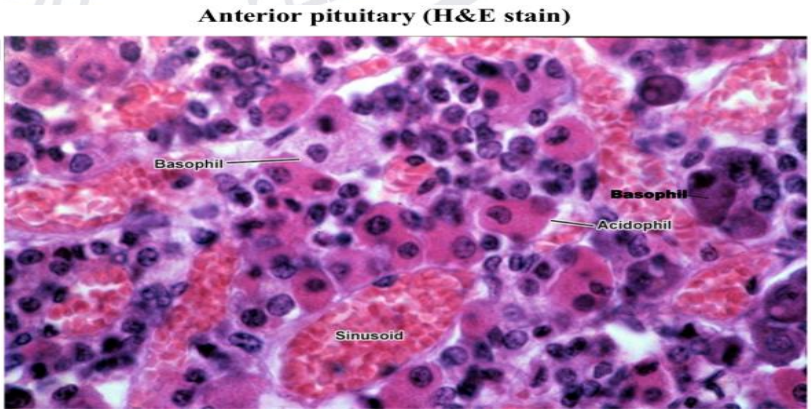
• Hypoglycaemic coma.

Type 1 Versus Type 2 Diabetes Mellitus

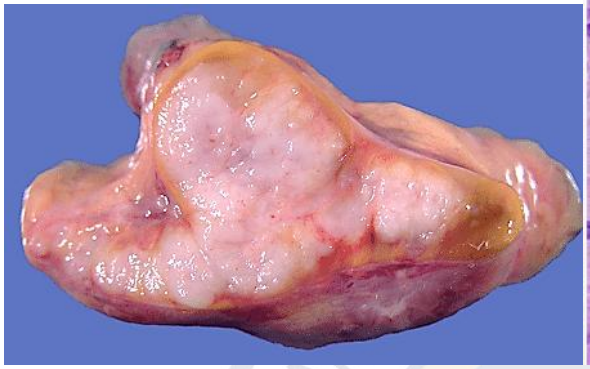
Features	T 1DM	T 2DM
Age Incidence Weight/ass. diseases Risk of coma	▪ Childhood and adolescence ▪ 5% to 10% of cases ▪ Normal or weight loss ▪ Diabetic ketoacidosis	▪ Usually in adulthood (40y) ▪ 90% of cases ▪ Obesity and metabolic syndrome ▪ Non-ketotic hyperosmolar coma
Beta cell mass	▪ Depletion	▪ Mild depletion
Insulin level	▪ Reduced	▪ Increased (early); normal or moderate decrease (late)
Islet autoantibodies	▪ Present	▪ Absent
Etiology	▪ Autoimmune destruction and loss of β cells due to failure of self-tolerance	▪ Insulin resistance ▪ β cell dysfunction
Genetic linkage	▪ MHC class I and II genes; HLADR3, 4	▪ Diabetogenic and obesity-related genes
Pathology (islets of Langerhans)	▪ Insulitis ▪ Decreased number and size of islets	▪ Normal islets at early stage ▪ Amyloid deposition in islets (late)

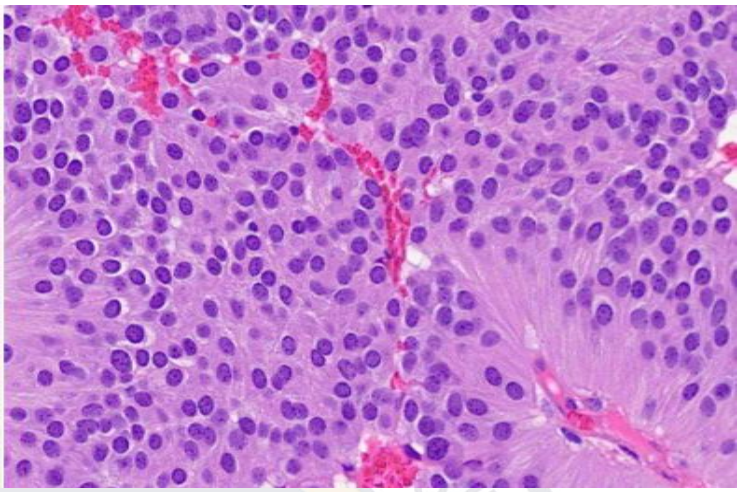
Photo gallery



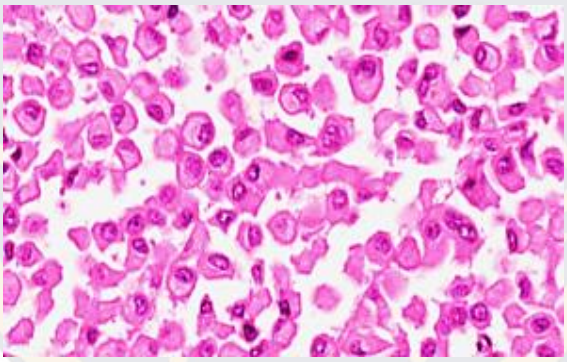


Normal pituitary gland

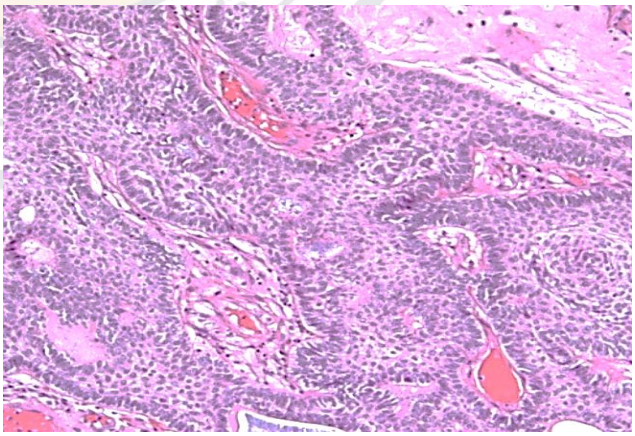




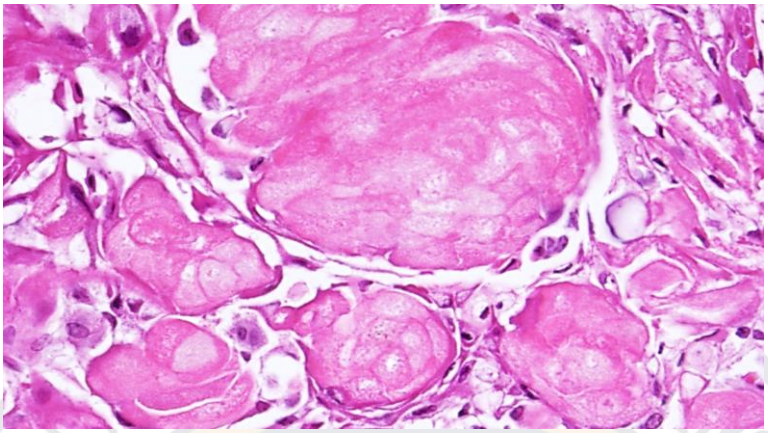
Pituitary adenoma NE & ME

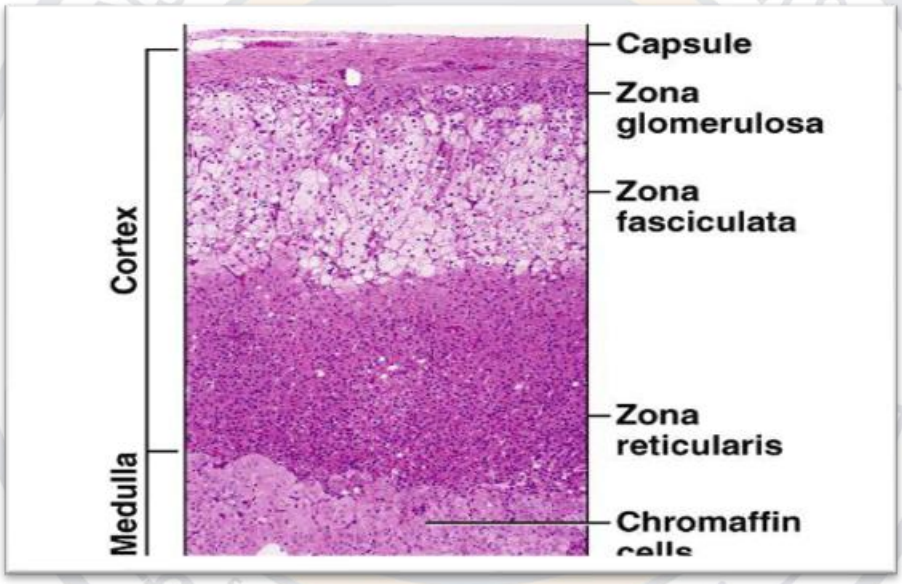


Pituitary adenoma (Crooke hyaline change)

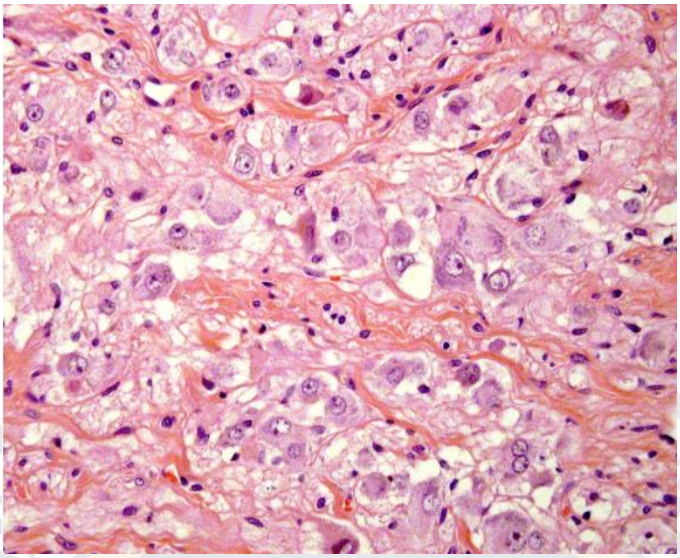


Craniopharyngioma NE & ME

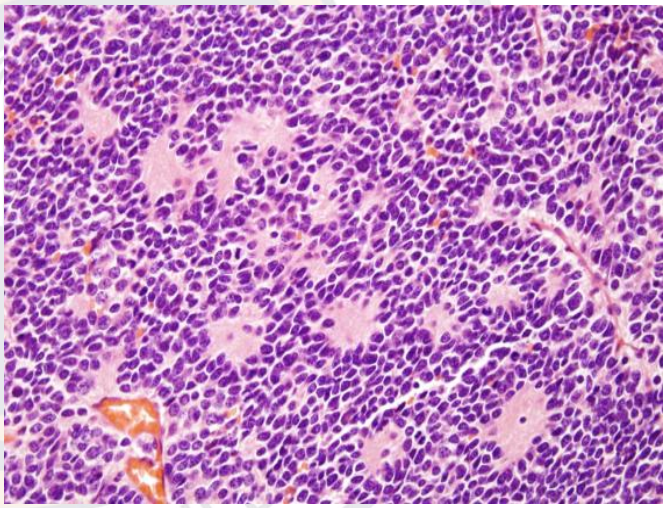




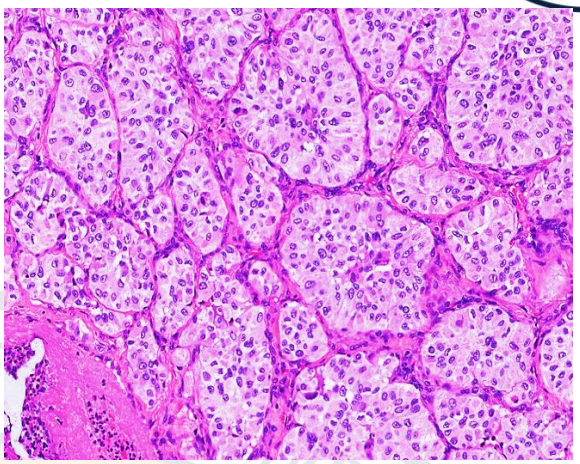
Normal histology of suprarenal gland



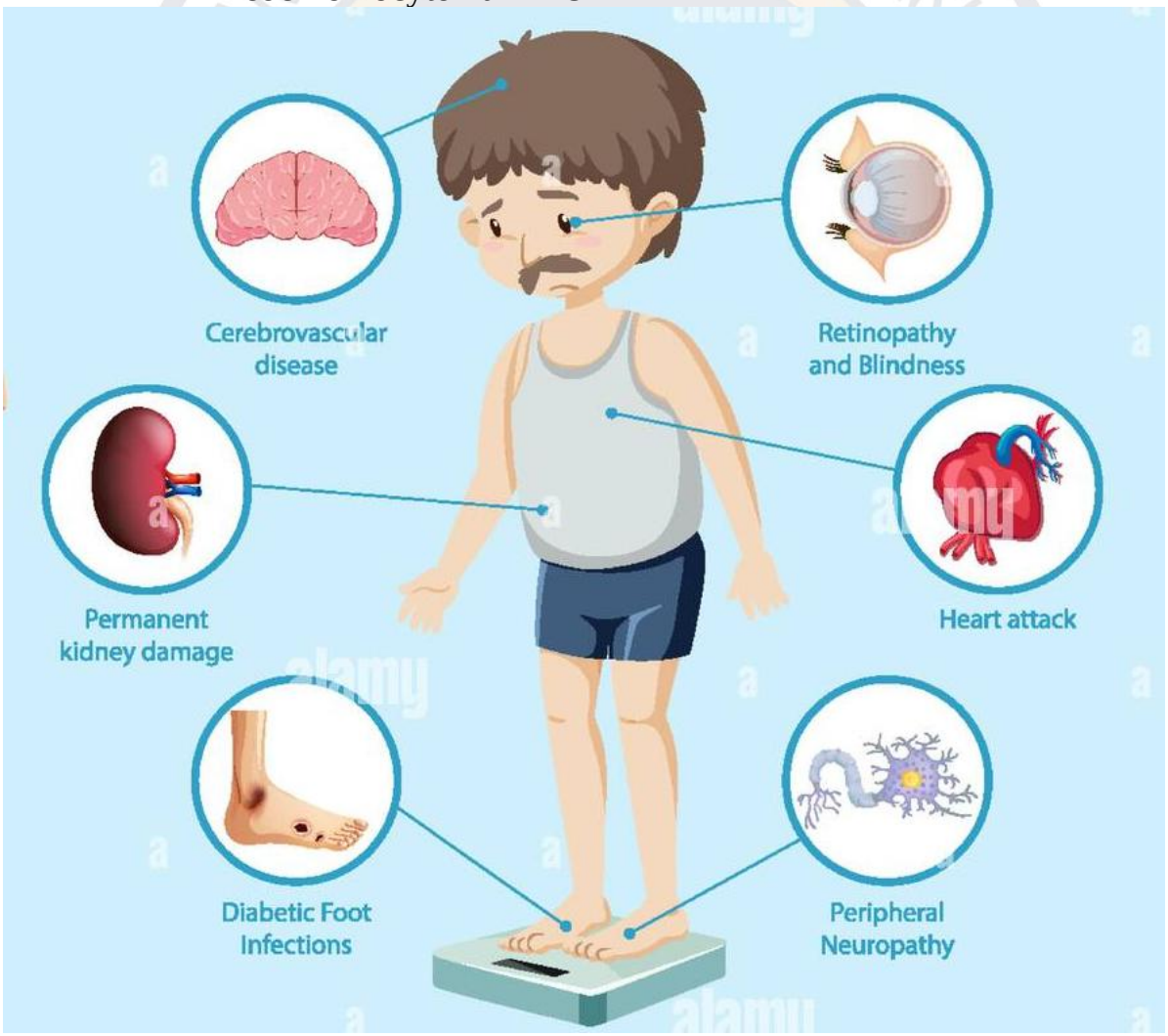
Ganglioneuroma



Neuroblastoma NE & ME



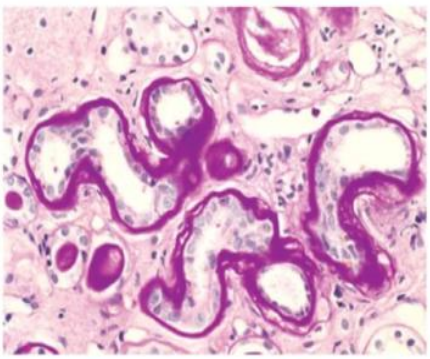
Pheochromocytoma NE & ME



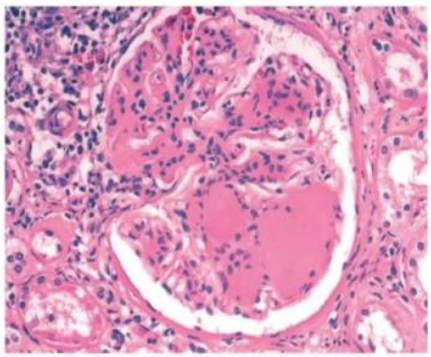
Complications of DM

Necrotizing papillitis

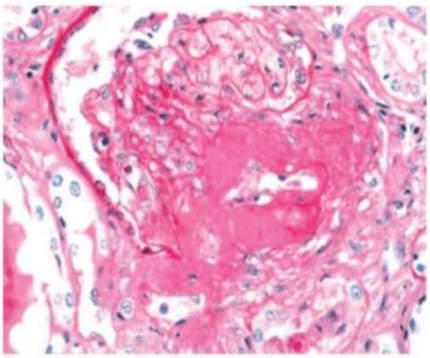
Pyelonephritis



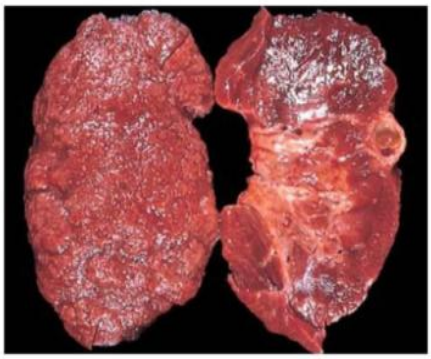
Thickening of tubular basement membranes



Nodular glomerulosclerosis

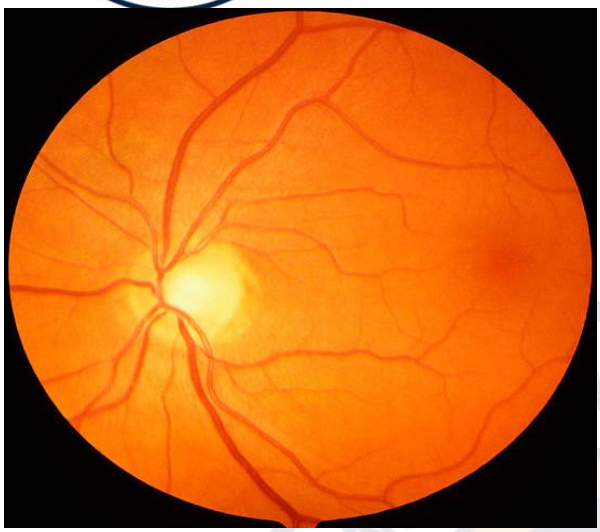


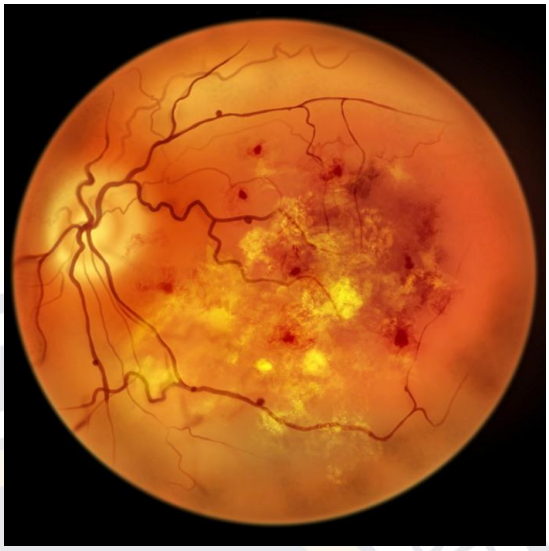
Severe renal hyaline arteriolosclerosis



Nephrosclerosis in long-standing DM

Diabetic nephropathy

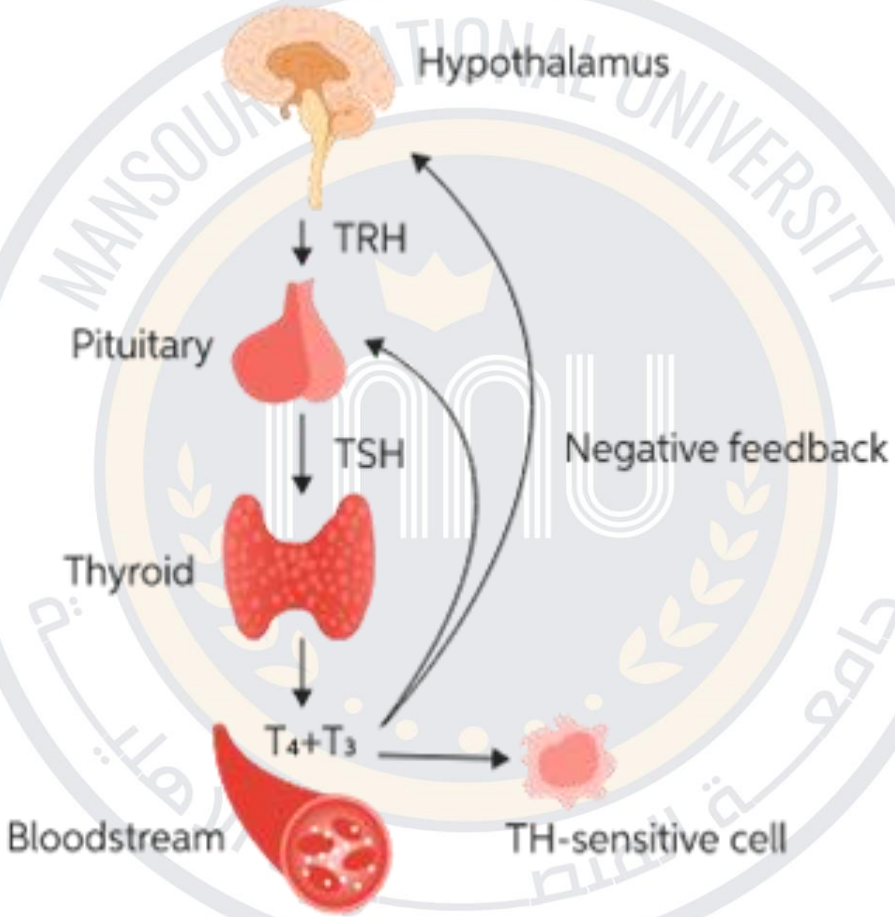




Normal retina vs diabetic retinopathy

Non-neoplastic thyroid diseases

Hypothalamo-pituitary-thyroid axis:



Hyperthyroidism and hypothyroidism:

Hyperthyroidism	Hypothyroidism
Primary - Graves disease -Toxic multinodular goiter -Toxic follicular thyroid adenoma Secondary TSH-secreting pituitary adenoma	Primary -Iodine deficiency -Hashimoto thyroiditis -Postablative -Genetic defects in thyroid develpment -Thyroid hormone resistance Secondary Pituitary failure.

Thyroiditis

Types:

-Acute / infectious thyroiditis

-Autoimmune thyroiditis (Hashitmoto thyroiditis).

-Riedel thyroiditis

-Subacute granulomatous thyroiditis

Acute Infectious Thyroiditis

Risk factors:

-Malnourished infant, debilitated elderly, immunosuppression, trauma

Etiology:

-Often Streptococcus haemolyticus, Streptococcus pneumoniae, Staphylococcus aureus

-Via blood or direct seeding from upper respiratory infections, causes sudden onset of pain and glandular enlargement

Gross description

-Normal or slightly enlarged thyroid gland

-May have suppurative areas

Microscopic description

-Neutrophils, possibly microabscesses and tissue necrosis

-Fungi are associated with necrosis, acute inflammation and granulomas

Hashimoto Thyroiditis

The most common cause of Hypothyroidism after iodine deficiency.

- More common in females

Pathogenesis

•Auto-immune thyroiditis

•Activation of helper (CD4+) T lymphocytes sensitized to thyroid antigens

•These helper T lymphocytes stimulate proliferation of cytotoxic (CD8+) T lymphocytes, which attack thyroid follicular cells.

Activated helper T lymphocytes also recruit reactive B lymphocytes to produce antibodies against thyroid antigens as anti-thyroglobulin and anti-thyroid peroxidase

Gross

1- Early… There is symmetrical diffuse enlargement of the thyroid gland with vague nodularity

-The affected areas are pale (gray or yellow) and firm

-They lack the glistening appearance of colloid

2- Late… The gland becomes symmetrically atrophic

Microscope:

-Follicles are atrophied. Follicles are lined by large cubical cells with eosinophilic granular cytoplasm (Hurthle cells).

-lnflammatory cells (lymphocytes, plasma cells, macrophages).

-Reactive lymphoid follicles.

Riedel Thyroiditis

-Rare of chronic disease of unknown cause.

-Riedel thyroiditis may be part of multifocal idiopathic fibrosclerosis.

Gross:

-The gland is stony hard and greyish white

-Adherent to the surrounding structures

Microscopic:

-Follicles are atrophied

-Excess fibrous tissue may extend outside the gland

-Lymphocytic infiltrate

Complications:

Compression manifestations: dysphagia, dyspnea, recurrent laryngeal nerve paralysis.

Subacute Granulomatous Thyroiditis

-A self-limited disorder in which patients present with a tender thyroid.

-Etiology is not known but clinical features of preceding respiratory infection suggest a possible viral etiology.

Gross:

-Moderate enlargement of the gland which is often focal and asymmetrical.

-The cut surface of the involved area is firm and greyish white.

Microscope:

-Early, Acute inflammatory destruction of the thyroid follicles.

-Late, Granulomas consist of central colloid material surrounded by histiocytes and scattered multinucleated giant cells.

-Advanced cases, Fibrosis.

Graves' Disease

-Autoimmune disease, more common in females.

-Due to auto-antibodies. Most common is TSI (thyroid stimulating immunoglobulin). Stimulate TSH receptors leading to diffuse hyperplasia and hyper functioning thyroid follicles with excess thyroid hormone secretion

Gross

-The thyroid gland is symmetrically enlarged.

-The gland appears fleshy.

-Cut surface is firm and dark red.

-Loss of the normal translucence of stored colloid.

Microscopic

- The gland is diffusely Hyperplastic and highly vascular

-The follicles are lined by tall columnar cells

-The colloid is depleted and scalloped (moth-eaten) at the periphery

-Hyperplastic papillae that project into the lumen of the follicles

-Lymphocytes and plasma cells infiltrate the interstitial tissue and may form reactive lymphoid follicles

Goiter

Goiter: Non inflammatory, non neoplastic enlargement of the thyroid gland

Goitrogen: agents that suppress thyroid hormone synthesis, and so elevating TSH levels and leads to hyperplastic changes of thyroid (goitrous enlargement) as cabbage and cauliflower.

Classification

-Simple (non toxic)

-Diffuse

-Multinodular

-Toxic (associated hyperthyroidism)

Diffuse Simple (Nontoxic) Goiter

Diffusely involves the thyroid gland without producing nodularity.

Common in females.

Causes

Physiologic Goiter: Usually seen at times of increased physiological demands as puberty, pregnancy.

The disease occurs in two forms:

Endemic form occurs in geographic areas where the soil, water, and food supply contain low levels of iodine

Sporadic form.

Diffusely involves the thyroid gland the gland has two phases:

1-**Hyperplastic stage**: there is diffuse and symmetric enlargement of the thyroid gland. There is hypertrophy and hyperplasia of the follicular epithelium with scant colloid.

2-**Colloid involution stage**: if iodine correction and decreased demand to thyroid hormones occur after a short period of hyperplasia, there is colloid accumulation and atrophy (involution) of follicular epithelium. Most patients are clinically euthyroid.

Simple Multinodular (Nontoxic) Goiter

-Repeated cycles of stimulation and involution of a diffuse goiter lead to rupture of some follicles followed by fibrosis, hemorrhage, scarring, and sometimes calcification.

-This produces an irregular enlargement of the thyroid gland (variable nodularity and scarring).

Gross

-The thyroid gland is asymmetrically enlarged with nodular surface

-The cut surface shows numerous irregular nodules contain glistening colloid

Fibrosis, calcification, hemorrhage & cystic degeneration may be present

Microscopic

•Nodular thyroid gland separated by fibrous tissue.

Hyperplastic nodules, tall columnar follicular epithelium, papillary structures, formation of small new follicles.

•Involuted nodules, large follicles distended by colloid and lined by flat follicular epithelium. Large colloid-containing follicles may fuse to form colloid cysts.

•Calcification, chronic inflammation, hemorrhage & cystic degeneration are common in the old standing cases

Complications

-Pressure effects: on trachea, esophagus and recurrent laryngeal nerve

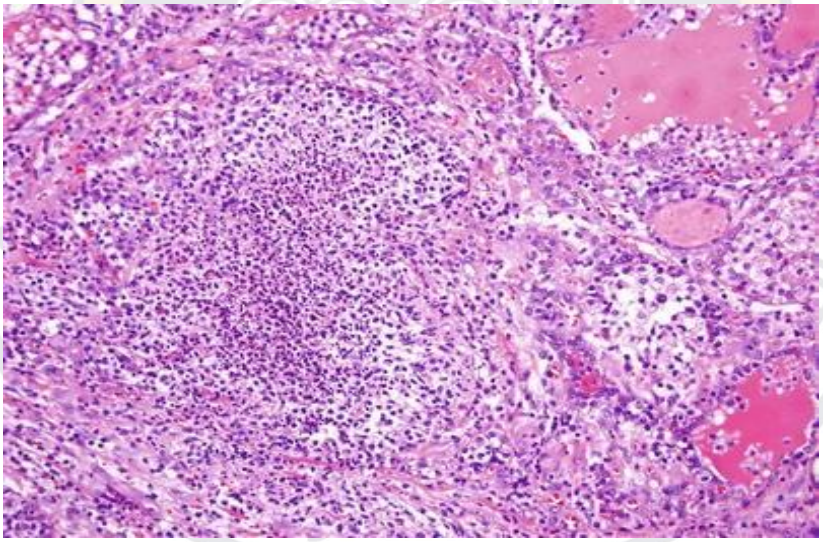
-Some of these nodules may become hyper functioning and cause hyperthyroidism (no exophthalmos)

-Malignancy: rare in 2% of cases

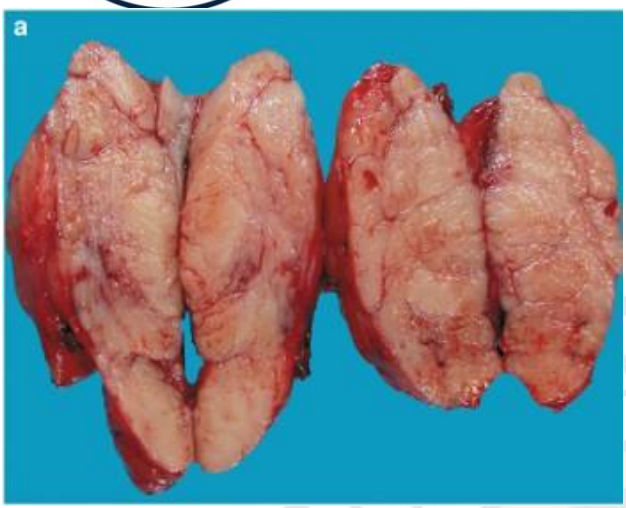
-

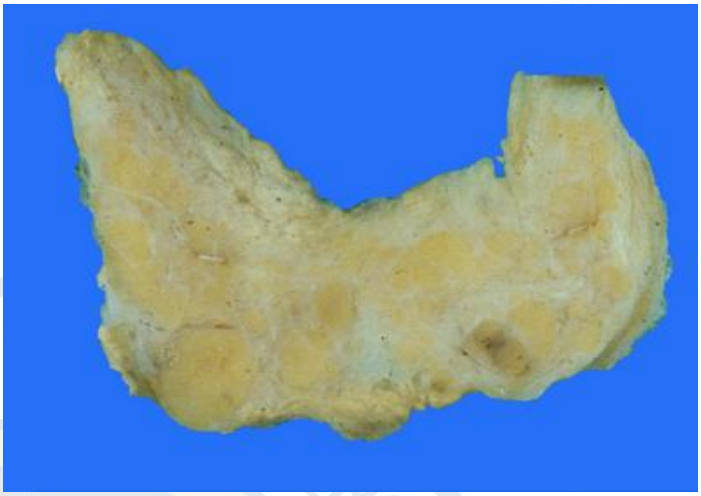
Photo gallery

Acute infectious thyroiditis

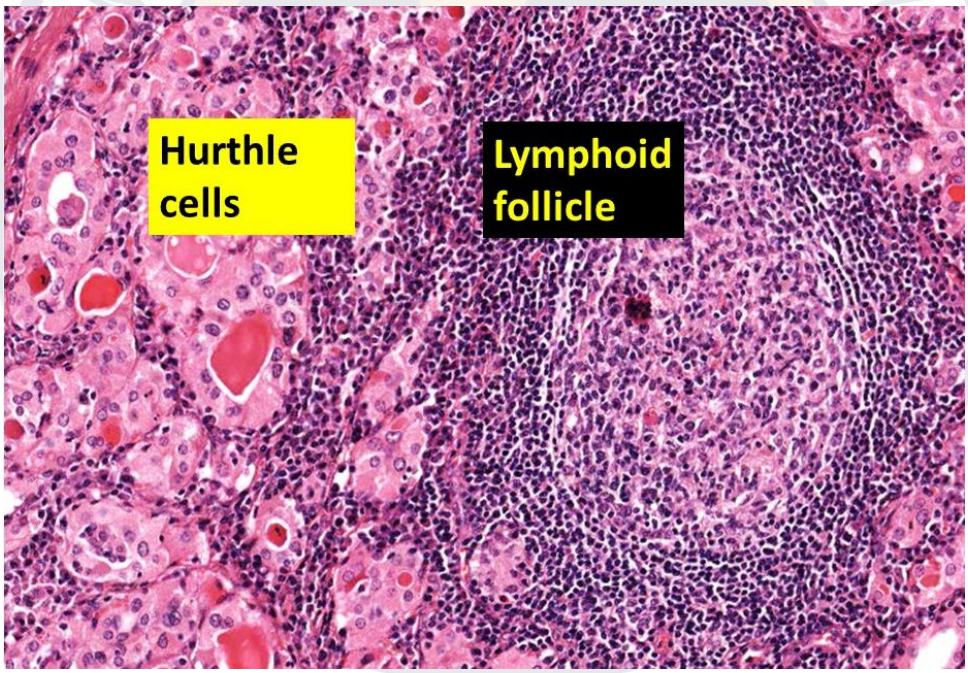


Acute infectious thyroiditis (ME)

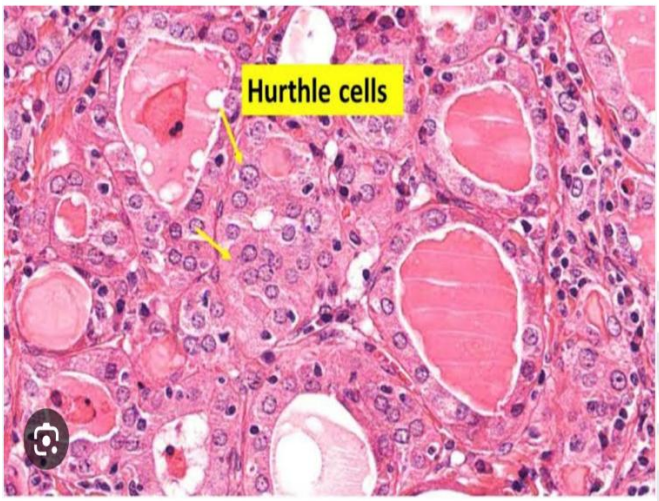


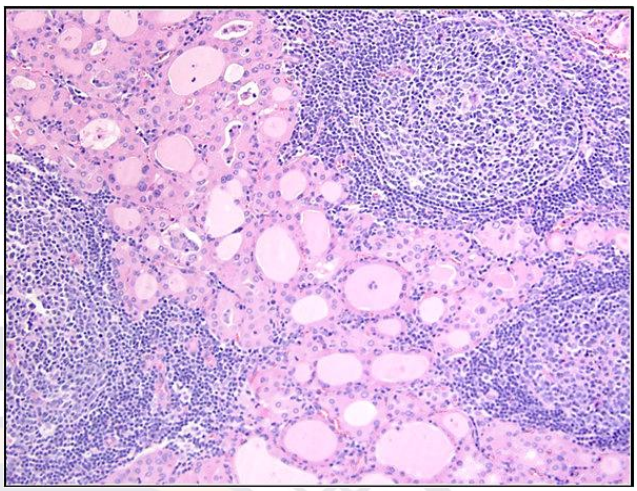


Hashimoto thyroiditis gross

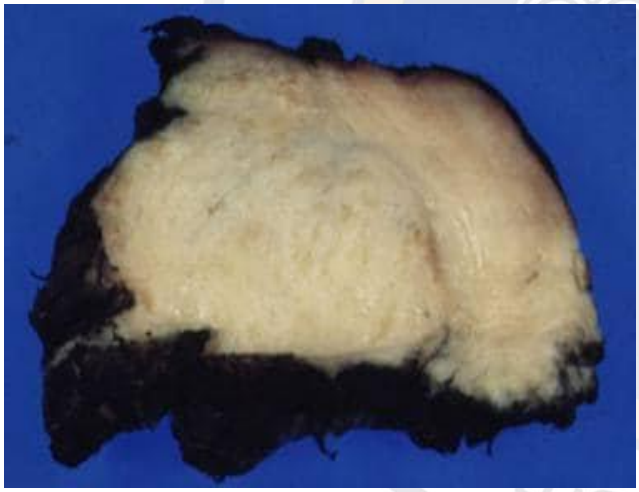


Hashimoto thyroiditis ME

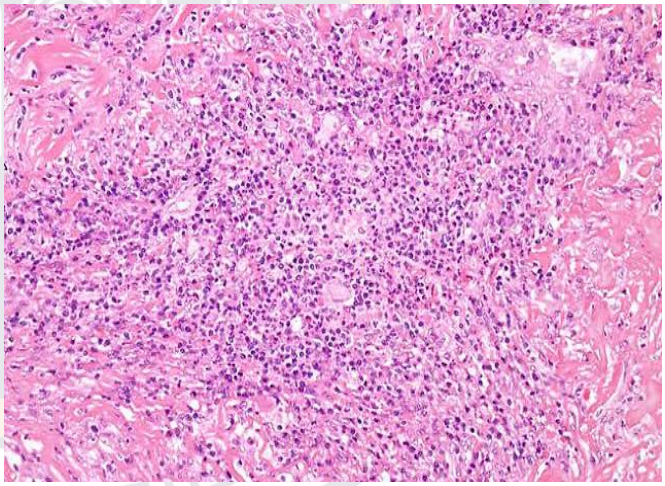




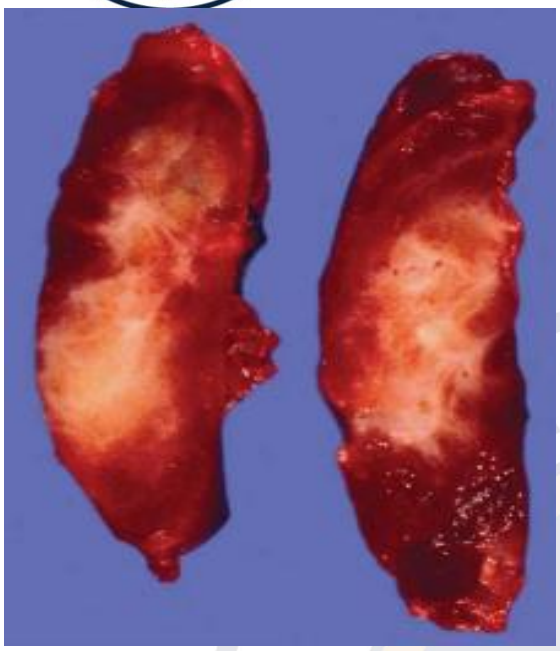
Hashimoto thyroiditis ME

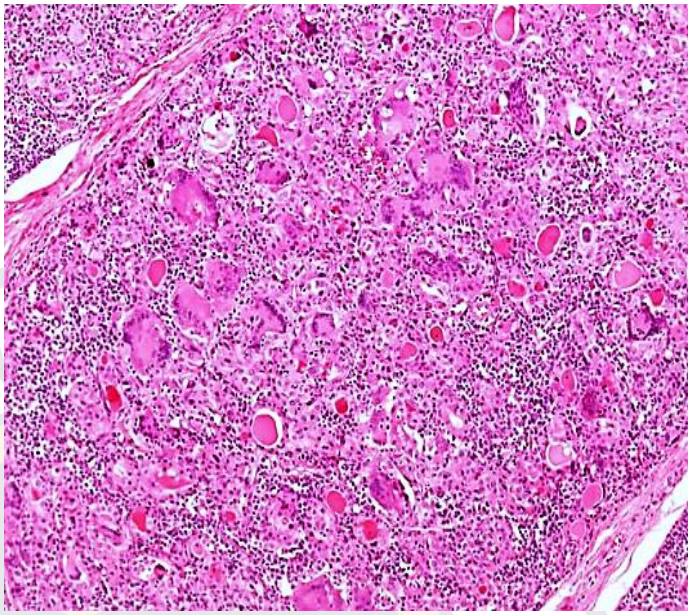


Riedel thyroiditis gross

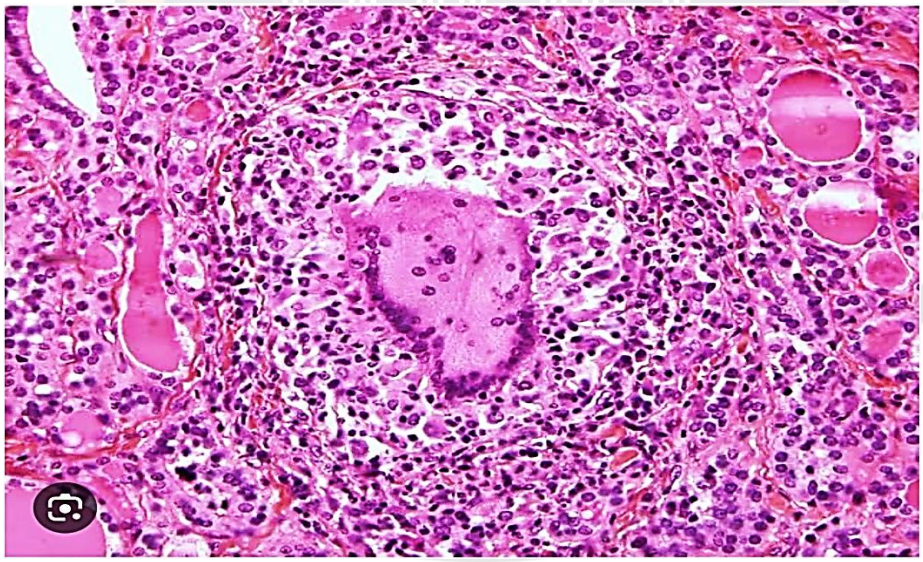


Riedel thyroiditis ME





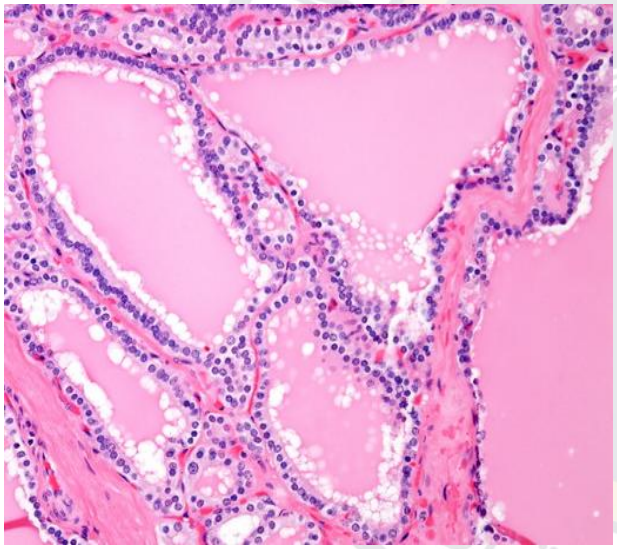
Subacute Granulomatous Thyroiditis gross and ME

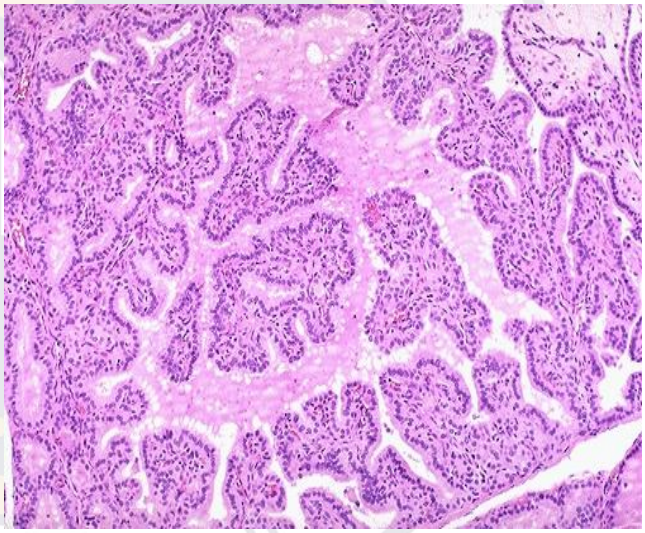


Subacute Granulomatous Thyroiditis ME

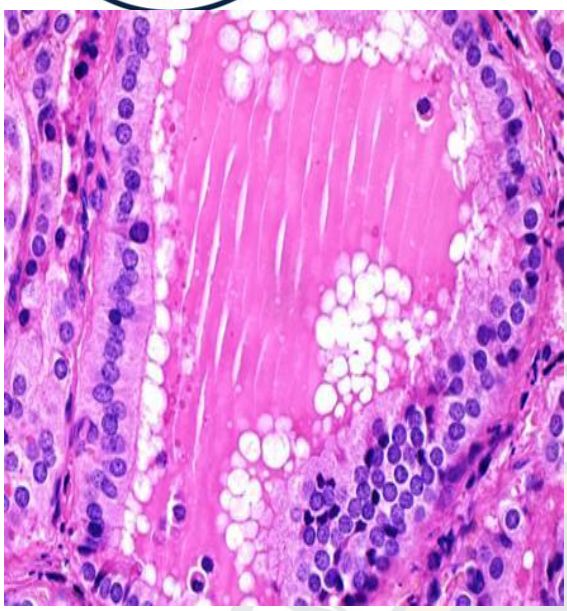
Graves' disease (exophthalmos)

Graves' disease (gross)





Graves' disease (ME)



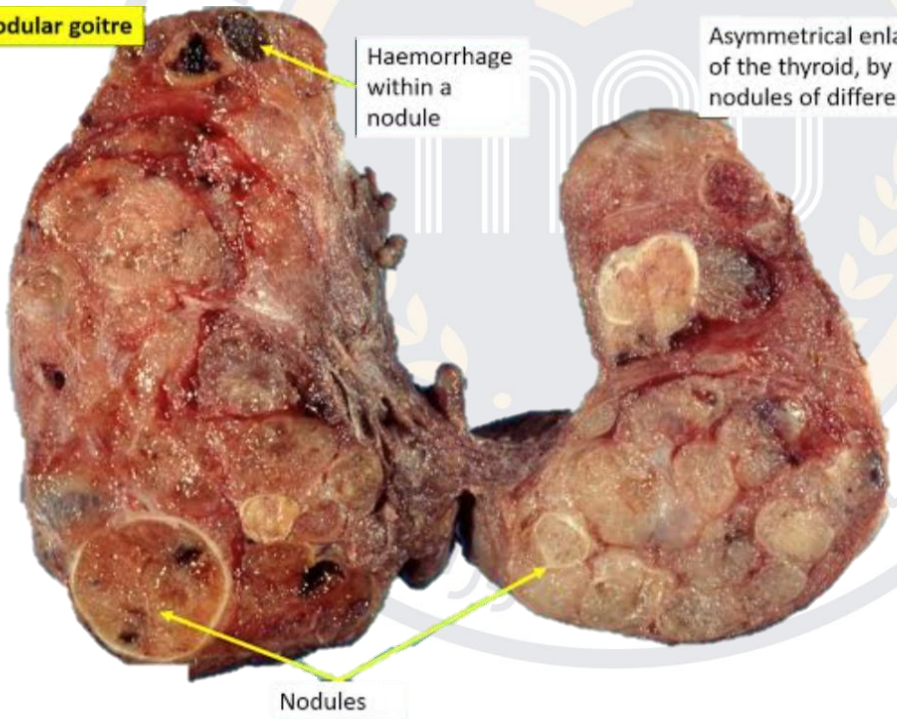
Graves' disease (ME)

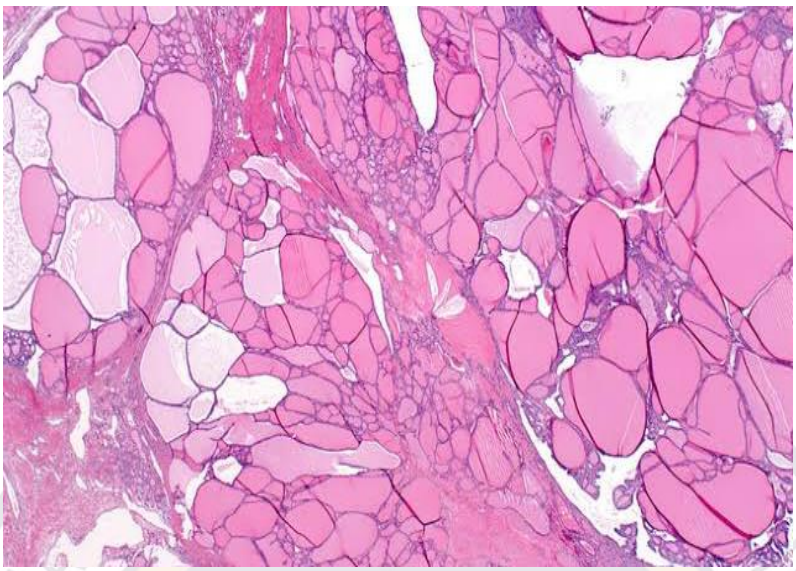
Diffuse simple goiter

Simple multinodular goiter

Simple multinodular goiter gross

- Multinodular goitre





Simple multinodular goiter ME

Neoplastic thyroid diseases

Classification of thyroid tumors

-Primary thyroid tumors

***Epithelial tumors**

-Benign epithelial tumors

-Follicular Adenoma.

-Hurthle cell Adenoma.

-NIFTP (Non-invasive follicular thyroid neoplasm with papillary like nuclear features).

-Hyalinizing trabecular tumor.

-Malignant epithelial tumors

-Follicular carcinoma

-Papillary carcinoma

-Medullary carcinoma

-Anaplastic carcinoma

***Mesenchymal tumors**

***Hematolymphoid tumors**

***Metastases (rare)**

Follicular Adenoma

Most common benign thyroid gland tumor.

Grossly, the follicular adenoma is characterized by four features:

1. Solitary nodule.
2. Complete encapsulation.
3. Difference between inside and outside the capsule.
4. Compression of the thyroid tissue outside the capsule.

Hemorrhage, fibrosis and cystic change are common.

Microscopically

Complete fibrous capsule

The tumor is formed of thyroid follicles (large or small) containing colloid (abundant or scanty).

-**Hurthle cell type**: the Hurthle cell type: the follicles are lined by oncocytic cells (Cells with abundant granular eosinophilic follicles are lined by oncocytic cells cytoplasm and central rounded vesicular nuclei).

*Careful evaluation of the capsule to differentiate follicular adenomas from follicular carcinomas, which demonstrate capsular and/or vascular invasion.

Follicular carcinoma

-The second most common type of thyroid carcinoma (10-15%).

-Common in females.

-Blood spread to distant sites (lung, bone).

-Worse prognosis than papillary thyroid carcinoma.

Grossly, it appears as well-defined, encapsulated tumor. On cut section, it is soft and pale tan to pink with areas of hemorrhages, necrosis, cyst formation and bulges from within its capsule.

Microscopically, resembles follicular adenoma

*The principal distinction from adenoma is at the interface of the capsule and normal parenchyma by demonstration of invasion of blood vessels in region of capsule or by finding capsular invasion

Papillary thyroid carcinoma

-The most common type of thyroid carcinoma (75-85%).

-It can occur at all ages including children.

-Common in females.

-Lymphatic spread to cervical lymph nodes.

-Good prognosis.

Grossly, ranges from microscopic foci < 1 cm to large nodule up to 10 cm in diameter, .can be multicentric with firm consistency. Cut surface is greyish-white

Sometimes the tumor is transformed into cyst, into which numerous papillae projection

Microscopically

-Papillary structures with thin fibrovascular cores

-Psammoma bodies: Concentrically calcified structures

Nuclear features

-Glassy/ground glass nuclei (Orphan Annie nuclei, washed out nuclei): very finely .dispersed chromatin

-Pseudo-inclusions: invaginations of the cytoplasm may give the appearance of intranuclear .inclusions

.-Grooved nuclei

.-Crowded & overlapping nuclei

Medullary thyroid carcinoma

.This tumor is derived from C cells or parafollicular cells

.They secrete calcitonin

-The disease can be sporadic or familial, Patients with the familial medullary carcinoma have MEN type 2 syndrome, which includes medullay carcinoma, adrenal pheochromocytoma and parathyroid adenoma

-The mean age of patients is 50 years, but familial cases appear earlier (mean age, 20 .years)

.-Both lymphatic and blood spread occurs

-Worse prognosis

Grossly, *It is* usually single nodule not encapsulated, but are usually circumscribed. Cut surface is firm and grayish white.

In MEN type 2, tumors are often multicentric and bilateral.

Microscopically, it is composed of nests, trabeculae, and sheets of spindle/polygonal cells.

- The stroma contains amyloid material

Anaplastic thyroid carcinoma

.They are undifferentiated tumors of the thyroid follicular epithelium

.Rare, less than 5% of thyroid carcinomas

.The tumor is predominantly found in old age

The features at presentation are usually those of extensive invasion of adjacent soft tissue, .neck muscles and structures of the neck

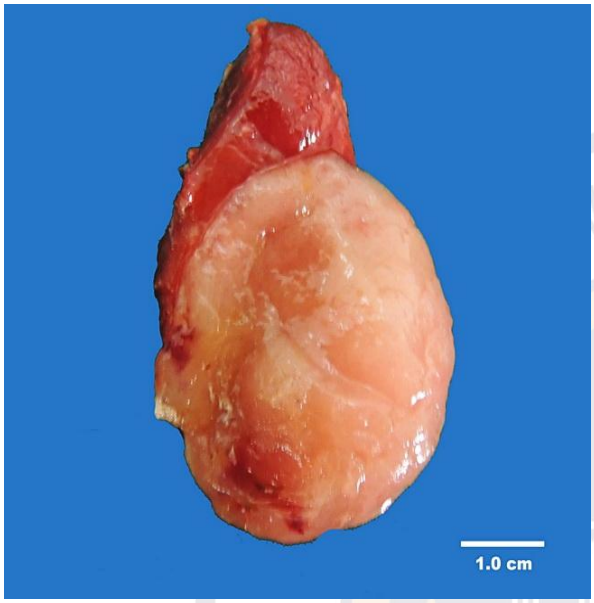
.Both lymphatic and blood spread occurs

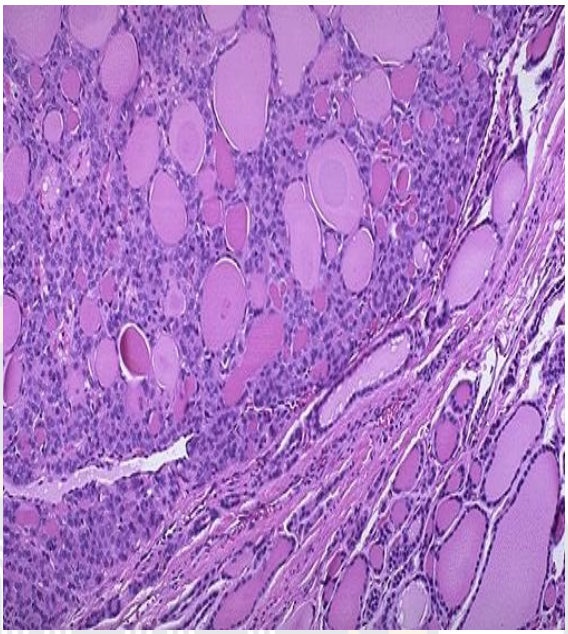
-Worse prognosis

Grossly, A huge infiltrative lesion. It is hard, and grayish-white and show areas of necrosis .and hemorrhage

Microscopically, It is composed of highly malignant spindle or giant cells, showing marked pleomorphism and numerous mitotic figures

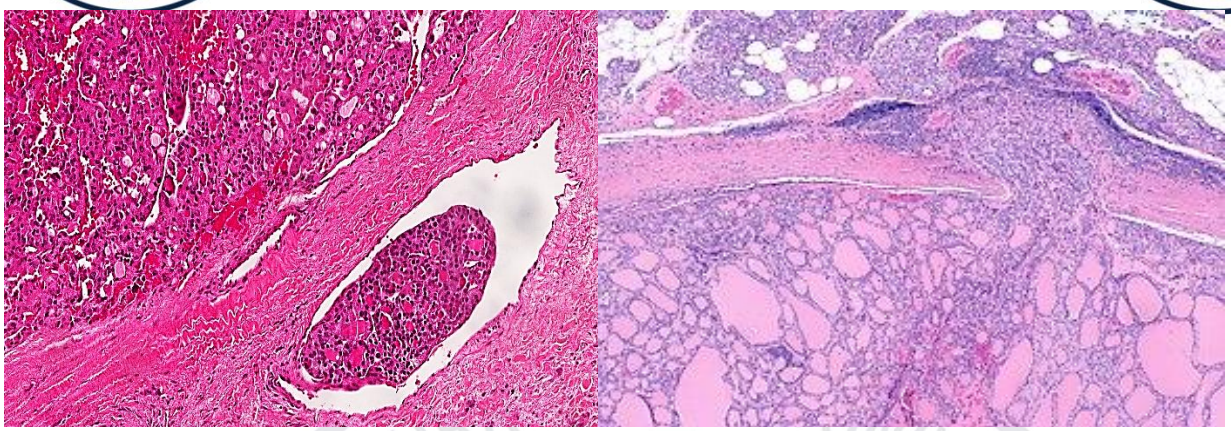
Photo gallery



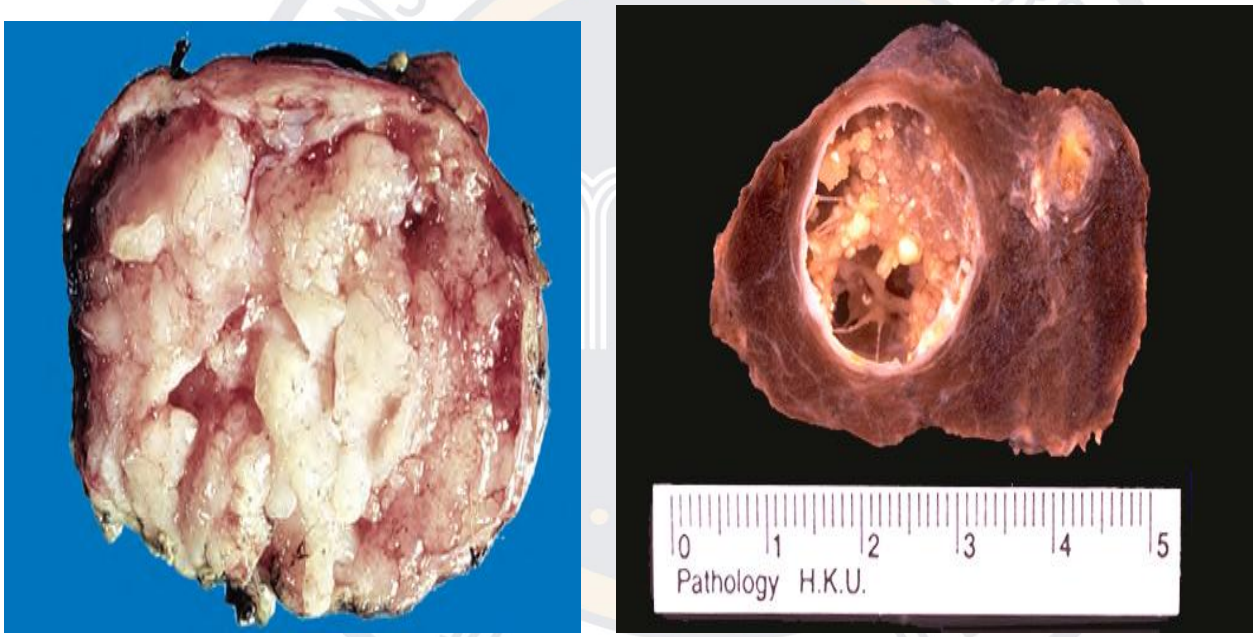


Follicular adenoma gross and ME

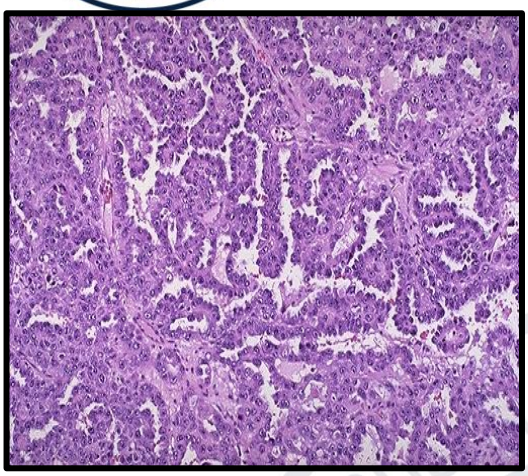
Follicular carcinoma gross

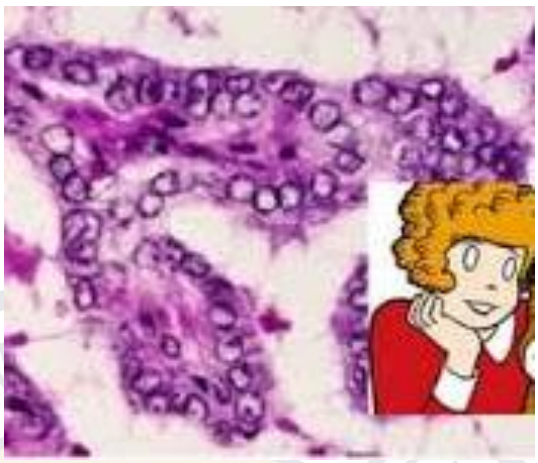


Follicular carcinoma(vacular and capsular invasion)

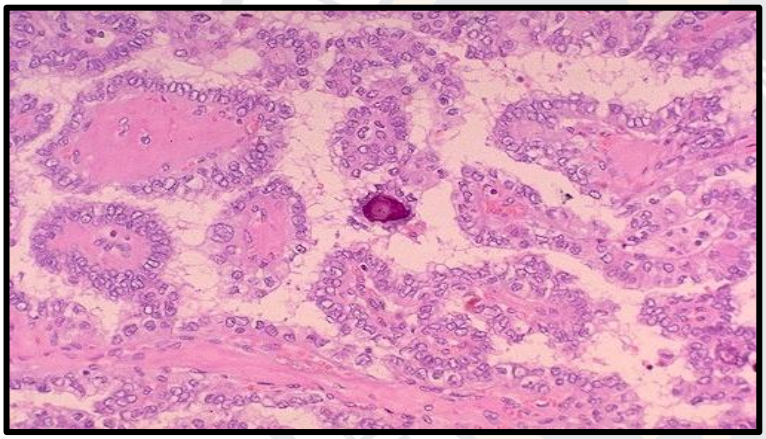


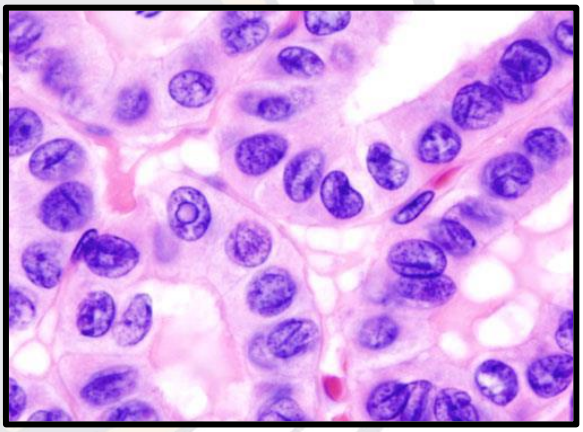
Papillary thyroid carcinoma (gross)

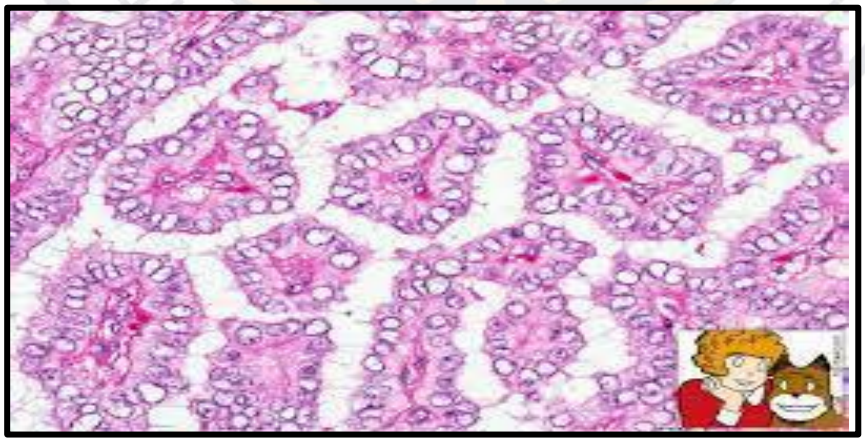




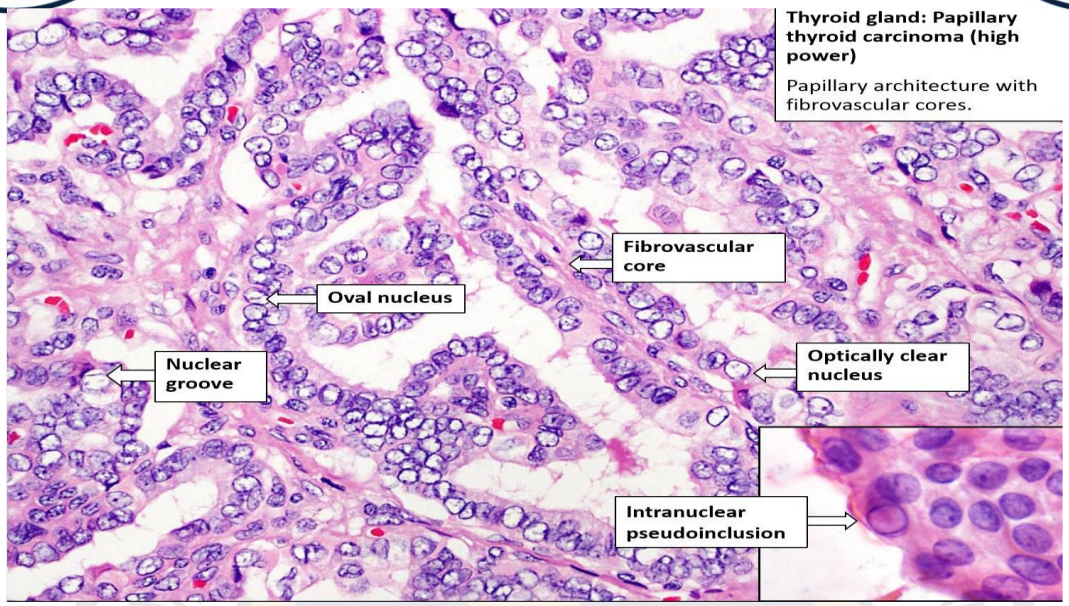
Papillary thyroid carcinoma (ME)



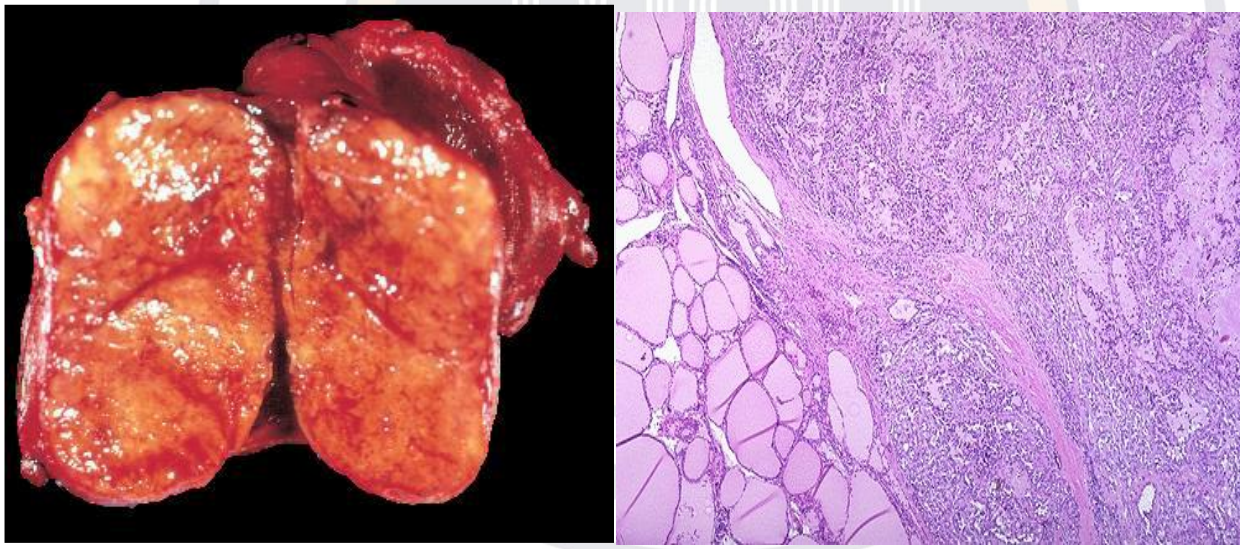




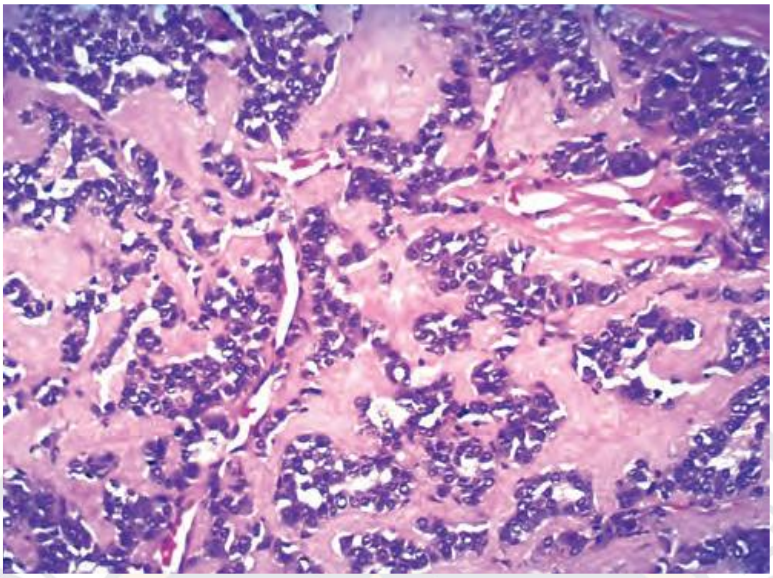
Papillary thyroid carcinoma (nuclear features)



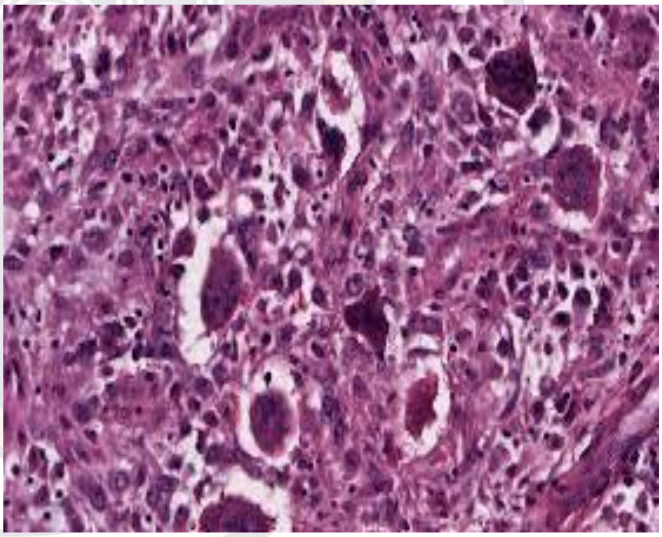
Papillary thyroid carcinoma (nuclear features)



Medullary thyroid carcinoma gross and ME



Medullary thyroid carcinoma (Amyeloid)



Anaplastic thyroid carcinoma gross and ME

Male genital system

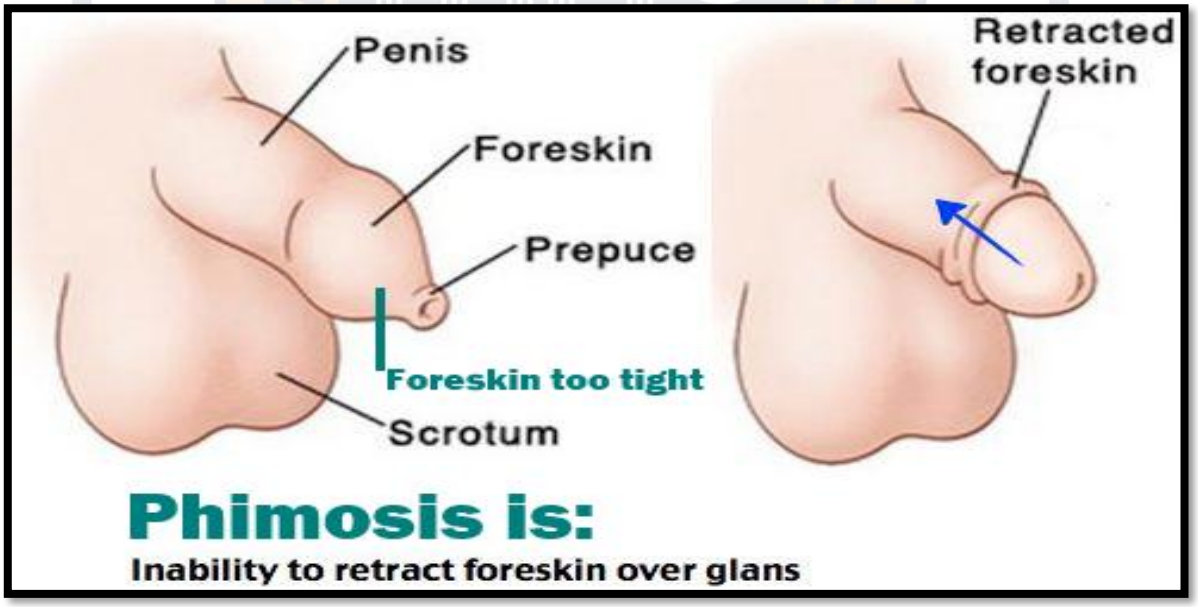
I. Congenital anomalies

1. Phimosis

☒ It is narrowing of the opening of the prepuce.

☒ **Complications:**

1. **Balanitis:** Inflammation of glans penis.
2. **Squamous cell carcinoma of the penis**
   - due to accumulation of **smegma** that predispose to both infection and carcinoma.
3. **Gradual urinary tract obstruction.**



Gross appearance of phimosis

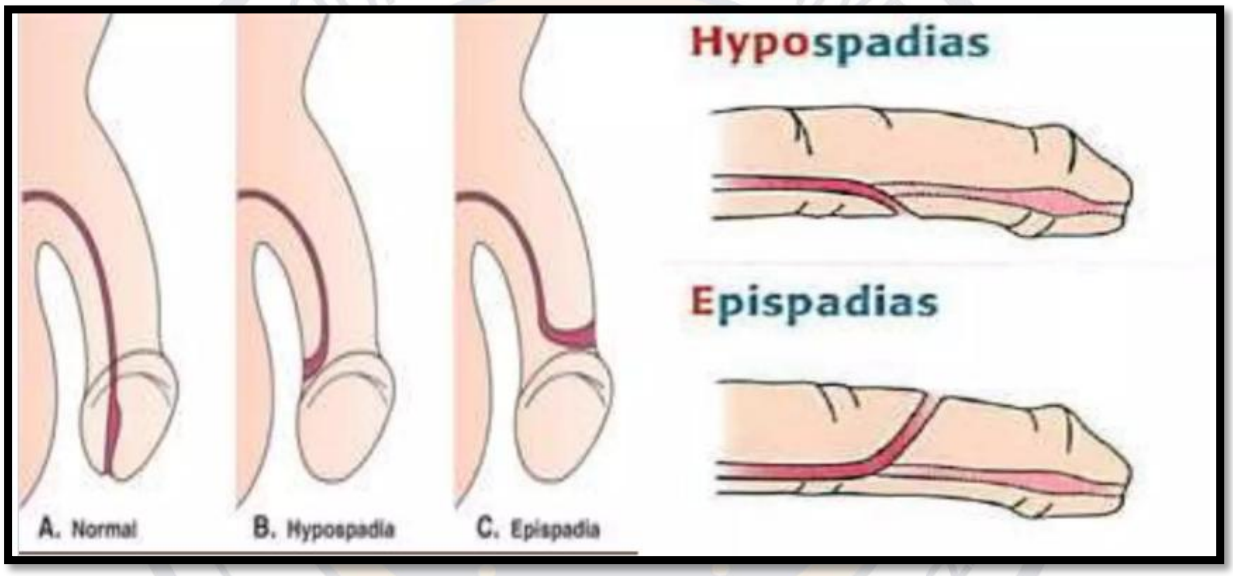
2. Hypospadias and epispadias of the penis:

☒ **Hypospadias:** the urethra opens at ventral surface of the penis.

☒ **Epispadias:** the urethra opens at dorsal surface of the penis.

☒ **Complications:**

1. **Urinary obstruction** (as the urethral opening is often constricted).
2. **Sterility** (when the orifice is near the base of the penis).



Gross appearance of hypospadias and epispadias

3. Cryptorchidism (undescended testis):

☒ **Most common** congenital abnormality of the genitourinary tract

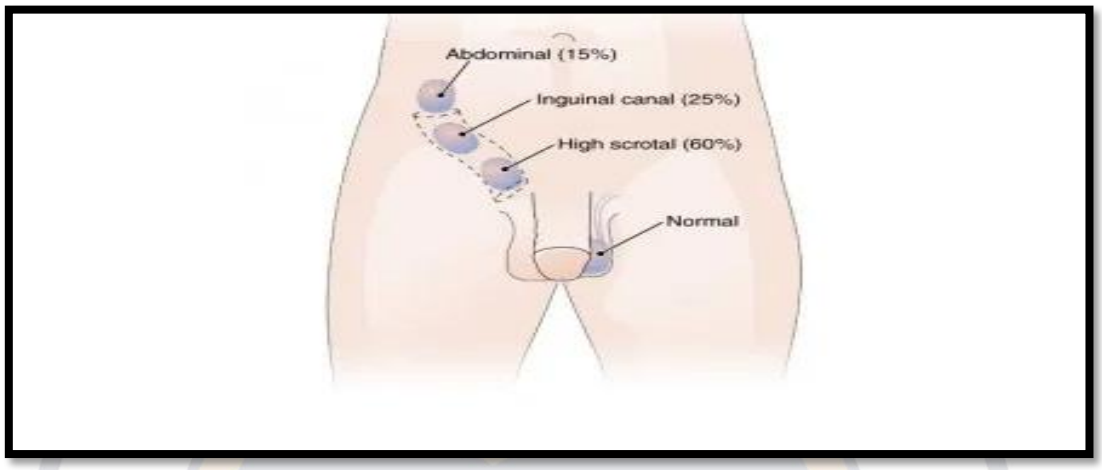
☒ **Def:**

- Failure of descent of one or both testis into the scrotum.
- The testis is found in the abdomen, pelvis, or in the inguinal canal.

☒ **Causes:**

1. **Hormonal disturbances:** Deficiency of gonadotrophic hormone of pituitary
2. **Obstruction of the pathway:** Organic obstruction prevents the descent.

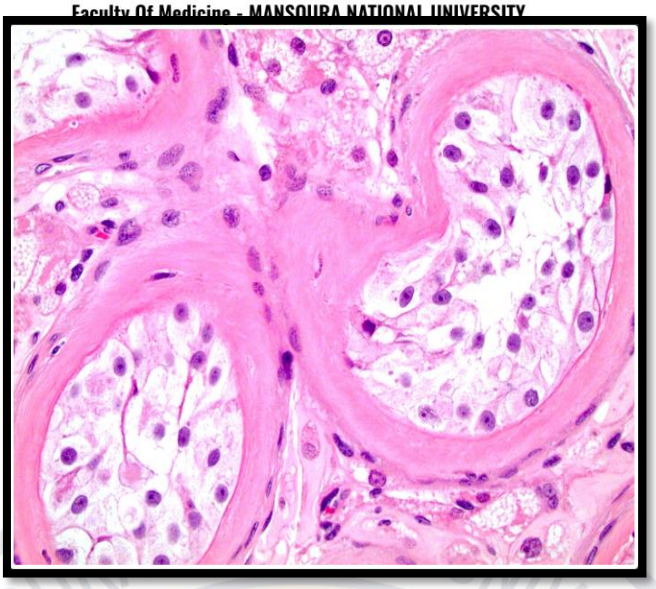
3. **Other defects:** Short spermatic vessels or vas deferens or mal development of the scrotum or cremaster muscle.



Sites of undescended testis

☒ **Microscopic picture**

- **Atrophy** of the seminiferous tubules with fibrosis.
- **Germ cell neoplasia insitu** which is likely a precursor of subsequent germ cell tumors



ME of cryptorchidism

II. Inflammation

A. Nonspecific inflammation

1. Prostatitis

☒ **Def:** Inflammation of the prostate.

☒ **Causes:**

- **Organisms:** E-coli, gonorrhea, staph. aureus, strept. pyogens…etc.
- **Routes of infection:**
  - Direct spread from cystitis, urethritis, urethral instrumentation.
  - Blood borne infection

☒ **Pathology:**

- Acute suppurative prostatitis which may form abscess.
- Chronic prostatitis follows acute.

2. Seminal vesiculitis:

☒ **Def:** Inflammation of seminal vesicles.

☒ **Cause:** It may be 2ry to prostatitis or blood borne.

3. Funiculitis:

☒ **Def:** Inflammation of spermatic cord

☒ **Cause:**

- Direct spread from epididymis.
- Lymphatic spread from seminal vesicles.
- Blood spread.

☒ **Effect:** It leads to diffuse thickening of spermatic cord.

4. Orchitis

1. **Bacterial orchitis:**

☒ **Cause:** Due to the spread of infection from:

- Epididymis directly
- Spermatic cord by lymphatic or through vas deferens
- Bloodborne

☒ **Pathology:** Acute inflammation with suppuration resulting in scarring and sterility.

2. **Viral: mumps orchitis**
3. **Traumatic orchitis**
4. **Autoimmune orchitis**

B. Specific inflammation

1. Tuberculosis.
2. Syphilis.
3. Filariasis
4. Bilharziasis.

III. Non inflammatory lesions

Benign (senile) nodular hyperplasia of the prostate

• Extremely common.

•≈50% of men at 50 Years are affected, ≈95% are affected above 70 Years.

•Gradual onset with slow progression

Pathogenesis:

•Hormonal changes with increase in 5 α-reductase enzyme in prostate that convert testosterone to dihydroxytestosterone (DHT)

•Accumulation of DHT(10 times more potent than androgens in combining to the androgen receptor and dissociate more slowly).

•Increasing the proliferation of epithelial & stromal cells and decreasing epithelial cells apoptosis.

Naked Eye:

•The gland is enlarged nodular, may show cystic change.

•Firm, rubbery in consistency.

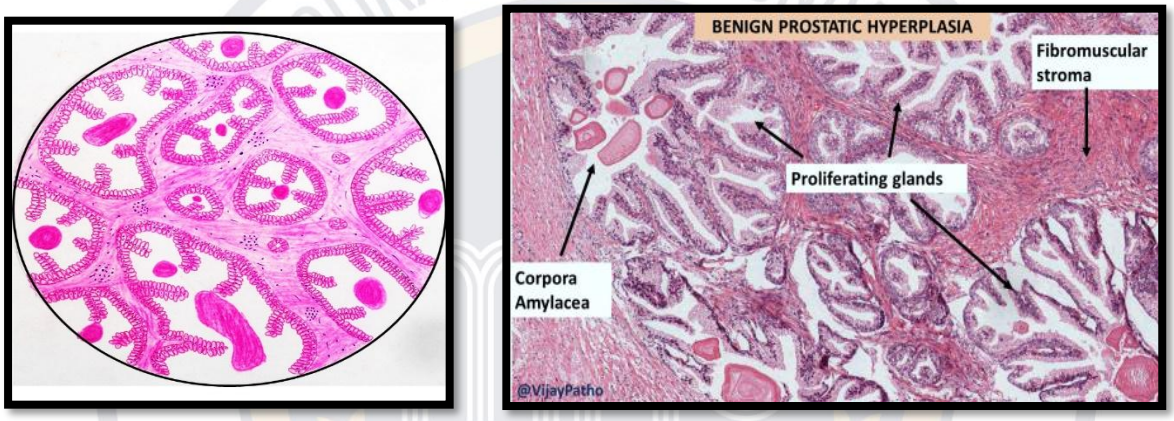
Microscopic Examination:

Hyperplasia of the acini which are larger than normal, variable in size and shape and lined by tall epithelium with frequent papillary projections.

The acini may contain numerous corpora amylacea.

Hyperplasia of the fibromuscular stroma with lymphocytes & plasma cells

NE of benign prostatic hyperplasia



ME of benign prostatic hyperplasia

Clinical picture:

•Obstructive symptoms (Prostatism) due to compression on prostatic urethra and internal urethral meatus (interferes with the sphincter mechanism).

Complications

Gradual urinary tract obstruction

• Urethra: elongated, compressed to a mere slit.

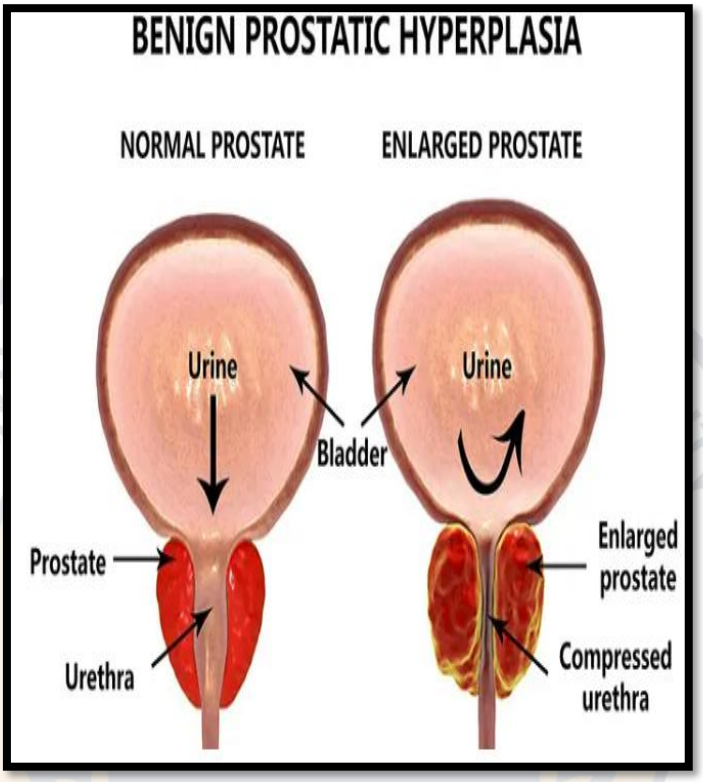
• Urinary bladder: trabeculations, diverticulations, cystitis, stones

• bilateral hydroureter, pyoureter.

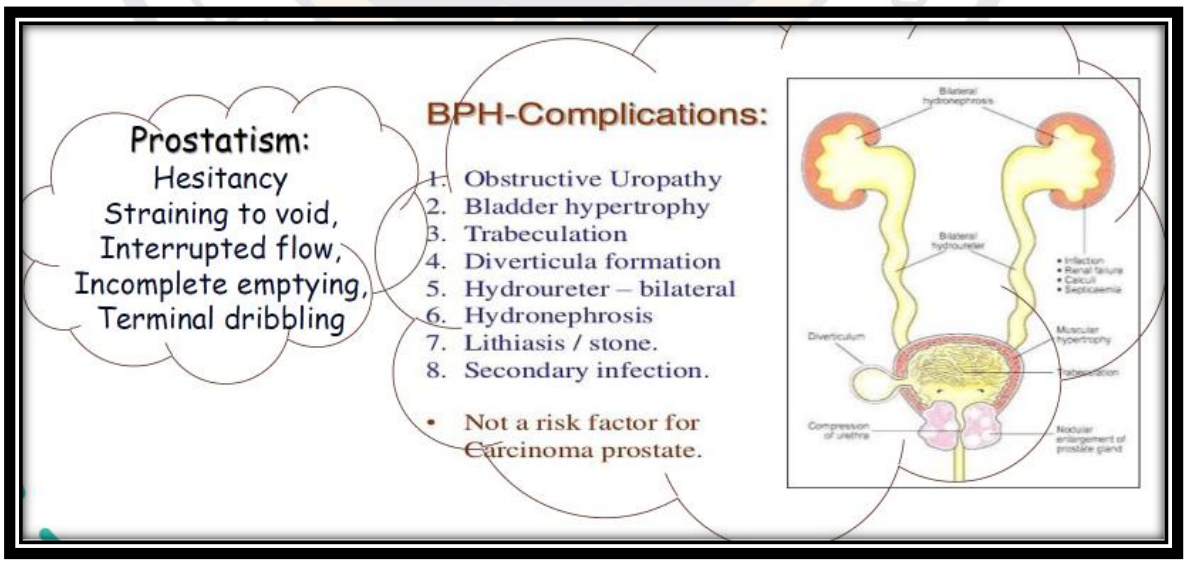
• bilateral hydronephrosis, pyonephrosis.

- Chronic renal failure.

No relation to malignancy



Complications of benign prostatic hyperplasia



Complications of benign prostatic hyperplasia

IV. Prostatic carcinoma

• The most common malignant tumor in males >50 years

Predisposing factors:

- ☒ Racial factors- More common in African
- ☒ •Endocrinologic factors- Androgens (so, Orchiectomy reduce the tumor size in Prostatic carcinoma patient).
- ☒ Environmental factors-high fat diet, exposure to polycyclic aromatic hydrocarbons
- ☒ Genetic basis- familial cases (Chromosome No 1 and 10)

Gross picture

- ☒ Affect the peripheral zone of the posterior lobe
- ☒ Uncapsulated mass palpable in rectal exam
- ☒ Multifocal, gritty and firm

Microscopic picture

- ☒ Adenocarcinoma; malignant glands are lined cells having prominent nucleoli.
- ☒ Tumor cell produce mucin and acid phasphatase•Gleason Score: is the system to grade the tumor based on the degree of differentiation among the cells.

Spread

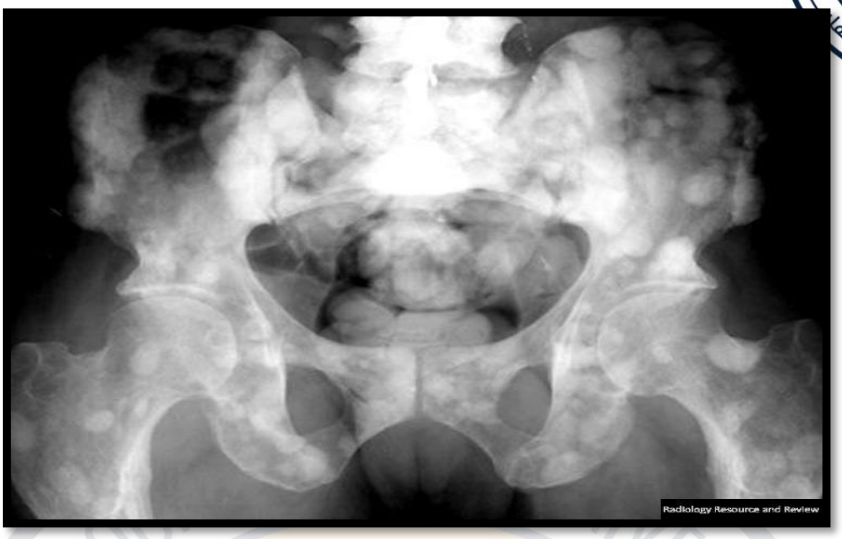
•Local spread: to prostatic urethra , seminal vesicles, floor of urinary bladder and rectum

•Lymphatic spread: To para-aortic, iliac lymph nodes

•Perineural invasion

•Hematogenous metastases: bone(most often found in the vertebrae & sacrum), lung, liver

•Bony metastases are often osteoblastic & are associated with elevated serum alkaline phosphatase

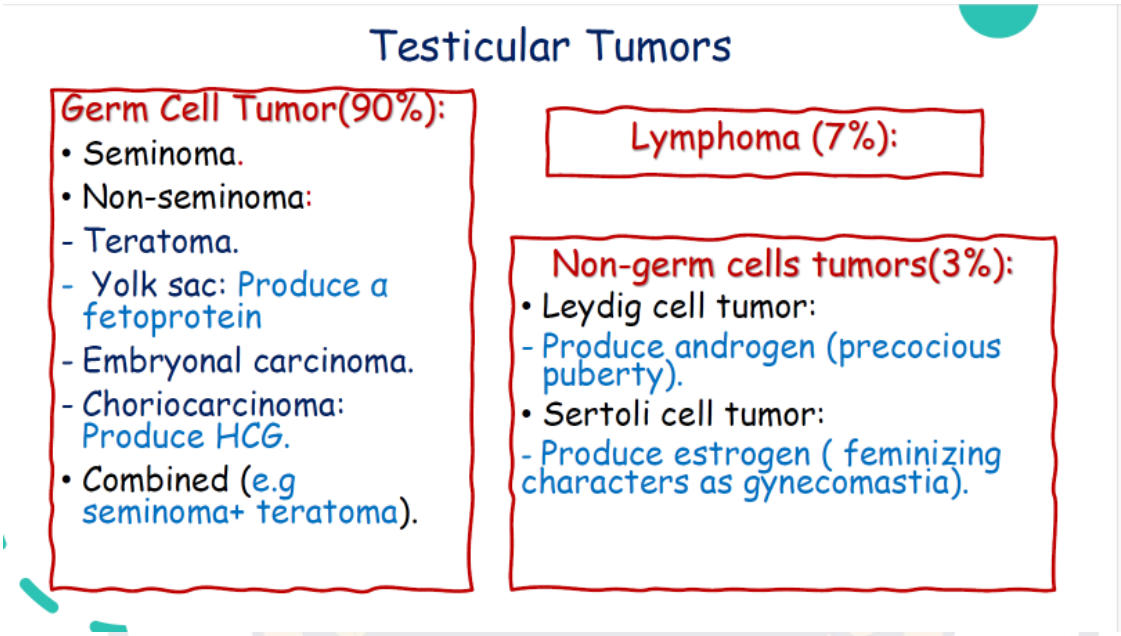


Radiograph of osteosclerotic bone metastasis in prostatic carcinoma

- **Tumor markers**
  - ☒ **PSA:** used as screening test and for assessing the response to treatment.
  - ☒ **CEA**
  - ☒ **Prostatic Acid phosphatase.**
  - ☒ **Alkaline phosphatase in bone metastasis**

V. Testicular tumours

Testicular tumors



Seminoma

Most common germ cells with gonadal differentiation.

Age: 40-50y. Unknown before puberty.

Radiosensitive.

Predisposing factors:

Genetic factors

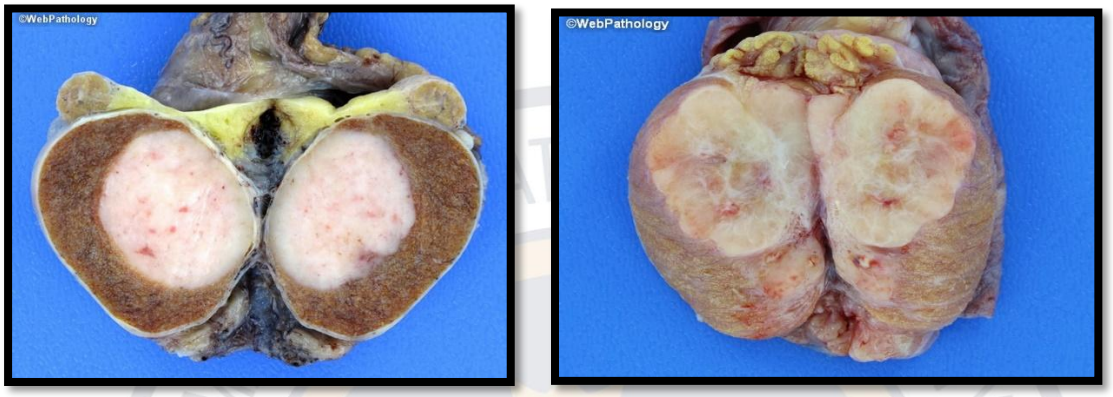
Undescended testis

Atrophic testis

Venereal diseases (infections).

NE:

Well defined, fleshy, homogenous cut section (potato like).

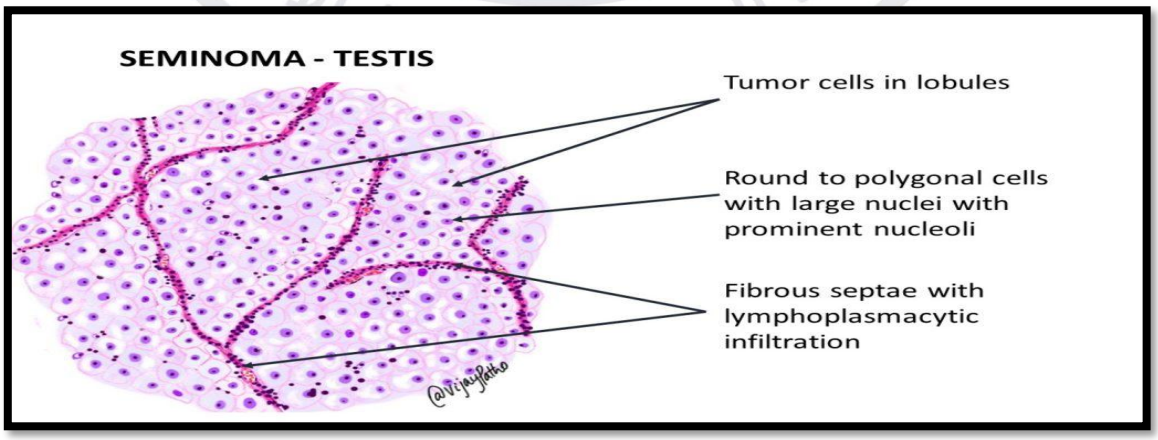


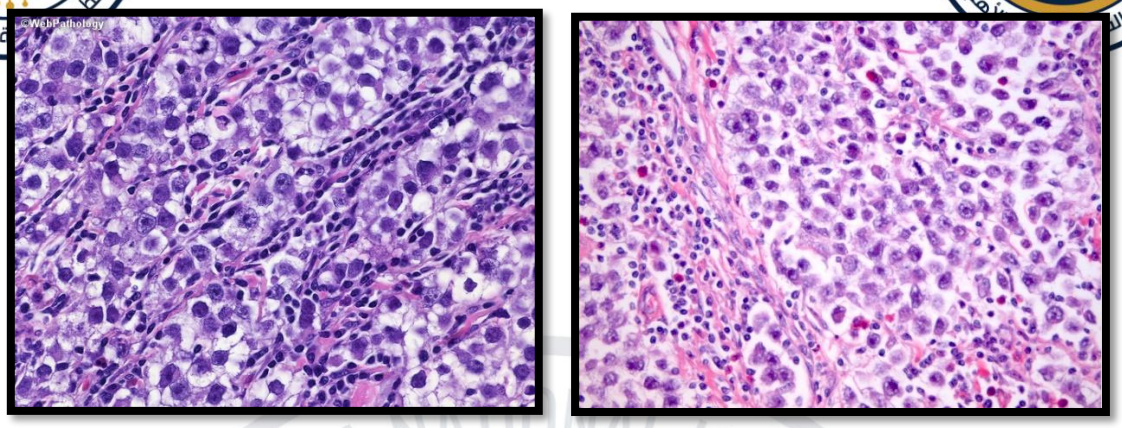
NE of seminoma

Microscopic picture

• Tumour is formred of nests and sheets of Spermatogenic cells with clear cytoplasm (due to glycogen content) with prominent cell membrane, large nucleus and prominent nucleolus.

• Tumour cells are separated by fibrous septa rich in lymphocytes and plasma cells





ME of seminoma

•Spread:

 Local : Invade testicular tissue to reach tunica vaginalis, epididymis, spermatic cord and scrotal skin.

Lymphatic :To common iliac and pancreatic L.N. Later to mediastinal and supraclavicular L.N

 blood : Lung, then brain and bones.

Non seminoma

-Less common germ cells with embryonic differentiation.

-Age: 20y, may occur before puberty.

-Radioresistant.

-**Teratoma**:formed of tissues derived from ectoderm, mesoderm and endoderm

-Yolk sac : secretes Alpha fetoprotein.

-**Embryonal carcinoma.**

-**Choriocarcinoma**: secretes human chorionic gonadotrophins (HCG).

-**Combined** (e.g seminoma+ teratoma).

Non germ cell tumors (sex cord stromal tumors)

• Most of These are benign, representing 3% of testicular tumors and arise from non germinal cells (Leydig and sertoli cells).

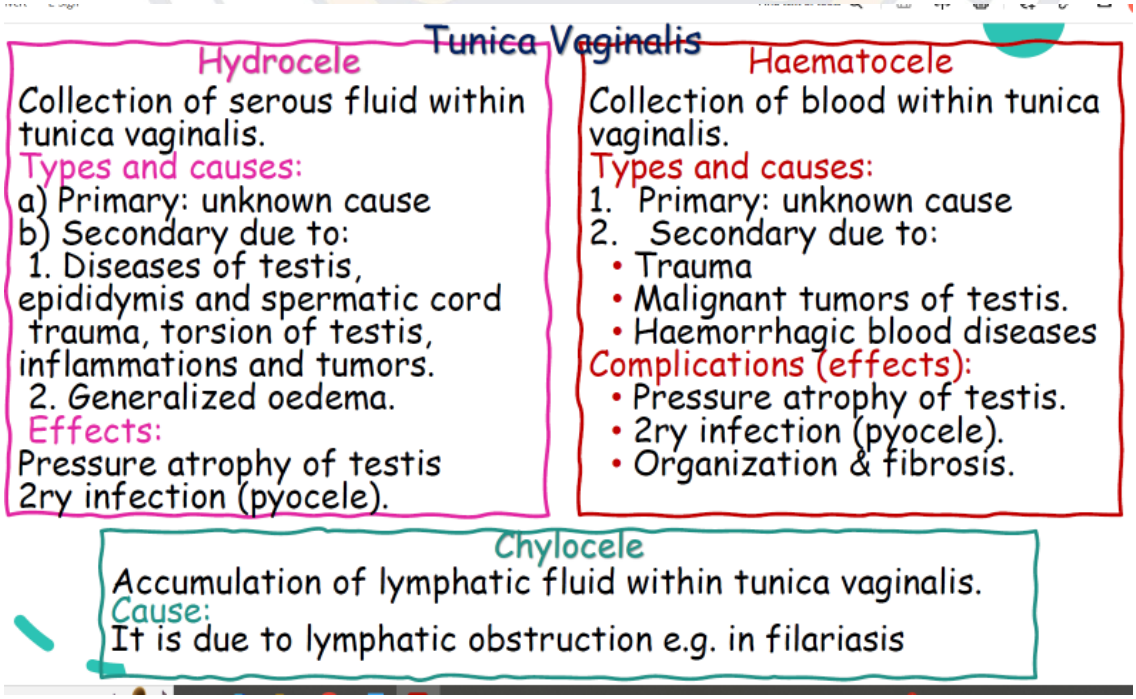
• They include:

(1) **Leydig (interstitial) cell tumor**: It produces androgens which leads to:

Before puberty it leads to sexual precocity.

After puberty, no body changes are detected.

(2) **Sertoli cell tumor**: It produces estrogen leading to feminizing characters.



Varicocele

Def: It is varicosity of the pampiniform plexus of veins in the spermatic cord.

Causes:

1. Primary: Occur in young unmarried men.

2. Secondary: Usually detected over the middle age. It is due to:

a) Pressure on the spermatic vein usually by a tumor of the kidney

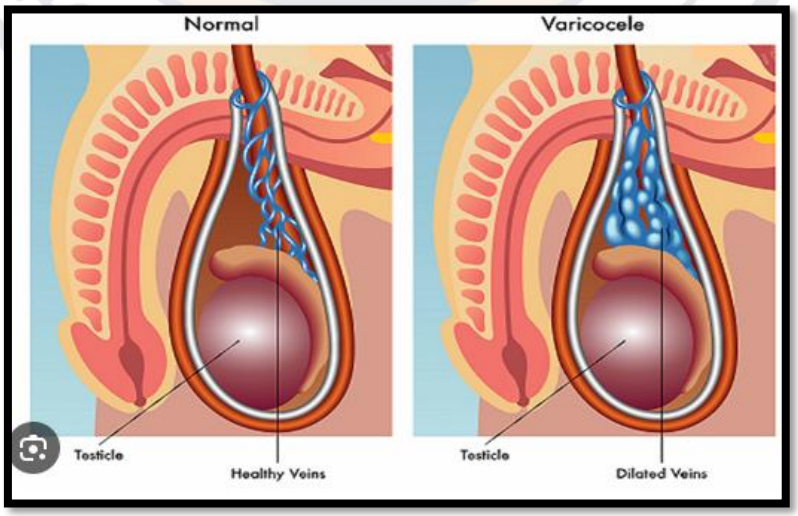
b) Right side heart failure

c) Venous thrombosis

Pathology:

a) Bag of warm like masses is felt in the scrotum

b) Detective spermatogenesis

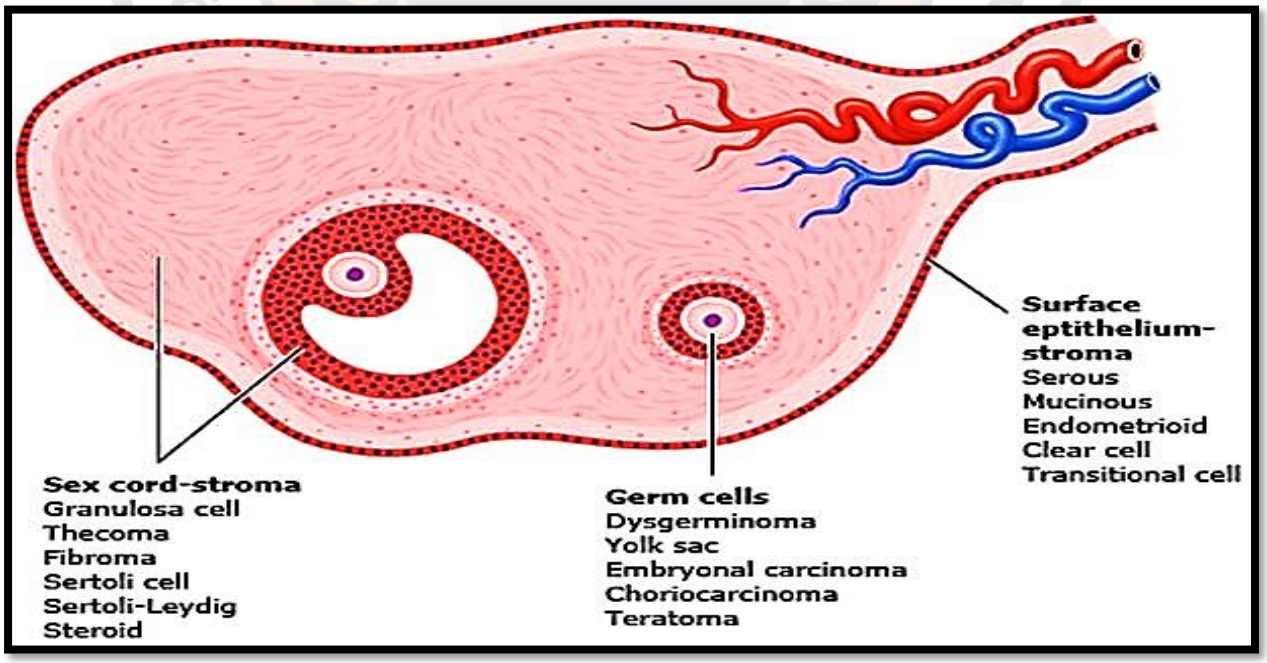


Varicocele

Ovary and fallopian tube

Ovarian tumors

- **Ovarian cancer accounts for 3% of all cancers in females**
  - ☒ Benign tumors occur mostly in young women between (20-25 years old).
  - ☒ Borderline tumors occur at slightly older ages.
  - ☒ Malignant tumors are more common in older women (45-65 years old).
- **Risk factors:**
  - ☒ Nulliparity
  - ☒ family history
  - ☒ Germline mutations in certain tumor suppressor genes.
- **Origin:**
  - ☒ Tumors of the ovary are remarkably varied as they may arise from any of the three cell types in the normal ovary:



1. Surface epithelial tumors

- Most common, accounting for >90% of ovarian tumors.
- The most widely accepted theory for the origin of surface epithelial tumors is the transformation of coelomic epithelium. This view is based on the embryologic pathway by which the müllerian ducts are formed from the coelomic epithelium and evolve into serous (tubal), endometrioid (endometrial), and mucinous (cervical) epithelia present in the normal female genital tract.
- **Types:**
  A. Serous tumors
  B. Mucinous tumors
  C. Endometrioid tumors
  D. Others

A. Serous tumors:

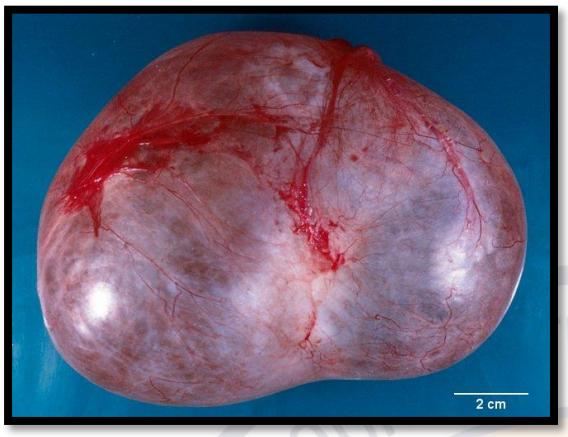
☒ They account for 30% of all ovarian tumors.

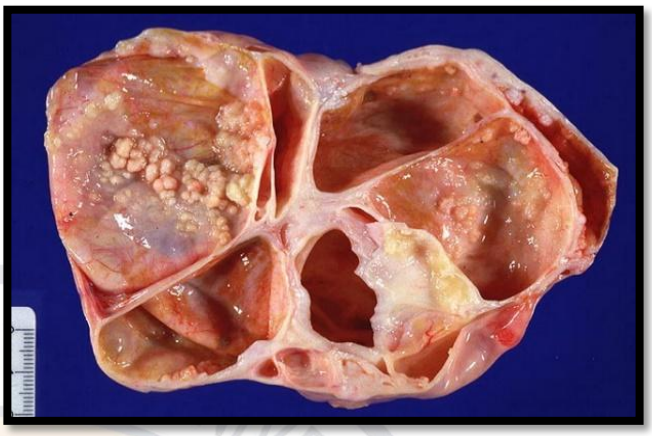
☒ **Age:** Benign lesions are usually between 30 and 40 years of age, and malignant serous tumors are more commonly seen between 45 and 65 years of age.

☒ **Pathogenesis:** The low-grade tumors arising in serous borderline tumors with only rare mutations in p53(tumor suppressor gene). In contrast, the high-grade tumors have a high frequency of mutations in the p53 gene.

☒ **N/E:**

- They are cystic lesion (cystadenoma) with smooth surface and serous fluid contents.
- Intarcystic papillary projections may be present (papillary cystadenoma).
- The outer surface of cystadenocarcinomas may show, in addition, nodules and outward papillary projections.
- **Bilaterality** is common in serous tumors.

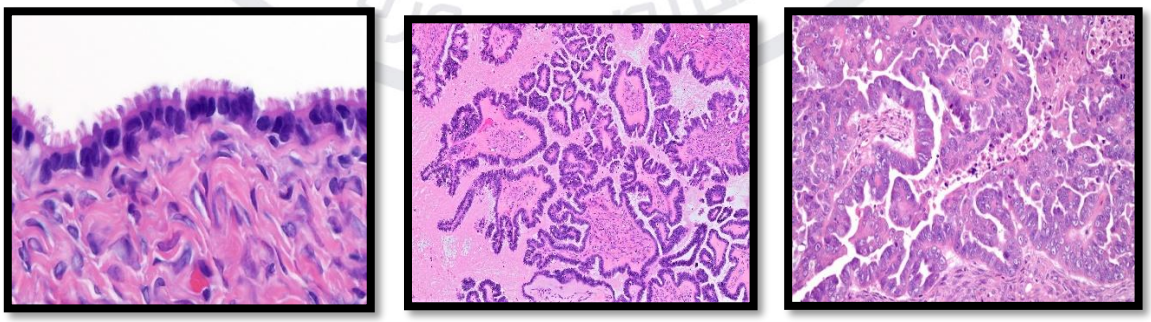




NE of serous cytadenoma *papillary cystadenoma*

☒ **M/E:**

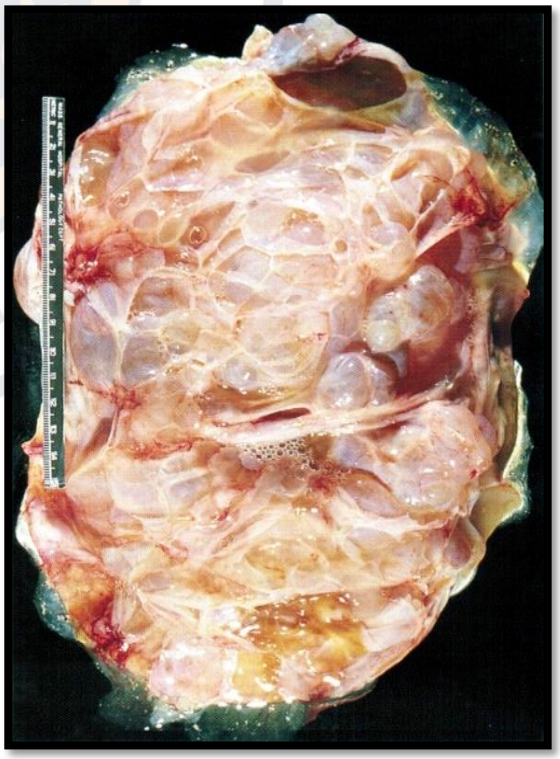
- **Benign tumors (serous cystadenoma)** contain a single layer of columnar epithelial cells that line the cyst or cysts. The cells often are ciliated occasionally forming microscopic papillae.
- **Malignant tumors** have multilayered epithelium with many papillae, solid areas and stromal invasion. Psammoma bodies (concentrically laminated calcified concretions) are commonly present.
- **Borderline tumors** show some of features of carcinomas but without stromal invasion.

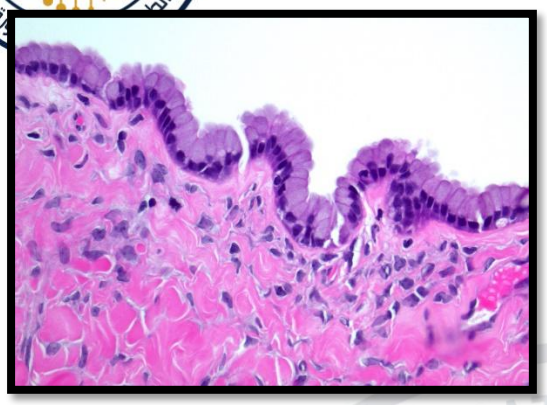
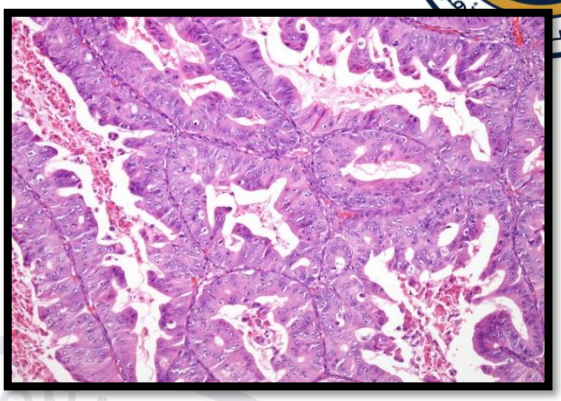


ME of benign, borderline, malignant serous tumors

B. Mucinous tumors:

- ☒ They account for 25% of all ovarian neoplasms.
- ☒ Only 10% of mucinous tumors are malignant; another 10% are borderline, and 80% are benign.
- ☒ Wide age range with a mean age at diagnosis of 50 years.
- ☒ Symptoms include abdominal pain, distension, pelvic mass.
- ☒ **NE:**
  - Mucinous neplasms tends more to be unilateral and larger. They appear as multiloculated cystic tumors (mucinous cystadenoma) filled with sticky, gelatinous fluid.
  - Rupture of the cyst may lead to pseudomyxoma peritonii, in most cases, this disorder is caused by metastatic spread of tumors in the gastrointestinal tract, primarily the appendix
- ☒ **M/E:**
  - **Benign lesions** are lined by tall columnar non ciliated epithelium with apical mucin similar to intestinal or cervical epithelium.
  - **Malignant tumors** usually show solid areas, necrosis and stromal invasion.
  - **Borderline tumors** show some of features of carcinomas but without stromal invasion



ME of benign and malignant mucinous tumors

C. Other tumors:

☒ **Endometrioid tumors**

- Most are malignant.
- Many cases occur in the setting of concurrent endometriosis.

☒ **Clear cell adenocarcinoma:**

- Uncommon, show cells with clear cytoplasm.

☒ **Brenner's tumor:**

- Most are benign.
- They consist of rounded islands of transitional epithelium embedded in dense fibrous stroma.

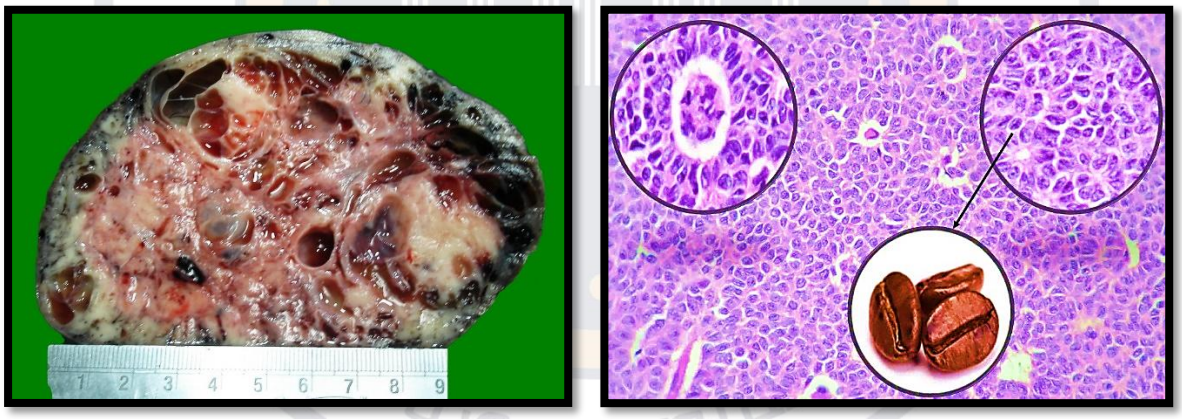
2. Sex cord stromal tumors

- Normally, the ovarian stroma, which is derived from the sex cords of the embryonic gonad differentiate into Sertoli and Leydig in male and granulosa and theca in female gonads, tumors resembling all of these cell types can be identified in the ovary.

- Moreover, because some of these cells normally secrete estrogens (granulosa and theca cells) or androgens (Leydig cells), their corresponding tumors may be either feminizing (granulosa–theca cell tumors) or masculinizing (Leydig cell tumors).

A. Granulosa cell tumor:

- ☒ 90% of all ovarian sex cord stromal tumors of low grade malignancy.
- ☒ **Age:** Menopausal women.
- ☒ **C/P:** Hyperestrogenism, associated endometrial hyperplasia and bleeding.
- ☒ **NE:** Well-circumscribed mass with solid and cystic areas, hemorrhage and necrosis
- ☒ **M/E:** Uniform ovoid cells with cleaved nucleus arranged in diffuse, trabecular or microfollicular pattern

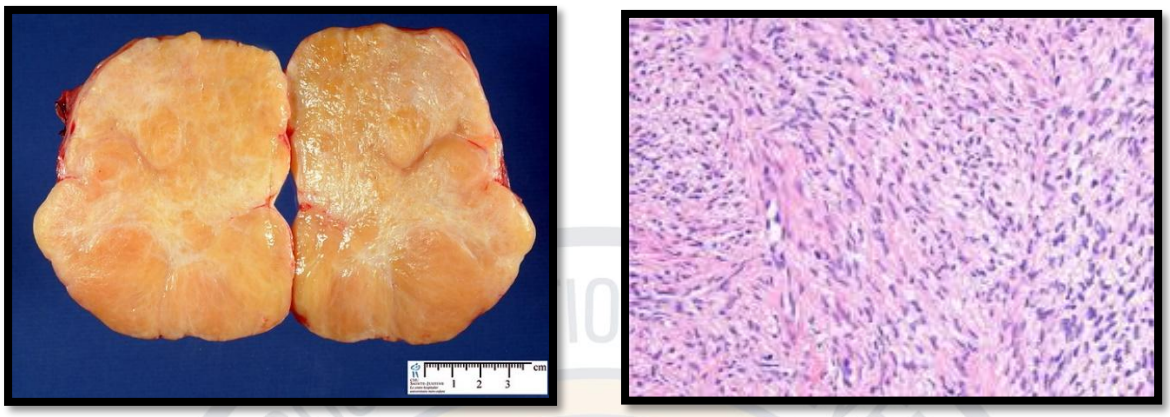


NE and ME of granulosa cell tumor

B. Thecoma-fibroma:

- ☒ **Theca cell tumor (thecoma):** benign tumor, mostly mixed with fibroma (fibrothecoma). Mostly are hormonally inactive but, may secrete estrogen
  - **NE:** Solid yellow lobulated mass.

- **M/E:** Ovoid to spindle cells with cytoplasmic lipid vacuoles.



NE and ME of thecoma-fibroma

☒ **Meig's syndrome:** Ovarian fibroma with hydrothorax and ascites.

C. Other Tumors:

☒ These may be Sertoli cell tumor (secretes estrogen), Leydig cell tumor (secrets androgen) or a combination of them. The majority are benign.

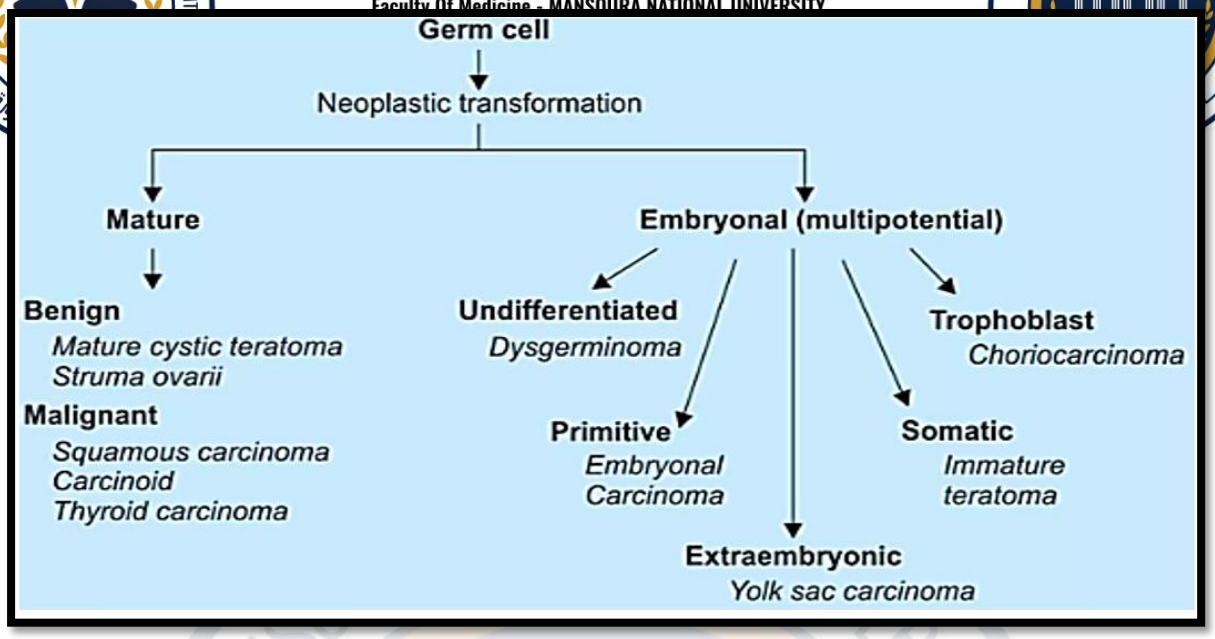
☒ Mixed male and female differentiation (Gynandroblastoma):

☒ Contain elements of granulosa, theca, Sertoli and Leydig tumors.

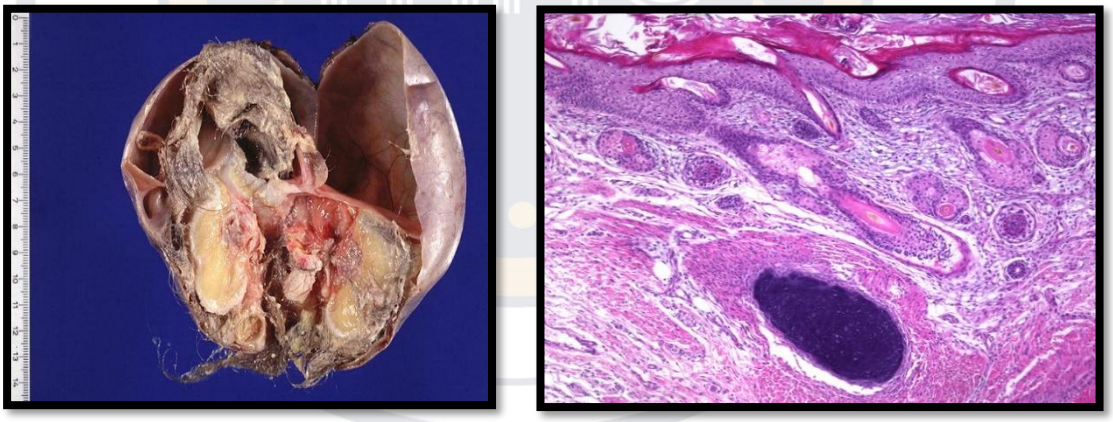
☒ It produces both hormones.

3. Germ cell tumors

- 30% of all primary ovarian neoplasms.
- >90% of ovarian GCT are mature cystic teratomas which are benign tumors. Remaining 5% are malignant.



1. **Mature teratoma:** It is usually cystic (dermoid cyst) and benign.
2. **Immature teratoma**: It is predominantly solid and malignant.
3. **Monodermal teratoma**: Characterized by one sided development. Examples are struma ovarii (only thyroid tissue) and some cases of mucinous cystadenoma (G.I.T. epithelium).



NE and ME of mature teratoma

4. **Other tumors:**

☒ Dysgerminoma

- Uncommon malignant non-functioning neoplasm occurs in children and young adults.

- Microscopically, it is similar to seminoma of testis (Sheets or cords of large clear cells, Stroma may contain lymphocytes).

☒ **Choriocarcinoma:** Differentiation towards trophoblasts. It secretes HCG hormones

☒ **Yolk sac tumor:** occur in children, adolescent and young adult, secretes alpha fetoprotein

5. **Unclassified tumors**

☒ Lymphomas, Hemangiomas, Lipomas, Leiomyomas,…etc

6. **Metastatic tumors**

☒ These tumors are usually bilateral.

☒ They reach both ovaries by transcoelomic spread, blood spread, retrograde lymphatic spread or direct spread.

☒ Site of primaries include uterus, G.I.T, gall bladder, pancreas, and lung.

☒ **Krukenberg tumor** is bilateral ovarian secondaries showing signet ring cells scattered in fibrous stroma. The primary is present in G.I.T, mainly stomach.

Non-Neoplastic Cysts of the Ovary

1. **Follicular cysts:**

☒ Extremely common finding.

☒ They are <2cm, lined by follicular cells, and filled with clear fluid.

☒ They commonly originate in unruptured graafian follicles.

2. **Corpus luteum cysts:**

☒ Dilatation of degenerated corpus luteum.

☒ Usually single and filled with blood.

3. **Polycystic ovary (stein- leventhal syndrome):**

- ☒ Affects women in reproductive age and is in the form of bilateral multiple small cystic follicles with cortical fibrosis.
- ☒ Oligomenorrhea, hirsutism and infertility are presenting symptoms.
- ☒ The condition is related to disturbance in androgen synthesis

N.B: Sometimes these cysts rupture, producing intraperitoneal bleeding and peritoneal symptoms (acute abdomen).

Fallopian tubes

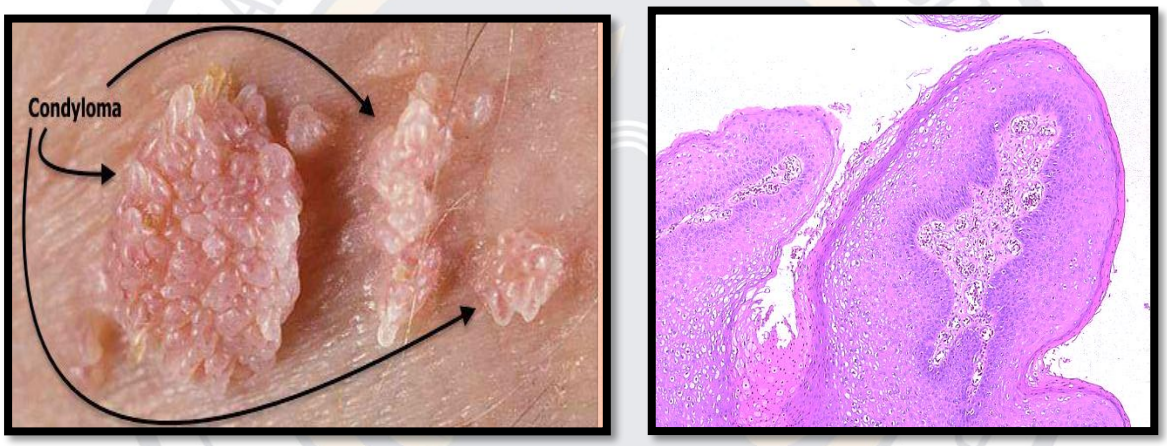
1. **Suppurative salpingitis,**
   - ☒ gonococcus accounts for more than 60% of cases.
   - ☒ These tubal infections are a part of pelvic inflammatory disease.
2. **Tuberculous salpingitis is an important cause of infertility.**
3. **Tumors of the fallopian tube**
   - ☒ are uncommon.
   - ☒ Primary adenocarcinoma of the fallopian tubes is rare.
4. **Serous tubal intraepithelial carcinoma**
   - ☒ considered as a precursor lesion to most of high grade serous tumors.

Vulva, vagina, cervix

Vulva

Benign lesions of the vulva

- ☒ Condyloma Accuminata which is virus related (low risk HPV).
- ☒ Squamous cell papilloma is not of viral origin.
- ☒ Hidraadenoma papilliferum.



NE and ME of condyloma accuminata

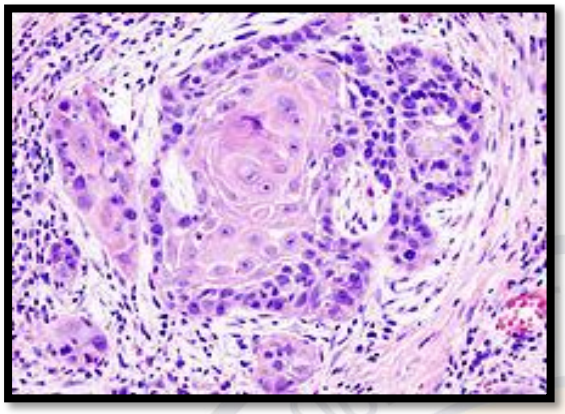
Carcinomas:

☒ Squamous cell carcinoma:

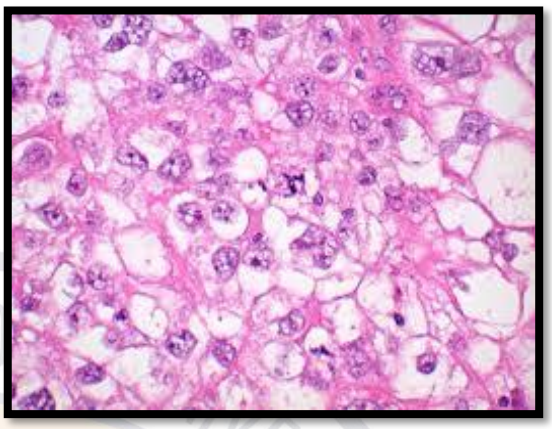
- Squmous cell carcinomas are, in a proportion of cases, related to (high risk HPV).
- They are preceded by a precursor lesion (vulvar intraepithelial neoplasia, VIN).

☒ Clear cell carcinoma:

- A variant of adenocarcinoma. It is preceded by a precursor lesion (vaginal adenosis). The condition is uncommon but is seen in up to 90% of patients exposed in utero to DES.



ME of SCC of vulva



ME of clear cell carcinoma of vulva

Vagina

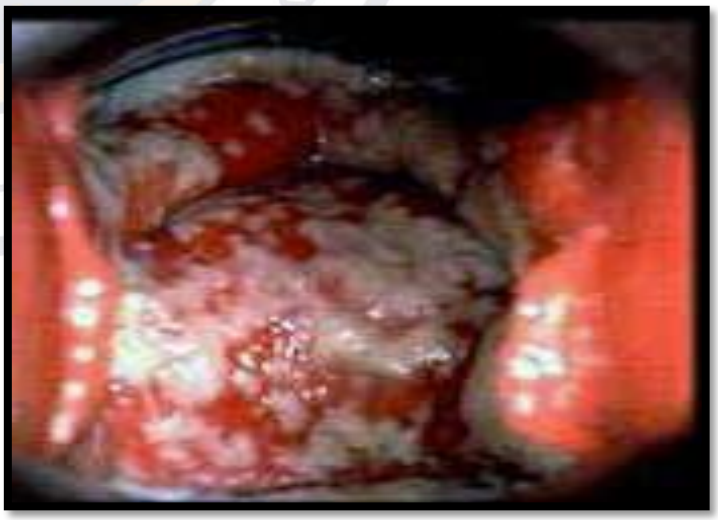
Vaginitis:

☒ **Caused by:**

- Monilia - trichomonas vaginalis
- Gonorrhea -Staph.
- Herpes simplex ... etc.

☒ **It occurs in:**

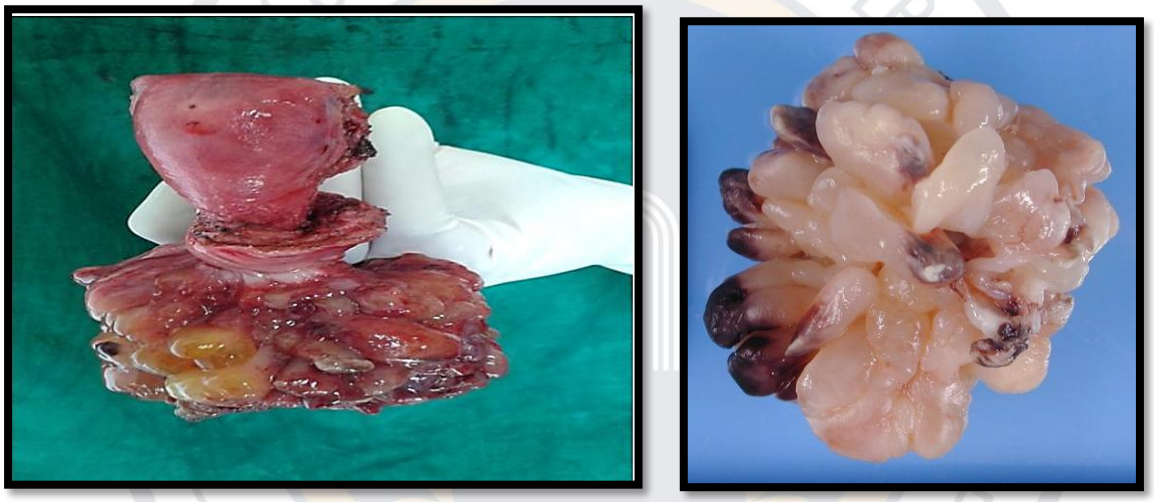
- Infants and young women (high glycogen content of vaginal epithelium.)
- Pre-pubertal and postmenopausal women (lack of oestrogen)
- Diabetic women
- In case of prolonged loop application.



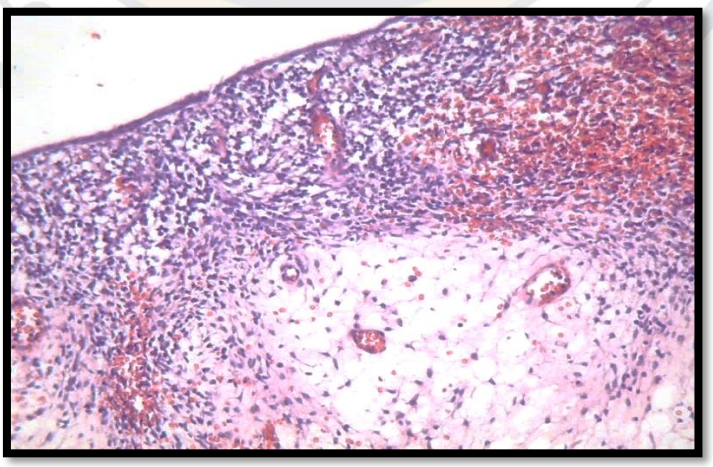
Gross appearance of vaginitis

Embryonal rhabdomyosarcoma (sarcoma botryoides):

- ☒ This tumor is uncommon occurring chiefly in girls from birth to adolescence (90% of cases occur under 5 years of age).
- ☒ **Grossly,** appears as a large polypoid (grapes-like), reddish, soft mass.
- ☒ **Microscopically,** it consists of malignant embryonal cells (small round to oval cells with hyperchromatic nuclei and scanty cytoplasm) in a myxoid stroma with rhabdomyoblastic differentiation.

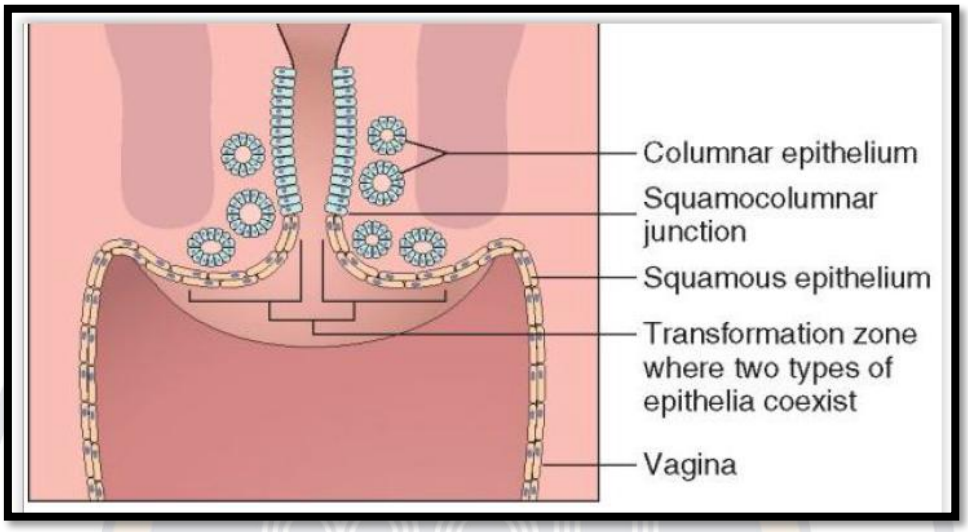


NE of Embryonal rhabdomyosarcoma



ME of Embryonal rhabdomyosarcoma

Cervix



Normal cervix

Cervicitis

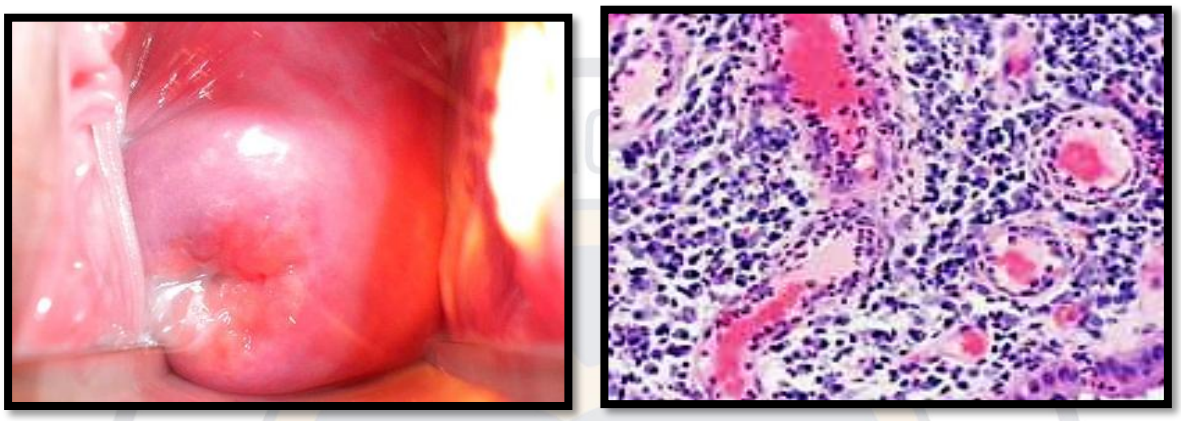
☒ Some degree of cervical inflammation may be found with no or little clinical consequence.

☒ **Cause:**

- E. coli, staph, strept. H. gonococci, chlamydiae, mycoplasmas, trichomonas vaginalis and herpes simplex virus may produce significant acute or chronic cervicitis.
- May be associated with upper genital tract disease, complications during pregnancy, and sexual transmission.
- Can be either acute or chronic

A. Acute cervicitis:

☒ The cervix is congested, swollen and shows profuse purulent discharge. The inflammation may resolve or more often passes to a chronic stage.



NE and ME of acute cervicitis

B. Chronic cervicitis:

☒ **Common**

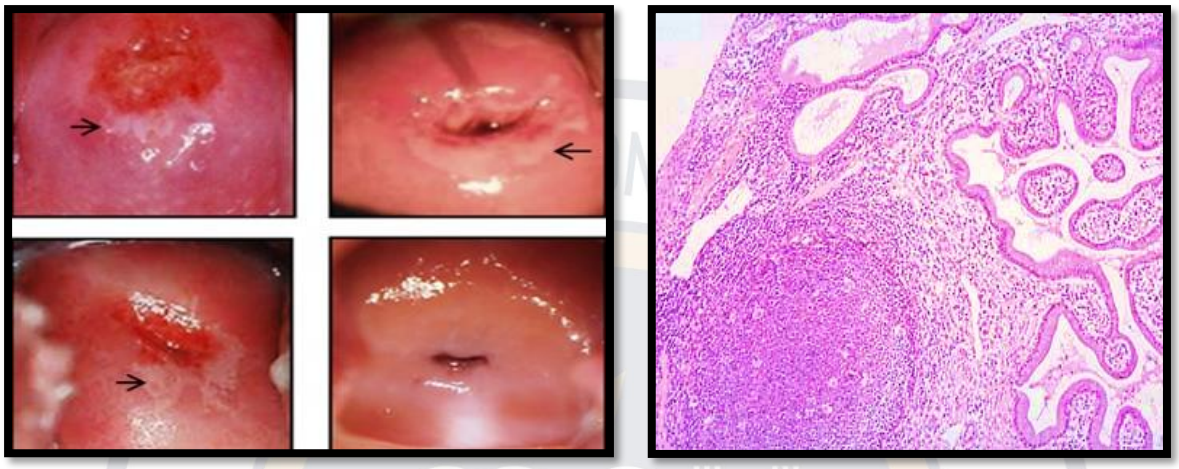
☒ **N/E:**

- The cervix is red, swollen ± ulcers, polyps orcysts. External os is wide, irregular with mucopurulent discharge.

☒ **M/E:**

- **Endocervix:**
  - Lining epithelium shows squamous metaplasia ± dysplasia.
  - Subepithelial tissue shows chronic inflammatory cells + endarteritis obliterans +fibrosis and some neutrophils. Some glands are cystically dilated (Nabothian cysts).
  - Inflammatory polyp

- **Ectocervix:**
  - Extension of endocervical mucosa to replace ectocervical epithelium around external os. Squamous metaplasia occurs later.



NE and ME of chronic cervicitis

Endocervical Polyps

☒ Benign exophytic growths

☒ Usually arise from the endecervix.

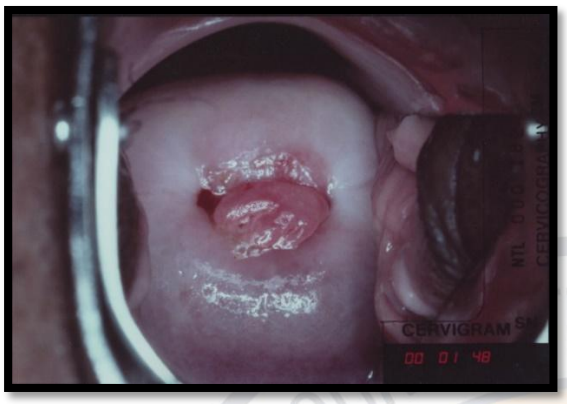
☒ Cause irregular vaginal bleeding.

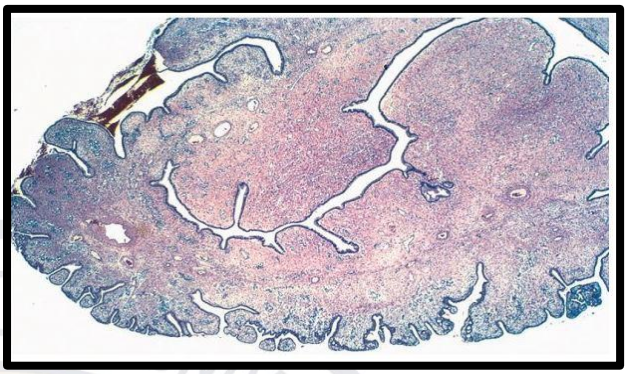
☒ **NE:**

- Polyps are soft, almost mucoid.

☒ **ME:**

- composed of central vascular and edematous connective tissue core containing chronic inflammatory cells and proliferated cervical glands.
- It is covered by columnar epithelium with areas of squamous metaplasia.

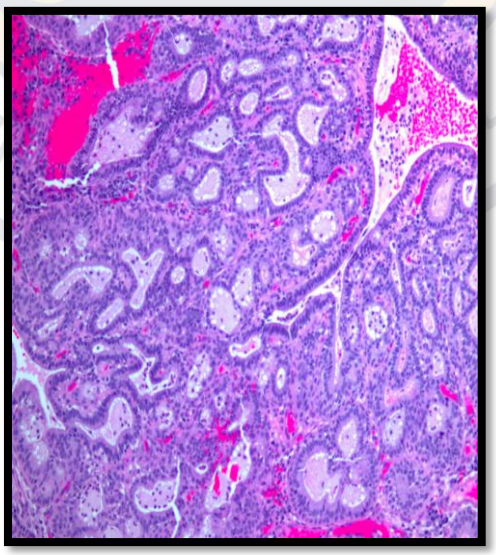




NE and ME of endocervical polyp

Microglandular Hyperplasia

- ☒ It is benign condition of the cervix in which there is closely packed proliferation of small endocervical glands.
- ☒ It is caused by progesterone administration such as during pregnancy, postpartum period or oral contraceptive pills administration.



ME of microglandular hyperplasia

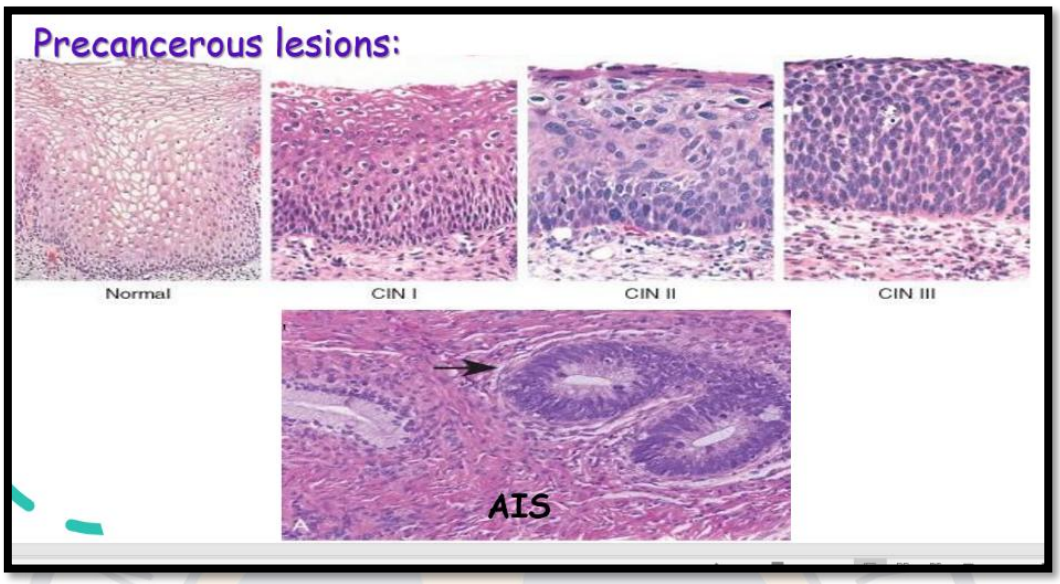
Carcinoma of the cervix

☒ Predisposing factors:

- Persistent infection with oncogenic HPVs (16 & 18). HPVs infect immature basal cells of the squamous epithelium. Integration of HPV DNA interferes with the p53 & RB genes.
- Smoking reduces local cervical immunity.
- Early age at first intercourse.
- Multiple sexual partners.
- Presence of other sexually transmitted disease like HIV and genital herpes.
- Having a partner with sexually transmitted disease.
- Long term Oral contraceptive pills use and multiple pregnancies
- Immunosupression .

☒ Precancerous lesions:

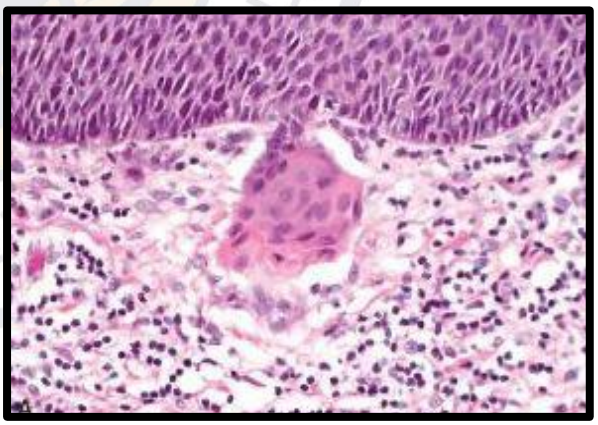
- **Cervical Intraepithelial Neoplasia (CIN)** is the precancerous lesion of cervical squamous cell carcinoma. It is classified as:
  - **CIN1** → minimal dysplasia in lower 1/3 → low risk to develop carcinoma, called low grade squamous intraepithelial lesion (LSIL)
  - **CIN2** → moderate dysplasia in lower 2/3
  - **CIN3** →the most severe where the atypical cells involve the whole thickness of the epithelium.
- **Both 2, 3 risk** to develop carcinoma, called **high grade squamous intraepithelial lesion (HSIL)**
- **Adenocarcinoma insitu (AIS):** is the precancerous lesion for invasive adenocarcinoma.



Precancerous lesions of cervix: ME of CIS and AIS

Invasive carcinoma

- ☒ One of the commonest cancer in females.
- ☒ The age peak of incidence is 45 years.



NE and ME of invasive cervical carcinoma

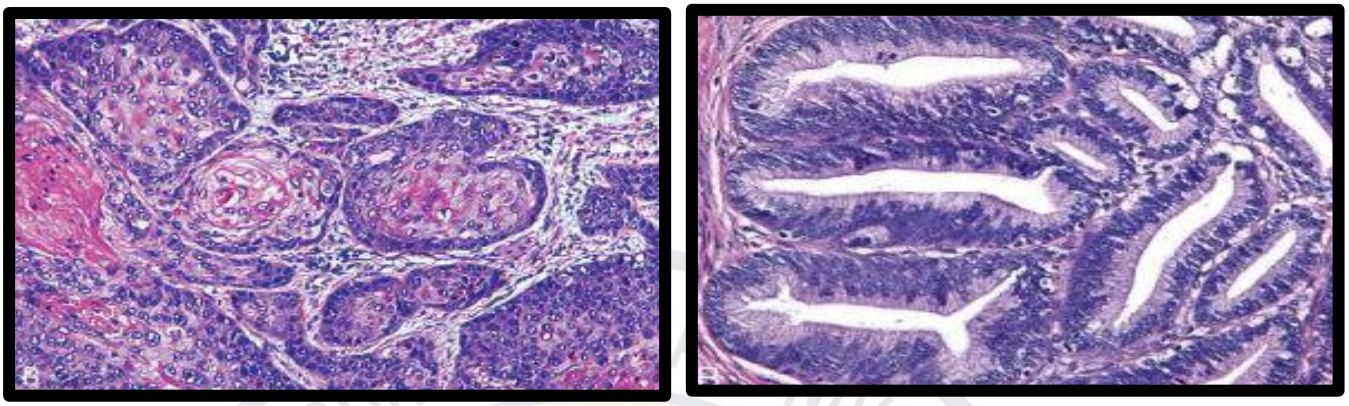
☒ **Gross:**

- **Site:**
  - Squamous columnar junction.
  - Endocervix with sq. metaplasia
- **Shape:**
  - **Carcinoma in situ:** a focal thickening & induration of cervix.
  - **Invasive carcinorna.**
    - Fungating (exophytic)
    - Infiltrating (endophytic) →induration & deformity of the cervix.
    - Ulcerating (malignant ulcer)

NE of invasive cervical carcinoma

☒ **Microscopically:**

- **Squamous cell carcinomas** either keratinizing or nonkeratinizing. The most common (80% of cases)
- **Adenocarcinomas (15% of cases)** are characterized by formation of glandular structures.
- **Other types (5%)** include adenosquamous carcinoma and neuroendocrine carcinoma.



ME of invasive cervical carcinoma

☒ **Spread:**

- Local to the peritoneum , bladder and rectum.
- Lymphatic to local and distant lymph nodes metastasis
- Hematogenous metastasis to liver lung and bone.

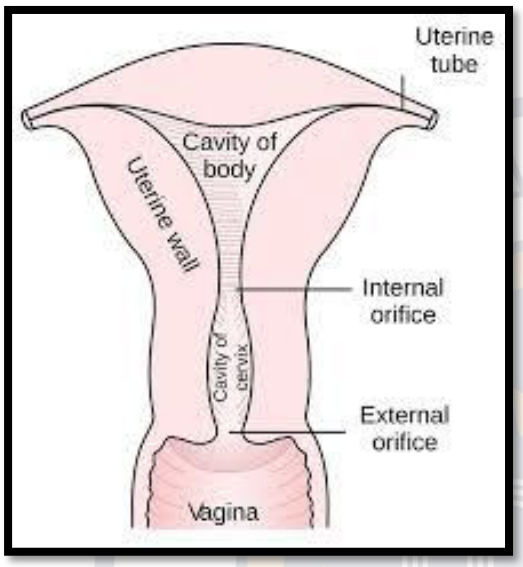
☒ **Prognosis:**

- Because of screening programs, most of patients are discovered in the early stages.
- Patients with stage IV cancer of poor prognosis die as a consequence of local extension of the tumor.

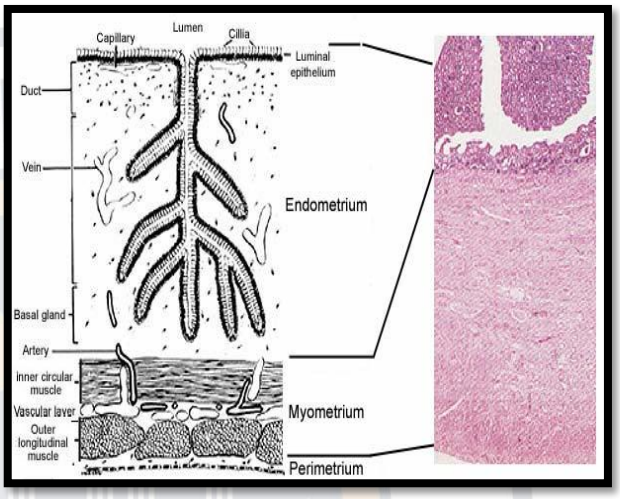
☒ **Prevention:**

- **Vaccination against HPV** introduced to girls at school age hopefully may reduce the cervical cancer risk.
- **Screening programs:**
  - **Aim**: to detect precancerous lesions or abnormal cells early.
  - **Method**: PAP smear and HPV testing.

Pathology of Uterine Corpus And Gestational Trophoblastic Diseases.



Structure of uterus



Structure of uterine wall

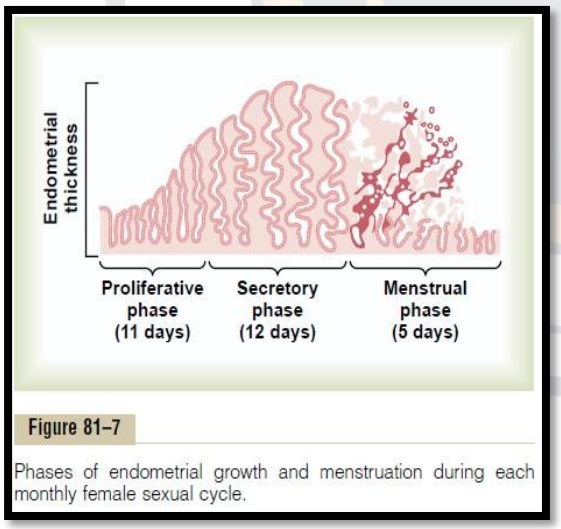
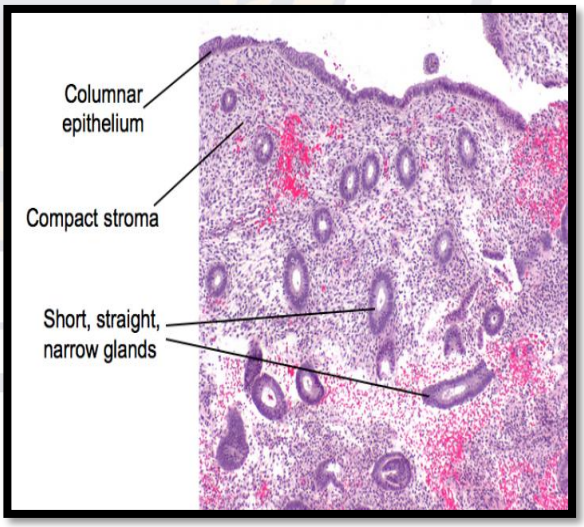


Figure 81–7

Phases of endometrial growth and menstruation during each monthly female sexual cycle.



Endometrium

Abnormal Uterine Bleeding (AUB)

- **Definition:** Any deviation from a normal menstrual cycle pattern.
- The key characteristics are regularity, frequency, heaviness of flow, and duration of flow.
- **The causes of abnormal bleeding may be:**
  - ☒ **Organic (Structural) abnormality**, such as chronic endometritis, submucosal leiomyomas, endometrial polyp or endometrial neoplasms.
  - ☒ **Functional disturbances (dysfunctional uterine bleeding)** as a result of abnormalities in the menstrual cycle or systemic diseases.

Dysfunctional uterine bleeding

- **Nonstructural'' causes of abnormal uterine bleeding (AUB)**
  1. Disorders of endometrial origin (disturbances of the molecular mechanisms responsible for regulation of the volume of blood lost at menstruation);
  2. Disorders of the hypothalamic-pituitary-ovarian axis
  3. Disorders of hemostasis (the coagulopathies).
- **Causes of abnormal uterine bleeding in different age groups:**

Age Group	Causes
Prepuberty	Precocious puberty (hypothalamic, pituitary, or ovarian origin)
Adolescence	Anovulatory cycle, coagulation disorders
Reproductive age	Complications of pregnancy (abortion, trophoblastic disease, ectopic pregnancy)
	Organic lesions (leiomyoma, adenomyosis, polyps, endometrial hyperplasia, carcinoma)
	Anovulatory cycle
	Ovulatory dysfunctional bleeding (e.g., inadequate luteal phase)
Perimenopausal	Anovulatory cycle
	Irregular shedding
	Organic lesions (carcinoma, hyperplasia, polyps)
Postmenopausal	Organic lesions (carcinoma, hyperplasia, polyps)
	Endometrial atrophy

Endometritis

• Inflammation of the endometrial lining of the uterus. is classified as acute or chronic

- **ACUTE ENDOMETRITIS**

It is uncommon, may progress to puerperal sepsis

Puerperal sepsis:

It is endometrial infection during puerperium (after labour or abortion), caused by strept. H., staph. Aureus, E. coli, pseudomonas

Predisposing causes:

1- Uterine retention of products of conception and blood clots provide a culture medium for bacteria.

2-Traumatic lacerations during childbirth.

N/E:

1- Uterus is bulky (subinvoluted), soft and flabby.

2- Uterine cavity contains septic necrotic material, remnants of placenta and pus.

3- Endometrium is hyperemic, edematous with necrosis and ulceration.

4- Myometrium show:

Septic inflammation which may form abscesses.

Myometrial veins contain septic thrombi.

NE of puerperal sepsis

M/E:

l- Uterine cavity contains septic material and pus.

2- Endometrium show:

Ulceration of surface epithelium with acute suppurative inflammation.

3- Myometrium show:

Suppurative myometritis which may lead to myometrial abscesses.

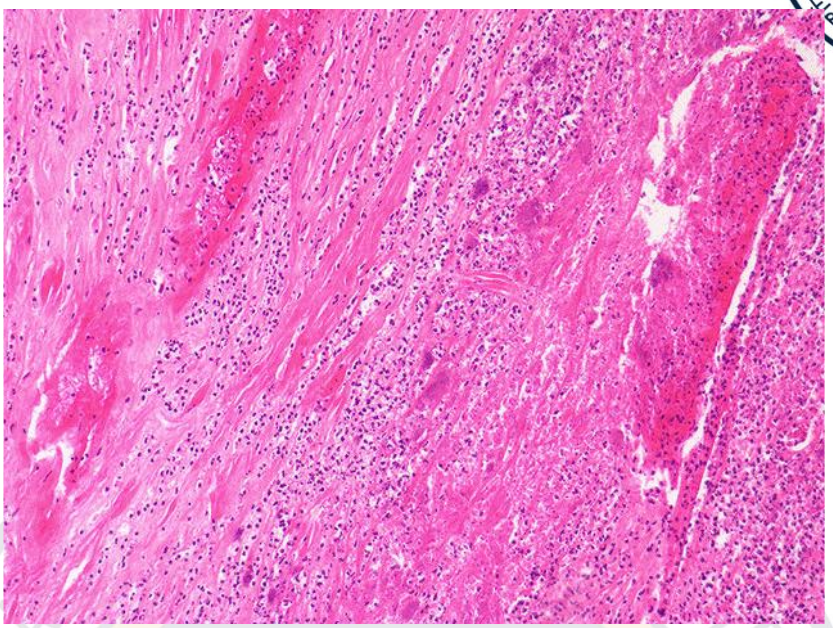
Myometrial veins contain septic thrombi.

Complications:

Direct spread to pelvic structures

Blood spread: - Pyeamia (septic thrombo phlebitis), Septicaemia.

Severe toxemia.



ME of puerperal sepsis

- **CHRONIC ENDOMETRITIS**

-Presented with bleeding, pain, discharge and infertility.

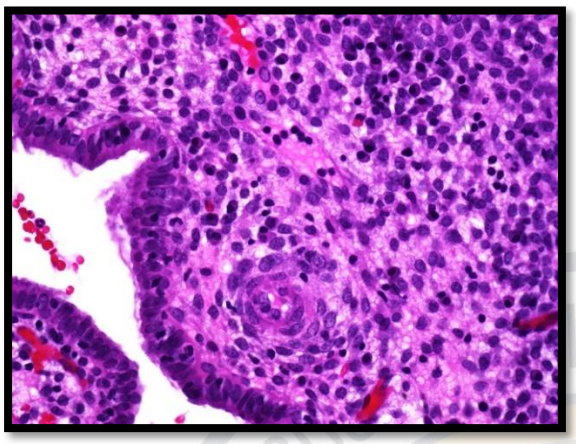
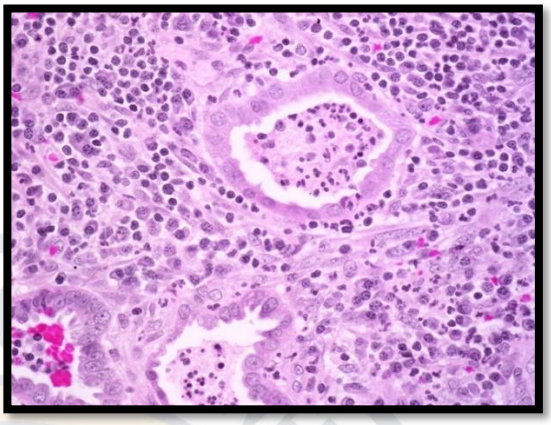
M/E: plasma cells.

- Causes:

Pelvic inflammatory disease(PID), in postpartum or post-abortion patients with retained gestational tissue.

-Women with intrauterine contraceptive devices

-Women with tuberculosis, Syphilis(rare)

Chronic endometritis ME

Endometriosis

- Endometriosis is the occurrence of endometrial tissue (glands and stroma) in a location outside the uterus.
- It responds to ovarian hormones somewhat like the uterine endometrium.

I. External Endometriosis

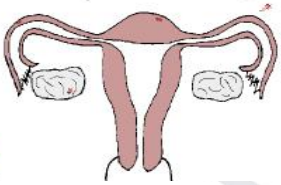
☒ Presence of endometrial tissue (glands and intervening stroma) **outside the uterus.**

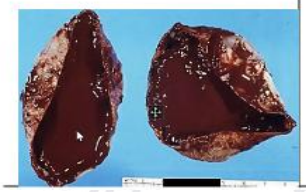
☒ Frequently is multifocal and often involves pelvic structures (ovaries, pouch of Douglas, uterine ligaments, tubes, and rectovaginal septum

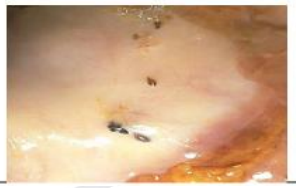
II. Internal Endometriosis (adenomyosis)

• Presence of endometrial tissue (glands and stroma) in the myometrium of uterine wall.

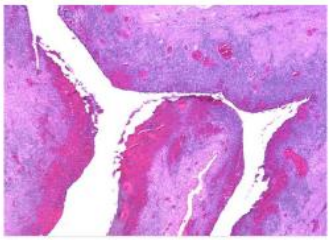
	External Endometrisis	Internal Endometriosis
Site	Outside the myometrium	Myometrium of body of uterus called **Adenomyosis**
Pathogenesis	1. The regurgitation theory: during menstruation, viable endometrial fragments pass via fallopian tube to implant on the peritoneum 2. Metaplasia of serosal cells leads to peritoneal lesions. 3. Vascular and lymphatic dissemination theory.	**Abnormal growth activity of the endometrium**, the basal zone of endometrium dips into the adjacent myometrium.
N/E	Hemorrhagic lesions (as the endometrial tissue undergoes cyclic menstrual bleeding). It excites excessive fibrous tissue around them •Ovarian endometriosis (chocolate cysts): cyst with dark red brown altered blood content. • Fibrous adhesion with surroundings.	• The uterus is symmetrically enlarged • The uterine wall is thickened • The lesions form dark red foci

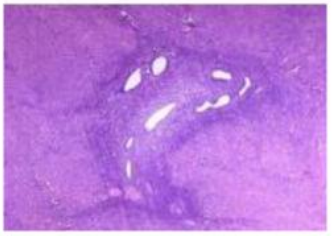


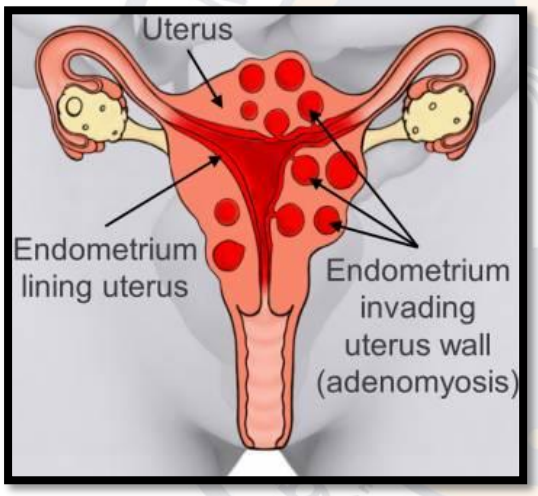


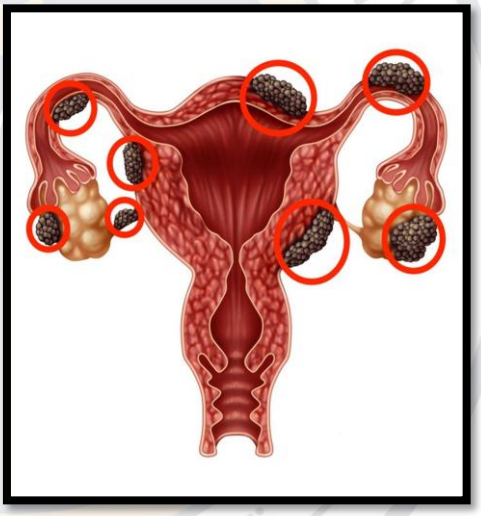


	External Endometrisis	Internal Endometrisis
M/E	• Lesion consists of endometrial glands and stroma with hemosiderin. • fibrosis and hemosiderin laden macrophage.	• Nests of endometrial glands and stroma in myometrium between muscle bundles







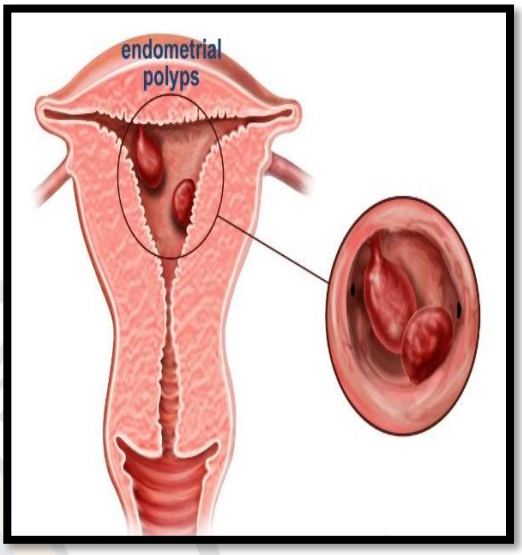


Intrnal endometriosis (adenomyosis) ***External endometriosis***

Endometrial Polyp

- Endometrial polyps are sessile masses of that project into the endometrial cavity.

- They may be single or multiple
- It may cause abnormal bleeding.
- **Types:**
  - ☒ Functional endometrium,
  - ☒ Hyperplastic endometrium, in association with endometrial hyperplasia
  - ☒ Endometrial polyps in association with the administration of tamoxifen, an antiestrogen therapy of breast cancer.

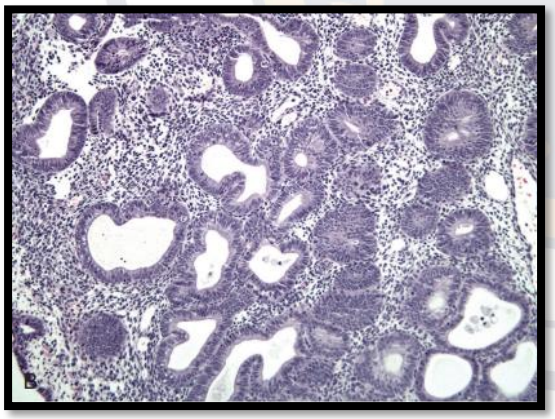


Endometrial Hyperplasia

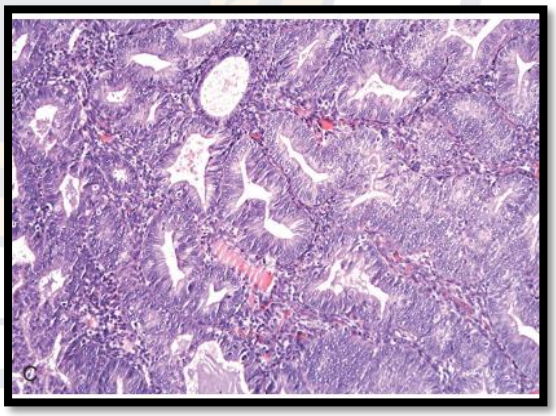
- **Definition:**
  - ☒ Increased proliferation of the endometrial glands relative to the stroma, resulting in an increased glandto-stroma ratio when compared with normal proliferative endometrium.
  - ☒ It is an important cause of abnormal uterine bleeding.
- **Causes:** prolonged unopposed estrogen stimulation
  - ☒ Repeated anovulatory menstrual cycles,
  - ☒ Obesity,
  - ☒ Estrogen secreting tumors
  - ☒ Polycystic ovarian disease

- **N/E:**
  - ☒ Endometrial hyperplasia appears as increased endometrial thickness
- **ME:**
  - ☒ Charcterized by glandular proliferation and crowding
  - ☒ Increased gland to stromal ratio
  - ☒ Endometrial hyperplasia is placed in two categories based on the presence of cytologic atypia:
    - **Hyperplasia without atypia**: carries a low risk (between 1% and 3%) for progression to endometrial carcinoma
    - **Hyperplasia with atypia**: also called endometrial intraepithelial neoplasia (EIN), is associated with a much higher risk (20%–50%).

Endometrial hyperplasia NE



Endometrial hyperplasia without atypia



EH with atypia

Endometrial tumors

Endometrial Tumors

1- Endometrial Carcinoma

2- Carcinosarcoma (Malignant Mixed Mullarian Tumor)

3- Endometrial Stromal Tumors

a-Benign: Stomal nodule

b-Malignant: Endometrial Stromal Sarcoma (ESS)

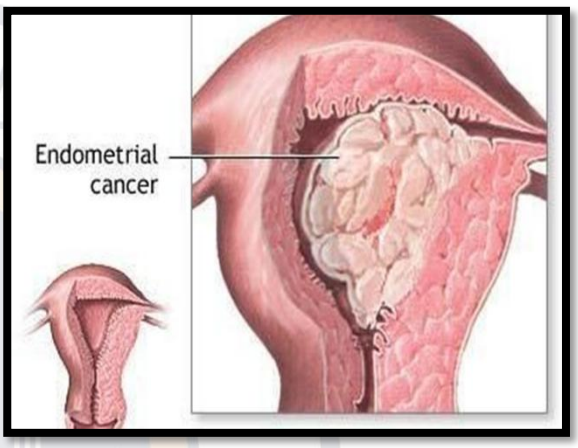
Endometrial carcinoma

- Endometrial carcinoma (EC) is the most common cancer of the female genital tract
- Endometrial carcinoma has two broad categories,
  - ☒ **Type I:** Endometroid carcinoma (about 80% of cases)
  - ☒ **Type II:** Serous carcinoma (about 20% of cases).

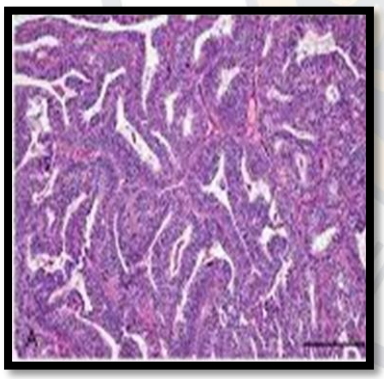
- **Precursor (precancerous, preneoplastic) lesions:**
  - ☒ **Type I carcinoma:** atypical endometrial hyperplasia (also known as endometrioid intraepithelial neoplasia, EIN)
  - ☒ **Type II carcinoma:** a surface endometrial lesion is called Endometrial intraepithelial carcinoma, EIC

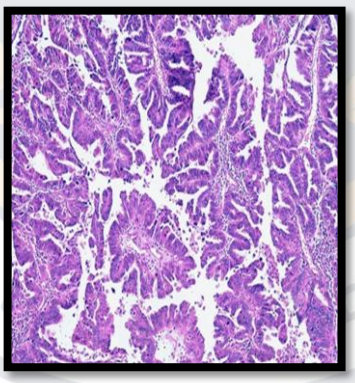
Endometrial carcinoma

- **NE:** It may be polypoid or infiltrative. Type II tends to be more bulky and diffuse.
- **ME:**
  - ☒ **Type I tumor:** resembling endometrial glands.
  - ☒ According to the degree of glandular differentiation, endometrioid carcinoma is graded into GI, GII and GIII.
  - ☒ **Type II:** is usually of serous histology (simulating tubal epithelial lining).

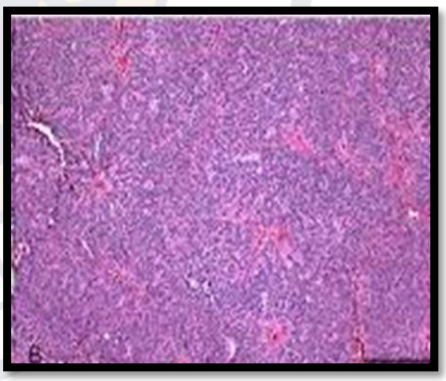


Endometrial carcinoma NE





Type I endometrial carcinoma



Type II endometrial carcinoma

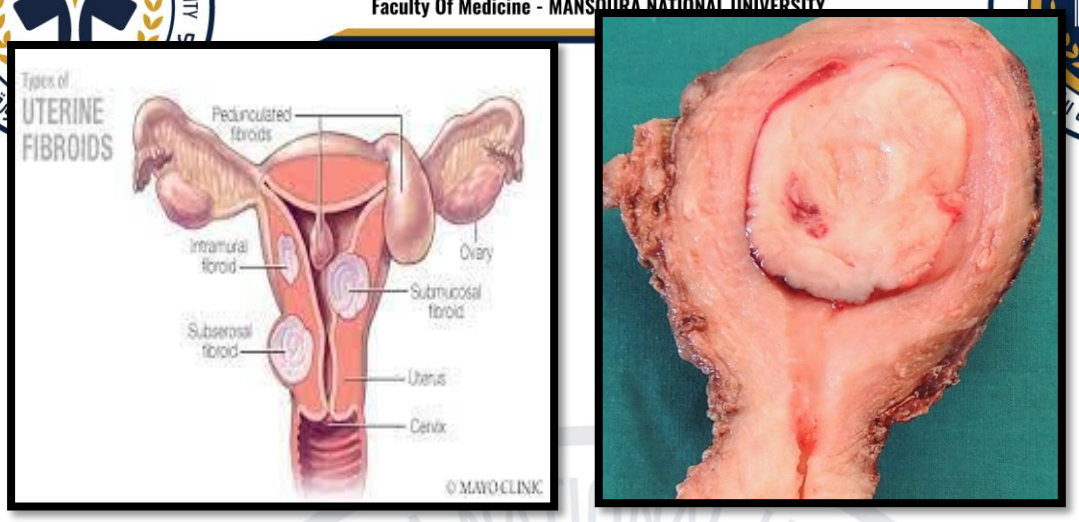
Characteristics	Type I	Type II
Age	55–65 years	65–75 years
Risk factors and Clinical settings	Unopposed estrogen Obesity Hypertension Diabetes	Atrophy Thin patients
Morphology	Endometrioid	Serous Clear cell
Precursor	Atypical endeomtrial hyperplasia Endometrioid intraepithelial neoplasia (EIN)	Endometrial intraepithelial carcinoma (EIC)
Molecular genetics	*PTEN*	*p53*
Behavior	Indolent Spreads via lymphatics	Aggressive Intraperitoneal and lymphatic spread

Tumors of Myometrium

- **Benign:** Leiomyoma
- **Maliganat:** Leiomyosarcoma

Leiomyoma

- Benign tumors that arise from the smooth muscle cells in the myometrium are properly termed leiomyomas, but because of their firmness often are referred to clinically as fibroids.
- Leiomyomas are the most common benign tumor in females, affecting 30% to 50% of women of reproductive age.



Leiomyoma NE

- **Etiology:**

☒ The tumor is linked to prolonged hyperestrinism.

- **Site:**

☒ **Commonly arise in the body of uterus and cervix. May be:**

- **Submucous** (project in the uterine cavity under the endometrium)
- **Intramural** (within the wall of the uterus)
- **Subserous** (projects to outside under the peritoneum)

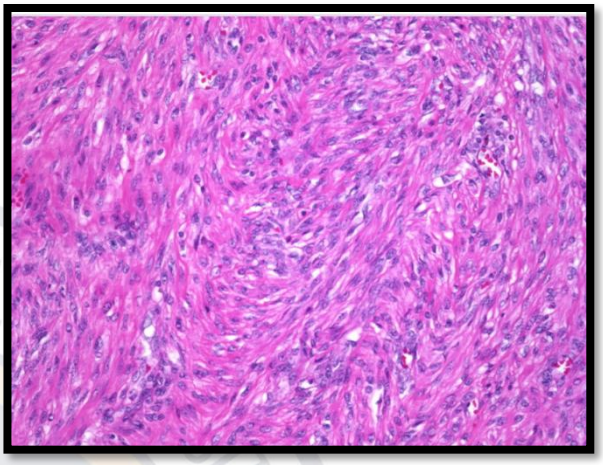
Submucous ***Intramural*** ***Subserous***

- **NE:**

☒ Rounded masses, surrounded by pseudo-capsule of compressed uterine muscle and interstitial tissue.

☒ **Cut surface:** whorly appearance and firm in consistency

- **ME:**
  - ☒ **Interlacing bundles of:** smooth muscle cells & fibroblasts.
  - ☒ **Secondary changes:** e.g. hyaline degeneration, cysts, necrosis, and calcification.
  - ☒ **Red degeneration** (hemorrhagic infarction) occurs particularly during pregnancy.

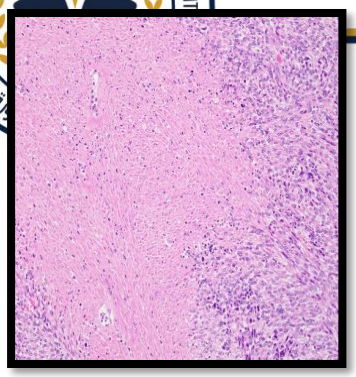
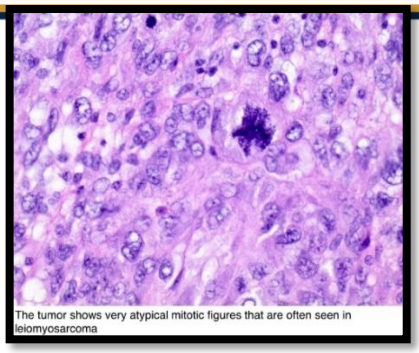


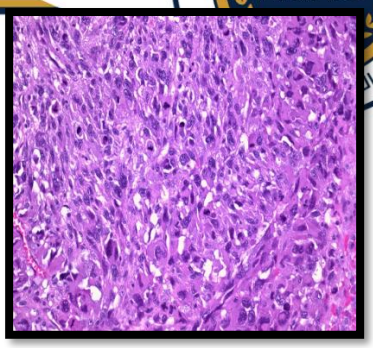
Leimyoma ME

- **Complications:**
  1. Abnormal uterine bleeding.
  2. Infertility due to prevention of implantation of fertilized ovum.
  3. Risk of abortion.
  4. Interfere with child birth.
  5. Iron deficiency anemia
  6. Malignant transformation to Leiomyosarcoma (rare, 1%).

Leiomyomsarcoma

- **On histologic examination:**
  1. Atypia,
  2. Increased mitotic figures
  3. Coagulative necrosis.



Leiomyosarcoma ME

Gestational trophoblastic diseases (GTD)

- **Definition: group of diseases characterized by:**
  - ☒ Proliferation of pregnancy-associated trophoblastic tissue
  - ☒ Has a malignant potential

Classification:

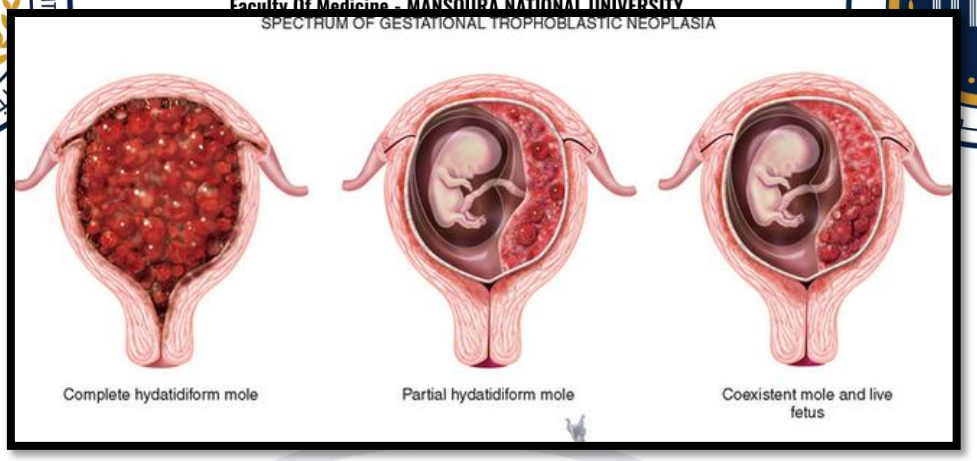
1.Molar GTD (Villous):Characterized by formation of chorionic villi

Hydatiform mole:- Complete - Partial -Invasive mole

2.Non- Molar GTD (Non- villous):

No villi

Choriocarcinoma



Molar pregnancy

<u>Hydatiform mole</u>

Called vesicular mole

Incidence:

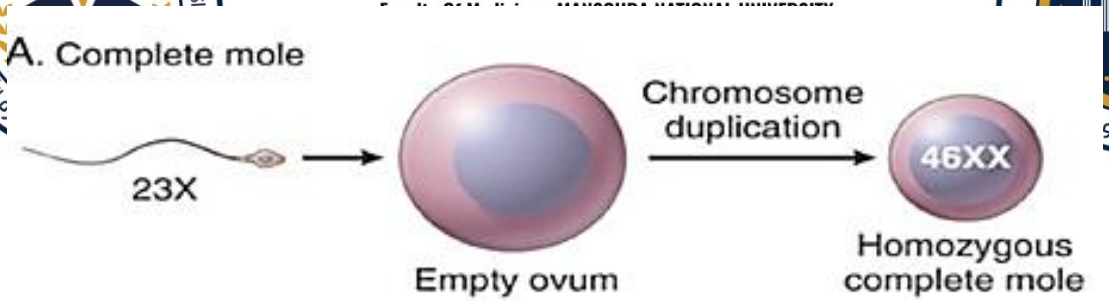
During reproductive period, (20-40 years)related to pregnancy.

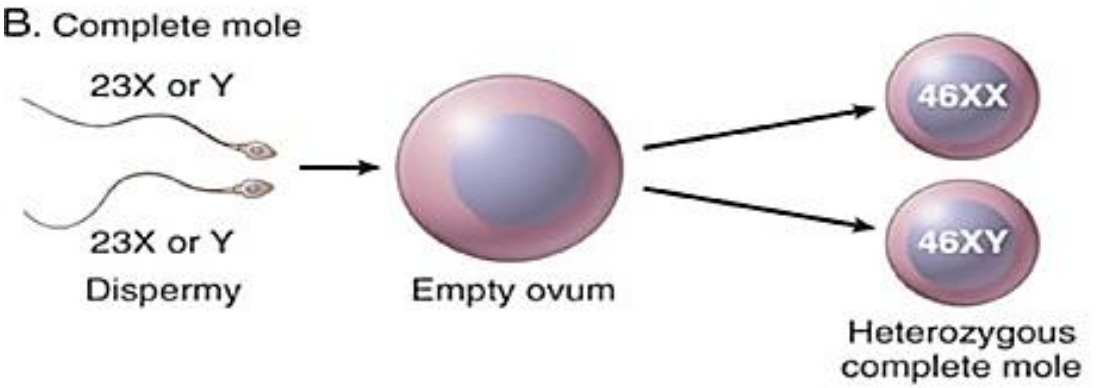
Types:

-Complete mole

One or two sperm fertilize an empty ovum (without DNA).

-All chromosomes are paternal (Diploid with 46 XX, 46 XY)

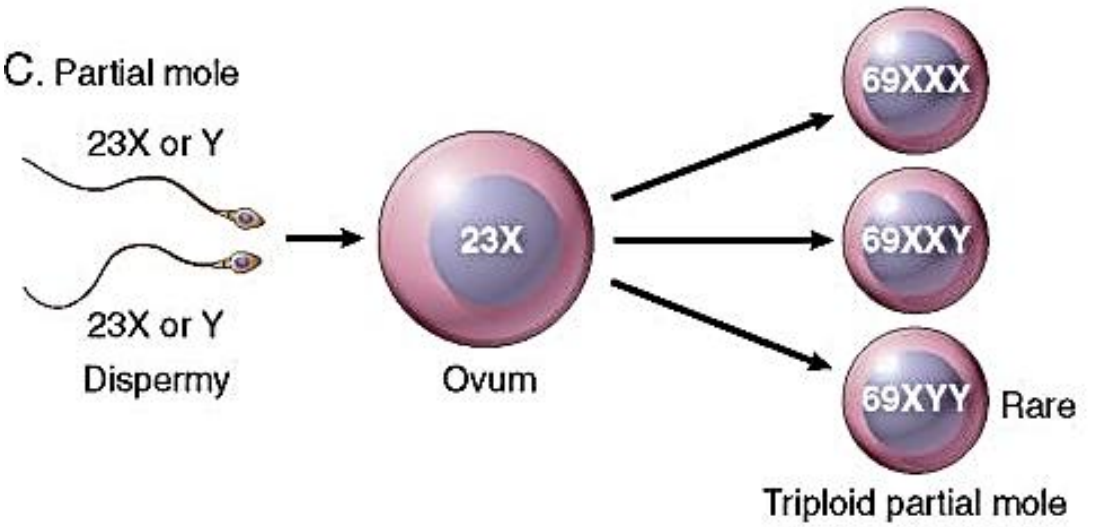




-Partial mole

Fertilization of an ovum by one diploid, or two haploid sperm,

-Triploid (69 XXX, 69 XXY or 69 XYY)



Complete Hydatiform mole

N/E:

-It is filled with a mass that resembles a punch of grape. It is formed of clusters of vesicles

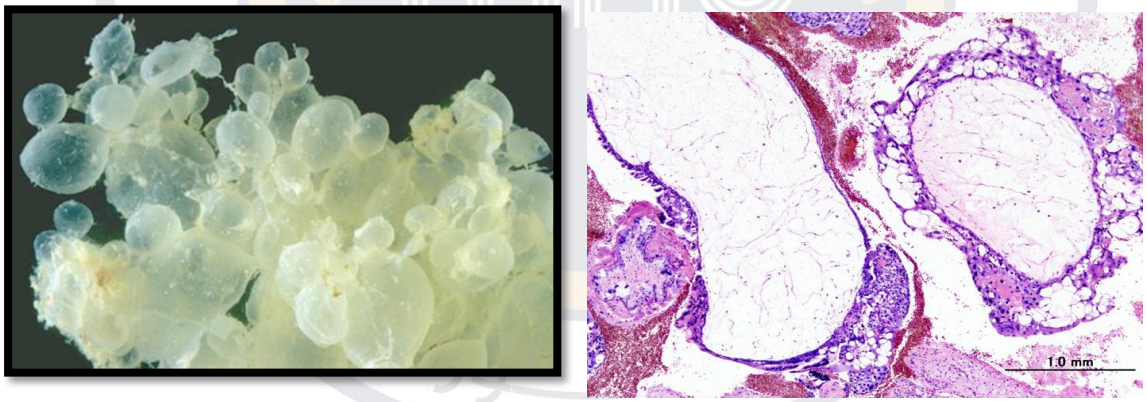
-No trace of embryo, amniotic sac or umbilical cord

M/E:

- Odema of some chorionic villi Prognosis:

- May complicate to invasive mole

- 5% pass into choriocarcinoma



Complete Hydatiform mole NE & ME

B- Partial Hydatidiform mole:

N/E:

-Normal placenta with few chorionic villi are swollen

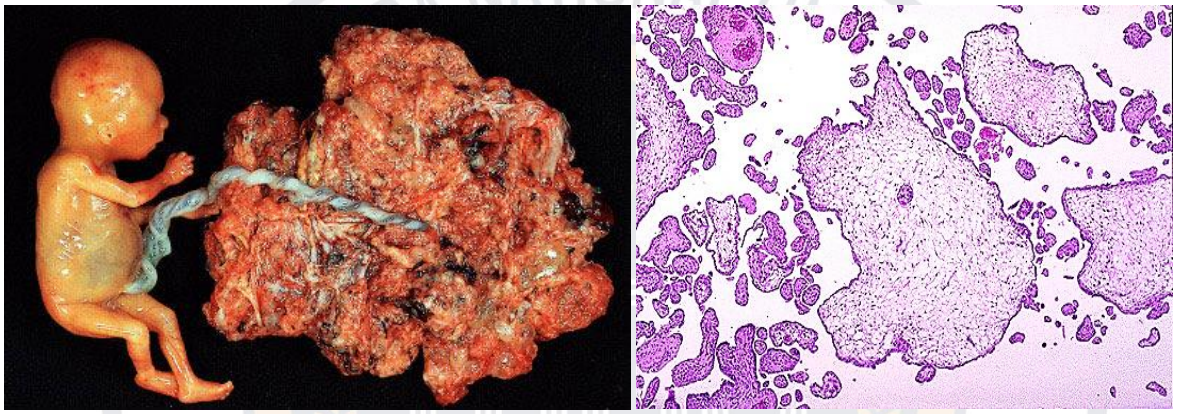
-Abnormal fetus is seen.

M/E:

- Normal chorionic villi with few abnormal swollen chorionic villi

Prognosis:

Very rare to pass into choriocarcinoma



Partial Hydatiform mole NE & ME

C- Invasive mole

(chorioadenoma destruens):

• It complicates complete mole.

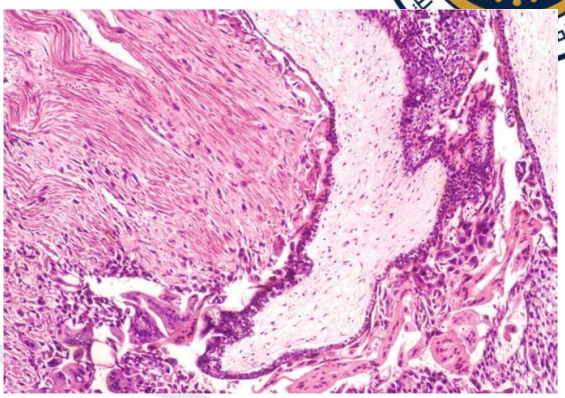
N/E:

- Clusters of vesicles attached deeply to the myometruim.

M/E:

Villi become invasive to myometrium and blood vessels

Prognosis: Spread to distant sites



Invasive mole

• <u>D- Choriocarcinoma</u>

• Gestational choriocarcinoma is a malignant neoplasm of trophoblastic cells

• Incidence:

• 50% arise in hydatidiform moles,

• 25% in previous abortions,

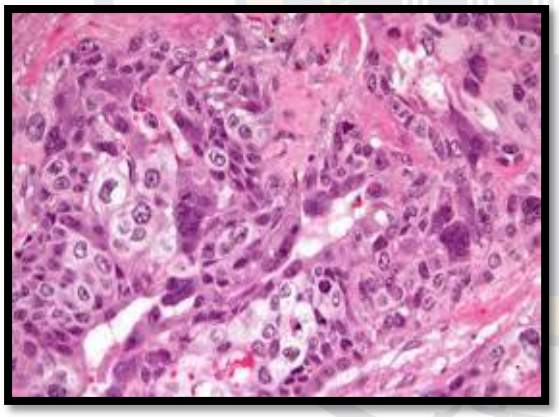
• approximately 22% in normal pregnancies

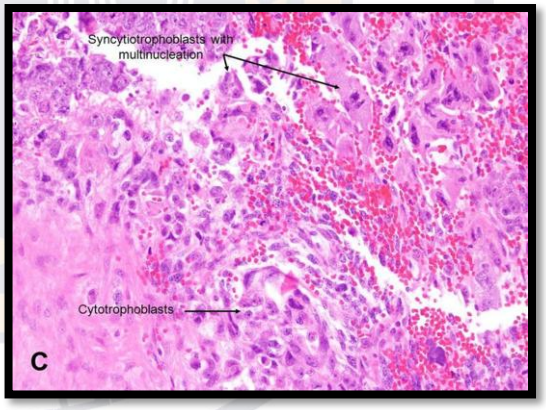
• **N/E:**

• Uterus contains a soft, friable, fleshy mass invading the uterine wall. very hemorrhagic, and necrotic

NE of choriocarcinoma

ME: Large sheets of malignant cytotrophoblasts and syncytiotrophoblasts with little or no stroma and wide areas of necrosis and hemorrhage.





ME of choriocarcinoma

Spread:

-Direct spread: Into uterine wall leading to perforation →peritoneal Metastases and peritoneal hemorrhage.

-Blood spread: The main method of distant spread, occurs early → Lung, liver, brain, bone, vulva and kidney are involved.

Effects:

Abnormal uterine bleeding, marked↑↑HCG hormone in blood and urine

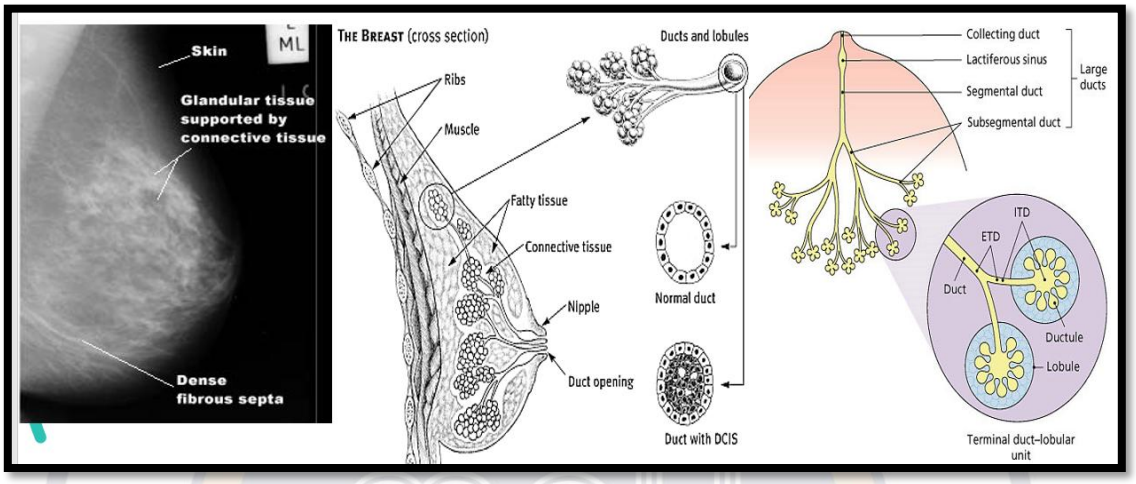
Prognosis:

1- Chemotherapy produce high percent cure rate.

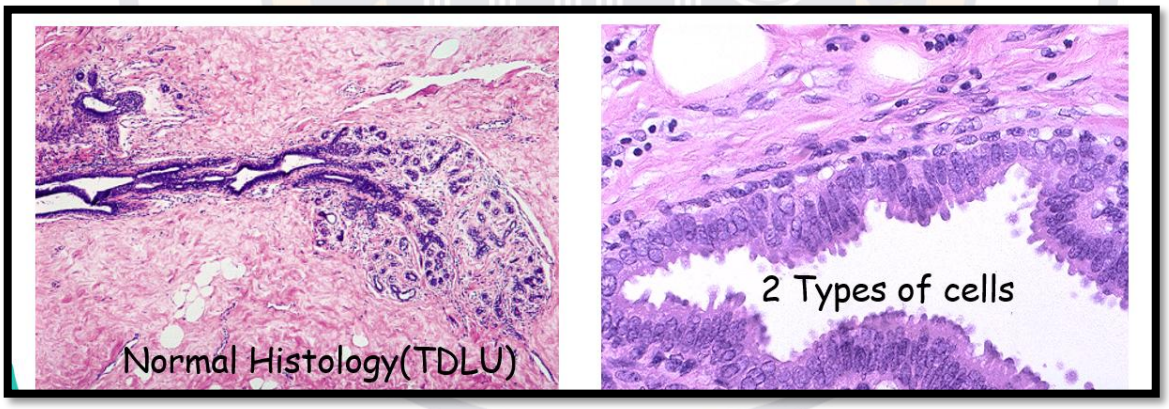
2- Spontaneous disappearance of tumor may occur due to immune reaction.

Pathology of the breast

Normal breast



Radiograph and illustration of normal breast



Histology of normal breast

Clinical presentation of breast disease

1. Lump (mass)
2. Pain
3. Discharge
4. Inflammatory changes
5. Gynecomastia (in male breast)

DD of breast lump

1. **Traumatic:** hematoma and traumatic fat necrosis.
2. **Inflammatory:** breast abscess, mammary ductectasia and granulomatous as T.B.
3. **Fibrocystic disease of the breast.**
4. **Neoplastic mass:** Fibroadenoma, duct papilloma, phylloides tumor and breast cancer

Non neoplastic breast lesions

I. Mastitis

- **Definition:** Inflammation of the breast could be infective or non-infective

A. Infective mastitis and breast abscess

☒ **Predisposing factors:**

It occurs during lactation especially in **primipara** due to:

- Ignorance of nipple hygiene.
- Nipple abrasion .
- Retained milk.

☒ **Cause:** Bacteria usually staphylococcus aureus.

☒ **Pathology:** Acute inflammatory changes which can progress to form single or multiple abscesses. It may be acute or chronic.

B. Non-Infective Mastitis

☒ Traumatic fat necrosis.

☒ Periductal plasma cell mastitis (Mammary ductectasia)

II. Mammary duct ectasia

- Periductal plasma cell mastitis
- Inflammatory disease usually affects multipara between 40 and 60 years of age.
- **Pathogenesis:**

☒ Inspissation of milk in the main excretory ducts.

☒ Dilatation of proximal ducts and rupture.

☒ Escape of milk leading to marked periductal chronic inflammation rich in plasma cells.

- **N/E:**
  - ☒ Lesion feels as **a bag of worms** in one or more segments of the breast.
  - ☒ **C/S:** dilated ducts containing **cheesy material.**
  - ☒ Later, the lesion forms a firm periareolar mass with nipple retraction and nipple discharge
- **M/E:**
  - ☒ Dilatation of ducts with destruction of their lining epithelium and may rupture.
  - ☒ Ducts are filled with granular debris and sometimes lipid laden foamy macrophages.
  - ☒ Periductal tissue is infiltrated by chronic inflammatory cells rich in plasma cells, occasional granulomas and fibrosis

III. Fibrocystic diseases of the breast

- Cystic Mammary Hyperplasia
- **Incidence:**
  - ☒ The most common breast disease.
  - ☒ It affects over half the women during reproductive period
  - ☒ It is not premalignant
- **Aetiology:**
  - ☒ Hyperestrogenemia.
- **Pathogenesis:**
  - ☒ Derangement of cyclic breast changes that occur normally during menstrual cycle.
- **Prognosis:**
  - ☒ **Epitheliosis** increase incidence of breast cancer which is more evident with atypical hyperplasia

N/E picture:

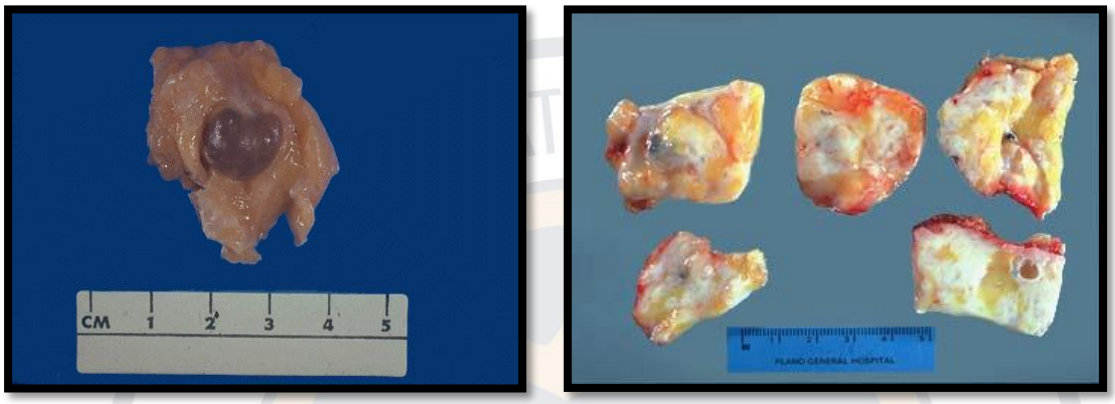
☒ Unilateral or bilateral. ☒ Single or multiple.

☒ No-encapsulated, ill defined, rubbery in consistency.

☒ **Mobile** ☒ **Firm to rubbery.**

☒ **C/S:** Grey white in colour.

☒ Show variable sized cyst containing serous or hemorrhagic fluid.



NE of fibrocystic disease

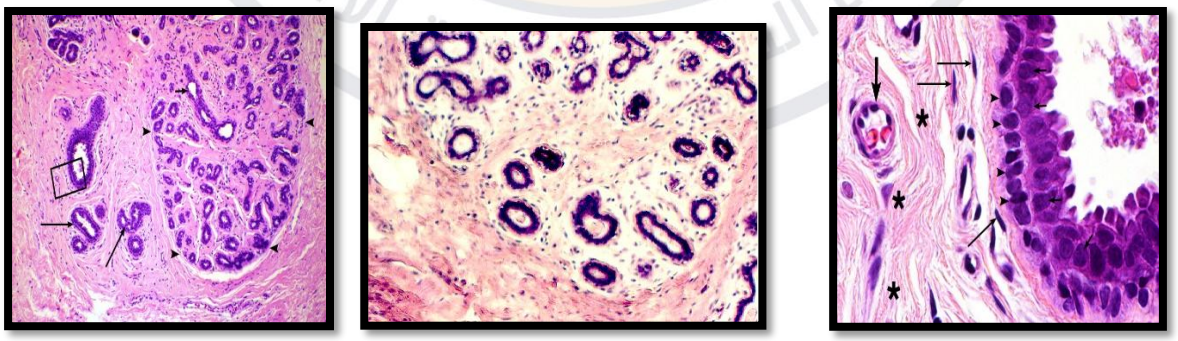
M/E:

☒ Fibrosis.

☒ Adenosis.

☒ Epitheliosis.

☒ Cystic formation.



ME of fibrocystic disease

Neoplastic breast lesions

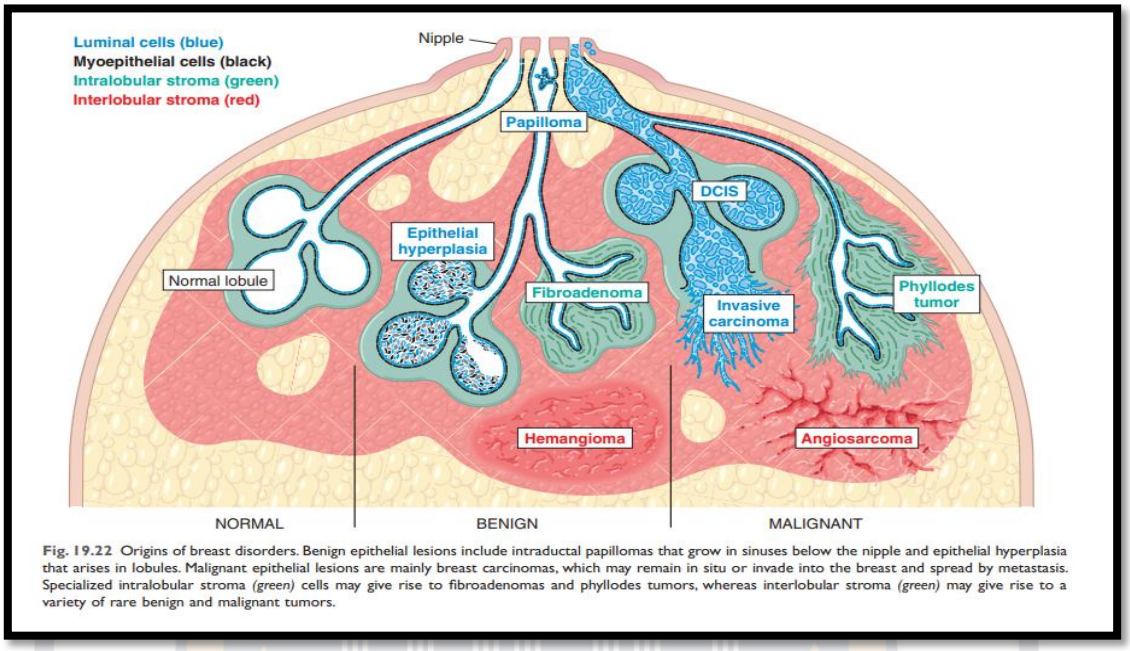


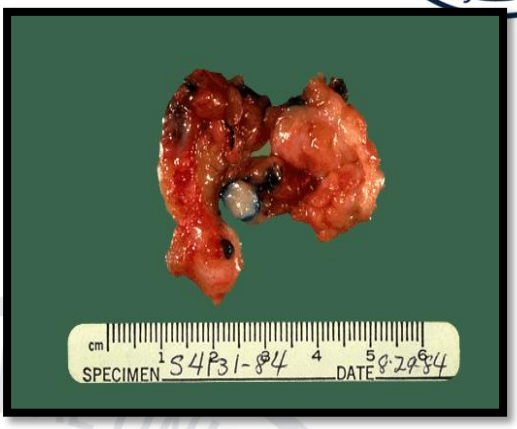
Fig. 19.22 Origins of breast disorders. Benign epithelial lesions include intraductal papillomas that grow in sinuses below the nipple and epithelial hyperplasia that arises in lobules. Malignant epithelial lesions are mainly breast carcinomas, which may remain in situ or invade into the breast and spread by metastasis. Specialized intralobular stroma *(green)* cells may give rise to fibroadenomas and phyllodes tumors, whereas interlobular stroma *(green)* may give rise to a variety of rare benign and malignant tumors.

Origin of breast disorders

I. Benign tumors

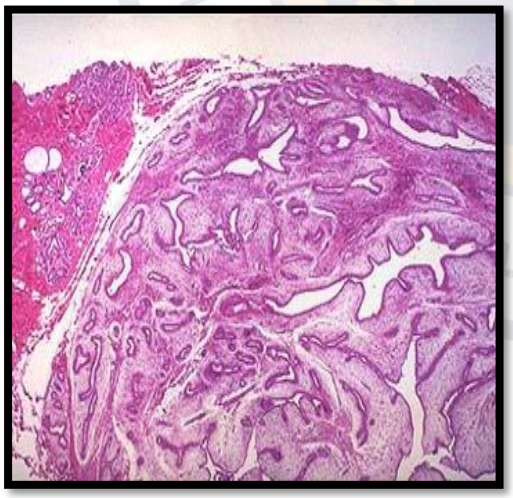
A. Fibroadenoma

- Commonest benign tumour of female breast.
- Mixed (fibrous and epithelial).
- Peak incidence is in 3rd decade.
- Caused by estrogen stimulation.
- **N/E:**
  - ☒ Usually single, well circumscribed, round or oval.
  - ☒ Encapsulated, well-defined.
  - ☒ Firm, freely mobile.
  - ☒ **C/S:** greyish white



NE of fibroadenoma

- **M/E:**
  - ☒ Mixed tumor formed of epithelial lined ducts separated by fibrous stroma.
  - ☒ Surrounded by true capsule.
  - ☒ It may be:
    - Pericanalicular.
    - Intracanalicular
    - Mixed



ME of fibroadenoma

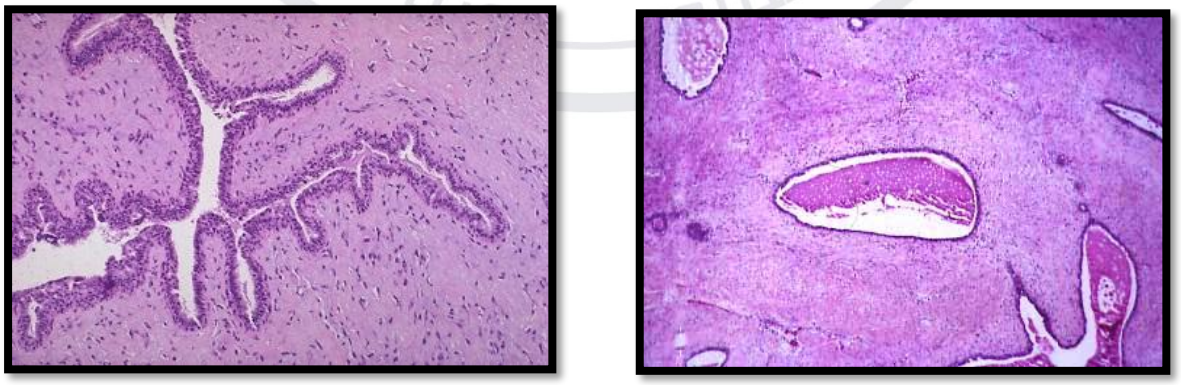
- **Prognosis:**
  - ☒ Does not recur after excision.
  - ☒ Malignancy is rare.

B. Phyllodes tumor (phyllodes is Greek for “leaf like”)

- less common than fibroadenomas
- A fibroepithelial tumor of unpredictable behavior.
- Detected in older females.
- **N/E:**
  - ☒ Large, rounded, circumscribed mass .
  - ☒ Consistency: firm
  - ☒ **C/S:** greyish white with slits and cysts.

Clinical and gross of phylloides tumor

- **M/E:** Fibroepithelial tumor with abundant the stromal element and cellular element forms leaf like projections.



ME of phylloides tumor

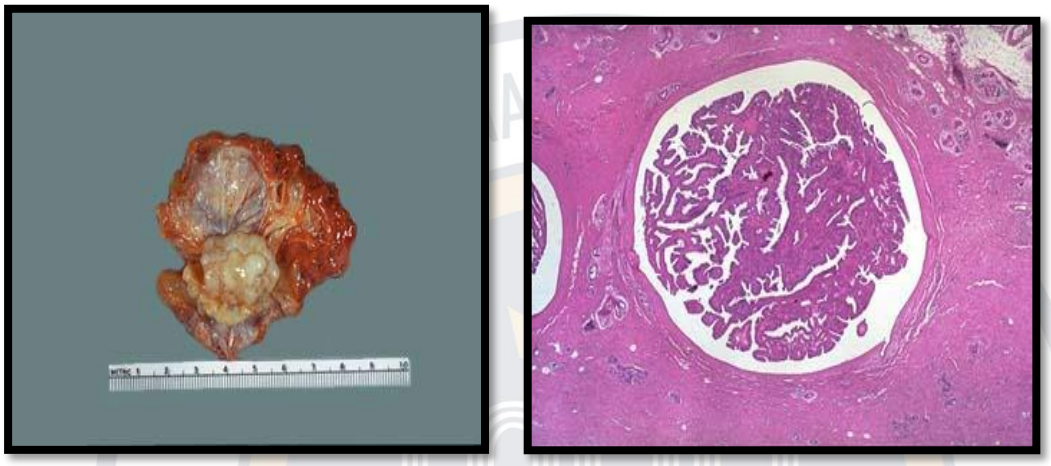
- **Changes suggesting malignancy are:**
  1. stromal hypercellularity
  2. anaplasia
  3. high mitotic activity,
  4. rapid increase in size
  5. infiltrative margins
- **Prognosis:** Most phyllodes tumors are benign but few are malignant with hematogenous spread.

C. Duct papilloma

- Intra-ductal growths.
- Frequently causes nipple discharge or small subareolar mass.
- Usually occurs in 4th or 5th decade.
- **N/E:**
  - ☒ **Site**: usually within a large duct (principal lactiferous duct or sinus) near the nipple.
  - ☒ **Shape**: Delicate branching papillary growth.
  - ☒ **Size**: small, usually less than 1cm.
  - ☒ **Consistency**: friable.
- **M/E:**
  - ☒ Branching papillae within the dilated duct formed of fibrovascular core covered by two layers of cells, luminal cuboidal or columnar and outer myoepithelial.

- **Prognosis:**

1. Involution leading to atrophy and hyalinization.
2. Rarely, it changes to duct papillary carcinoma.



NE and ME of intraduct papilloma

II. Breast Carcinoma

- 20% of all cancers in women
- **Risk factors:**

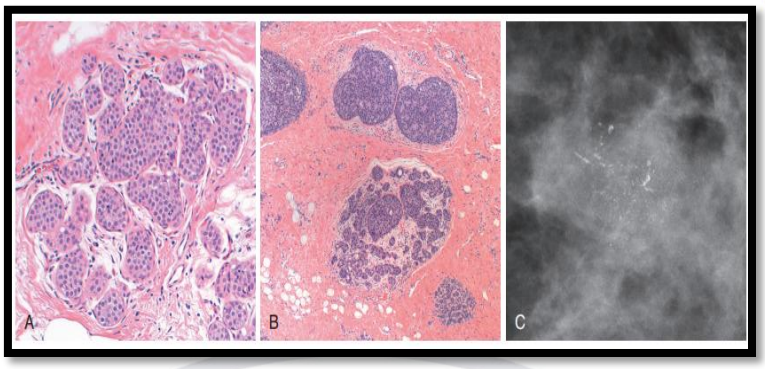
1. **Age**:
   - ☒ risk increases with increasing age, especially after menopause except in familial cases.
   - ☒ Very rare before age 25
2. **Genetic and familial predisposition:**
   - ☒ Positive family history.
   - ☒ Familial cases are characterized by increase incidence in:
     - 1st degree relatives.
     - Younger age (premenopausal).
     - Bilateral breast cancer.
     - Genetic mutations, BRCA1 and BRCA2

3. **Reproductive life:**
   - ☒ More in nullipara.
   - ☒ More with late age of birth of first child .
   - ☒ More with long reproductive period of life with early menarche.
4. Prolonged exposure to **exogenous estrogen postmenopausally.**
5. **Ionizing radiation** to the chest only women in whom irradiation occurred before age of 30 during breast development are affected.
6. **Other risk factors:**
   - ☒ Obesity due synthesis of estrogen in adipose tissue.
   - ☒ A diet rich in fat.
   - ☒ Alcohol consumption.
   - ☒ Cigarette smoking.
7. **Precancerous lesions:**
   - ☒ Proliferative fibrocystic change especially with **atypical hyperplasia**.
   - ☒ Carcinoma in situ: - In situ **duct** carcinoma - In situ **lobular** carcinoma.
   - ☒ Carcinoma of the **other** breast.
   - ☒ Benign tumors such as duct papilloma

Classification of breast carcinoma

A. <u>Noninvasive</u>

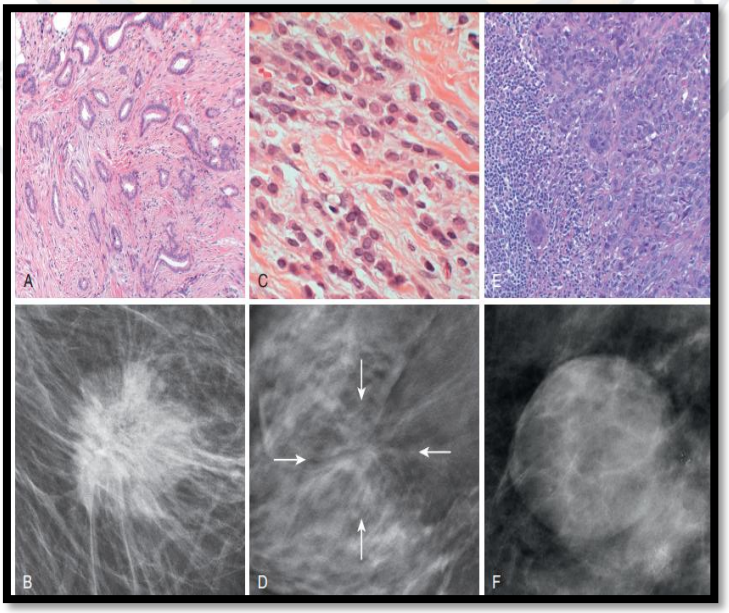
1. Ductal carcinoma in situ
2. Lobular carcinoma in situ



ME and radiograph of non invasive breast carcinoma

B. <u>Invasive</u>

1. Invasive ductal carcinoma
   - ☒ includes all carcinomas that are not of a special type —70% to 80%
2. Invasive lobular carcinoma— ~10% to 15%
3. Carcinoma with medullary features— ~5%
4. Mucinous carcinoma (colloid carcinoma) — ~5%
5. Tubular carcinoma— ~5%
6. Other types.



ME and radiograph of invasive breast carcinoma

1. Noninvasive (in situ) carcinoma

1. Ductal carcinoma insitu (DCIS)

☒ It is a preinvasive neoplasm which has not yet broken through basement membrane of the ducts.

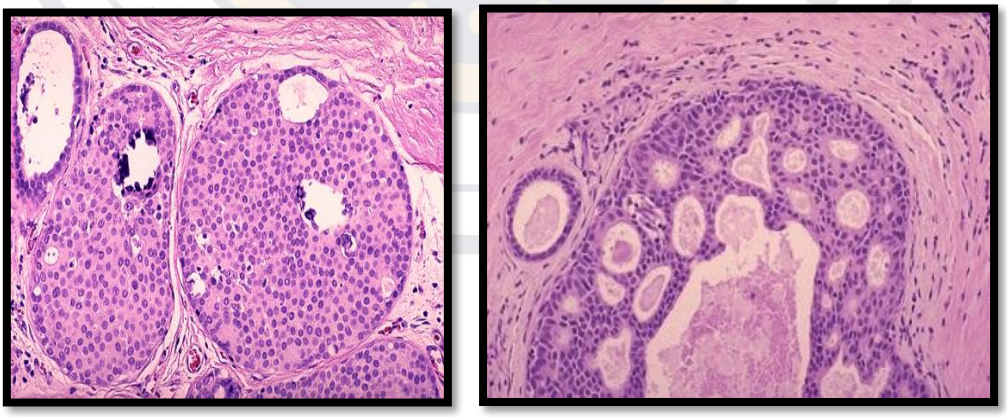
☒ **N/E:**

- small **hard masses**
- Bloody or serous **nipple discharge**
- **C/S:** shows dilated ducts filled with papillary structures (papillary intraduct carcinoma) or necrotic tissue (comedocarcinoma).

☒ **M/E:**

- The ducts are dilated and distended by **malignant cells <u>without</u>** invasion of the basement membrane.
- The malignant cells are arranged within the ducts in the following patterns papillary, cribriform or solid that may have central necrosis called **Comedo** type. Calcification of central necrosis may occur

☒ **Prognosis:** Good with complete excision



ME of ductal carcinoma insitu

2. Paget's disease:

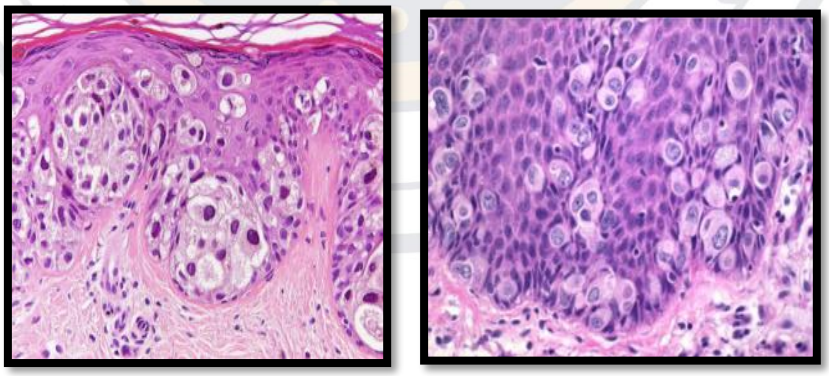
☒ It is **intraduct carcinoma** extends to the epidermis covering the nipple and areola which shows eczema (the skin appears red, swollen, granular, fissured, eroded, ulcerating and oozing)

Skin and nipple appearance in Paget disease

☒ **M/E:**

- The epidermis is thickened and show round, large pale vacuolated cells called **Paget's cells.**

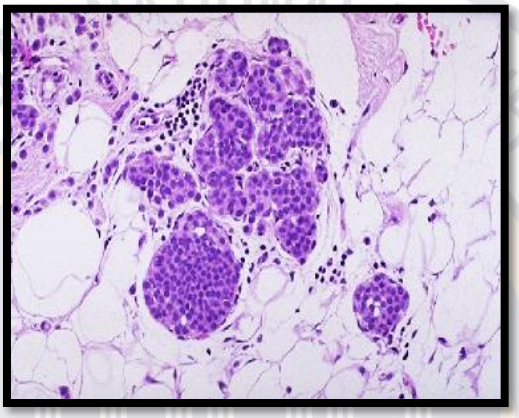
☒ **Prognosis**: Good with complete excision



ME of Paget disease

3. lobular carcinoma insitu (LCIS):

- ☒ **N/E:** hard breast mass.
- ☒ **M/E:** in one or more breast lobules all terminal ductules and acini are distented with malignant cells which are non-cohesive monomorphic with bland round nuclei



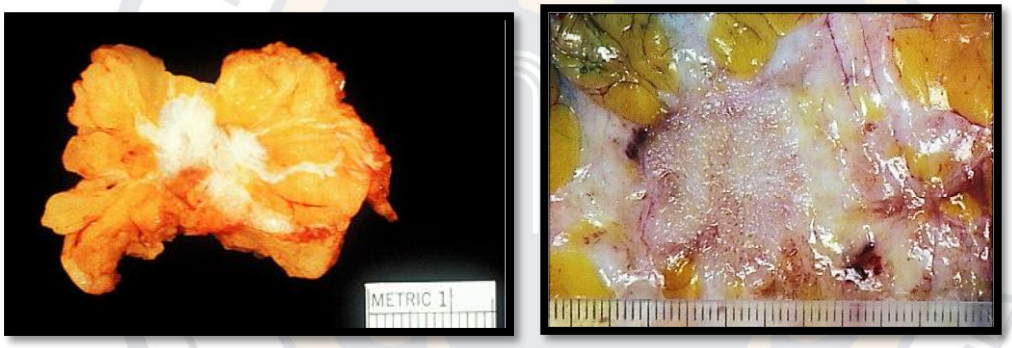
ME of lobular carcinoma insitu

- ☒ **Prognosis:** LCIS is both a marker of an increased risk of carcinoma in both breasts and a direct precursor of some cancers

2. Invasive carcinoma

☒ **N/E:**

- Ill-defined mass greyish white.
- **Stony hard** in consistency.
- Fixed.
- **C/S:** retracted hard with gritty sensation, with hemorrhage, necrosis.
- **Skin changes** (late with locally advanced tumors): the skin covering the breast shows dimpling, retraction of the nipple, ulceration, cancer en cuirasse or peau d'orange
- In addition, some microscopic types have other NE features



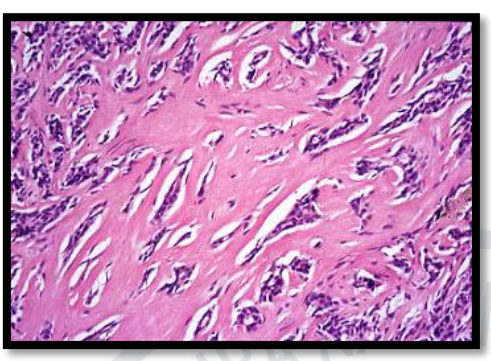
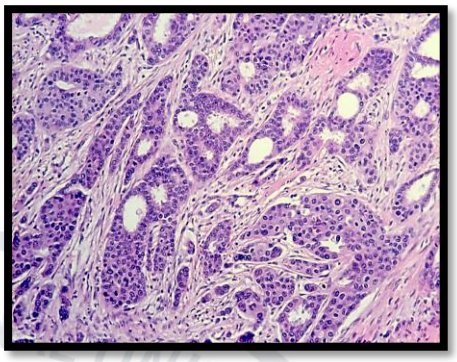
NE of invasive breast carcinoma

1. Invasive ductal carcinoma (NST)

☒ The commonest type (65%-80% of all mammary carcinoma).

☒ **M/E:**

- Groups, cords, tubules and sheets of malignant cells separated by desmoplastic stroma.
- The tumour cells are rounded or polygonal with uniform or pleomorphic nuclei.
- Mitotic figures range from absent to multiple

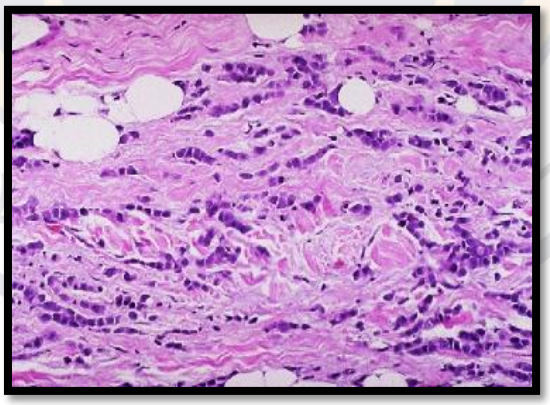
2. Invasive lobular carcinoma

☒ **N/E:** Usually multicentric and bilateral

☒ **M/E:**

- Strands of malignant cells of Indian file pattern separated by fibrous tissue stroma.
- The cells are small, uniform with little pleomorphism

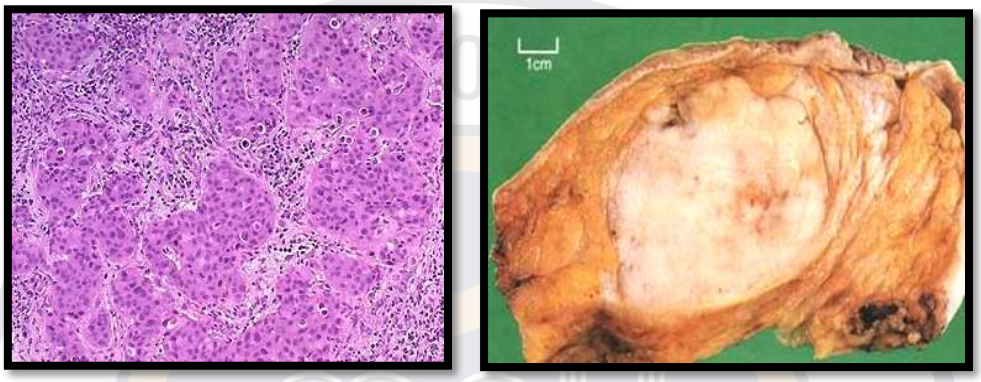
☒ **Prognosis:** worse than invasive duct carcinoma



ME of invasive lobular carcinoma

3. Carcinoma with medullary features

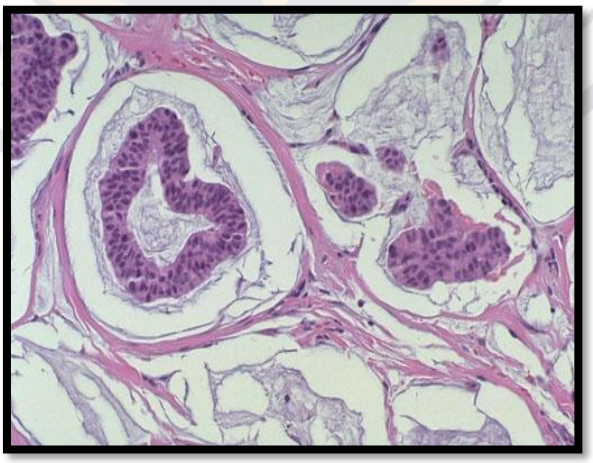
- ☒ **ME:** They consist of sheets of large anaplastic cells associated with pronounced lymphocytic infiltrate.
- ☒ **Prognosis:** good prognosis



ME and NE of carcinoma with medullary features

4. Mucinous carcinoma (colloid carcinoma)

- ☒ **N/E:** Circumscribed soft gelatinous mass.
- ☒ **M/E:** Lakes of mucin with scattered small islands of malignant cells
- ☒ **Prognosis:** is good.



ME of mucinous carcinoma

5. Tubular carcinoma

☒ **ME:** The tumor cells are arranged in well formed tubules and have low-grade nuclei.

☒ **Prognosis:** is good

- **Spread of invasive carcinoma**

☒ **Direct spread**

- Deep fascia, pect. Ms, pleura.& chest wall.
- Overlying skin causing cancer en cuirasse (thick, hard skin fixed to underlying structures).

☒ **Lymphatic spread:**

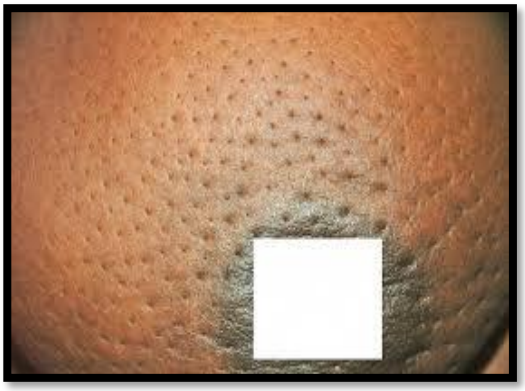
- Common and early, It occurs by 2 ways:

a. Lymphatic Embolization: It leads to metastasis in:

- L.N., axillary, int. mammary, medias. & supraclav.
- Opposite breast.
- Liver and peritoneum

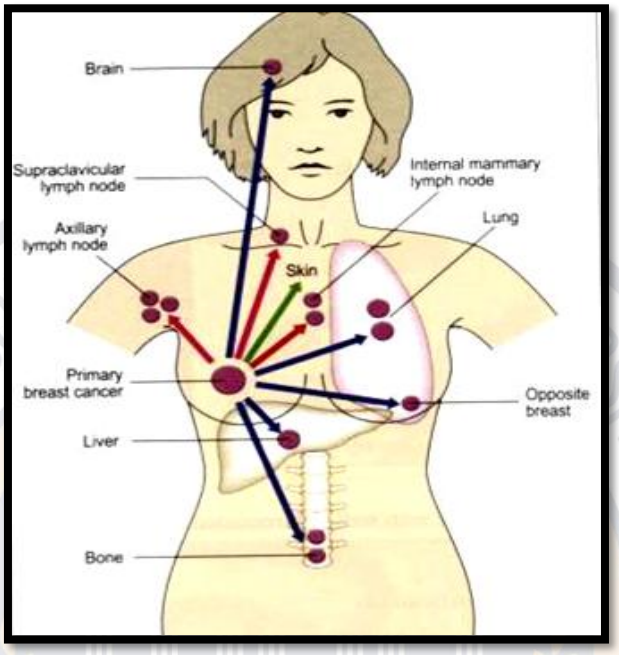
b. Lymphatic permeation (skin lymphatic): It Leads to:

- Small malignant nodules under the skin.
- **Peau d'orange** due to lymphatic edema of the skin except at site of hair follicle



☒ Blood spread

- Occurs early or late.
- Metastasis to lung, liver, bone, brain & adrenal gland



Staging

☒ TNM System

- **T:** Primary tumor size
  - T0 (in situ) to T4 (very large)
- **N:** Lymph node involvement:
  - N0 (no nodal involvement) to N3 (multiple involved lymph nodes)
- **M:** Distant metastases,
  - M0 (no distant metastases) to M1 and M2 (multiple metastases)

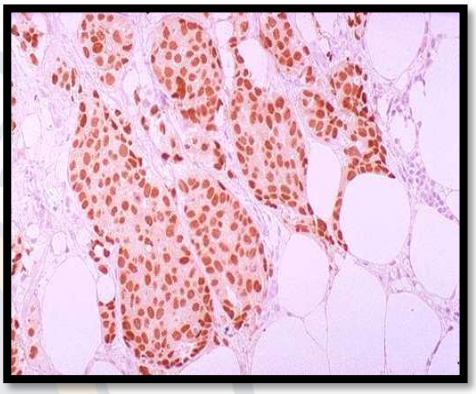
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	Any	M0
Stage IV	Any	Any	M1

Stag	Definition	5-year Surv (%)	7-year Surv (%)
I	Tumor 2 cm or less without spread	96	92
II	Tumor 2-5cm with regional lymph node involvement but without distant metastases, OR > 5 cm in diameter without spread	81	71
III	Any size with skin/chest wall fixation, & axillary or internal mammary nodal involvement, without distant metastases	52	39
IV	Tumor of any size with or without regional spread but with evidence of distant metastases	18	11

- **Diagnosis**
  - ☒ Mammorgraphy
  - ☒ Ultrasound
  - ☒ Biopsy
  - ☒ Immunohistochemistry
  - ☒ Molecular techniques Gene mutation detection

Estrogen Receptor & Prognosis

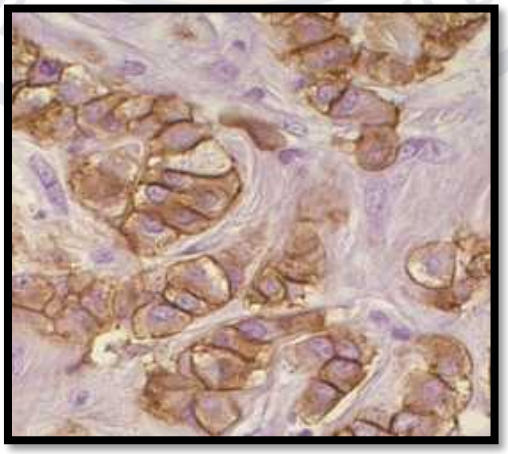
- ☒ Estrogen receptor expression is **proportional to differentiation** of tumor
- ☒ Proportional to **prognosis and response to tamoxifen** (receptor antagonist) therapy.
- ☒ Demonstrated by **IHC special stain**.



IHC for Estrogen receptors

HER2

- ☒ The HER2 proto-oncogene encodes a cell surface receptor and inhibits growth of breast cancer cells that over express this protein
- ☒ overexpressed in approximately 25%-30% of breast cancers.
- ☒ Herceptin is the first monoclonal antibody that targets the extracelluar domain of the HER2 protein

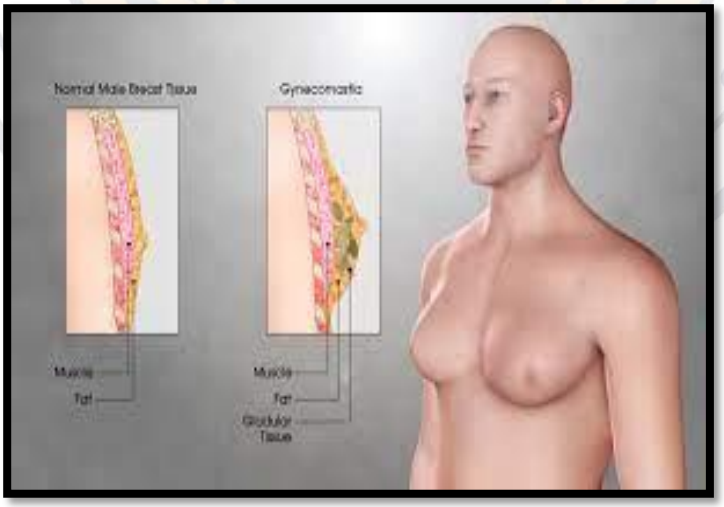


IHC for HER2

Male breast

A. Gynecomastia

- **Def:** enlargement of male breast.
- **AE:**
  - ☒ Physiological: at puberty.
  - ☒ Increase estrogen level in
    - Liver cirrhosis
    - Estrogen producing tumors
    - Estrogen therapy
  - ☒ Digitalis therapy.
  - ☒ Klienefilter syndrome.
- **NE:** Disc like subareolar mass, Unilateral or bilateral



- **M/E**
  - ☒ Variable degree of epithelial hyperplasia in ducts.
  - ☒ Prominent stroma.

B. Carcinoma of male breast

- Occurs in old age.
- Common with estrogen therapy.
- It has bad prognosis as the tumor infiltrate locally early due to small breast size

FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

MICROBIOLOGY

Genital system infections

Normal flora (Microbiome) of the genital system:

A. Vagina:

- ☒ Aerobic Lactobacilli (**Doderlein's bacilli**) form the main flora.
- ☒ Responsible for the **acidic pH of the vagina** due to fermentation of glycogen to lactic acid.
- ☒ **Not** present at pre-puberty and **diminishes** after menopause (present only in the productive female life).
- ☒ High acidity of the vagina produced by Lactobacillus is **inhibitory** to some bacteria as Streptococci and Staphylococci as well as the potentially pathogenic yeast, Candida albicans. Also, it (maintains the sperm viability) In addition, anaerobic Streptococci, Coliform, Diphtheroids and yeast are present as normal vaginal flora.

B. The flora of the anterior urethra:

- ☒ Consisting of Staphylococcus epidermidis, Enterococcus faecalis and some alpha-hemolytic streptococci. Their numbers are not plentiful.
- ☒ In addition, some enteric bacteria (e.g. E. coli, Proteus) and corynebacteria, which are probably contaminants from the skin, vulva, or rectum.

Classification of genital system infections and causative organisms in each type.

A. Venereal diseases:

- ☒ Gonorrhea caused by Neisseria gonorrheae.
- ☒ Syphilis caused by Treponema pallidum.
- ☒ Soft sore caused by Haemophilius ducreyi
- ☒ Lymphogranuloma venereum caused by Chlamydia.
- ☒ Nongonococcal uretheritis (NGU) caused by Chlamydia and Mycoplasma genitalium
- ☒ AIDS.
- ☒ HBV.
- ☒ HSV type 2 (HSV-2).

B. Non-venereal disease

- ☒ **In male**: Prostatitis and urethritis
- ☒ **In female:** salpingitis, oophritis & endometritis. Causative organisms:
  - *Staphylococcus aureus*
  - *Proteus.*
  - *Streptococcus pyogenes*
  - *E. coli.*
  - *Pseudomonas pyocyanea*.

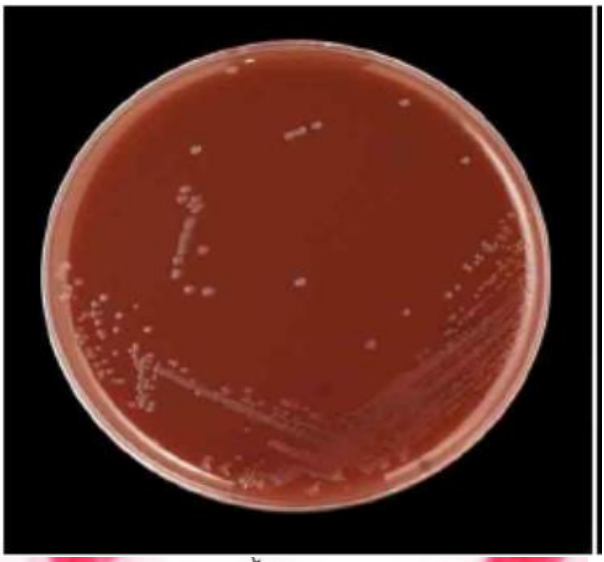
Neisseria gonorrhea

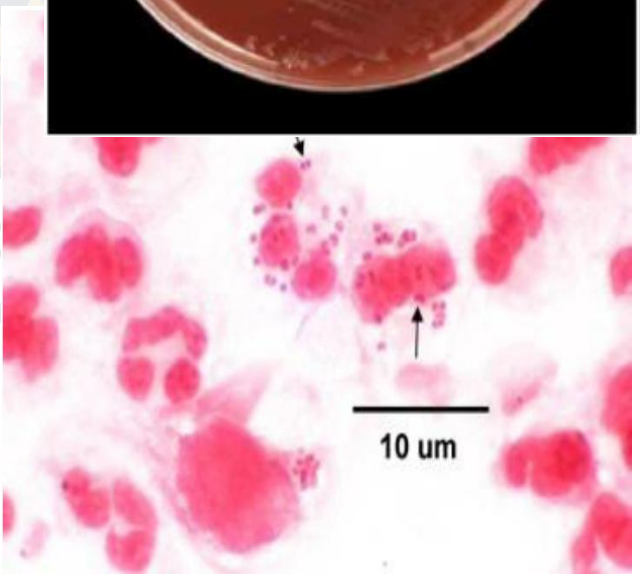
Morphology of N. gonorrhea (Gonococci):

- ☒ **Shape & Gram stain:** Gram-negative cocci (kidney-shaped)
- ☒ **Arrangement:** Diplococci
- ☒ **Motility:** Non-motile
- ☒ **Spore formation:** Non spore-forming.
- ☒ **Capsule:** not capsulated

Culture characters:

- ☒ **O2:** aerobe,
- ☒ **Optimum temperature is** 37ºC,
- ☒ **CO2:** 10% CO2 is required for growth.
- ☒ **Culture media :**
  - **Ordinary media**: Cannot grow on it
  - **Enriched media**: Grow on chocolate agar
  - **Selective media**: Grow on Thayer-Martin media





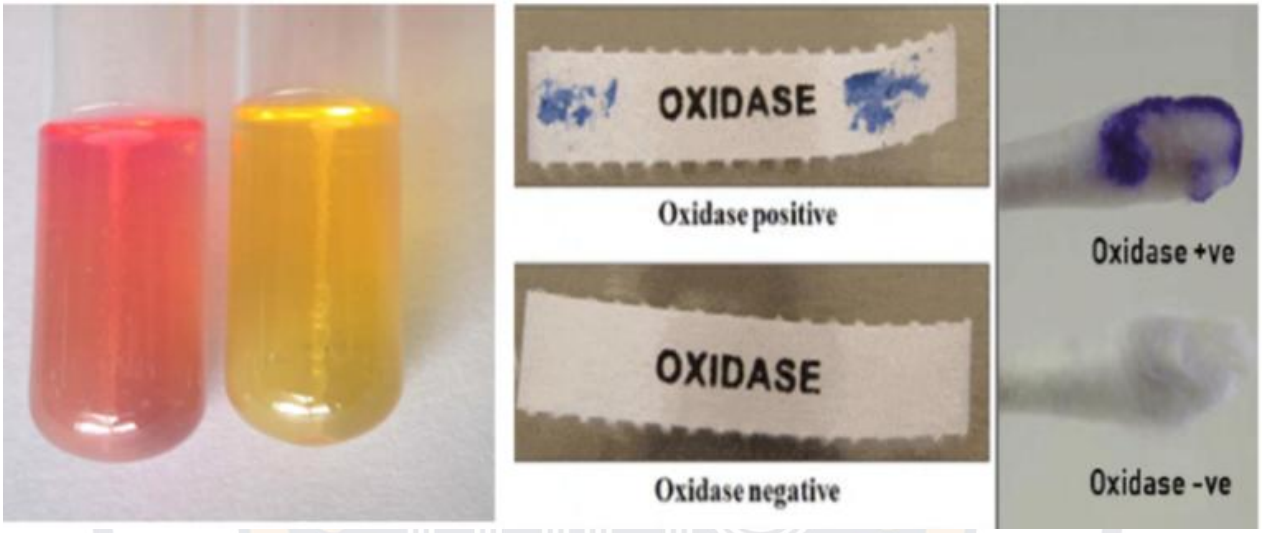
- **Virulence factors:**
  - ☒ **Pili (fimbriae) and outer membrane proteins:** adhesion.
  - ☒ **Endotoxin:** Lipooligosacchrides.
  - ☒ **IgA proteases:** inactivate human IgA.

- **Manifestations: Gonorrhea**
  - ☒ **Male**: Acute urethritis:
    - Characterized by profuse purulent discharge
  - ☒ **Female**: Cervicitis:
    - Characterized by profuse vaginal mucopurulent discharge & sometimes acute urethritis & dysuria.
  - ☒ **Newborn**: Ophthalmia neonatorum:
    - Occur in newborns who are exposed to infected secretions in the birth canal.

- **Laboratory diagnosis of N. gonorrhea.:**

1. **Specimens:**
   - ☒ **In acute disease:** There is profuse pus and secretions from urethra or cervix.
   - ☒ **In chronic disease:** There is scanty or no discharge.
     - In males: Sample may be morning drop of the urethra, centrifuged deposit of urine, or by prostatic massage.
     - In females: Cervical secretion is obtained after cervical irritation.
2. **Direct film stained by Gram stain:**
   - Detection of **intracellular Gram-negative diplococci** is diagnostic.

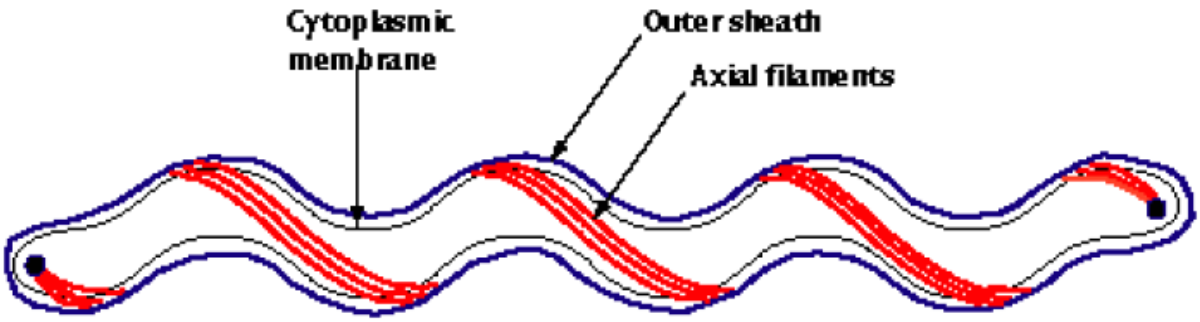
3. **Culture**: As before.
4. **Identification of the colonies** by:
   - Film stained by **Gram stain** to show characteristic morphology.
   - **Biochemical reactions**: ferments Glucose with acid production only, oxidase positive.



Treponema pallidum

Morphology:

- ☒ Slender, Spiral filaments with regular coils (coils are small and large in numbers), motile.
- ☒ Can not be seen by light microscopy but can be seen unstained by dark-field microscopy.
- ☒ Can not be stained by Gram stain, can be stained by Giemsa and Fontana stains.
- ☒ In tissues can be visualized by silver impregnation methods.
- ☒ Have axial filaments, which are otherwise similar to bacterial flagella
- ☒ Filaments enable movement of bacterium by rotating in place.



- **Culture characters:**
  - Pathogenic Treponema have **not** yet been cultured in vitro on artificial media.
  - **Pathogenic strains:** can grow in testicles of rabbit or cultured rabbit epithelial cells
  - The cells have a **high lipid content** (cardiolipin, cholesterol), which is unusual for most bacteria.
  - Microaerophilic
  - **Fastidious** organism with narrow optimal ranges of pH (7.2 to 7.4), and temperature (30 to 37°C).

- **Pathogenesis: Syphilis**
  - **Causative agent:** T. pallidum, strictly a human disease.
  - **Mode of transmission:** by sexual contact. Organisms penetrate mucous membranes or enter minute breaks in the skin.
  - **Less than 10 organisms** are capable of producing infection.

- **The disease passes into 3 clinical stages:**

A. Primary Syphilis: **chancre** (painless, indurated ulcer)

  - develops at the site of inoculation and associated with regional lymphadenopathy.
  - This lesion is filled with treponemes and is, therefore, highly contagious.

B. Secondary Syphilis: mucocutaneous rash.

- ☒ mucous patches on mucous membranes and wart-like lesions called condylomata in moist intertriginous areas.
- ☒ All these lesions are highly contagious.

C. Tertiary syphilis: is characterized by long-term complications:

- ☒ **Gumma** (granulomatous-like lesion)
- ☒ Cardiovascular and neurosyphilis.
- ☒ Can affect all areas of the body and be fatal.

- **NB: Congenital syphilis**: through placenta: fetus may die or borne live with congenital anomalies

Methods of laboratory diagnosis:

1. Specimens:

☒ Exudate from chancre, mucous patches, blood for serology.

2. Direct smear:

☒ Examined by:

- Dark ground microscope for motile Treponema.
- Fluorescent microscope for smears stained with fluorescein-labelled anti treponemal antibodies.

3. Serological tests:

☒ Syphilitic patients produce 2 types of antibodies:

- **Specific antibodies:** (react only with treponemal antigens)
- **Non-specific (reagin) antibodies**: (react with lipid antigens e.g., cardiolipin).

a. Non treponemal antigen tests:

- Measure non-specific antibodies (directed against lipid antigens, principally **cardiolipin**).
- **Examples:**
  - Venereal Disease Research Laboratory (VDRL).
  - Rapid Plasma Reagin (RPR).
  - Complement fixation test (Wasserman reaction).
- **Use:**
  - screening.
  - epidemiological purposes.
  - Evaluate the effect of treatment.

b. Treponemal antigen tests:

- Detect specific antibodies (antibodies directed against protein constituents of T. pallidum).
  - **Examples**:
    - Fluorescent T. pallidum antibody absorption (FTA- ABS).
    - Micro-hemagglutination for T. pallidum (MHA-TP).
    - Treponema pallidum immobilization tests (TPI)
  - **Use:**
    - Confirmation.

☒ The sensitivity of the tests varies with the stage of the disease.

☒ The results of non-treponemal tests usually parallel the extent of infection; titers tend to be highest during secondary syphilis and subside during subclinical infection (latency) or following antibiotic therapy.

☒ The treponemal tests often remain **reactive for life**.

Treatment

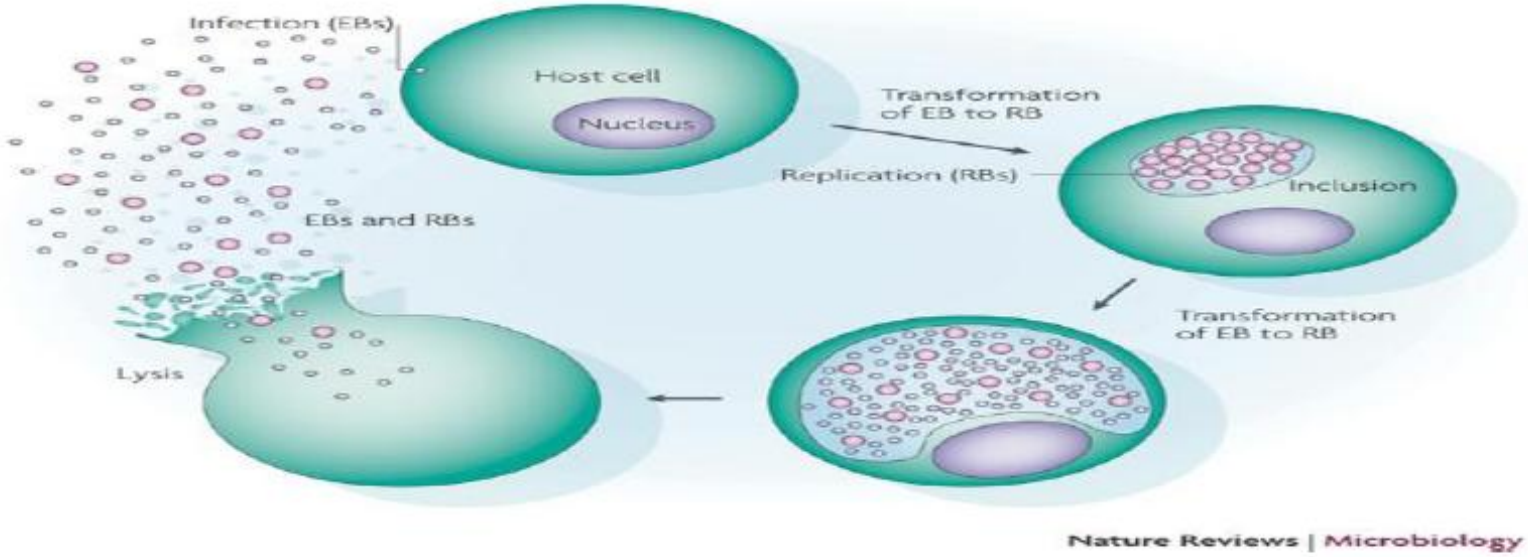
☒ **Penicillin** is the drug of choice in the treatment of syphilis.

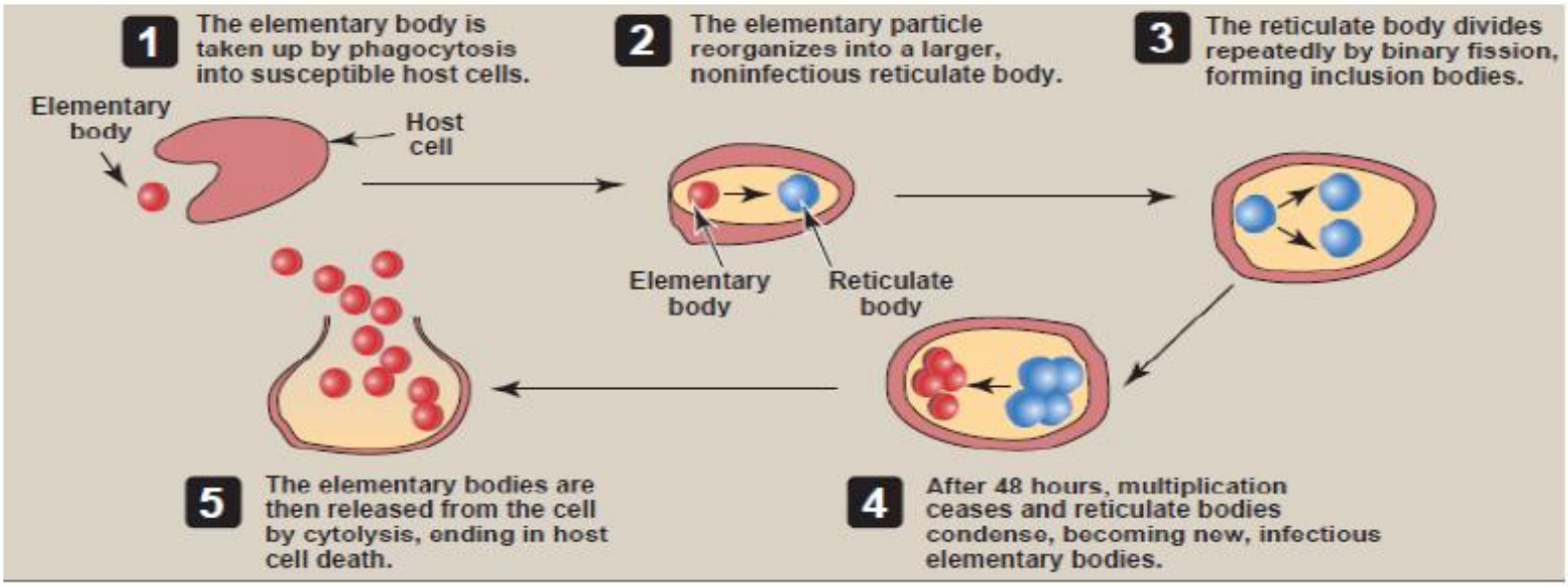
☒ Penicillin was found to be effective in **eradicating syphilis** of **all** clinical stages as well as the congenital infection.

Chlamydia trachomatis

- **Chlamydial infections in genital system:**
  - ☒ Lymphogranuloma venereum, is a venereal disease spread sexually characterized by genital lesions and regional lymph node involvement (buboes).
  - ☒ Non gonococcal urethritis in men and acute salpingitis and cervicitis in women.
- **Chlamydiae resemble viruses in the following:**
  - ☒ Obligate intracellular
  - ☒ Cannot make ATP
  - ☒ Grow in cell culture
  - ☒ No peptidoglycan
- **Chlamydiae resemble bacteria in the following:**
  - ☒ Have DNA, RNA, ribosome.
  - ☒ Have Inner and outer membrane & cell wall.
  - ☒ Susceptible to Antibiotics
  - ☒ Multiply be binary fission.

Life cycle of chlamydiae:





Elementary body	Reticulate body (RB)
Small	Large
Extracellular	Intracytoplasmic
Infectious form	Non-Infectious form
Non-replicating	Metabolically active and replicating
Released from ruptured infected cell	Within cells, the site of replication appears as an inclusion body, which can be stained and visualized microscopically

- **Laboratory diagnosis:**

1. **Specimens:**
   - ☒ Scrapping from the urogenital tract.
   - ☒ Urethral or Cervical exudates.
2. **Microscopic examination:**
   - ☒ **Inclusion bodies** in scraped tissue cells are detected by staining with **Giemsa** or **iodine** or by staining with **fluorescent monoclonal antibodies**.

3. **Culture:**
   - ☒ **On McCoy cells:** after incubation, typical cytoplasmic inclusions are seen.
   - ☒ **Yolk sac of embryonated egg:** have been used to isolate Chlamydia.
4. **Serological tests:**
   - ☒ Detection of chlamydial antigen directly in specimens by using specific **immunofluorescent antibodies** prepared against C.trachomatis.
   - ☒ Detection of anti-Chlamydia antibodies in sera from infected humans by the **complement fixation** or **micro-immunofluorescence tests**.
5. **Molecular techniques:**
   - ☒ **DNA probes:** It is possible to diagnose C -trachomatis in tissue specimens by hybridization with a specific DNA probe.
   - ☒ **PCR:** is used for diagnosis.

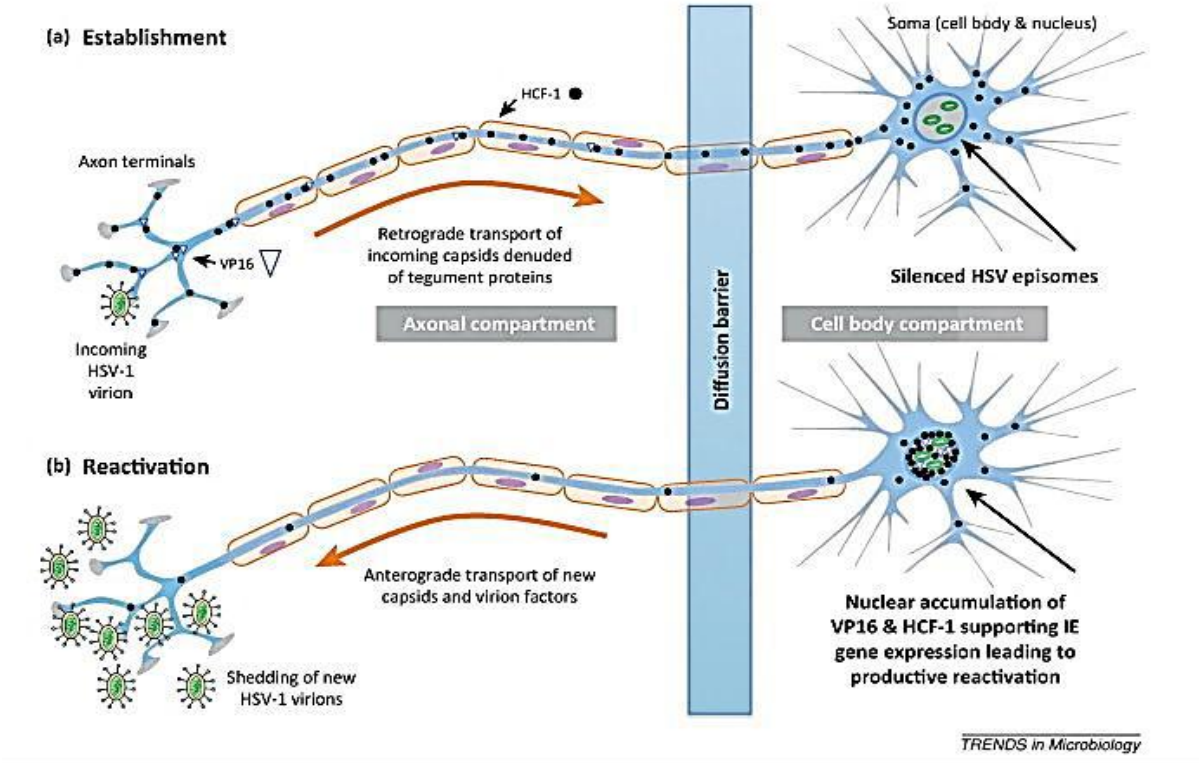
Treatment

- ☒ There is **no** available vaccines
- ☒ It is important to take precautions against sexually transmitted infections because chlamydia is so common and it doesn't produce symptoms.
- ☒ **Tetracycline and erythromycin** are the drugs of choice.
- ☒ **Penicillin is not** effective.

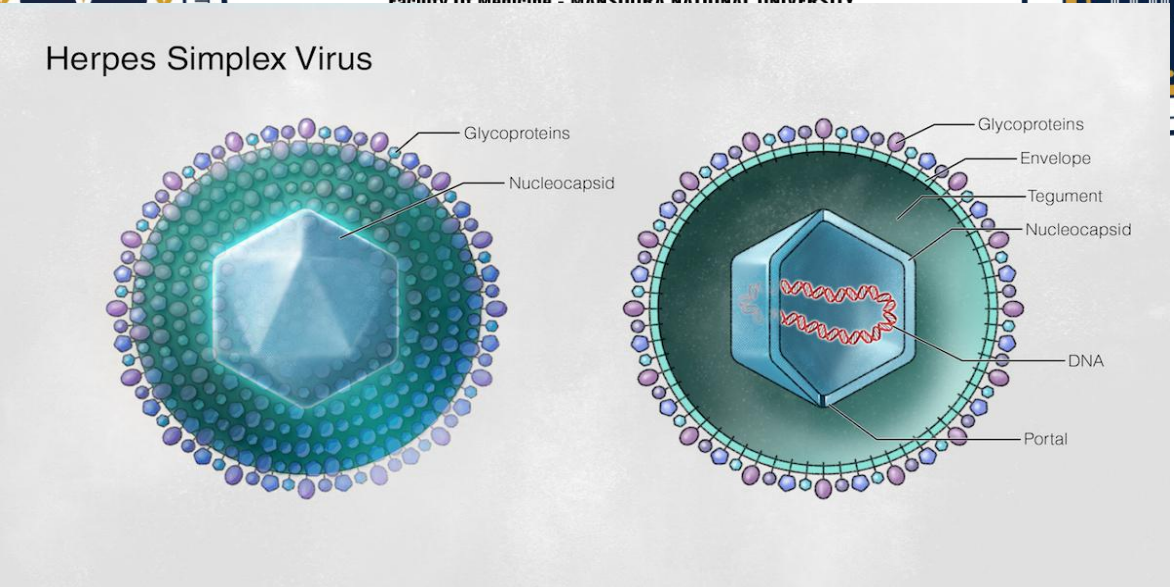
Viral Genital Infections

Herpes viruses

- **Eight** human herpesvirus species are known.
- **All** have the ability to **enter a latent state** following primary infection and to be **reactivated** at a later time.



- **Structure:**
  - ☒ **Virion:** icosahedral.
  - ☒ **Genome:** Double-stranded DNA, linear.
  - ☒ **Envelope:** Contains glycoprotein spikes.



- **Classification of Herpesviruses:**

  ☒ **They have been divided into three subfamilies:**

Alpha herpesvirinae	**Beta herpesvirinae**	**Gamma herpesvirinae**
Herpes simplex virus type 1 (HSV-1 or HHV-1).	**Cytomegalovirus** (HHV-5).	**Epstein-Barr virus** (HHV-4).
Herpes simplex virus type 2 (HSV-2 or HHV-2).	Human herpes virus type 6 (HHV-6).	**Kaposi's sarcoma-associated herpes virus** (KSHV) or (HHV-8).
Varicella – Zoster virus (VZV or HHV-3).	Human herpes virus type 7 (HHV-7).	

Herpes simplex viruses:

- There are 2 distinct herpes simplex viruses, type 1 and type 2.
- The two viruses cross-react serologically but some unique proteins exist for each type.
- **Transmission and Pathogenesis:**

	HSV-1	**HSV-2**
Mode of transmission	Primarily in saliva (kissing)	By sexual contact
Multiplies **locally** in the **mucous membrane** or **abraded skin** causing vesicular lesions.		
Site of lesion	Mainly orofacial lesions	Genital lesions
However, **both** types of HSV can infect **oral or genital** mucosa depending on regions of **contact**.		

Clinical syndromes:

	HSV-1	HSV-2

Primary infection	• **Acute gingivostomatitis.**
	• **Herpes libialis** (cold sores).
	• **Herpetic whitlow**: is a pustular lesion of the skin of finger or hand of medical personnel.
	• **Keratoconjunctivitis, encephalitis.**
	• **Disseminated infections**, such as esophagitis and pneumonia in immune-compromised.
		• **Genital herpes**: vesiculo-ulcerative lesions on external genitalia as well as the cervix.
		• **Neonatal infection**:
		  ○ Originates chiefly from contact with vesicular lesions within the birth canal.
		  ○ Neonatal herpes varies from a severe generalized disease often involving the CNS to an asymptomatic infection.
		• **Aseptic meningitis**.

Latency	**Trigeminal** ganglia.	**Sacral** ganglia.
Reactivation	In response to stimuli as common colds, hormonal changes, and sunlight.	
	• Cold sores. • Keratitis.	• Occur more frequently. • Often asymptomatic but still results in viral shedding.

Cold sore **Vesicular lesion**

- **Laboratory diagnosis:**
  - ☒ **Sample:** vesicular fluid.
  - ☒ Detection of **viral particles** by electron microscope.
  - ☒ Detection of **viral antigens** by immunofluorescence in vesicular fluid.
  - ☒ Detection of **HSV DNA by PCR.**

☒ **Virus isolation** from herpetic lesions.

☒ **Serologic diagnosis** (Detection of IgM or 4-folds rising titer of IgG).

☒ **Histological staining (Giemsa stain)** of scrapings or swabs from the base of skin lesions.

- **Treatment**

☒ **Acyclovir, Famciclovir, and Valacyclovir** are the treatment of choices.

☒ It shortens the duration of the lesion and decreases shedding of the virus.

☒ No drug treatment prevents recurrences.

☒ No effect on the latent state.

Human papilloma virus (HPV)

Morphology:

- ☒ HPV is a small, Icosahedral **non-enveloped** virus with a circular **double-**stranded DNA genome.
- ☒ There are more than 100 different types of HPV.
- ☒ The **most common** sexually transmitted virus.

Mode of Transmission:

- ☒ It requires **direct contact** with infected individuals e.g. sexual contact or contaminated surfaces e.g. common bathroom floors.

Clinical significance:

HPV type	Clinical lesion	Benign/ Malignant
Type-1	Planter wart.	Benign
Type- 2, 4	Skin warts.	Benign
Type-16, 18	Carcinoma (cervix, penis) (70%).	**Malignant**
Type-6, 11	Anogenital condylomas (90%) and laryngeal papilloma.	**Low oncogenic** potential

☒ **Condylomata (genital wart)** are irregular, soft, pink growths that are found on external genitalia or the anus.

HPV and cancer:

☒ HPV virulence factors include proteins **(E6 and E7)** that are capable of **inactivating** tumor suppressor proteins (**P53**) → uncontrolled cell division and the development of cancer.

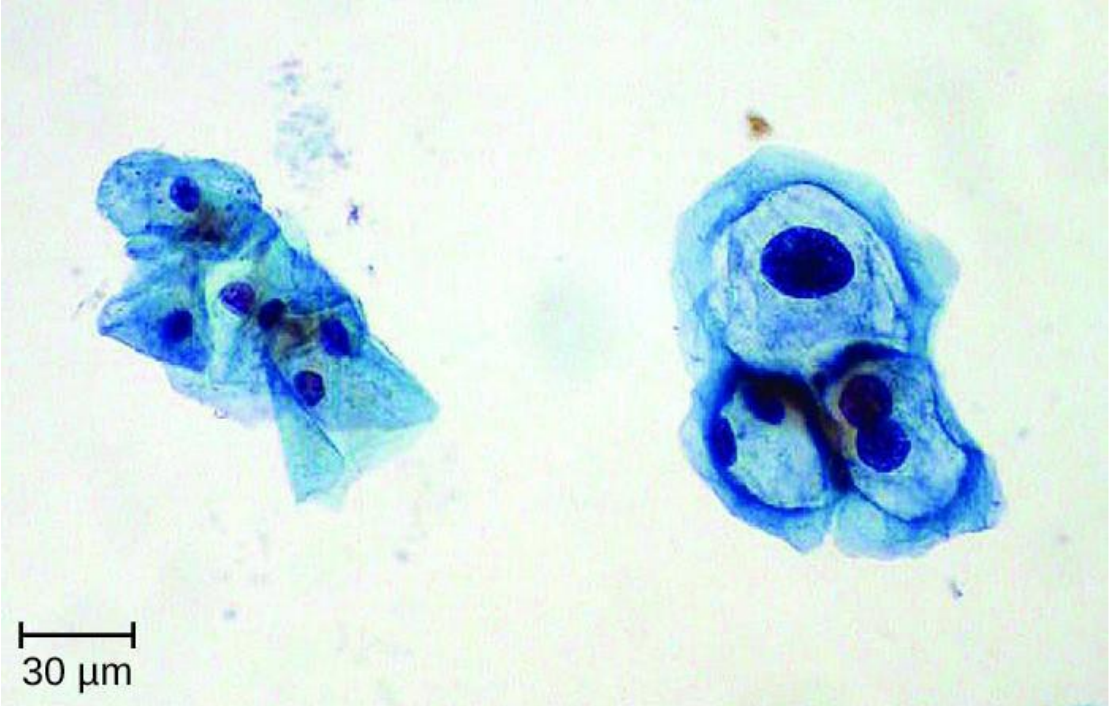
Laboratory Diagnosis:

☒ Virus has not been isolated in cell line.

☒ Serologic tests rarely done (large number of serotypes).

☒ PCR to detect virus DNA is available.

☒ Screening by Pap smear for all women above 30 in USA (koilocytes).



In this image, the cervical cells on the **left are normal** and those on the **right** show **enlarged nuclei and hyperchromasia** (darkly stained nuclei) typical of HPV-infected **koilocytes**.

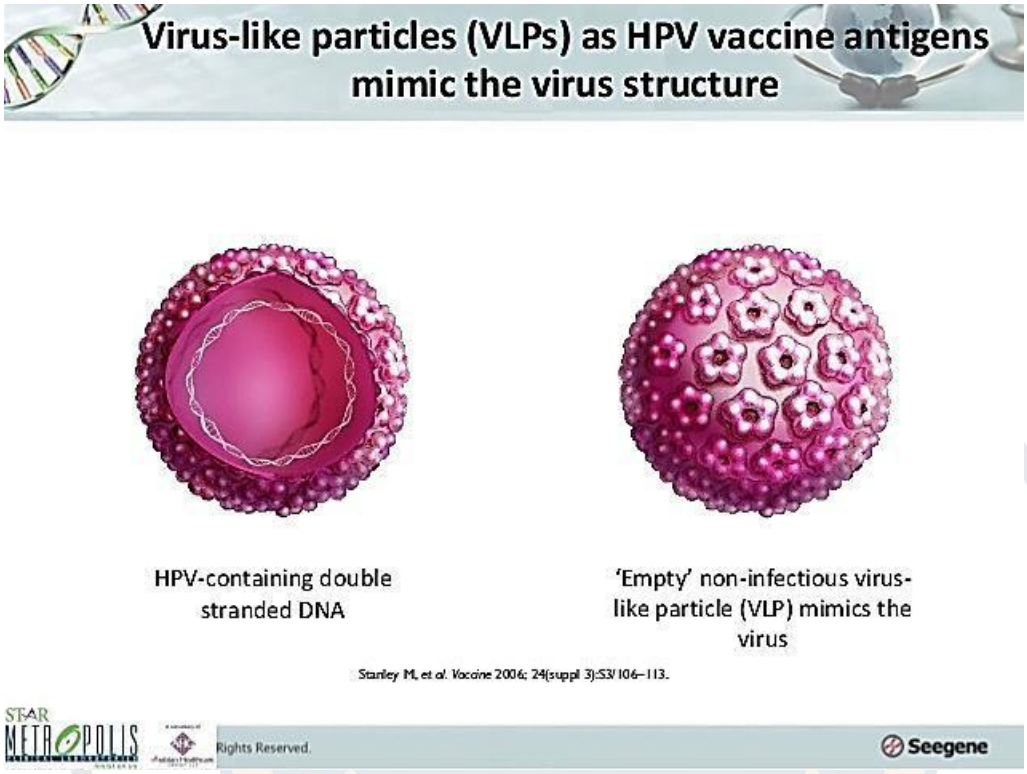
- **HPV vaccine:**

☒ Virus-like particle (VLP) vaccine. (L1 and/ Or L2 protein).

☒ There are **3 versions** of the L1-only HPV vaccine.

- **Gardasil:** HPV16, 18, 6 and 11.
- **Cervarix:** HPV 16, 18.
- **Gardasil 9:** HPV16, 18, 6, 11, 31, 33, 45, 52, and 58.

☒ Given to females **10 - 25** years of age.



- **Treatment:**

☒ Most HPV infections resolve **spontaneously**.

☒ **Topical medications:**

- **imiquimod** (which stimulates the production of **interferon**).

☒ **Cryotherapy or surgery,** but these approaches are less effective for genital warts than for other types of warts.

☒ **Electrocauterization and carbon dioxide laser therapy.**

Case scenario:

A 37-year-old man came to the outpatient clinic for dermatology and venereology, stating that a soft pink growth had appeared on the shaft of his penis. He reported to have had multiple extramarital encounters.

1. **What is the causative organism in this case.**
   - human papillomavirus.
2. **Describe its morphology.**
   - small, Icosahedral non-enveloped virus with a circular double-stranded DNA genome.
3. **Mention its mode of transmission.**
   - It requires direct contact with infected individuals e.g. sexual contact or contaminated surfaces e.g. common bathroom floors.
4. **Mention its relation to malignancy.**
   - HPV virulence factors include proteins (E6 and E7) that are capable of inactivating tumor suppressor proteins (P53) → uncontrolled cell division and the development of cancer.
5. **How to treat this case.**

- Most HPV infections resolve spontaneously.
- Topical Medication: **imiquimod (which stimulates the production of interferon).**
- **Cryotherapy** or **surgery**, but these approaches are less effective for genital warts than for other types of warts.
- **Electrocauterization** and carbon dioxide **laser** therapy.

Questions:

1- Describe the morphology of herpes viruses.

2- Mention diseases caused by primary infection with HSV-2.

3- Illustrate laboratory diagnosis of a case infected with HSV-2.

4- Illustrate human papillomaviruses vaccines.

5- Explain the clinical significance of human papillomaviruses.

Infection in Pregnancy

Congenital Viral Infections

Viral infections in pregnancy are major causes of maternal and fetal morbidity and mortality.

- **The clinical manifestations vary depending on:**
  - ☒ **Viral agent** (Some viruses results in congenital malformation).
  - ☒ **Gestational age at infection:** the early is the infection, the more dangerous is the outcome.
- **Mode of transmission:**
  - ☒ **Infections that develop in the neonate can be transmitted through:**

Trans-placental Through placenta	Perinatal (from vaginal secretions or blood)	Postnatal (from breast milk or other sources)

- **Causative organisms:**
  - ☒ **Infections causing congenital defects are described with "TORCH"**

T (Toxoplasma), O (Others), R (Rubella), C (Cytomegalovirus), H (Herpes).

- ☒ **Other viruses** now known to cause congenital infections include:

- Parvovirus B19 (B19V).
- Varicella-zoster virus (VZV).
- Adenovirus.
- Human immunodeficiency virus (HIV).
- Zika virus.
- Hepatitis E virus.

Outcomes

Spontaneous abortion.	**Premature birth.**	**Intrauterine growth restriction (IUGR).**	**Abnormalities in the CNS, the skeletal and endocrine systems, and the internal organs (e.g., cardiac defects, vision and hearing loss).**

Prevention

General Measures:

- Hygiene measures (washing hands).
- Do not sharing drinking glasses or eating utensils with young children.
- Do not kissing young children on the mouth or cheek.
- Affected infants require regular follow-ups to monitor for hearing loss, ophthalmological abnormalities, and developmental delays.

Specific Measures: Primary (vaccination for varicella and rubella (prior to pregnancy).

Cytomegalovirus (CMV)

Structure:

- ☒ **Virion:** icosahedral
- ☒ **Genome:** Double stranded DNA, linear
- ☒ **Envelope:** Contains
- ☒ **Glycoprotein spikes.**

Transmission and pathogenesis:

Early in life:	Later in life:
• **Trans-placental** • **Within birth canal** • **Via breast milk.**	• **Saliva (most common route).** • **Sexually.** • **Blood transfusion.** • **Organs transplant.**

Clinical Significance:

A) Primary infection:
☒ **In healthy individuals may cause:** • **Asymptomatic infection** with intermittent shedding in saliva and urine. • **Infectious mononucleosis-like syndrome:** similar to EBV infection but heterophil antibodies negative.
☒ **Infection of immunodeficient patients:** • **Hepatitis and pneumonia** are common, In AIDS, (diarrhea and retinitis may occur). • **Congenital infections:** **the most common intrauterine viral infection:** • **In-utero, it causes:** abortion, still birth or cytomegalic inclusion disease: (Mental retardation, microcephaly, blindness and deafness). • **Perinatal infection** from the birth canal or from the milk: usually subclinical infection.
B) Latency and Reactivation:
Latency is established in monocytes, macrophages and kidney. Reactivation: repeated episodes of asymptomatic virus shedding over prolonged periods of times.

Laboratory diagnosis:

Direct Detection:	Virus isolation in cell culture:	Serological test
1. **Fluorescent antibody & histological staining** of inclusions in giant cells in urine and in tissue. 2. **PCR** for detection of CMV nucleic acid in tissues or body fluid as CSF.	**CPE is 2-3 weeks** (Typical swollen and translucent cells with intranuclear inclusion bodies (Owl eye) appearance.	**detect rising IgG titer or IgM.**

Diagnosis of CMV during pregnancy:

☒ **Mother:**

- Positive IgM
- PCR.

☒ **Fetus:**

- **Amniotic fluid** sample is taken and CMV is demonstrated either by PCR or isolation on tissue culture.

Prevention and treatment:

☒ **Prevention:** General preventive measures for intra-uterine viral infections.

☒ **Treatment:** Ganciclovir: is effective in immunocompromised patients.

Parvoviruses

Structure:

- ☒ **Virion:** icosahedral
- ☒ **Genome:** Single-stranded DNA, linear
- ☒ **Non-enveloped**

Clinical Significance:

Dependo-viruses:	**Autonomous parvoviruses:**
They require helper virus for their replication which usually an adenovirus (e.g. Adeno-associated virus).	They are capable of independent replication (e.g. human parvovirus B19).

Human B19

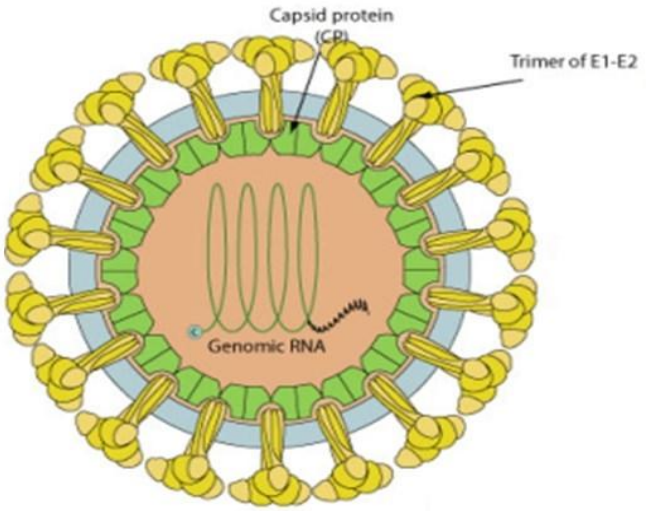
- **Human B19 virus targets immature cells of the erythroid lineage (RBCs).**
- **Diseases caused:**
  - ☒ Transient aplastic crisis in patients with sickle cell disease.
  - ☒ **Erythema infectiosum (fifth disease or slapped cheek disease**).
    - A common childhood disease.
    - Associated with bright red rash of the cheeks.
    - Exacerbation of rash by sunlight, heat and stress.

  - ☒ Hydrops fetalis and fetal death:
    - Due to severe anemia if Infection occurs during pregnancy
    - May leads to miscarriage (spontaneous abortion) if occurs before 20th week. Or stillbirth after 20th week of gestation.
- **Laboratory diagnosis:** PCR
- **Prevention:**
  - ☒ The best approach is to recommend all pregnant women to avoid contact with children with current symptoms of infection.
  - ☒ The risk to the fetus is reduced by:
    - Correct diagnosis of the anemia (by ultrasound scans)
    - Correct treatment (blood transfusions).

Rubella virus

Structure:

- ☒ **Virion:** icosahedral nucleocapsid. Spherical shape.
- ☒ **Genome:** positive-sense, single stranded RNA
- ☒ **Enveloped with** hemagglutinin-containing spike-like projections.
- ☒ Belongs to **Togavireadea family**



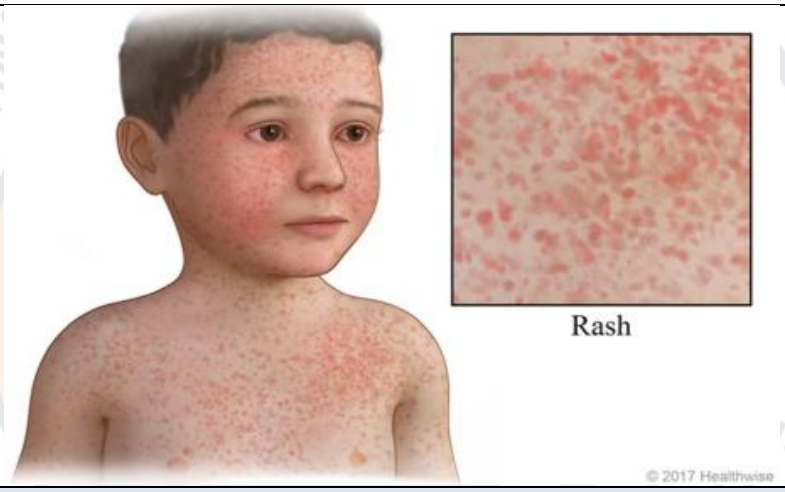
Transmission:

- ☒ The virus is transmitted via respiratory droplets.
- ☒ Initial replication of the virus occurs in the oropharynx and local lymph nodes.
- ☒ From there it spreads via the blood to the internal organs (including placenta) and skin.
- ☒ I.P. 14-25 days after infection, patient is infectious for most of this time.

Clinical Significance

☒ **The disease is characterized by:**

- In 95% of adolescent patients 14-25 days (average: 18 days) after infection
- Characteristic pink continuous maculopapular rash appears.
- Posterior auricular lymphadenopathy are characteristic of the disease
- In children, a mild febrile illness - less severe than measles.
- In adults other than pregnant women: symptoms are rare.



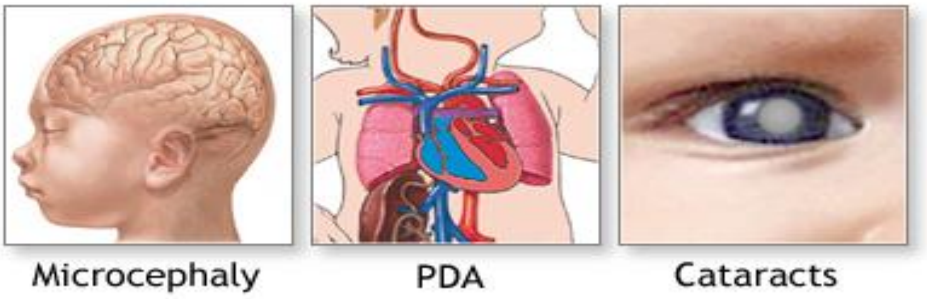
Congenital rubella syndrome:

☒ Virus crosses placenta and multiplies in the fetus.

☒ Up to 85% of infants infected in the first trimester of pregnancy get congenital rubella syndrome (CRS) with low birth weight, deafness, CNS involvement, cardiac abnormality, eye abnormality and abortion.

☒ The earlier in pregnancy infection occurs, the worse the prognosis becomes.

☒ Fetus is persistently infected (presumably due to immature immune response) and continues to excrete virus after birth (a risk to doctors, nurses and other patients).



Prevention and control:

☒ MMR vaccine:

- Trivalent live attenuated vaccine (MMR)
- Usually given by sub cutaneous injection.
- It is given at 12 – 15 months.
- A single dose of the MMR vaccine gives around
- 90% protection against measles and mumps and
- 95-99% against rubella.
- (For women infected during 1st trimester of pregnancy, therapeutic abortion is recommended).

Case scenario, Clinical Correlate, Practice points

A 35-year-old woman during her second pregnancy experienced no complication until 10 weeks of gestation.

Routine CMV serologic tests were performed. CMV immunoglobulin (IgG) and CMV-(IgM) were demonstrated in both samples obtained during 10th and 14th weeks of gestation.

Questions:

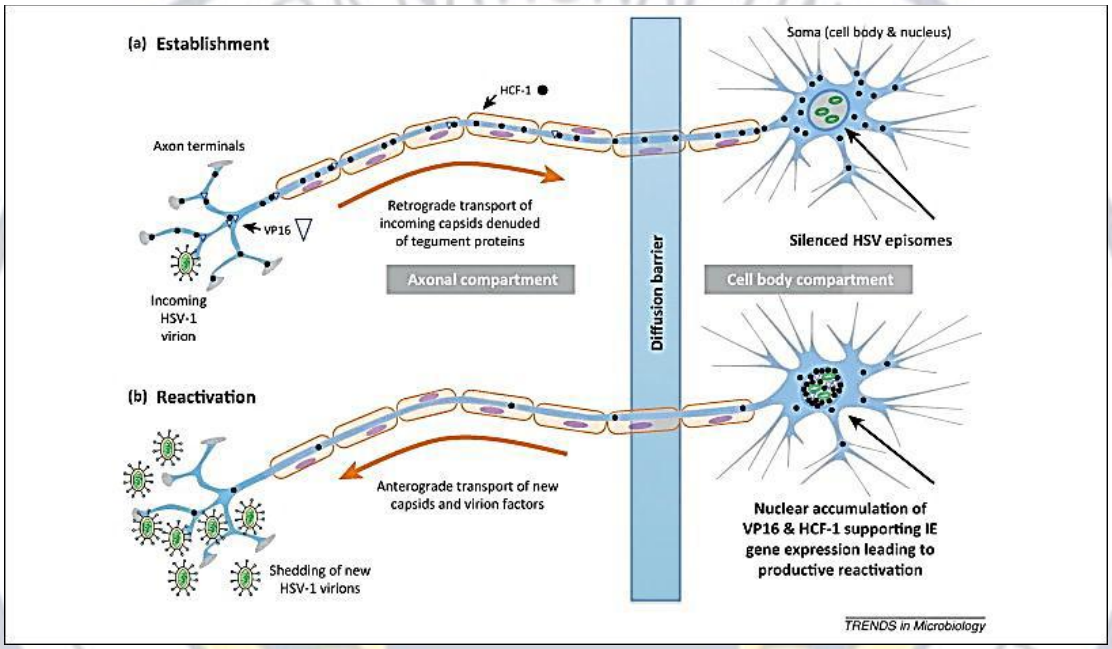
- What are the confirmatory tests that should be done?

- What are the modes of transmission of this virus?

Herpes viruses

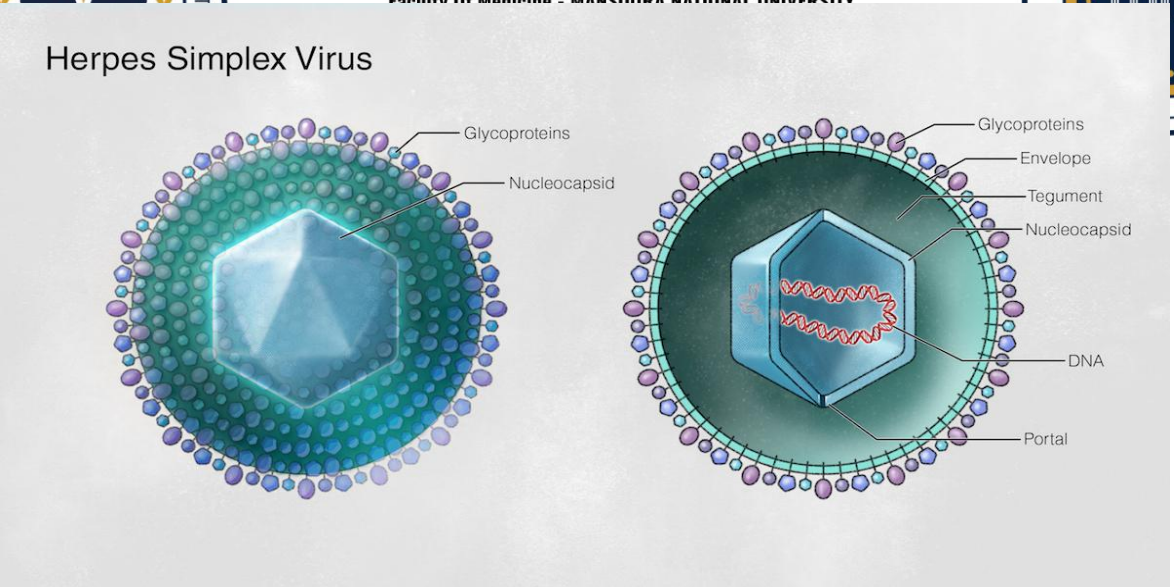
- Eight human herpesvirus species are known.

All have the ability to enter a latent state following primary infection and to be reactivated at a later time.



Structure:

- Virion: icosahedral.
- Genome: Double-stranded DNA, linear.
- Envelope: Contains glycoprotein spikes.



Classification of Herpesviruses:

- They have been divided into three subfamilies:

Alpha herpesvirinae	Beta herpesvirinae	Gamma herpesvirinae
Herpes simplex virus type 1 (HSV-1 or HHV-1).	Cytomegalovirus (HHV-5).	Epstein-Barr virus (HHV-4).
Herpes simplex virus type 2 (HSV-2 or HHV-2).	Human herpes virus type 6 (HHV-6).	Kaposi's sarcoma-associated herpes virus (KSHV) or (HHV-8).
Varicella – Zoster virus (VZV or HHV-3).	Human herpes virus type 7 (HHV-7).	

Herpes simplex viruses:

- There are 2 distinct herpes simplex viruses, type 1 and type 2.

- The two viruses cross-react serologically but some unique proteins exist for each type.

Transmission and Pathogenesis:

	HSV-1	HSV-2
Mode of transmission	Primarily in saliva (kissing)	By sexual contact
Multiplies locally in the mucous membrane or abraded skin causing vesicular lesions.		
Site of lesion	Mainly orofacial lesions	Genital lesions
However, both types of HSV can infect oral or genital mucosa depending on regions of contact.		

Clinical syndromes:

HSV-1	HSV-2

Primary infection	• **Acute gingivostomatitis.** • **Herpes libialis** (cold sores). • **Herpetic whitlow**: is a pustular lesion of the skin of finger or hand of medical personnel. • **Keratoconjunctivitis, encephalitis.** • **Disseminated infections**, such as esophagitis and pneumonia in immune-compromised.	• **Genital herpes**: vesiculo-ulcerative lesions on external genitalia as well as the cervix. • **Neonatal infection**: ▪ Originates chiefly from contact with vesicular lesions within the birth canal. ▪ Neonatal herpes varies from a severe generalized disease often involving the CNS to an asymptomatic infection. • **Aseptic meningitis**.
Latency	Trigeminal ganglia.	Sacral ganglia.
Reactivation	In response to stimuli as common colds, hormonal changes and sunlight.	
	• Cold sores. • Keratitis.	• Occur more frequently. • Often asymptomatic but still results in viral shedding.

Cold sore

Vesicular lesion

Laboratory diagnosis:

- **Sample**: vesicular fluid.
- Detection of viral particles by electron microscope.
- Detection of viral antigens by immunofluorescence in vesicular fluid.
- Detection of HSV DNA by PCR.
- Virus isolation from herpetic lesions.

- Serologic diagnosis (Detection of IgM or 4-folds rising titer of IgG).
- Histological staining (Giemsa stain) of scrapings or swabs from the base of skin lesions.

Treatment

- Acyclovir, Famciclovir, and Valacyclovir are the treatment of choices.
- It shortens the duration of the lesion and decreases shedding of the virus.
- No drug treatment prevents recurrences.
- No effect on the latent state.

Human papilloma virus (HPV)

Morphology:

- HPV is a small, Icosahedral **non-enveloped** virus with a **circular** double-stranded DNA genome.
- There are more than 100 different types of HPV.
- The **most common** sexually transmitted virus.

Mode of Transmission:

- It requires direct contact with infected individuals e.g. sexual contact or contaminated surfaces e.g. common bathroom floors.

Clinical significance:

HPV type	Clinical lesion	Benign/ Malignant
Type-1	Planter wart.	Benign
Type- 2, 4	Skin warts.	Benign
Type-16, 18	Carcinoma (cervix, penis) (70%).	Malignant
Type-6, 11	Anogenital condylomas (90%) and laryngeal papilloma.	Low oncogenic potential

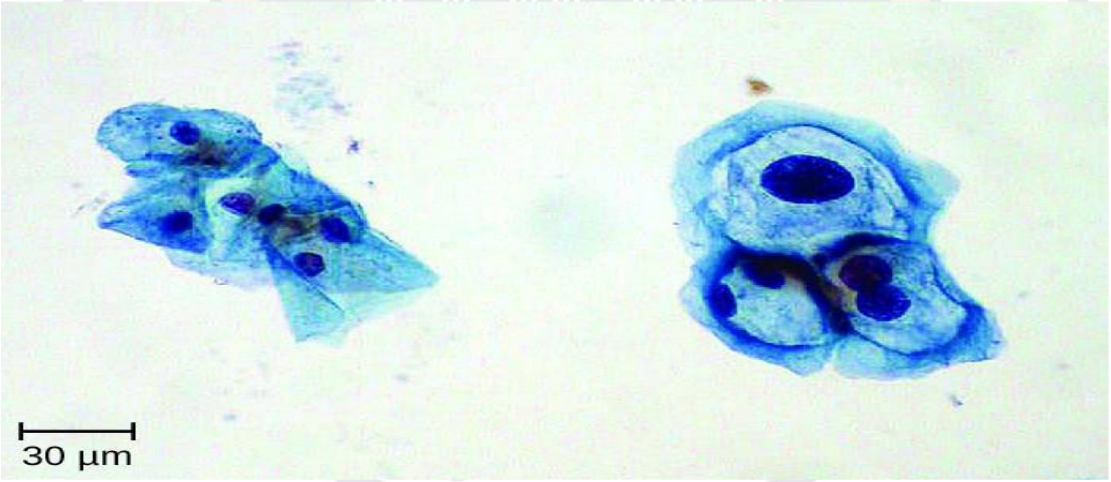
- Condylomata (genital wart) are irregular, soft, pink growths that are found on external genitalia or the anus.

HPV and cancer:

- HPV virulence factors include proteins (E6 and E7) that are capable of inactivating tumor suppressor proteins (P53) → uncontrolled cell division and the development of cancer.

Laboratory Diagnosis:

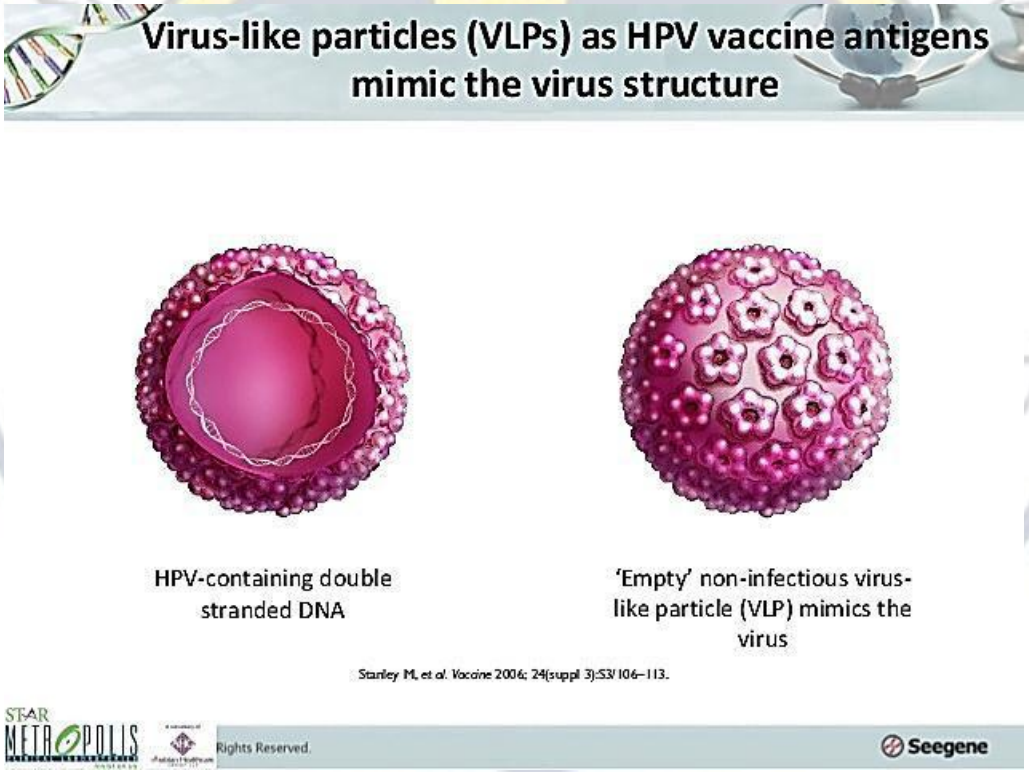
- Virus has not been isolated in cell line.
- Serologic tests rarely done (large number of serotypes).
- PCR to detect virus DNA is available.
- Screening by Pap smear for all women above 30 in USA (koilocytes).



✓ **In this image, the cervical cells on the left are normal and those on the right show enlarged nuclei and hyperchromasia (darkly stained nuclei) typical of HPV-infected koilocytes.**

HPV vaccine:

- Virus-like particle (VLP) vaccine. (L1 and/ Or L2 protein).
- There are 3 versions of the L1-only HPV vaccine.
  - **Gardasil:** HPV16, 18, 6 and 11.
  - **Cervarix:** HPV 16, 18.
  - **Gardasil 9:** HPV16, 18, 6, 11, 31, 33, 45, 52, and 58.
- Given to females 10 - 25 years of age.



Treatment:

- Most HPV infections resolve **spontaneously**.
- **Topical** medications:
  - **imiquimod** (which stimulates the production of interferon).
- **Cryotherapy** or **surgery**, but these approaches are less effective for genital warts than for other types of warts.
- **Electrocauterization** and carbon dioxide **laser** therapy.

Case scenario:

A 37-year-old man came to the outpatient clinic for dermatology and venereology, stating that a soft pink growth had appeared on the shaft of his penis. He reported to have had multiple extramarital encounters.

1. **What is the causative organism in this case.**

   - Human papillomavirus.

2. **Describe its morphology.**

   - Small, Icosahedral non-enveloped virus with a circular double-stranded DNA genome.

3. **Mention its mode of transmission.**

   - It requires direct contact with infected individuals e.g. sexual contact or contaminated surfaces e.g. common bathroom floors.

4. **Mention its relation to malignancy.**

   - HPV virulence factors include proteins (E6 and E7) that are capable of inactivating tumor suppressor proteins (P53) → uncontrolled cell division and the development of cancer.

5. **How to treat this case.**

   - Most HPV infections resolve spontaneously.

   - Topical Medication: **imiquimod (which stimulates the production of interferon).**

- **Cryotherapy** or **surgery**, but these approaches are less effective for genital warts than for other types of warts.

- **Electrocauterization** and carbon dioxide **laser** therapy.

Questions:

Describe the morphology of herpes viruses.

Morphology of herpes viruses:

- Virion: icosahedral.
- Genome: Double-stranded DNA, linear.
- Envelope: Contains glycoprotein spikes.

Mention diseases caused by primary infection with HSV-2.

Diseases caused by primary infection with HSV-2:

- **Genital herpes**: vesiculo-ulcerative lesions on external genitalia as well as the cervix.
- **Neonatal infection**:
  - Originates chiefly from contact with vesicular lesions within the birth canal.
  - Neonatal herpes varies from a severe generalized disease often involving the CNS to an asymptomatic infection.

- **Aseptic meningitis**.

Illustrate laboratory diagnosis of a case infected with HSV-2.

Laboratory diagnosis of a case infected with HSV-2:

- **Sample**: vesicular fluid.
- Detection of viral particles by electron microscope.
- Detection of viral antigens by immunofluorescence in vesicular fluid.
- Detection of HSV DNA by PCR.
- Virus isolation from herpetic lesions.
- Serologic diagnosis (Detection of IgM or 4-folds rising titer of IgG).
- Histological staining (Giemsa stain) of scrapings or swabs from the base of skin lesions.

Illustrate human papillomaviruses vaccines.

HPV vaccines:

- Virus-like particle (VLP) vaccine. (L1 and/ Or L2 protein).
- There are 3 versions of the L1-only HPV vaccine.
    - **Gardasil:** HPV16, 18, 6 and 11.
    - **Cervarix:** HPV 16, 18.
    - **Gardasil 9:** HPV16, 18, 6, 11, 31, 33, 45, 52, and 58.
- Given to females 10 - 25 years of age.

6- Explain the clinical significance of human papillomaviruses.

Clinical significance of human papillomaviruses:

HPV type	Clinical lesion	Benign/ Malignant
Type-1	Planter wart.	Benign
Type- 2, 4	Skin warts.	Benign
Type-16, 18	Carcinoma (cervix, penis) (70%).	Malignant
Type-6, 11	Anogenital condylomas (90%) and laryngeal papilloma.	Low oncogenic potential

Infection in Pregnancy

Congenital Viral Infections

Viral infections in pregnancy are major causes of maternal and fetal morbidity and mortality.

The clinical manifestations vary depending on:

- **Viral agent** (Some viruses results in congenital malformation).
- **Gestational age at infection:** the early is the infection, the more dangerous is the outcome.

Mode of transmission:

Infections that develop in the neonate can be transmitted through:

Trans-placental Through placenta	Perinatal (from vaginal secretions or blood)	Postnatal (from breast milk or other sources)

Causative organisms:

Infections causing congenital defects are described with "TORCH"

T (Toxoplasma), O (Others), R (Rubella), C (Cytomegalovirus), H (Herpes).

Other viruses now known to cause congenital infections include:

- Parvovirus B19 (B19V).
- Varicella-zoster virus (VZV).
- Adenovirus.
- Human immunodeficiency virus (HIV).
- Zika virus.
- Hepatitis E virus.

Outcomes			
Spontaneous abortion.	**Premature birth.**	**Intrauterine growth restriction (IUGR).**	**Abnormalities in the CNS, the skeletal and endocrine systems, and the internal organs (e.g., cardiac defects, vision and hearing loss).**

Prevention:

General Measures:

- Hygiene measures (washing hands).
- Do not sharing drinking glasses or eating utensils with young children.
- Do not kissing young children on the mouth or cheek.
- Affected infants require regular follow-ups to monitor for hearing loss, ophthalmological abnormalities, and developmental delays.

Specific Measures: Primary (vaccination for varicella and rubella (prior to pregnancy).

Classification of human Herpes viruses

- Eight human herpesvirus species are known.
- All have the ability to enter a latent state following primary infection and to be reactivated at a later time.

Classification of Herpes viruses

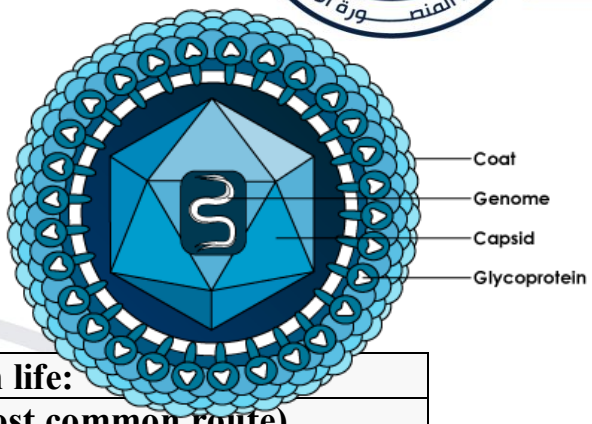
They have been divided into three subfamilies:

Alpha herpesvirinae	***Beta herpesvirinae***	***Gamma herpesvirinae***
Herpes simplex virus types 1 (HSV-1 or HHV-1)	Cytomegalovirus (HHV-5)	Epstein-Barr virus (HHV-4).
Herpes simplex virus	Herpes simplex virus	Herpes simplex virus
Varicella – Zoster virus	Varicella – Zoster virus	

Cytomegalovirus (CMV)

Structure:

- **Virion:** icosahedral
- **Genome:** Double stranded DNA, linear
- **Envelope:** Contains
- **Glycoprotein spikes.**



Transmission and pathogenesis:

Early in life:	Later in life:
Trans-placental **Within birth canal** **Via breast milk.**	**Saliva (most common route).** **Sexually.** **Blood transfusion.** **Organs transplant.**

Clinical Significance:

Primary infection:

In healthy individuals may cause:

- **Asymptomatic infection** with intermittent shedding in saliva and urine.
- **Infectious mononucleosis like syndrome:** similar to EBV infection but heterophil antibodies negative.

Infection of immunodeficient patients:

Hepatitis and pneumonia are common, In AIDS, (diarrhea and retinitis may occur).

Congenital infections: **the most common intrauterine viral infection:**

In-utero, it causes: abortion, still birth or cytomegalic inclusion disease: (Mental retardation, microcephaly, blindness and deafness).

Perinatal infection from the birth canal or from the milk: usually subclinical infection.

B) Latency and Reactivation:

Latency is established in monocytes, macrophages and kidney. Reactivation: repeated episodes of asymptomatic virus shedding over prolonged periods of times.

Laboratory diagnosis:

Direct Detection:	Virus isolation in cell culture: CPE is 2-3 weeks	Serological test to detect

1. **Fluorescent antibody & histological staining** of inclusions in giant cells in urine and in tissue. 2. **PCR** for detection of CMV nucleic acid in tissues or body fluid as CSF.	(Typical swollen and translucent cells with intranuclear inclusion bodies (Owl eye) appearance.	**rising IgG titer or IgM.**

Diagnosis of CMV during pregnancy:

Mother:

- Positive IgM
- PCR.

Fetus:

- Amniotic fluid sample is taken and CMV is demonstrated either by PCR or isolation on tissue culture.

Prevention and treatment:

Prevention: General preventive measures for intra-uterine viral infections.

Treatment: Ganciclovir: is effective in immunocompromised patients.

Parvoviruses

Structure:

- **Virion:** icosahedral
- **Genome:** Single stranded DNA, linear
- **Non-enveloped**

Clinical Significance:

Dependo-viruses:	Autonomous parvoviruses:
They require helper virus for their replication which usually an adenovirus (e.g. Adeno-associated virus).	They are capable of independent replication (e.g. human parvovirus B19).

Human B19

Human B19 virus targets **immature cells of the erythroid lineage (RBCs).**

Diseases caused:

- Transient aplastic crisis in patients with sickle cell disease.
- Erythema infectiosum (fifth disease or slapped cheek disease).
  - A common childhood disease.
  - Associated with bright red rash of the cheeks.
  - Exacerbation of rash by sunlight, heat and stress.

- Hydrops fetalis and fetal death:
  - Due to severe anemia if Infection occurs during pregnancy
  - May leads to miscarriage (spontaneous abortion) if occurs before 20th week.
  - Or stillbirth after 20th week of gestation.

Laboratory diagnosis: PCR

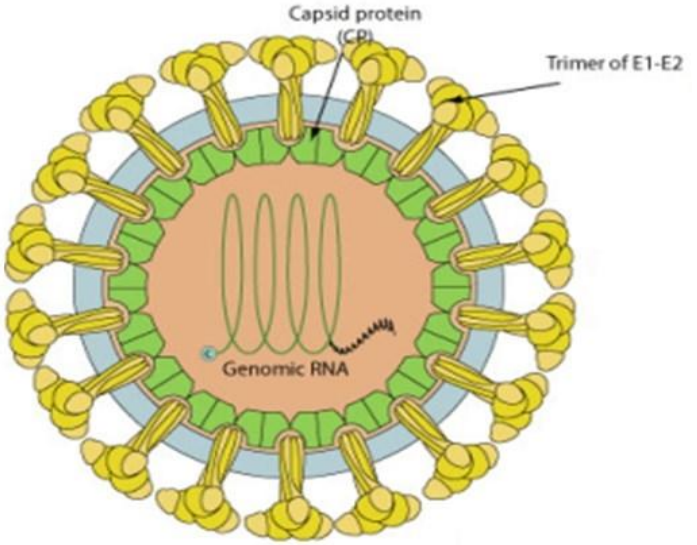
Prevention:

- The best approach is to recommend all pregnant women to avoid contact with children with current symptoms of infection.
- The risk to the fetus is reduced by:
  - Correct diagnosis of the anemia (by ultrasound scans)
  - Correct treatment (blood transfusions).

Rubella virus

Structure:

Virion: icosahedral nucleocapsid. Spherical shape.
Genome: positive-sense, single stranded RNA
Enveloped with hemagglutinin-containing spike-like projections.
Belongs to **Togavireadea family**



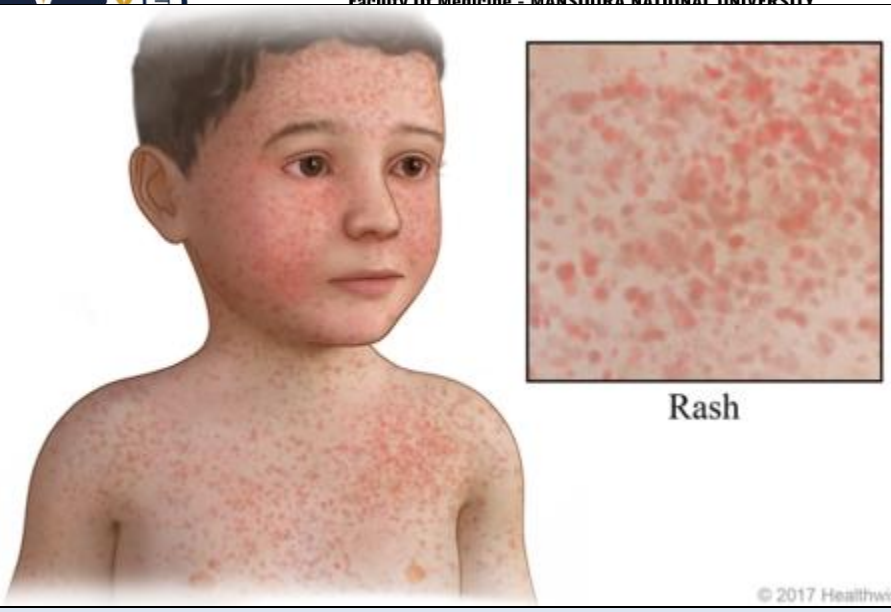
Transmission:

- The virus is transmitted via respiratory droplets.
- Initial replication of the virus occurs in the oropharynx and local lymph nodes.
- From there it spreads via the blood to the internal organs (including placenta) and skin.
- I.P. 14-25 days after infection, patient is infectious for most of this time.

linical Significance

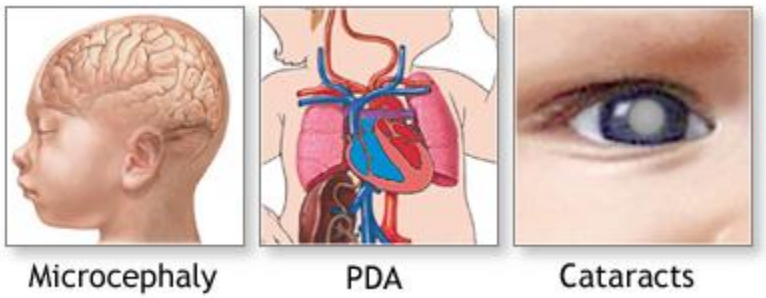
The disease is characterized by:

- **In 95% of adolescent patients** 14-25 days (average: 18 days) after infection:
  - Characteristic pink continuous maculopapular rash appears.
  - Posterior auricular lymphadenopathy are characteristic of the disease
- **In children**, a mild febrile illness - less severe than measles.
- **In adults** other than pregnant women: symptoms are rare.



ongenital rubella syndrome:

- Virus crosses placenta and multiplies in the fetus.
- Up to 85% of infants infected in the first trimester of pregnancy get congenital rubella syndrome (CRS) with low birth weight, deafness, CNS involvement, cardiac abnormality, eye abnormality and abortion.
- The earlier in pregnancy infection occurs, the worse the prognosis becomes.
- Fetus is persistently infected (presumably due to immature immune response) and continues to excrete virus after birth (a risk to doctors, nurses and other patients).



Prevention and control:

MMR vaccine:

- **Trivalent live attenuated vaccine (MMR)**
- **Usually given by sub cutaneous injection.**
- **It is given at 12 – 15 months.**

- **A single dose of the MMR vaccine gives around 90% protection against measles and mumps and 95-99% against rubella.**
- **(For women infected during 1st trimester of pregnancy, therapeutic abortion is recommended).**

Case scenario, Clinical Correlate, Practice points

A 35-year-old woman during her second pregnancy experienced no complication until 10 weeks of gestation.

Routine CMV serologic tests were performed. CMV immunoglobulin (IgG) and CMV-(IgM) were demonstrated in both samples obtained during 10th and 14th weeks of gestation.

Questions:

- What are the confirmatory tests that should be done?

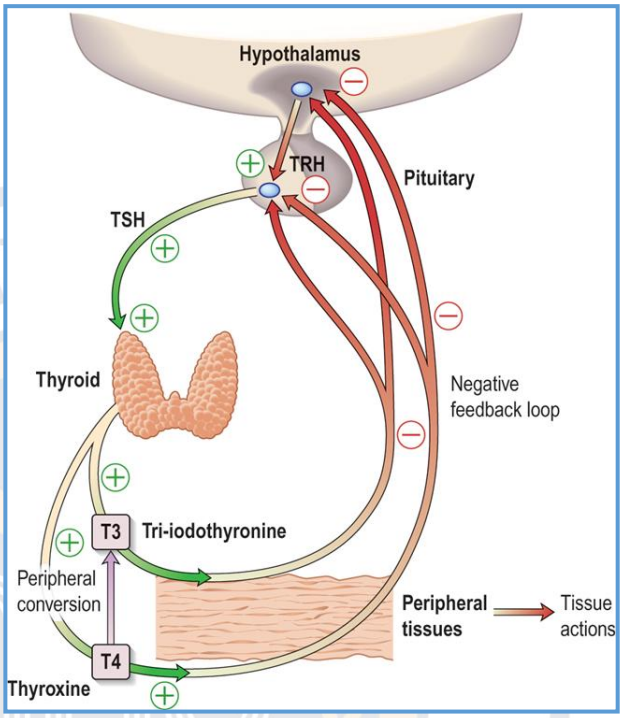
- What are the modes of transmission of this virus?

FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

PHARMACOLOGY

Thyroid disorders

Overview:

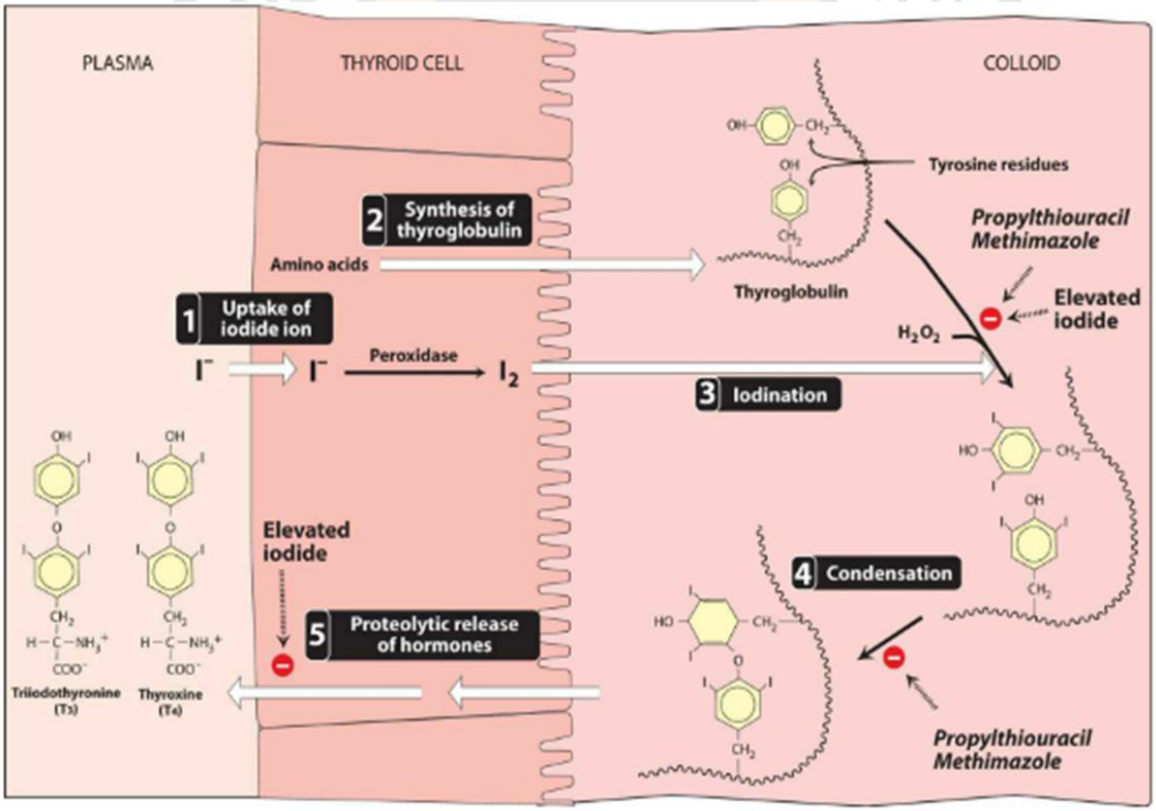


- The thyroid gland controls level of tissue metabolism → facilitates normal growth and maturation.
- The two major thyroid hormones are **triiodothyronine (T3**; the most active form) and **thyroxine (T4).**
- The thyroid gland is made up of multiple follicles → each follicle consists of a single layer of epithelial cells surrounding a lumen filled with colloid; thyroglobulin (the storage form of thyroid hormone).
- Thyroid function is controlled by the thyroid stimulating hormone (TSH), which is synthesized by the anterior pituitary.
- TSH secretion is controlled by the hypothalamic thyrotropin- releasing hormone (TRH)
- TSH action → stimulation of iodide (I−) uptake by the thyroid gland.

Biosynthesis & secretion of thyroid hormones

1. Iodide (I^-) is up taken from the circulation by the thyroid follicular cells.
2. Peroxidase → catalyzes oxidation of iodide ($I^{-)}$ to iodine (I^2).
3. Iodine (I^2) then crosses into the colloid, thyroglobulin.

4. Peroxidase → catalyzes iodination of tyrosine residues of thyroglobulin → monoiodothyronine & diiodothyronine.
5. Peroxidase → catalyzes coupling of mono- & diiodotyrosine → form triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine).
6. Thyroglobulin is stored as colloid in thyroid follicles.
7. When stimulated by TSH → thyroglobulin undergoes proteolysis → release of T4 (80%) and T3 (20%)
8. In peripheral tissues → T4 is converted to T3 (more active) by 5′-deiodinase enzymes



N.B: ↓ secretion of thyroid hormone → **hypothyroidism** → results in bradycardia, cold intolerance, and mental and physical slowing.

N.B: ↑ secretion of thyroid hormones → **hyperthyroidism** → can cause tachycardia, loss of body weight, nervousness, tremors, and heat intolerance.

Hyperthyroidism/Thyrotoxicosis

Graves' disease → An autoimmune disease → The most common cause of thyrotoxicosis

The clinical manifestations of Graves' disease result from:

- ↑ Secretion of the thyroid hormones → ↑ physiologic effects of T3 &T4 (a generalized ↑ of all metabolic processes).
- Sympathetic overactivity.
- ↓ TSH levels are due to negative feedback.

Three treatment modalities are used to control hyperthyroidism of Graves' disease:

1. **Antithyroid drugs** → are the favored therapy.

   Thioamides (Methimazole and propylthiouracil)

   Administered for a prolonged period → 1 to 2 years.

   + propranolol at the onset of treatment → a β-adrenergic receptor blocker to ↓ symptoms of sympathetic overactivity (↓ tachycardia and hypertension) in symptomatic patients.

2. **Radioactive iodine therapy (I^{131})**

   SE → 80% to 90% of patients become hypothyroid and require lifelong thyroid hormone replacement.

   CI→

   - Pregnant/breast feeding women.
   - Ptns with thyroid cancer
   - Ptns with moderate to severe Graves-related eye disease
   - Ptns with heart disease (unless controlled)

3. **Surgery** → Subtotal or total thyroidectomy → Least favored therapy

Treatment of choice for →

- ptns with very large gland causing pressure symptoms.
- ptns with large multinodular glands
- sometimes in females who desire pregnancy within the next year.
- Ptns with thyroid cancer
- Ptns with moderate to severe Graves-related eye disease

SE →

- Hypothyroidism
- Transient/Permanent hypoparathyroidism
- Recurrent laryngeal nerve paralysis

I. Antithyroid drugs

1. **Thioamide drugs** → ↓ synthesis of thyroid hormones

Methimazole & propylthiouracil (PTU)

MOA →

Methimazole & PTU → accumulated in thyroid gland → inhibit peroxidase enzyme → inhibit iodination of tyrosine and coupling iodotyrosine → block synthesis of T4 & T3

PTU (but NOT methimazole) → inhibits peripheral conversion of T4 to T3

- N.B. Effects of thioamides are delayed → takes 4 - 8 weeks till the circulating T3 & T4 levels return to normal.

- Start with higher doses till patient is euthyroid (remission of Graves' disease), then ↓ gradually at monthly intervals to reach the steady state dose.
- Duration of treatment → 12 to 24 months
- About 45% of patients → achieve a permanent remission.

Indications →

- To induce remission in Graves' disease
- Preoperative → to ↓ T4 & T3 levels before surgery or RAI treatment

SE →

- Rash, arthralgia, and fever → in up to 5% of ptns.
- Lupus erythematosus–like syndrome or GIT distress → less frequently
- Benign and transient leukopenia → mild ↓ in WBCs count
- Severe agranulocytosis → granulocyte count < 250/μL.

  Reversible → managed by stopping treatment.

  PTU > methimazole

  Rare → 0.1-0.3% of patients

  Develops during the first 3 months of therapy.

  Monitor with complete blood count.

  Advice patients to contact physician if he experiences fever, malaise, sore throat, or other flu like symptoms.

- Hepatotoxicity and fatal liver failure

  PTU > methimazole

1% of ptns

Monitor for liver toxicity for the first 6 months.

FDA recommends that PTU be reserved for patients who are allergic or intolerant of methimazole except in pregnant lady ??.

	Methimazole	**PTU**
MOA	Block T4 & T3 synthesis	Same + inhibits the peripheral conversion of T4 to T3.
Efficacy	More effective	Less effective
$T_{1/2}$	Longer → 8 h → once daily	Short → 2 h → 2-3 times/day
Plasma protein binding	Not bound → crosses placenta and appears in breast milk	80% bound.
Use in pregnancy	x3 more likely to cause birth defects (esp. during 1st trimester of pregnancy)	Drug of choice just before and during 1st trimester of pregnancy.
Liver toxicity	Lower risk	Higher risk
leucopenia	Lower risk	Higher risk

2. **Iodide salts (Potassium iodide (KI) & Lugol's solution (5% KI & 5% elemental iodine)** → ↓ release of thyroid hormones

MOA →

- Rapidly ↓ iodination of tyrosine residues of thyroglobulin (Acute Wolff-Chaikoff Effect)
- ↓ Release of T4 & T3 from thyroid gland → most important effect.
- Rapid symptomatic improvement → within 2 to 7 days after starting iodide.
- The effect is limited to several weeks → the thyroid gland escapes from the inhibitory effects of iodides.

Indications → a short-term therapy to →

- Treat patients with thyroid storm
- Preoperative → for 7 - 14 days to ↓ size & vascularity of thyroid gland
- After RAI treatment → KI for 3 - 7 days

SE →

Usually, mild

- Skin rashes and other hypersensitivity reactions
- Salivary & lacrimal gland swelling, sore gums & teeth → **iodism.**
- Metallic taste
- Ulcerations of mucous membranes

3. Beta (β)-blockers → MOA of β-blockers in hyperthyroidism →

- β-blockers → propranolol & atenolol → used to ↓ CVS symptoms associated with hyperthyroidism
- Propranolol, but NOT other beta blockers → ↓ peripheral conversion of T4 to T3

If beta blockers are CI → Calcium channel blockers can be used → diltiazem

Radioactive iodine (I^{131}). (RAI)
Single dose → safe, effective & cheap

MOA :

I131 → colorless & tasteless → orally administered → rapidly absorbed from the gut and selectively concentrated in the thyroid gland → emits low penetration radiation that destroy thyroid tissue → T4 & T3 levels gradually return to normal over several weeks (4-8 weeks).

Adjunctive therapy to I131:

1. Thioamide drugs (before & after RAI) → should be stopped 3-7 days before RAI & reinstituted 3-7 days after it.
2. Beta blockers → to control symptoms of hyperthyroidism till full effect to RAI is achieved.
3. Iodide salts (KI) → used after RAI to ↓ radioactive thyroid hormone release. KI should NOT be used before RAI → because nonradioactive iodide would compete with I131 for uptake by thyroid gland.

SE :

80% to 90% of ptns become hypothyroid → require lifelong thyroid hormone replacement.

CI:

- Pregnant women → but it is NOT teratogenic if pregnancy occurs after I^{131} therapy.
- Young children
- Ptns with thyroid cancer
- Ptns with moderate to severe Graves-related eye disease
- Ptns with heart disease (unless controlled)

Treatment of Severe hyperthyroidism (Thyroid storm)

An acute, life-threatening complication of hyperthyroidism.

1. **Inhibition of thyroid hormone synthesis:**
   - **PTU** 800 mg initially → followed by 200 - 300 mg 4 times daily.
   - **PTU is preferred over methimazole** → has the added benefit of blocking peripheral conversion of T 4 to T 3
2. **Inhibition of stored thyroid hormone release:**
   - **KI** → important to **administer PTU/methimazole 1 hr before the iodide** → to prevent iodide incorporation in the synthesis of additional thyroid hormone.
3. **IV Corticosteroids** → to inhibit peripheral conversion of T4 to T3
4. **Suppression of CV effects of thyroid hormone:**
   - Oral/IV **propranolol**, cardio selective; metoprolol, diltiazem
5. **Fluid replacement**
6. Correct underlying precipitating event.
7. Treatment of **hyperthermia** with cooling blankets or acetaminophen

Hypothyroidism/Myxedema

A clinical syndrome caused by deficiency of thyroid hormones.

Adult-onset hypothyroidism is mostly due to auto-immune disease.

Iatrogenic causes of hypothyroidism:

- I^{131} therapy
- Thyroidectomy
- Iodine deficiency/excess
- Lithium
- Amiodarone

Treatment of hypothyroidism (Replacement therapy):

Thyroid hormone preparations → ***levothyroxine (T4), liothyronine (T3)***

MOA→

- T4 → the major circulating form of thyroid hormone → in peripheral tissues → deiodinase (5'DI) enzyme convert T4 to T3 → the more biologically active form of thyroid hormone.
- T3 → **bind to nuclear receptors, thyroid hormone receptors (TRs)** → **control of transcription of genes** involved in many metabolic processes → maintain normal growth & development.

Levothyroxine (T4) → Synthetic T4 → drug of choice for thyroid hormone replacement

- Relative potency → 1
- **t1/2 → 8 days**
- **Once daily** administration

- Coffee, & dietary fiber → ↓ absorption of levothyroxine → recommended to be taken on empty stomach.
- Levothyroxine → often starts with lower dose, esp. in old ptns & those with long-standing/severe hypothyroidism → then gradually increase dose → to prevent excessive stress on the CVS.
- Response to levothyroxine therapy → monitored after 6 - 8 weeks → clinical improvements & ↓ serum TSH levels.

Liothyronine (T3) → Synthetic T3

- Relative potency → 4
- **t1/2 → 1 day**
- **1-3 times** daily

Treatment of Myxedema coma:

Severe hypothyroidism → metabolic decompensation & mental status change

Carries ***a high mortality rate*** despite treatment.

1. High dose (500 - 800 µg ***IV***) ***levothyroxine*** → loading dose → followed by 100 µg/day of levothyroxine.
2. ***Hydrocortisone*** (100 mg ***IV*** three times daily)
3. ***IV fluids.***
4. Correct underlying precipitating event.
5. Supportive →

- ***Respiratory*** assistance
- Treatment of ***hypothermia*** with warming blankets

Pharmacotherapy of DM

Definition of DM: → a group of disorders that develop due to either

- Insulin deficiency → T1DM
- Insulin resistance → inadequate actions of insulin in stimulating the uptake of glucose by peripheral tissues → T2DM

Leading to → hyperglycemia + disturbances in metabolism of CHO, fat, and protein.

Types of DM

	Type 1 (IDDM)	Type 2 (NIDDM)
Pathophysiology:	Autoimmune condition against the pancreatic beta cells. The damaged pancreas doesn't make insulin.	The pancreas usually produces some insulin. But either the amount is not sufficient, or the body's cells are resistant to it.
Onset (age):	< 30 years	>30 years (adult-onset)
Body built:	Usually undernourished	Usually obese
Insulin therapy:	Essentially required.	Required in 20% of patients
Oral drugs:	Not required.	Essentially required.

Gestational DM: appears during pregnancy and disappears after labor.

Secondary DM: 2ry to drugs, infections, endocrine diseases, etc.

Diagnosis of DM

Clinical symptoms

1-Polyuria, polydipsia, polyphagia and loss of weight.

2-Complications of DM e.g. recurrent infections, angiopathy, retinopathy, nephropathy, DKA, etc.

Laboratory investigations:

- Fasting blood glucose > 126 mg/dL
- 2-hour post-prandial glucose level > 200 mg/dL
- Random blood glucose > 200 mg/dL
- Hemoglobin A1c (HbA1c) level >6.5%

HbA1c → the percentage of hemoglobin in circulating erythrocytes that is glycosylated → an index of the average blood glucose level over the preceding 2 to 3 months.

Diagnostic criteria for type I Diabetes

The same +

- Usually characterized by insulin deficiency and dependency
- Document levels of insulin and C-peptide
- Test for autoantibodies (Insulin, Glutamic acid decarboxylase, Pancreatic islet cells)
- A1C is not recommended for diagnosing type 1diabetes

Management of T1DM

- **Type 1 diabetes management is highly individualized.**

1-Carbohydrate counting.

2-Insulin: Intensive treatment with a combination of multiple mealtime bolus and basal injections or continuous insulin infusion through an insulin pump or two or three premixed insulin injections per day may be used.

3-Blood sugar monitoring for Type 1 diabetes management: Closely throughout the day by Blood glucose meter or Continuous glucose monitoring (CGM): The sensor continuously records blood glucose levels

- **Improved glycemic control in patients with T1DM**

1-The target (HbA1c) for all children with T1DM, is recommended to be 7 %.

2-↓ long-term microvascular & macro vascular complications

- **Adjunctive therapies for patients with type 1 diabetes**

Under investigation but are not currently recommended SGLT2, Pramlintide , metform, long-term benefits are unclear.

- **Pancreas and islet cell transplantation**

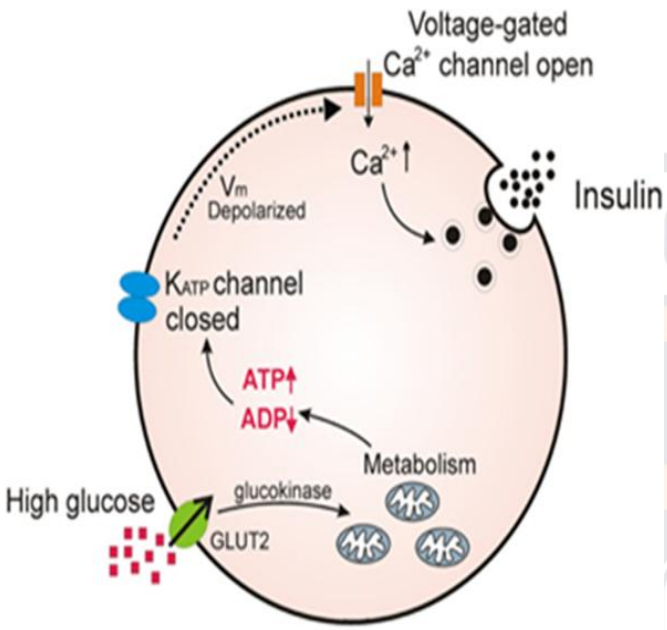
Effective in restoring insulin production and normalizing glucose levels, requires lifelong immunosuppressive therapy. Therefore, it is currently recommended only for patients who also require renal transplantation.

Insulin

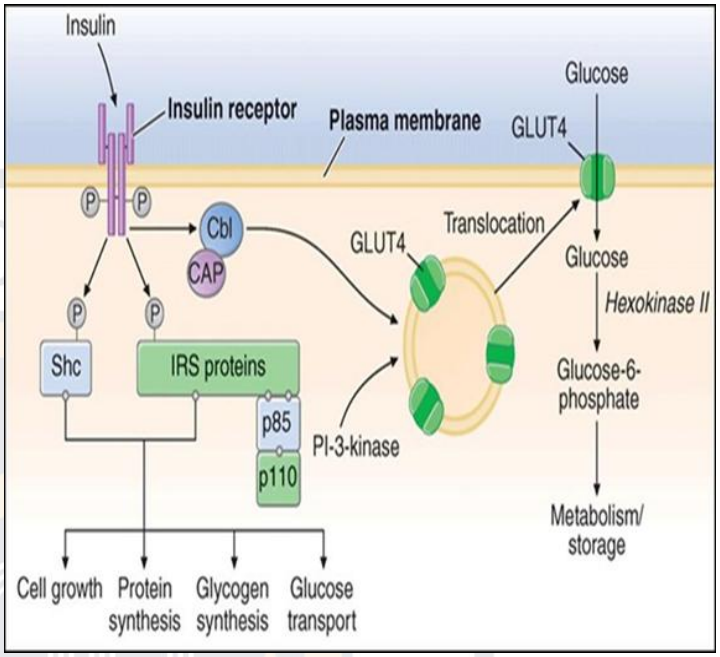
Mechanism of action

- When blood glucose ↑ → more glucose enters pancreatic β cell via GLUT2 → glycolysis → ↑ the ATP/ADP ratio → inhibition of the ATP-sensitive K+ channel (KATP) → membrane depolarization → activation of voltage-gated Ca++ channels → ↑ intracellular Ca++ → insulin secretion.
- Released insulin rapidly reaches liver, muscles, and adipose tissue → binds to and activates insulin receptor (a tyrosine kinase receptor) →

Promote translocation of glucose transporters (GLUT4) from intracellular vesicles to the plasma membrane → ↑ glucose uptake into the cell.



Insulin secretion



Insulin receptor

Pharmacokinetics of insulin

1-Insulin administration

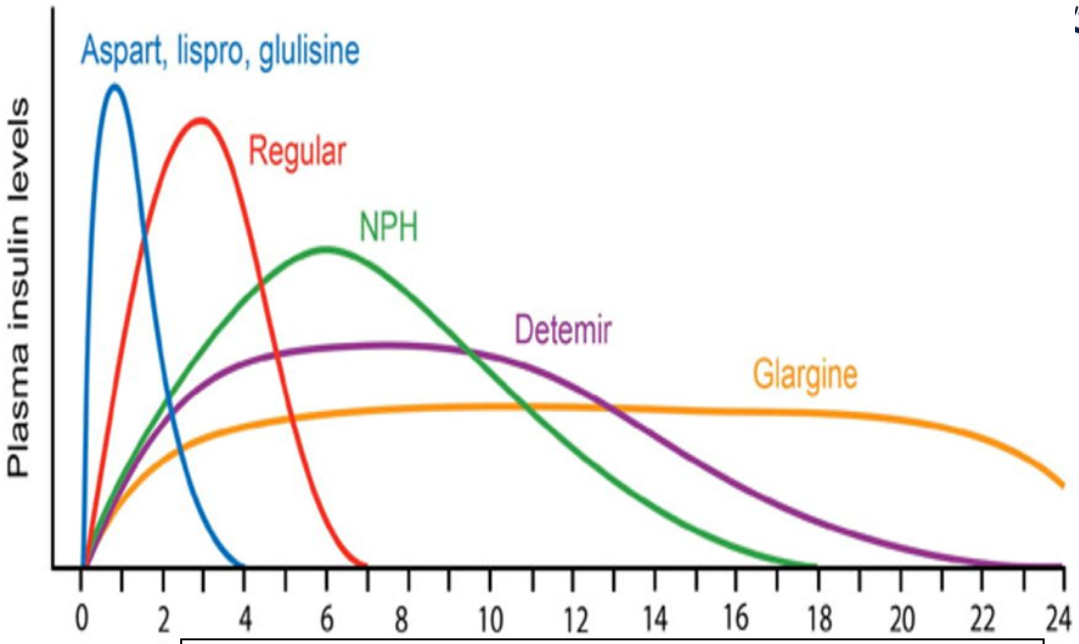
Insulin can be administrated in the following ways:

- Sc. injected with a standard U-100 syringe or insulin pens, the standard insulin concentration is 100 units/mL (U-100)
- IV → emergency treatment of diabetic ketoacidosis → (regular insulin only)
- Pump: Insulin SC infusion pumps are devices that deliver insulin continuously and on demand. They mimic the pancreas, 64% of persons with type 1 DM in USA use an insulin pump.
- Rapid-acting inhaled insulin: This type of insulin (Afrezza) is inhaled through mouth quicker than other types of insulin

2-Insulin preparations

- With different pharmacokinetics to meet different physiological functions of insulin →
- Maintenance of constant low plasma glucose levels during fasting
- Lowering blood glucose peaks after meals.

Insulin type	**Onset**	**Preprandial injection timing**	**Peak**	**Duration**
Rapid-acting • Lispro • Aspart • Glulisine	10-15 min	At start of meal	1-2 h	3-5 h
Short-acting Regular	30 min	30 min before meal	2-4 h	6-8 h
Intermediate-acting NPH	1 h	30 min before meal	6 h	Up to 18 h
Long-acting • Glargine • Detemir • Degludec	2 h	Once daily	Peakless	Up to 24 h



Pharmacokinetics of different insulin preparations

Premixed insulin preparations (biphasic)

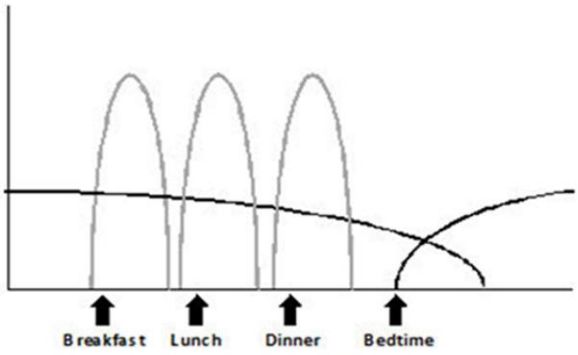
- A premixed preparations of intermediate-acting insulin (NPH) + short- or rapid-acting insulin, are available as vials for injection with syringes or as insulin pens.
- Faster onset & longer duration of action
- Greater ease of use → but are less likely to achieve good glycemic control.
- NPH/regular 70/30, NPH/regular 50/50, NP/lispro 75/25, NP/lispro 50/50, NP/aspart 70/30

3-Insulin regimens

- Insulin regimens for DM, need to provide 'peaks' of insulin to deal with the glucose absorbed at mealtimes, and lower 'basal' levels in between.
- A 'basal–bolus' regimen
  Daily long-acting insulin injection, and rapid-acting insulin taken with breakfast, lunch, and evening meals. The advantage is flexibility.
- A 'twice-daily' regimen

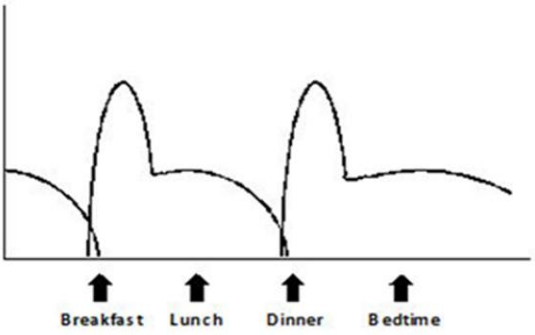
TWO daily injections of a premixed preparation NPH/regular (or NPH/lispro) → ⅔ of the total daily dose is given before breakfast and ⅓ before dinner

Figure 1: Basal-Bolus Regime



Plasma insulin concentrations over time with a basal bolus insulin regime

Figure 2: Premixed twice daily regime



Plasma insulin concentrations over time with a twice daily insulin mix regime

4-Insulin requirement

- A total daily dose of 0.3 to 0.5 units/kg is generally enough (max first dose of 10 units)
- Current Guidelines for Insulin Initiation and titration type II DM (Tolerate) ADA recommends initiation of basal insulin at 10 units/day or 0.1–0.2 units/kg/day, adjusted by 10–15% or 2–4 units once or twice weekly to reach a target FPG in patients

Insulin indications

1-Absolutely indicated in all cases **of T1DM**

2-**T2DM patients** if →

- Insulin is essential for treatment of T2DM from the start if: HbA1c 10%, whose blood glucose is >300 mg/dL, or who are symptomatic of hyperglycemia
- Not controlled on antidiabetic drugs, A1C remains uncontrolled after >3 months of triple combination therapy, insulin is considered alone or in combination
- In pregnancy

- In complications like diabetic ketoacidosis → regular insulin i.v. is preferred
- Stressful conditions like infections and surgery etc.

3- **Treatment of acute hyperkalemia**

Adverse effects of insulin

1-Hypoglycemia: The most serious complication

2-Hypersensitivity reactions (rare).

3-General weight gain

4-Insulin resistance

5-Hypokalemia: Insulin causes shift of K+ from extra- to intracellular fluid.

6-Local adverse effects:

- Allergy: at the site of injection

Treatment: Change the type of insulin &Local corticosteroids.

- Lipodystrophy: (atrophy or hypertrophy) of s.c. tissue after repeated injections.

Treatment: rotating the injection site.

- Local infection.

Hypoglycemia

- The most serious complication
- **Causes:**

  1-Large dose of insulin or sulfonylurea.

  2- Missed meal while taking insulin or sulfonylureas.

  3-Vigorous muscular exercise without dietary adjustment.

  N.B Renal impairment, insulin clearance is reduced, so there is an increased risk of hypoglycemia.

- **Manifestations:**

  1-Sympathetic over-activity: tremors, cold sweating, mydriasis, tachycardia, etc.

  2-Severe hypoglycemia can cause unconsciousness, convulsions, brain damage, and death.

- **Management**

  1-If the patient is conscious → give oral sugar solution.

  2-With impaired consciousness swallowing is unsafe given 1 mg glucagon by intramuscular injection or 20 ml dextrose 50% bolus then10% dextrose IV 100ml per hour

Treatment of T2DM

- Improved glycemic control in patients with T2DM ↓ long-term microvascular complications
- Therapeutic lifestyle modification is essential
- Treated mainly with anti-diabetic drugs
- Starting with one or two antidiabetic drugs (acc. to the degree of hyperglycemia) → there is a progressive loss of beta-cell function in T2DM over years → need for adding a 3rd antidiabetic drug and → ultimately, use of insulin
- For younger T2DM patients → a target goal for HbA1c in T1DM is 7.0%
- For older T2DM patients with complicating medical conditions → HbA1c 8% may be an acceptable and safer target

Therapeutic Lifestyle Changes

1-**Weight loss** (overweight &obese patients) → Reduce by 5% to 10%

2-**Physical activity** → 150 min/week of moderate-intensity exercise (eg, brisk walking) plus flexibility and strength training

3-Diet

Carbohydrate →Specify healthful carbohydrates (fresh fruits and vegetables, whole grains) 7-10 servings per day, preferentially lower-glycemic index foods: multigrain bread, apple, brown rice.

Fat → Specify healthful fats (nuts, avocado, fish) Limit saturated fats (butter, fatty red meats, plant oils, fast foods)

Protein →Consume protein in foods with low saturated fats (fish, egg whites, beans) Avoid processed meats

Antidiabetic drugs

1-Insulin sensitizers

- Biguanides → metformin
- Thiazolidinediones → pioglitazone

2-Drugs ↑ urinary glucose excretion

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors → gliflozins

3-Incrtetin-based therapy

- Glucagon-like peptide-1 analogs (GLP-1) (tides)
- DPP- IV (dipeptidyl peptidase-4) Inhibitors (Gliptins)

5-Insulin secretagogues

Sulfonylureas &Meglitinides

6-Drugs ↓ intestinal glucose absorption

α-glucosidase inhibitors → acarbose

Insulin sensitizers

A-Metformin (a biguanide)

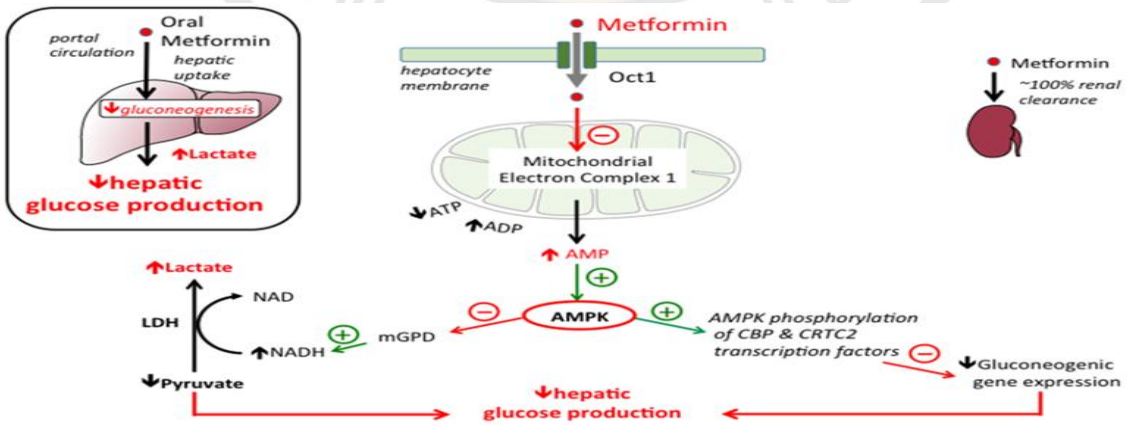
Mechanism of action

1-1ry & most imp. effects → in the liver → inhibition of gluconeogenesis → ↓ hepatic glucose output

- Maybe due to inhibition of the mitochondrial electron complex 1 → activation of 5′adeno-sine monophosphate-activated kinase (AMPK) → ↓ transcription of genes for gluconeogenesis

2-↑ Insulin sensitivity & ↑ glucose uptake in skeletal muscle and adipose tissue

3-↓ Glucose absorption from the intestines



Mechanism of action of metformin

- Does not stimulate insulin secretion & does not cause hypoglycaemia.
- Desirable metabolic changes (weight loss),
- Increasing body weight increases IR, worsening type 2 DM, insulin and insulin secretagogus (e.g. sulphonylureas), cause weight gain, with long-term adverse effects.
- Metformin cause weight loss , ↓risk of CVD, the first-choice treatment unless contraindicated.

Uses of metformin

1-1st-line drug for ttt of T2DM → esp. for obese with insulin resistance (alone or in combination)

2-To enhance weight loss in obese patients.

3-Treatment of polycystic ovary syndrome (POS)

Prescription of metformin

- Start at a low dose and increasing gradually with or after food to minimize transient GI upset
- A common regimen is 500 mg orally once daily with breakfast, increasing the dose by 500 mg weekly. The usual maximum dose is 1 g twice daily with meals.
- A modified-release preparation may be tried if GI adverse effects are problematic.

Adverse effects of metformin

1-GIT SEs →

- The most common
- Diarrhea (30%), nausea, vomiting and flatulence.
- Usually subsides over time.

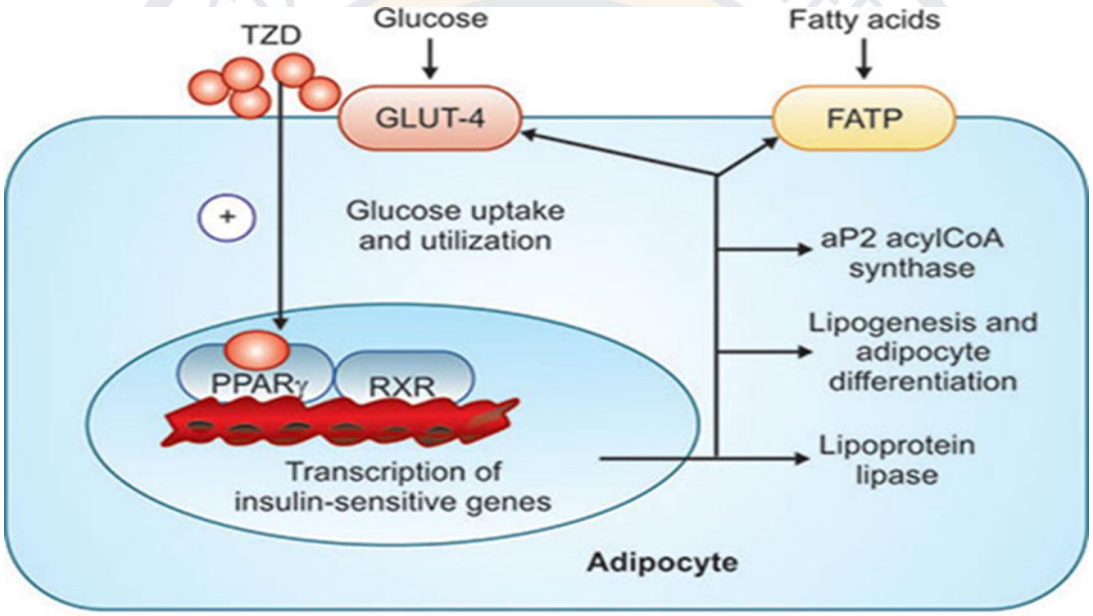
2-Lactic acidosis →

- Very rare (only 3 cases per 100,000)
- Due to interference with hepatic mitochondrial glucose oxidation
- CI in patient with renal or hepatic disease, or alcoholics → higher risk of lactic acidosis

B-Thiazolidinediones (Pioglitazone)

Mechanism of action

- Agonists at the peroxisome proliferator–activated receptor-γ (PPAR-γ) → ↑ transcription of insulin-responsive genes → ↑ peripheral insulin sensitivity (60%) in patient with T2DM.
- ↑ Number of GLUT4 glucose transporters in cell membranes of muscle and adipose tissue → ↑ peripheral uptake of glucose



Mechanism of action of thiazolidinedione

Adverse effects

1-Cardiovascular SEs → ↑ plasma volume, edema and ↑ risk of developing heart failure → not used as 1st-line therapy in T2DM & CI in patient with/at risk of heart failure.

2- Increased body weight

3-Risk of bladder cancer → slight ↑ → pioglitazone

4-Osteoporosis & fractures → as it ↓ bone mineral density

Drugs that ↓ glucose reabsorption

Sodium–glucose co-transporter 2 inhibitor

- Canagliflozin, dapagliflozin and empagliflozin.
- The newest oral drugs for T2DM

Indication:

Type 2 diabetes, in combination with other antidiabetic drugs (e.g. metformin, insulin) an option for monotherapy if metformin is not tolerated.

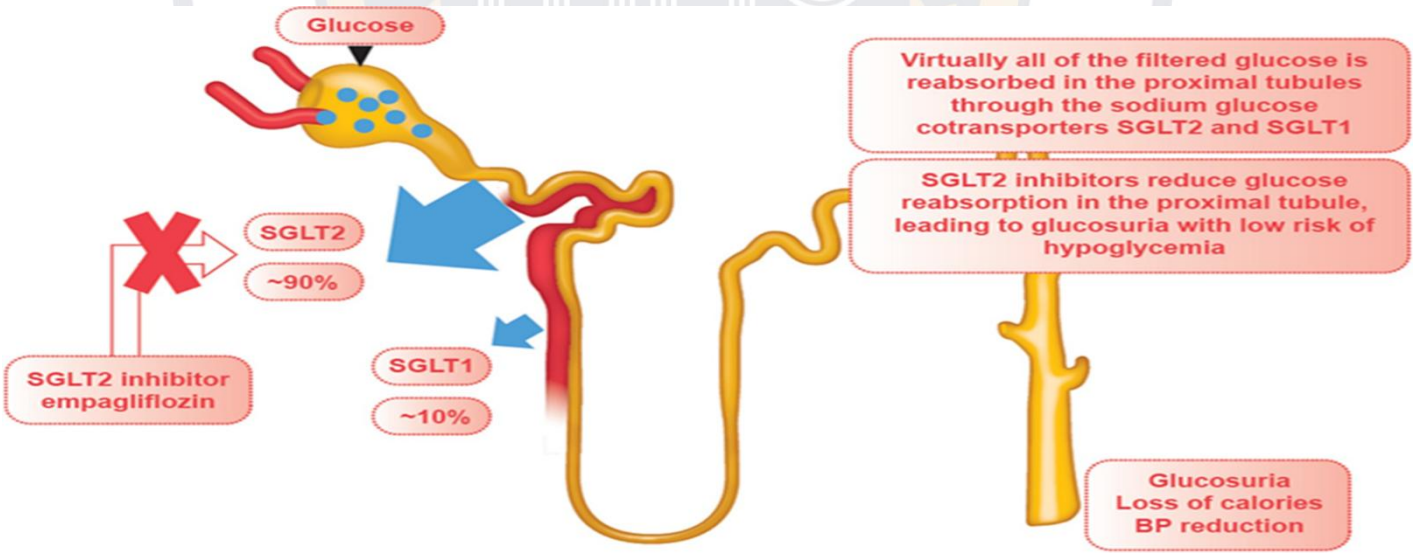
NB. SGLT-2 → responsible for reabsorption of 90% of filtered glucose in PCT

Mechanism of action

1-SGLT2 inhibitors → selectively inhibit SGLT2 → ↓ renal glucose reabsorption → ↑ urinary glucose excretion → ↓ blood glucose levels

2-High glucose in renal tubules → osmotic diuresis → ↑ urine volume → ↓ blood pressure

3-Loss of calories in urine → ↓ weight



Mechanism of action of SGLT2 inhibitors

Advantages of SGLT2I

1-Reno- protective effect: Increased sodium delivery to distal tubule triggers tubule-glomerular feedback mechanisms that reduce intra-glomerular pressure.

2-Favorable effects on renal and cardiovascular outcomes in type 2 DM heart failure and CKD.

3-The effect of SGLT2 inhibitors diminishes at lower serum glucose concentrations → low risk of hypoglycemia

Adverse effects of SGLT2 inhibitors

1-Osmotic diuresis causing thirst and increase the risk of hypovolemia and electrolyte disturbance with intercurrent illness.

2-↑ incidence of UTIs and genital yeast infections → as they ↑ urinary glucose levels & facilitate microbial growth.

NB. Based on the fact that → efficacy of SGLT-2 inhibitors is dependent on renal glomerular filtration of glucose → SGLT-2 inhibitors are CI with glomerular filtration rates < 50 mL/min.

Incretin-based therapy

- The incretins (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)) are released by the intestine throughout the day, but particularly in response to food.
- Act on specific Rs pancreatic β cells → ↑ insulin secretion (glucose-dependant insulin secretion)
- They promote insulin secretion and suppress glucagon release, lowering blood glucose.
- Incretins are rapidly inactivated by hydrolysis by the enzyme DPP-4.

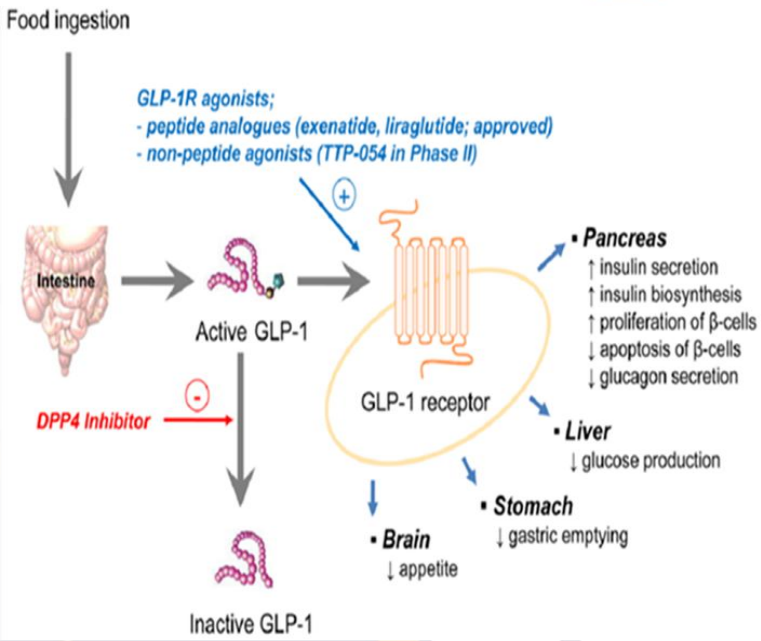
Other effects of incretins:

1-↑ proliferation of β cells.

2-↓ glucagon secretion

3-GLP-1 →

- Delays gastric emptying
- ↓ appetite
- ↓ blood pressure
- ↑ lipolysis in adipose tissue



A-Glucagon-Like Peptide 1 Agonists (Incretin Mimetics)

(-Tides: Liraglutide, exenatide)

Indications:

1-In type 2 DM combination with metformin (or other antihyperglycaemic) or Monotherapy if metformin is contraindicated or not tolerated.

2-To enhance weight loss in obese patients.

- Administered SC , once or twice daily
- Newer GLP-1 analogues → Dulaglutide → linked to Ig or albumin → very slowly eliminated → half-life of a week → once weekly

Mechanism of action:

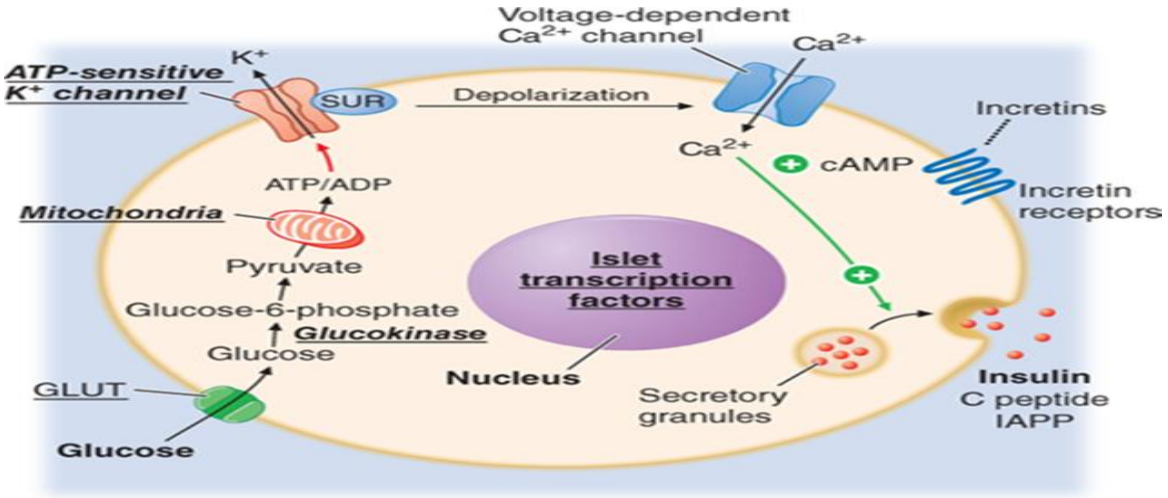
1- Synthetic analogues of human GLP-1 + resistant to degradation by DPP-IV → prolonged duration of action

2-GLP-1 analogues → bind to GLP-1 receptors on beta cell → ↑ intracellular cAMP →

- cAMP-mediated activation of calcium channel → glucose-dependent insulin release (low risk of hypoglycaemia)
- ↓ Glucagon secretion

3-Delays gastric emptying

4-↓ appetite, promoting satiety,weight loss and significant decrease in cardiovascular risk



Mechanism of action of GLP 1 analouge

Side effects: (They are expensive)

1- GI side effects nausea, vomiting, diarrhea → ↓ over time → start with low dose

2-Pancreatitis slight ↑ → require further investigations

3-Thyroid C-cell tumors → only in rodents

4- Skin reactions at injection sites.

B-Dipeptidylpeptidase-4 inhibitors

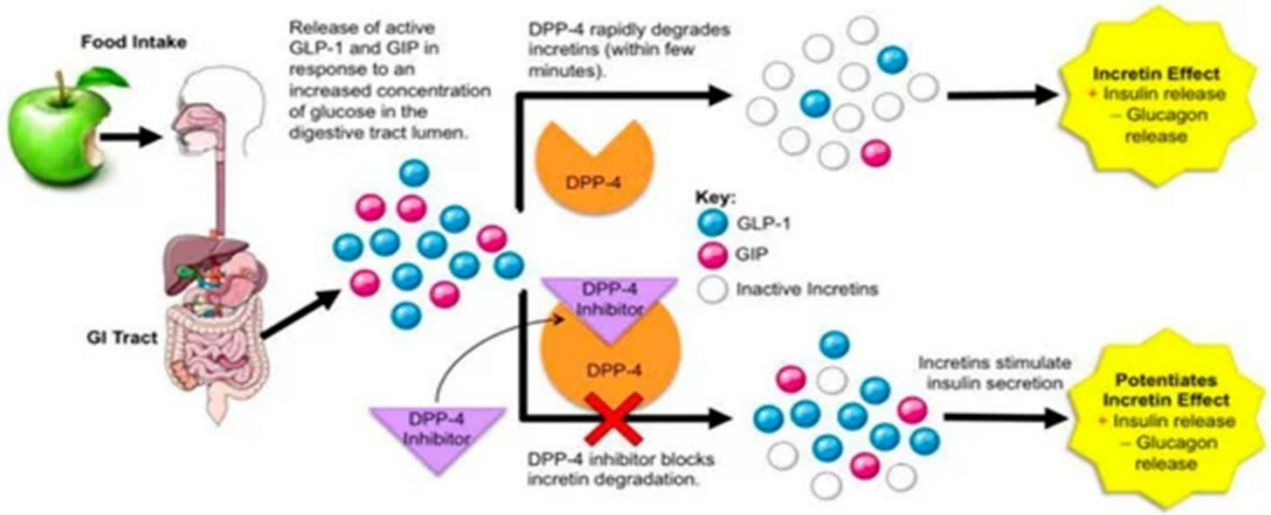
Sitagliptin, linagliptin, alogliptin

Indications:

In type 2 DM combination with metformin (or other antihyperglycaemic) Monotherapy if metformin is contraindicated or not tolerated.

Mechanisms of action:

- Competitive inhibitors of DPP-IV (that inactivates incretins) → 2x to 3x ↑ in incretin levels → glucose-dependant insulin release ↑
- The incretins actions are glucose dependent, occurring when blood glucose is elevated, DON'T stimulate insulin secretion at normal blood glucose level, Less likely to cause hypoglycaemia



Mechanism of action of DPP4 inhibitors

Adverse effects:

1-GI upset, headache.

2-Small risk of acute pancreatitis (0.1%–1)

Insulin secretagogus

A-Sulphonylureas

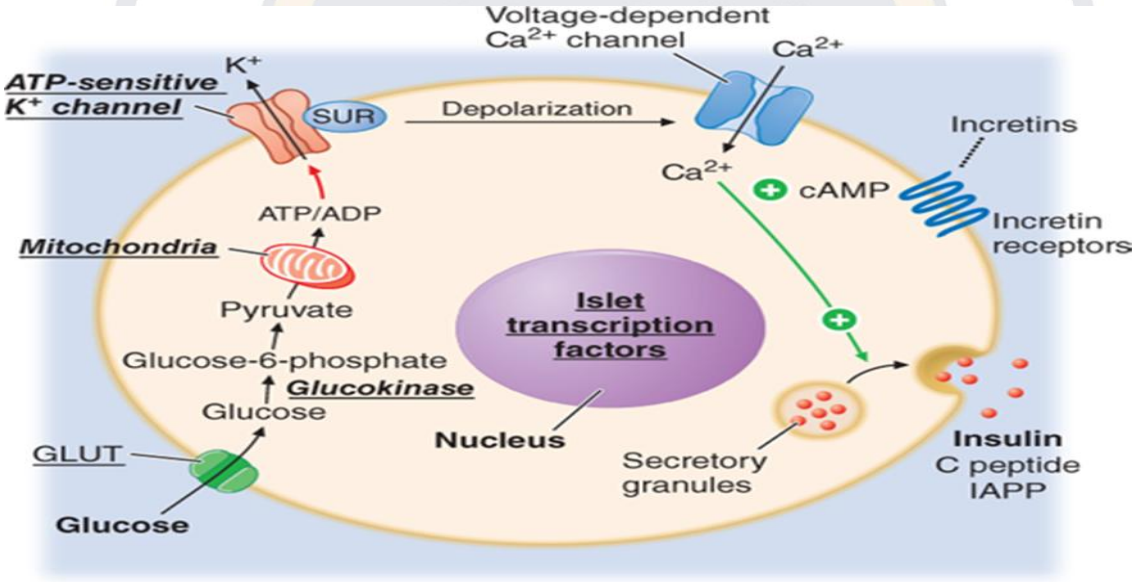
Glyburide, glipizide and glimepiride

Indications:

- Type 2 DM, combination therapy with metformin (and/or other antihyperglycaemic agents) or as monotherapy if metformin is contraindicated.

Mechanism of action:

Bind to SU receptors on the KATP channels → channel closure → membrane depolarization & Ca++ entry → ↑ insulin release.



Mechanism of action of sulphonylurea

Adverse effects:

1-Hypoglycemia →The most common

Result from overdose, skipped meals, inadequate ingestion of carbohydrate, renal or hepatic disease.

2-Weight gain →Common→ released insulin → ↑ lipogenesis

3-Skin rashes

4-Hematologic reactions → leukopenia, thrombocytopenia, and hemolytic anemia.

5-GIT disturbances → nausea, vomiting, and cholestasis.

B-Meglitinides (Repaglinide)

The same as sulphonylurea but the differences are

1-Rapid onset and short duration of action→ control postprandial hyperglycemia→ taken just before each meal

2-Less hypoglycemia

3-Less weight gain

4-They don't contain sulfur, so they can be used in patients allergic to sulfonylureas.

Drugs that ↓ glucose absorption

α-glucosidase inhibitors (Acarbose)

Mechanism of action:

Competitive inhibitor of α- glucosidase enzyme → an intestinal enzyme that converts oligosaccharides and disaccharides to glucose → ↓ digestion & absorption of dietary starch and disaccharides → ↓ postprandial blood glucose.

Side effects:

1-Flatulence and abdominal bloating → most common → result from delivery of greater amounts of carbohydrate to colon → exert an osmotic attraction for water and are metabolized by bacteria.

2-↓ iron absorption.

Drugs affecting Ca homeostasis &treatment of osteoporosis

Primary hormonal regulators of Ca+2 metabolism

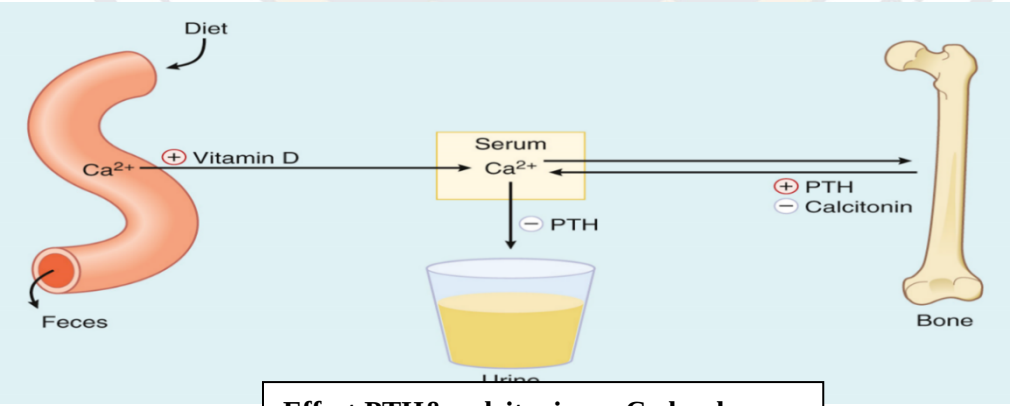
1-Parathormone (PTH)

It is a single chain polypeptide secreted by the parathyroid glands its secretion is controlled by the serum level of Ca+2

Mechanism of action:

Acts on specific receptors on bone and kidney increasing serum Ca and decreasing serum PO4 as follows:

- Bone: increase bone resorption
- Intestine: increase calcium absorption indirectly, by stimulating the renal synthesis of 1α, 25-vitamin D.
- Kidney: increase Ca reabsorption and PO4 excretion.



Effect PTH& calcitonin on Ca level

Therapeutic uses:

1-PTH (84 amino acids)

In hypoparathyroidism as an adjunct to Ca and vit D to reverse hypocalcemia.

2-Teriparatide recombinant PTH (34 amino acids).

- It is an anabolic agent stimulating bone formation in treatment of osteoporosis.
- The skeletal effects of teriparatide depend on the frequency and duration of administration. Low and intermittent subcutaneous administration of teriparatide for up to 2 years preferentially stimulates osteoblastic more than osteoclastic.
- In contrast, long-term exposure to excessive amounts of PTH as occurs in hyperparathyroidism can stimulate bone resorption more than bone formation

2-Vitamin D (fat –soluble vitamin) found in 2 forms:

1-Vitamin D2 (ergocalceferol): plants.

2-Vitamin D3 (cholecalceferol): animals and can be synthesized in human skin by the action of UV rays.

- The two forms must be activated by 2 OH at site 25 (Liver) and 1 (Kidney).

Mechanism of action:

Acts on DNA receptors to synthesis protein for Ca transport:

- Bone: when bone Ca is deficient (rickets) Vit D increase Ca deposition.
- Intestine: increase calcium absorption.
- Kidney: increase reabsorption of Ca and PO4.

Therapeutic uses:

1-Treatment of hypocalcemia.

2-Treatment of osteoporosis.

3-Treatment of rickets (children) and osteomalacia (adults).

3-Calcitonin (CT)

It is a single chain polypeptide secreted by the C-Cells of the thyroid its secretion is controlled by the serum level of Ca+2.

Mechanism of action:

Acts on specific receptors on bone and kidney ↓ serum Ca and PO4:

- Bone: decrease bone resorption
- Intestine: decrease calcium absorption.
- Kidney: decrease reabsorption of Ca and PO4.

Therapeutic uses:

Salmon CT (subcutaneous& intramuscular or intranasal) can be used for treatment of:

1-Hypercalcemia

2-Osteoporosis

Secondary hormonal regulators of Ca2+ metabolism

1-Glucocorticoids

Prolonged administration of glucocorticoids can cause osteoporosis in adults and retarded growth in children due to

- ↑ Renal Ca 2+ excretion
- Antagonize intestinal Vit D stimulated Ca absorption
- ↓ Bone formation (inhibit the osteoblast).

It can be used to treat hypercalcemia associated with lymphoma

2-Estrogen

- Estrogen receptors is present in bone (↓ bone resorption) so it is used in the treatment of postmenopausal osteoporosis
- Prolonged use may cause many side effects (e.g. breast cancer and endometrial carcinoma).

3-Selective estrogen receptor modulators (SERMs) (Raloxifene)

- Mixed agonist-antagonist.
- Stimulate estrogen receptors in bones and block them in the breast and uterus

Non- hormonal regulators of Ca2+ metabolism

1-Bisphosphonates (Alendronate)

- They are analogs of pyrophosphate in which the P-O-P bond is replaced by the stable P-C-P bond.
- Once absorbed, about half of the drug is deposited in bone where bisphosphonates adsorb to hydroxyapatite and become a permanent part of the bone structure, and the remainder is excreted in the urine.
- Bisphosphonates are slowly released from bone during bone remodeling, and the terminal half-life appears to be greater than 10 years.

Mechanism:

They inhibit many osteoclastic cell and induces apoptosis of the osteoclasts.

Uses:

1-Treatment of osteoporosis

2-Treatment of hypercalcemia associated with malignancy and bone lesions associated with bone metastasis.

Side effects:

1-Gastrointestinal distress.

2-High doses can cause renal impairment and osteonecrosis of the jaw.

2-Densumab

Mechanism of action

- Monoclonal antibody
- Denosumab binds to RANKL with high affinity and blocks it from binding to its receptor RANK, thus inhibiting osteoclast maturation and bone resorption.

Uses

1-Skeletal-related events secondary to multiple myeloma or bone metastases.

2-Hypercalcemia of malignancy (don't response well to bisphosphonate)

3-Osteoporosis

3-Cinacalcet

Mechanism of action:

- It works by an agonist action at the calcium-sensing receptor in the parathyroid gland increasing the activation of these calcium-sensing receptors to extracellular calcium.
- This leads to decreased secretion of PTH and lowering of serum calcium levels.

Uses:

1-Treatment of hyperparathyroidism.

2-Treatment of hypercalcemia in patients with parathyroid cancer.

4-Diuretics

- Thiazides can decrease renal Ca2+ excretion through ↑ the effect of PTH in stimulating renal Ca2+ reabsorption
- Loop diuretics (frusemide)→ hypocalcemia (increase renal Ca excretion)

5-Sodium Fluoride

Mechanism:

Fluoride is stored in bone and teeth where it replaces the hydroxyl group in calcium phosphate salts (hydroxyapatite) to form fluorapatite. Fluorapatite deposited on the tooth surface is more resistant to erosion than hydroxyapatite.

Uses:

1-Prevention of dental caries. Fluoride has been added to the drinking water supply in many localities, and it can be applied directly to the tooth surface as a gel.

2-Treatment of osteoporosis??

Treatment of hypercalcemia

Management of acute hypercalcemia:

1-Hydration: 0.9% saline infusion & electrolyte replacement

2-Bisphosphonates

3-Calcitonin

4-Denosumab

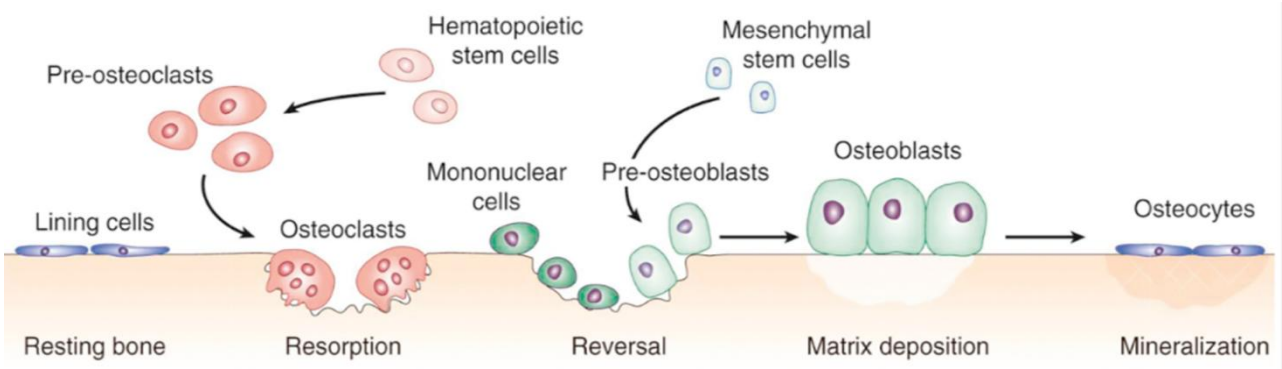
5-Cinacelcet

6-Glucocorticoids: In cases where hypercalcemia is due to lymphoma or granulomatous diseases, oral prednisone (20-40 mg daily)

Treatment of osteoporosis

Definition: it is a condition of low bone mass that results in fractures with minimal trauma.

It occurs in postmenopausal women (due to estrogen lack) and in old age.



Bone metabolism

Prevention and treatment of osteoporosis:

1-Replacement therapy

A-Diet rich in calcium

B-Vitamin D

2-Antiresorptive drugs

A-Bisphosphonates (the first line)

B-Selective Estrogen Receptor Modulators (Raloxifene)

C-Calcitonin

D-Denosumab

3- Anabolic drug

Teriparatide

4-Anabolic antiresorptive

Strontium ranelate

Gonadal hormones & inhibitors

Estrogens

Preparations:

A. Natural estrogens:

- ☒ **Estradiol** (principal estrogen in premenopausal women).
- ☒ **Estrone** (the primary circulating estrogen after menopause).
- ☒ **Estriol**

B. Semisynthetic estrogens: Ethinyl estradiol and mestranol.

C. Synthetic estrogens: diethyl stilbosterol

Pharmacokinetics

- ☒ are readily absorbed through the gastrointestinal tract, skin, and mucous membranes.
- ☒ Bioavailability of estradiol after oral administration is low due to first-pass metabolism.
- ☒ To reduce first-pass metabolism, estradiol may be administered via a transdermal patch, topical formulation (gel or spray), intravaginal preparation (tablet,cream, or ring), or injection.
- ☒ Estradiol and its metabolites subsequently undergo glucuronide and sulfate conjugation and are also subject to enterohepatic recirculation.

Mechanism of action

☒ After dissociation from their binding sites on sex hormone–binding globulin or albumin in the plasma, estrogens(e.g estradiol) diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins.

Physiologic effects

☒ **Normal development of genital tract and breast.**

☒ **Development of ♀ secondary sex characters.**

☒ **Metabolic effects:**

- Increase bone mass and prevent bone resorption.
- Increase blood glucose and TGs.
- Salt and water retention.

☒ **Increase blood coagulation and platelet adhesiveness.**

Therapeutic uses

☒ Contraceptive pills.

☒ Dysfunctional uterine bleeding.

☒ Replacement therapy in ovarian hypofunction.

☒ Postmenopausal symptoms e.g. atrophic vaginitis and osteoporosis.

☒ Cancer prostate.

Adverse effects and contraindications:(see contraceptive pills).

Anti-estrogens

I. Clomiphene citrate (Clomid)

Mechanism of action:

Clomiphene blocks estrogen receptors in hypothalamus and pituitary →↑ FSH and LH → stimulate ovulation.

Uses:

Used to stimulate ovulation in infertile women with normal pituitary function.

Adverse effects:

Ovarian enlargement and hot flushes.

II. Selective estrogen receptor modulators (SERMs):

SERMs are ligands for the estrogen receptor that have agonist activity in one tissue but may have antagonist activity or no activity in another tissue.

Examples: tamoxifen and raloxifene.

A. Tamoxifen

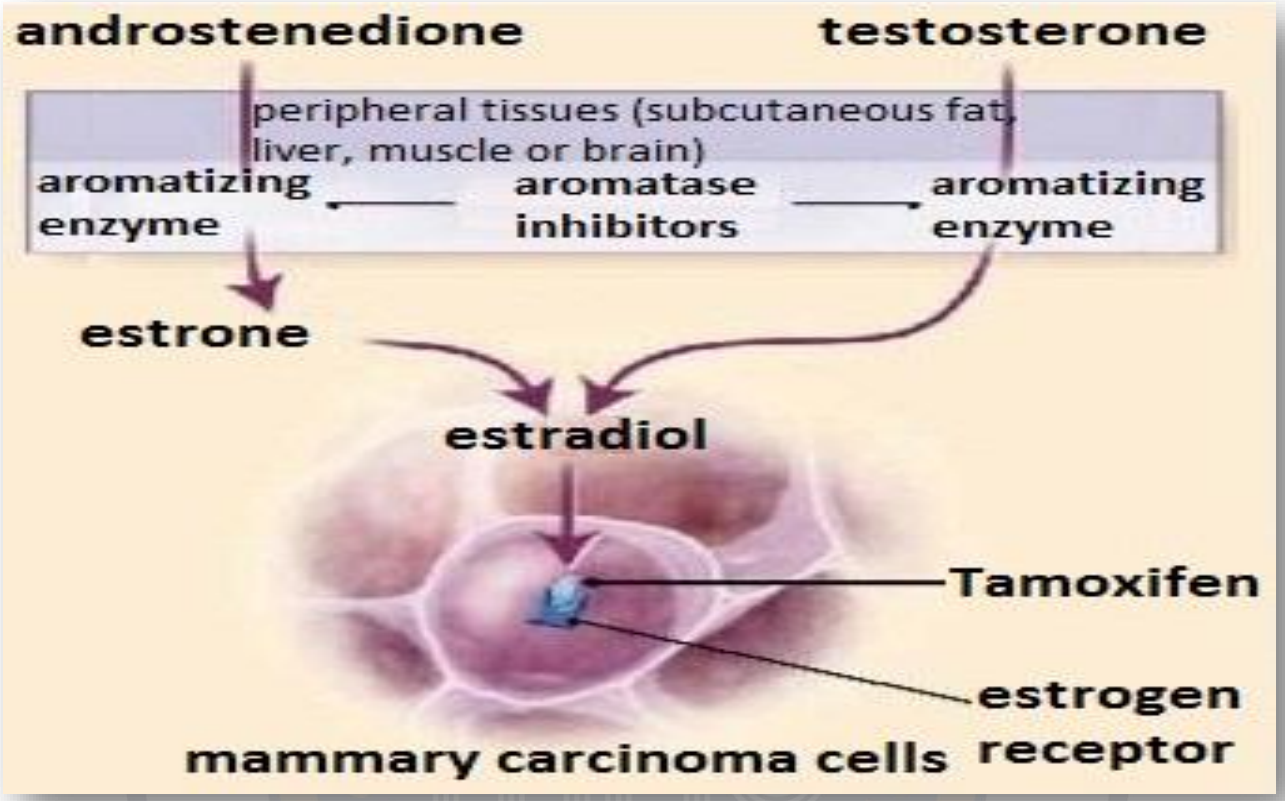
It is an estrogen antagonist in the breast but is an agonist in the uterus and bone.

☒ Uses:

- Used in the treatment of advanced, estrogen receptor positive breast cancer and for primary prevention of breast cancer in women at high risk.

☒ Adverse effects:

- Increases the risk of endometrial cancer.
- Thrombotic complications (e.g deep vein thrombosis and pulmonary embolism).



B. Raloxifene

It is an agonist in bone but has no effect on the uterus.

☒ **Uses:**

- It is used for the treatment and prevention of postmenopausal osteoporosis.

☒ **Adverse effects:**

- Hot flashes
- Thrombotic complications

III. Aromatase inhibitors

- Aromatase is the enzyme that catalyzes the production of estrogens from androgenic precursors within the ovary and peripheral tissues.
- Aromatase inhibitors are a new class of oral estrogen synthesis inhibitors.
- **Examples: Anastrazole , letrozole and Exemestane**

A. Anastrazole and letrozole (Femara):

☒ are nonsteroidal competitive inhibitors of aromatase.

B. Exemestane:

☒ is a steroidal, irreversible aromatase inhibitor.

☒ **Uses:**

- Used for treatment of postmenopausal women with estrogen-receptor positive breast cancer who have received two to three years of tamoxifen.

Progesterone and progestins

Preparations

- ☒ **Natural**: progesterone injection
- ☒ **Synthetic**: medroxy progesterone acetate.

Mechanism of action: Like estrogens

Therapeutic uses

- ☒ Contraceptive pills.
- ☒ Dysfunctional uterine bleeding
- ☒ Dysmenorrhea and endometriosis.
- ☒ Threatened abortion.

Adverse effects

- ☒ Headache
- ☒ Depression
- ☒ Weight gain
- ☒ Changes in libido

Antiprogesterone: Mifepristone

Mechanism of action:

- ☒ It is a competitive blocker of progesterone receptors.

Uses:

- ☒ It is used with misoprostol to induce medical abortion in the first trimester.

Androgens and anabolic steroids

Preparations:

- ☒ **Natural** androgens: androsterone and testosterone
- ☒ **Synthetic** androgens: testosterone propionate.
- ☒ **Anabolic** steroids: nandrolone and stanazol.

Mechanism of action

- ☒ Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell.
- ☒ Testosterone itself is the active ligand in muscle and liver, But in other tissues it must be metabolized to derivatives, such as DHT (dihydrotestosterone). For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, testosterone is converted by 5α-reductase to DHT, which binds to the receptor.

Uses of androgens and anabolic steroids:

1. Males with primary hypogonadism or secondary hypogonadism (androgens)
2. Chronic wasting associated with human immunodeficiency virus or cancer. (anabolic steroids)
3. Illicit use by athletes: to increase muscle bulk and strength. (anabolic steroids)

Adverse effects

1. Reduction in spermatogenesis after stopping.
2. Virilizing effects in females.
3. Precocious puberty and premature closure of epiphysis in children.
4. Cholestatic jaundice.

Contraindications

1. Prostatic tumors (benign and malignant).
2. Liver diseases
3. Children.

Antiandrogens

A. 5 α-reductase inhibitors:

- **Example:** Finasteride
- It inhibits 5 α-reductase enzyme responsible for conversion of testosterone into the active form dihydrotestosterone (DHT).
- **Uses:**

☒ Treatment of benign prostatic hyperplasia.

☒ Treatment of male baldness.

☒ Treatment of hirsutism in females.

B. Testosterone receptor blockers

1. **Cyproterone acetate:**

☒ is a competitive blocker of testosterone receptors.

☒ Used in male hypersexuality, and hirsutism in females.

2. **Flutamide:**

☒ is a competitive blocker of testosterone receptors.

☒ Used in cancer prostate.

3. **Others: Spironolactone**

☒ is a competitive blocker of both aldosterone and testosterone receptors. Used in hirsutism in females

Drugs In Pregnancy

Taking medications during pregnancy is necessary:

• For fetal health and development e.g., Vitamins and nutritional supplements

• To treat mother's health problem e.g., hypertension

✓ All drugs pass across the placenta to some extent, and therefore some exposure will occur

Drug passage of the placental barrier

Factors regulating passage of the drugs to the fetus:

• Drug size: Most drugs with a MW

• Lipid solubility: the lipophilic drugs have more chance to cross placenta

• Binding to the maternal plasma proteins.

There are two major considerations regarding drugs in pregnancy:

- The effects that the drugs have on the pregnancy.
- The effects that the pregnancy has on the drugs.

How does drug affect pregnancy?

Teratogenicity: Defects that could happen to a developing fetus after exposure to a teratogen, which is most commonly a drug.

Types:

• Physical malformations e.g., Cleft lip

• Functional defects e.g., impaired intellectual development

Examples of drugs with teratogenic effect

Thalidomide-induced Phocomelia

Hare lip ---phenytoin

Antiseizure drugs, valproic acid

Mechanism of teratogenicity

❑ Before implantation: (0-14 day):

The effect is all-or-none

❑ Early pregnancy: (3-10 weeks):

It is the most dangerous period because it is a period of organogenesis.

❑ Late pregnancy:

Gross anatomical abnormalities are less liable to occur.

Functional defects rather than anatomical abnormalities.

FDA (Food &drug administration)- Pregnancy categories of drugs

The FDA (American Committee) has established five drug categories (A, B, C, D & X) to indicate the potential of causing birth defects.

Pregnancy category	Definition
A	▪ Drug proved to be safe in animal and human e.g. Folic acid.
B	▪ Animal studies have shown fetal risk, but adequate studies in human have not shown a risk to the fetus. e. g. paracetamol and penicillin
C	▪ Animal studies have shown a risk to the fetus but there are no adequate studies in humans e.g. Antihistamines
D	▪ There is evidence of fetal risk, but benefits are thought to outweigh the risks. e.g. lithium (anti-mania).
X	▪ Studies in animals or humans demonstrate fetal abnormalities. ▪ contra-indicated (should not be used) in pregnancy.e.g. thalidomide.

How does pregnancy affect drugs?

➢Absorption

Drug absorption may decrease in a pregnant woman due to:

• Decreased gastric acidity

• Reduces gastric and small intestine motility.

➢Distribution

• 50% Increase in plasma volume and body water: Water soluble drugs are distributed and "diluted" more than in the non-pregnant state → adjustment of drug dose may be needed

• The capacity of the protein to bind drugs in the maternal system decreases.

➢Metabolism

• Some microsomal enzymes (Cytochrome P450) activity increased→ increase metabolism of certain drugs

• Other enzymes of Cytochrome P450 activity may decreased → decrease metabolism of certain drugs

➢Excretion

• The renal blood flow and GFR increase up to 50% →The kidneys may excrete drugs more rapidly

General advice to decrease the risk of teratogenicity

• Avoid all drugs if possible, including social drugs (e.g., smoking, alcohol, caffeine)

• Avoid drugs in the first trimester

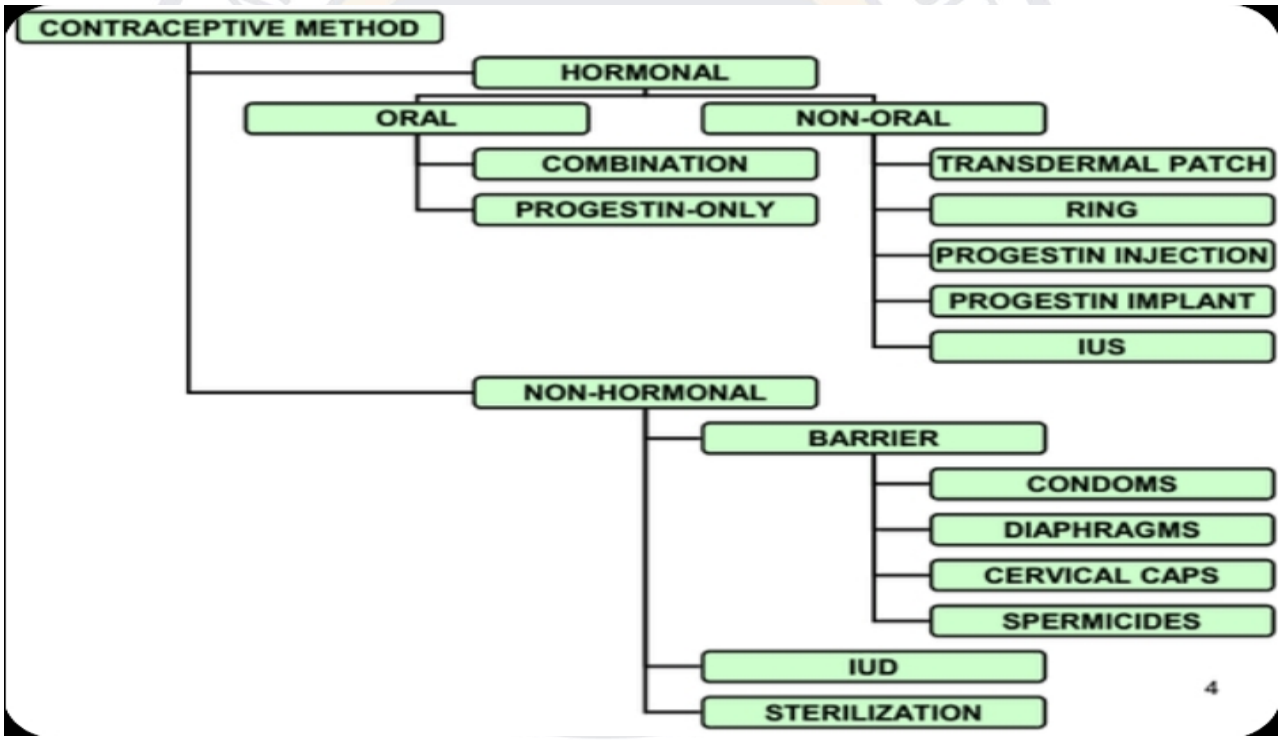
• Choose drugs of proven safety or least toxicity

• Use short courses and the smallest doses.

❖ The risk/benefit ratio must be considered when drugs are used in pregnancy.

Hormonal Contraceptives

- ☒ Contraceptives are drugs, devices, or devices that release drugs that are used to prevent conception, the fertilization of the ovum by the sperm and resulting pregnancy.
- ☒ Thus, contraceptive methods may be hormonal or non-hormonal.
- ☒ They are available in the following forms:



Hormonal contraceptives may be:

- **Oral:**

I. Combined regimen type

II. Single entity perpetrations

- **Non – oral:**

I. Transdermal patch

II. Vaginal ring

III. Injectable progestin

IV. Progestin implants

V. Progestin intrauterine system

ORAL CONTRACEPTIVES

I. Combined regimen type

- ☒ involves the administration of pills containing combination of Estrogen and Progestogen.
- ☒ With most oral contraceptives, active pills are taken for 21 to 24 days, followed by 4 to 7 days of placebo, for a total regimen of 28 days.

- ☒ The combination agents are further divided into monophasic forms (constant dosage of both components during the cycle) and biphasic or triphasic forms (dosage of one or both components is changed once or twice during the cycle).

II. Single entity preparations

A. Progestogen-only pills (POPs):

☒ A POPs (the mini-pill) is taken daily

☒ can be used in patients who are **breast-feeding** (doesn't affect lactation) or when estrogen is contraindicated.

☒ Major problems are a slightly higher failure rate and a much higher incidence irregular bleeding.

B. Emergency pills (postcoital pills or morning-after pills):

☒ is effective if taken within 72 hr of unprotected intercourse and repeated 12 h later.

☒ Nausea and vomiting are common

NON-ORAL CONTRACEPTIVES

I. Transdermal patch

☒ Deliver **ethinyl estradiol** and **progestin**, through the skin.

☒ They are applied weekly for 3 weeks, one patch is applied each week to the abdomen, upper torso, or buttock.

☒ No patch worn during the fourth week to allow withdrawal bleeding.

II. Vaginal ring

☒ Containing **ethinyl estradiol** and **progestin**

☒ Continuous serum hormone levels can be achieved for longer periods of time.

☒ The ring is inserted for 3 weeks and then removed for 1 week to allow withdrawal bleeding.

☒ Vaginal infections, and irritation are common

III. Injectable progestin

☒ **Medroxyprogesterone** im every 3 months.

☒ Effective, safe and suitable for unreliable women.

☒ Menstrual irregularities, weight gain are common.

☒ Infertility may persist for many months after the final dose.

IV. Progestin implants

☒ placed subdermally, usually in the upper arm.

☒ Irregular bleeding and headache are common.

V. Progestin intrauterine system

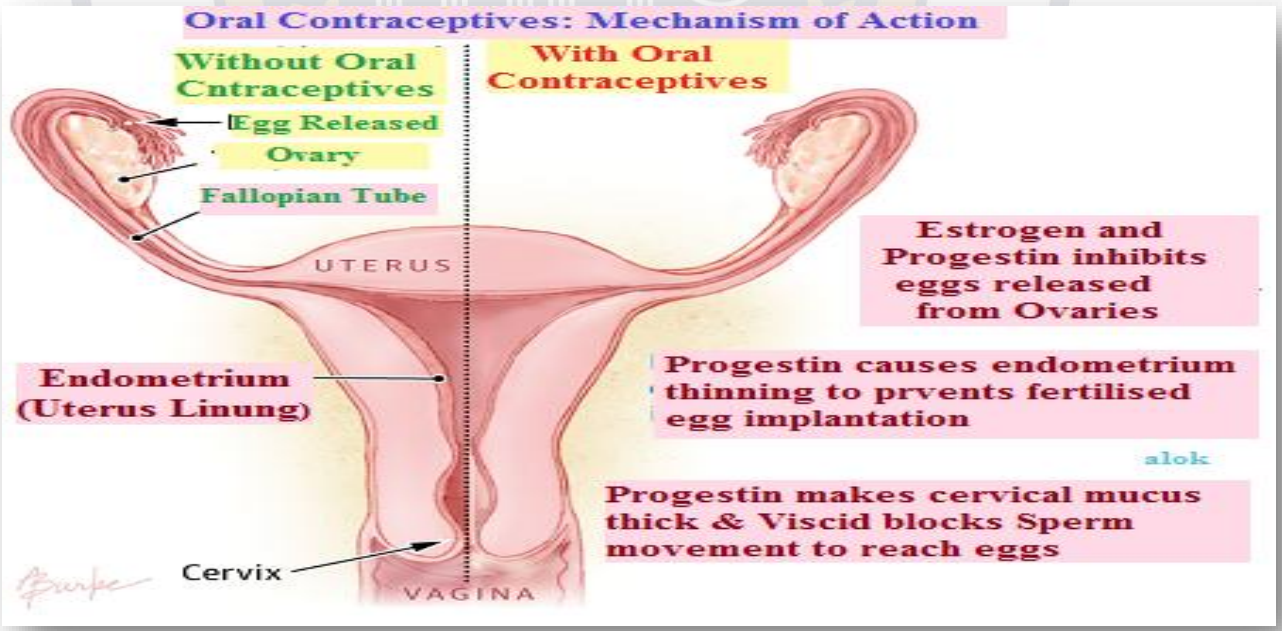
☒ Delivers low, continuous doses of **progestins** locally.

☒ Induces endometrial atrophy and decreases bleeding, which is a significant problem associated with standard copper containing devices.

❖ Progestin implants and intrauterine devices are known as long-acting reversible contraceptives as they are effective for 3 to 5 years and normal menstrual cycles and fertility return rapidly after removal.

Mechanism of action

- ☒ They inhibit ovulation by exerting –ve feedback on LH (progesterone) and FSH (estrogen) secretion.
- ☒ Produce endometrial changes and interferes with coordinated contraction of the cervix, uterus, and fallopian tubes →↓ sperm transport and fertilization.
- ☒ Increase thickness of cervical mucus to inhibit sperm penetration.



Side effects

A. CVS (combined hormonal contraceptive):

☒ the most serious side effects especially in women above 35 years and in women who are smokers:

- Hypertension
- increase risk of myocardial infarction.
- Thrombosis and thromboembolic catastrophes.

B. CNS:

- Migraine headache (combined hormonal contraceptive).
- Ischemic stroke (combined hormonal contraceptive).
- Mood changes and depression.

C. GIT:

- Nausea and vomiting.
- Cholecystitis and gall stones.
- Cholestatic hepatitis and hepatotoxicity.

D. Endocrinal:

- Hyperglycemia and DM.
- Weight gain and edema due to salt and water retention.
- Inhibition of lactation in lactating women (combined hormonal contraceptive).
- Menstrual irregularities: spotting bleeding, breakthrough bleeding, amenorrhea, and dysmenorrhoea.
- Acne, and hirsutism.

E. Cancer (combined hormonal contraceptives):

- increased risk of breast cancer.

❖ **N.B:** By contrast, the combined contraceptives reduce the risk of ovarian cancer and endometrial cancer

Contraindications of combined contraceptives

- Hypertension or ischemic heart disease (IHD).
- History of embolism, thrombosis or cerebral hemorrhage.
- History of cancer breast or estrogen-dependent neoplasm.
- Migraine headache.
- Chronic liver disease and gall stones.
- Diabetes mellitus.
- Obese, smokers, or women over 35 years.
- Depression.

Drug-interactions that cause failure of contraception:

- If taken with enzyme inducers e.g. rifampin, phenytoin, etc.
- If woman taking broad spectrum antibiotics e.g tetracyclines (kill bacteria flora)
- Paraffin oil (laxative) ↓ intestinal absorption of contraceptive pills.

Oxytocics and Tocolytics

Oxytocic

- **Drugs that stimulate the pregnant uterus and are important in obstetrics.**
- **They include:**
  - **Oxytocin**
  - **Ergometrine**
  - **Prostaglandins**
  - **Mifeprostone**

1. Oxytocin:

Oxytocin is a posterior pituitary hormone that induces powerful contractions of uterine muscle and induces milk ejection from the breast (a nasal spray preparation of oxytocin is available to **stimulate milk let-down in nursing mothers**)

Mechanism of action:

- By stimulation of Oxytocin receptors (G protein coupled receptors)
- It acts synergistically with prostaglandins to release Ca^{2+} from intracellular stores in the myometrial cells and promote muscle contraction.

2. Ergometrine:

Mechanism of action:

- It also causes vasoconstriction by α-adrenoceptor stimulation, which further limits hemorrhage.
- It also causes prolonged and forceful contraction of uterine smooth muscles.

N.B– Ergometrine should **not be used to induce labor**. It should be given at the time of placenta delivery (3rd stage of labor) and never before that. If it is given before delivery of the placenta, it causes severe spasm of uterine smooth muscles and retained placenta.

3. Prostaglandins

- Production of PGF and PGE by the cells of the amnion and decidua is increased near term.
- Synthetic PGs E and F are used as oxytocic agents e.g.

1. Gemeprost and Misoprostol [PGE_1 analogues]
2. Dinoprostone [PGE_2]
3. Carboprost [$PGF_2\alpha$]

Mechanism of action:

- Prostaglandins act at PG receptors ⟹ release Ca^{2+} from intracellular stores in the myometrial cells ⟹ promote muscle contraction.
- Prostaglandins ripen and soften the cervix, further aiding the expulsion of uterine contents.
- Prostaglandins also upregulate oxytocin receptors.

N.B. PGs are contraindicated with uterine scar.

Indications of oxytocics

A. Induction of abortion: Gemeprost (intravaginally) or misoprostol (following mifepristone) are used.

B. Induction of labour: Dinoprostone and **Oxytocin** are used

C. Bleeding due to incomplete abortion:

Ergometrine and oxytocin (Syntometrine) given intramuscularly, before surgery.

D. prevention and treatment of postpartum haemorrhage: Oxytocin, ergometrine and carboprost (in those unresponsive to oxytocin and ergometrine) are used.

Side effects of oxytocics

A. Nausea and vomiting, vaginal bleeding, uterine pain.

B. Oxytocin can cause hypotension and tachycardia. Its antidiuretic hormone-like effect on water excretion by the kidney causes water retention and consequent hyponatremia.

C. Ergometrine may cause vasoconstriction with an increase in blood pressure (if vasospasm of the coronary arteries, resulting in angina).

D. Prostaglandins ***(Carboprost)*** may be associated with an increased incidence of uterine rupture during labor in women who have had a previous cesarean section.

Tocolytics

- More than 10% of pregnancies result in preterm birth, defined as delivery before 37 weeks of gestation.
- Preterm birth is associated with significant complications such as neonatal respiratory distress syndrome, pulmonary hypertension, and intracranial hemorrhage.
- Drugs that inhibit labor or slowdown contractions of uterus are called tocolytics. They include:

1. **Calcium Channel Blocker**
2. **Magnesium Sulfate**
3. **Beta agonists**
4. **Oxytocin antagonist**
5. **Indomethacin**

- **N.B. Hydroxyprogesterone caproate** once-weekly injections are approved by the FDA to reduce the risk of preterm delivery in women with a history of at least one spontaneous preterm birth.

1. Calcium Channel Blocker

E. E.g. Nifidipine

F. Mechanism of action:

- They reduce uterine contractions by inhibiting Ca^{2+} influx in uterine muscle cells.
- They reduce neonatal respiratory distress syndrome more than other tocolytics.

2. Magnesium Sulfate

- Mg sulfate reduces uterine contractions by inhibition of Ca^{2+} influx in uterine muscle cells related to its actions as a divalent cation to compete with Ca^{2+} in myometrial cells.
- Used also for prevention and treatment of **seizures "in preeclampsia & eclampsia".**

3. Beta agonists

G. E.g. Terbutaline, Ritodrine

Mechanism of action:-

- β_2 -Adrenoceptor agonists relax the uterus and are given intravenous infusion by obstetricians to inhibit premature labor.
- They can delay delivery by 48 h, a time that can be used to administer glucocorticoid therapy to the mother to mature the lungs of the baby and reduce neonatal respiratory distress.
- Increases cAMP via activation of β_2-adrenoceptors leading to relaxation of uterine smooth muscle

4. Oxytocin Antagonists E.g. - Atosiban

H. Mechanism of action:

- Atosiban is a peptide analogue of oxytocin
- It acts as an oxytocin receptor antagonist, reducing the release of intracellular Ca^{2+}.
- **Atosiban** is given initially by intravenous bolus injection followed by an infusion for not more than 48 h.

5. Indomethacin

- **NSAIDs** such as **indomethacin** block the production of PGs (inhibit both COX-1 and COX-2).
- used to inhibit uterine contractions based on the role of PGs in stimulating contractions.
- It is used to relieve cramps associated with menstruation (dysmenorrhea)

Indications of Tocolytics

1. As a preventative therapy with progesterone in women with prior spontaneous preterm birth.
2. As an acute intervention to suppress established uterine contractions associated with cervical change occurring before 37th week of gestation.

Side Effects of Tocolytics

All available tocolytic agents cause maternal and/or fetal adverse effects.

A. Maternal adverse effects:

- Tachycardia, hypotension, and pulmonary edema (**with beta agonists**).
- Nausea, vomiting and hyperglycemia (**with atosiban**)
- Hypotension and muscle weakness (**with Mg sulfate**)

B. Fetal adverse effects:

- renal dysfunction and premature closure of the ductus arteriosus (**with indomethacin**).

FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

BIOCHEMISTRY

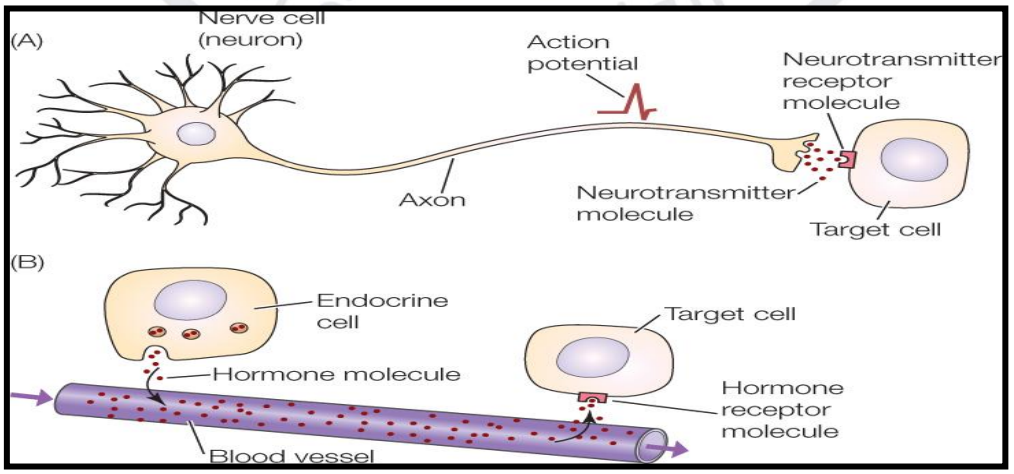
Hormone Action & Signal Transduction

Contents

- **Introduction.**
- **Hormones and its classifications.**
- **Hormone receptors.**
- **Mechanism of hormone action.**

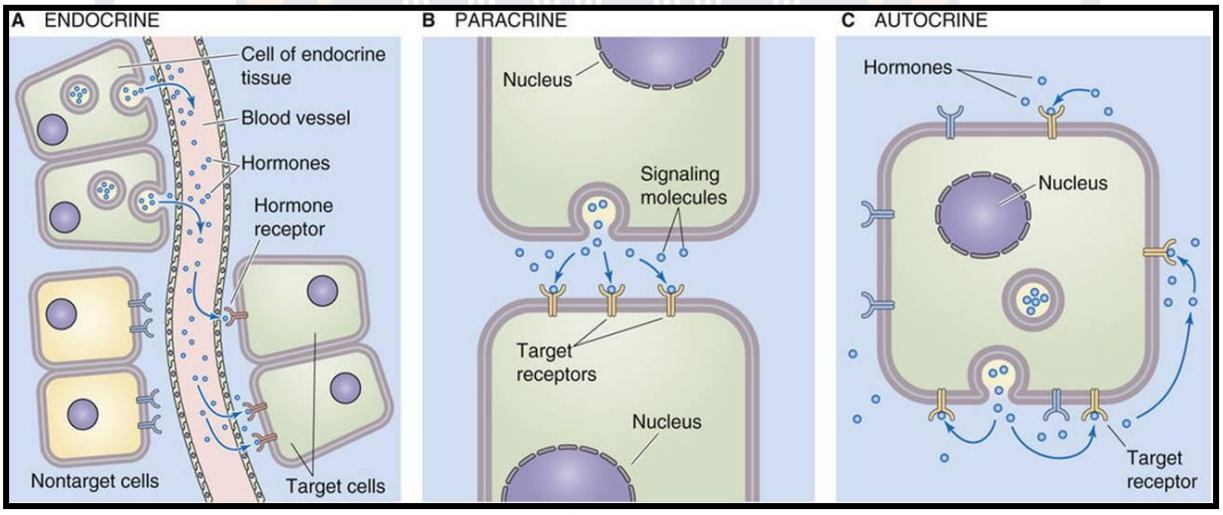
Introduction

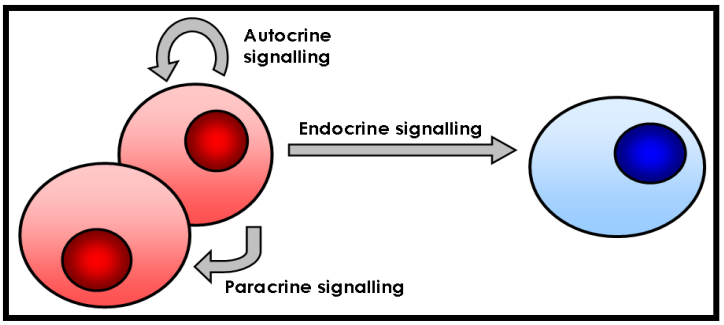
- Survival of multi-cellular organisms depends on their ability to adapt to the constantly changing environment.
- Intercellular communication mechanisms are necessary for this adaptation.
- Nervous system and endocrine system provide this intercellular communication through chemical messengers (neurotransmitters and hormones, respectively).



❖ There are four Different signaling mechanisms:

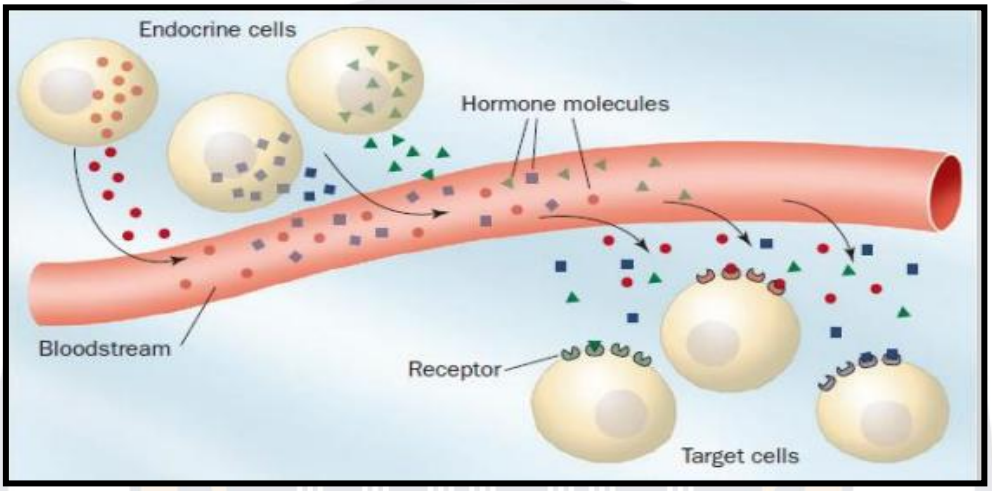
1. Endocrine signaling
2. Paracrine signaling
3. Synaptic signaling
4. Autocrine signaling





Hormones

- They are signaling molecules (chemical messengers) synthesized and secreted from the endocrine glands.
- Hormones are released into the circulation to act on the **target cell**.



- The target cell for the hormone (ligand) is **the cell that has the specific receptors for this hormone**.

↓

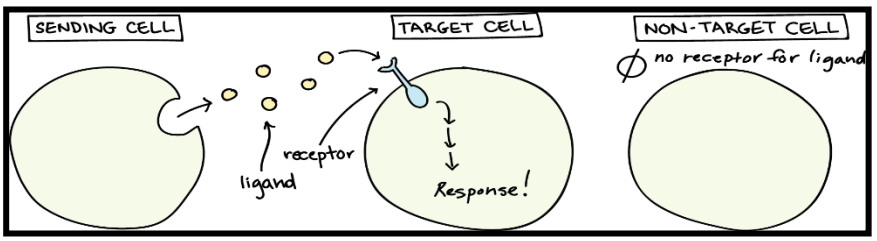
Ligand-receptor interaction

↓

Intacellular signaling

↓

Response

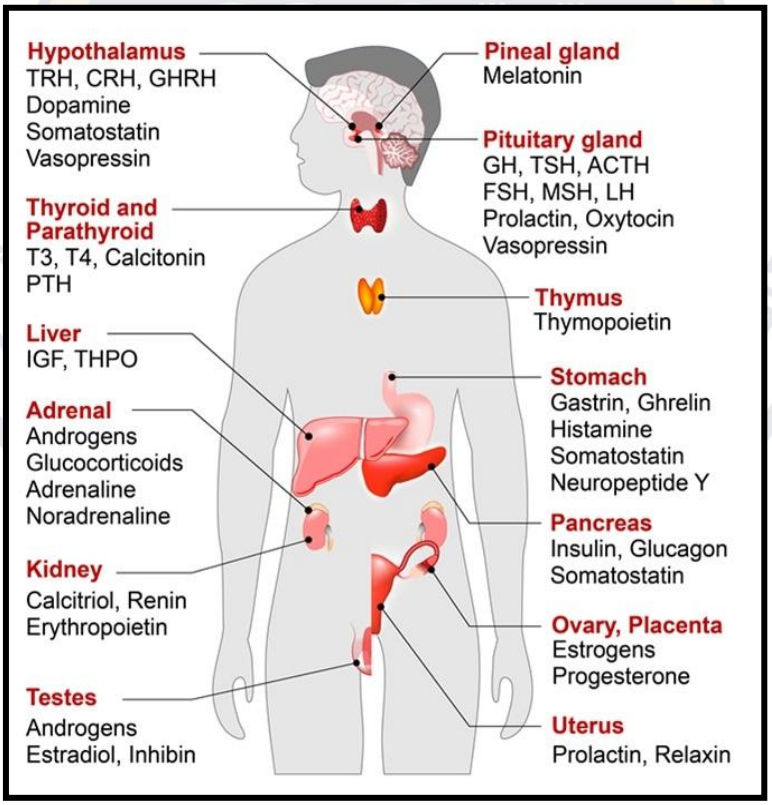


➢ Classifications of hormones:

✓ Hormones can be classified according to the chemical nature, solubility, location of its receptors and the mechanism of hormone action.

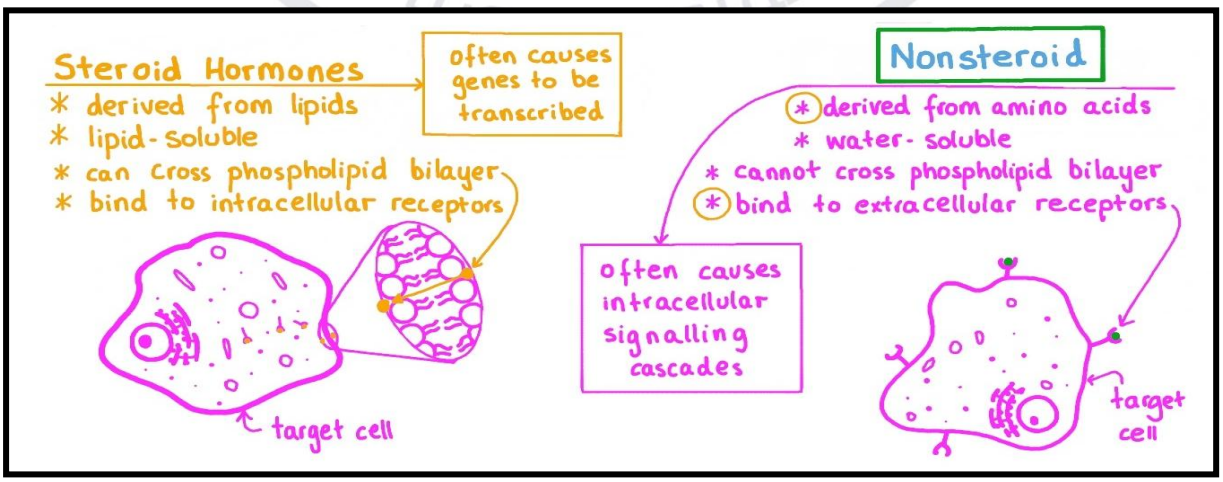
1- According to Chemical nature.

2- According to Mechanism of action.



1- According to chemical nature:

Steroid hormones	Non-steroid hormones
-They are derived from cholesterol. **1. Glucocorticoids** **2. Mineralocorticoids** **3. Sex hormones** **Androgens (testosterone)** **Estrogens** **progesterone**	I. **Protein Hormones:** **1.Large polypeptides:** **-ex. Growth hormone – Insulin – Glucagon – Parathyroid hormone – Prolactin.** **2.Small polypeptides: (small number of aa)** **-ex. ADH (9 aa) – Oxytocin (9 aa) – TRH (3 aa).** **3.Glycoprotein hormones:** **-ex. FSH – LH – TSH – HCG.** **II. Amino Acid Derived Hormones:** -These hormones are derived from aa. **-ex. Thyroid hormones – Adrenaline – Noradrenaline – Dopamine from Tyrosine aa** **-ex. Melatonin from Tryptophan aa**



2- According to mechanism of action:

	Group I	**Group II**
Solubility	Fat soluble (lipophilic)	Water soluble (hydrophilic)
Transport in plasma	Bounded to plasma protein Long plasma half-life (hours to days)	Free (no need to bind plasma protein) Short plasma half-life (minutes)
Receptor	Intracellular	cell membrane
Mediator	Hormone itself bind to receptor on the DNA forming Hormone- Receptor complex	Second messenger
Mechanism of action	Binding with receptors in the nucleus→ Activate genes	Modifing the enzyme activity (phosphorylation→ ↑ or↓ enzym activity)
Response	Slower response, takes hours (Control of gene expression)	Fast response, takes minutes NB. Some act by controlling gene expression , so takes hours
Example	Steroid and thyroid hormones	Protein hormones & catecholamines

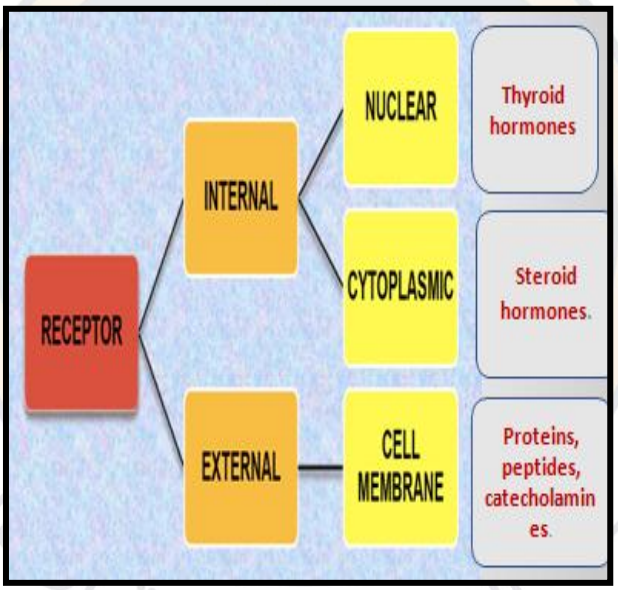
Hormone receptors

❖ They are:

✓ cell-associated **recognition molecules**.

✓ **protein** in nature.

✓ located **inside the cell either in the cytosol or in the nucleus** (intracellular receptors) or located **in the plasma membrane** of the cell (cell-membrane receptors).



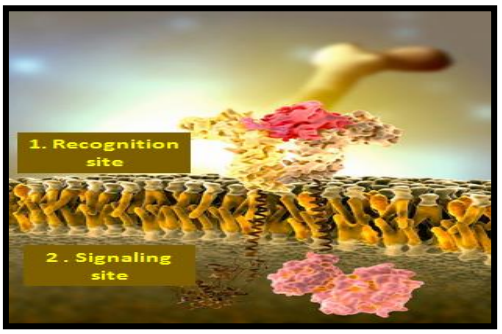
❖ Each receptor has two functional sites:

Recognition site:

It binds the hormone specifically.

Signaling site:

It couples hormone binding to intracellular effect.

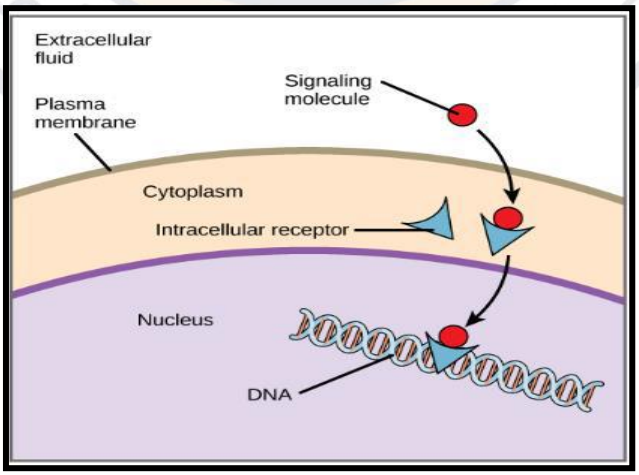


Mechanism of hormone action

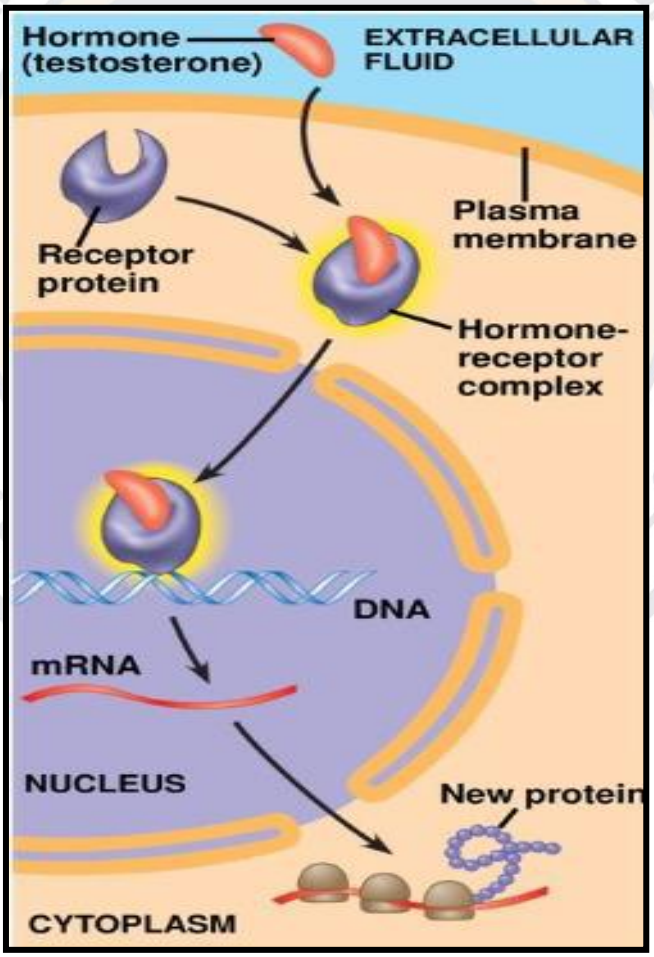
Group I Hormones (bind to intracellular receptors)	Group II Hormones (bind to membrane receptors)

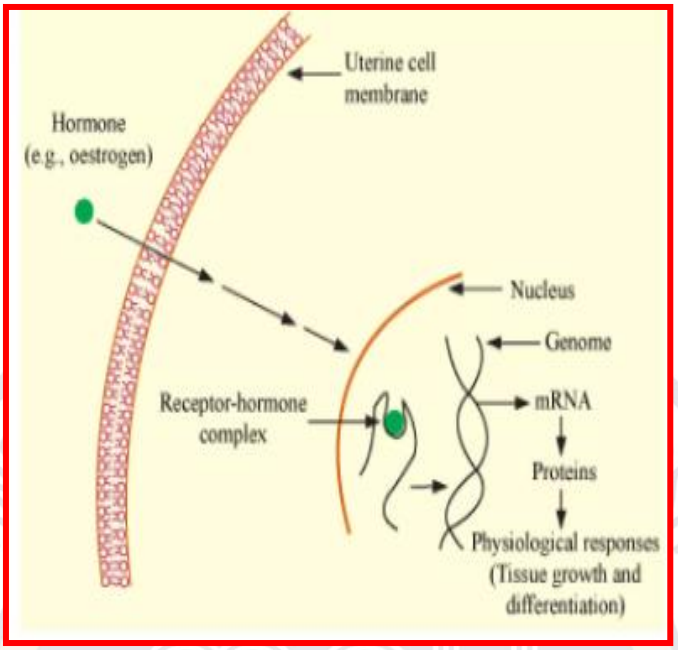
Mechanism of action of Group I Hormones

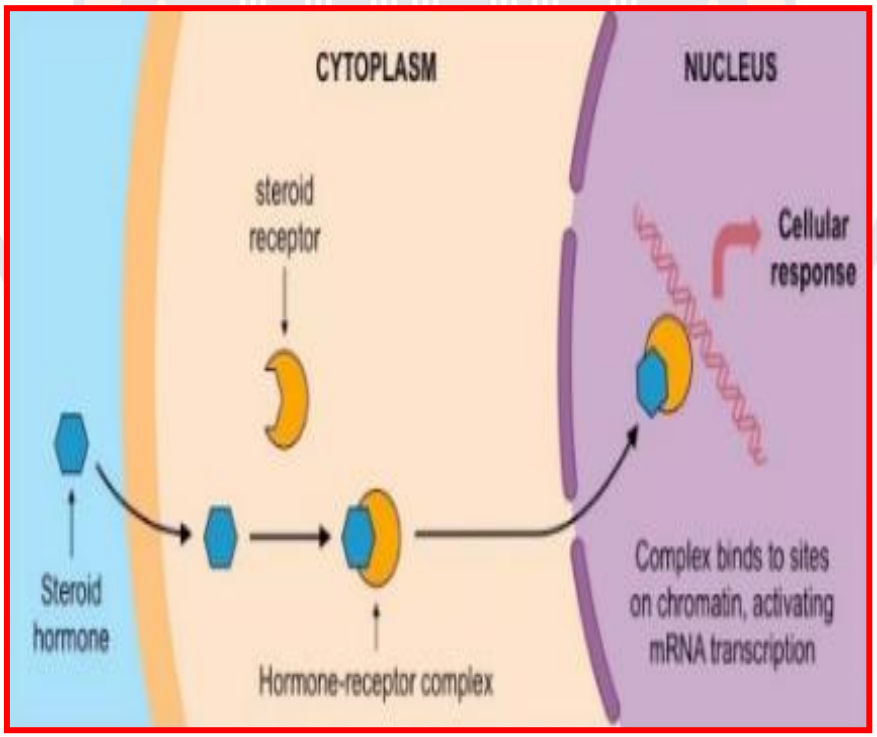
- The lipophilic group I hormones are transported in blood bounded to plasma proteins.
- They diffuse through the plasma membrane of cells, bind their specific, high-affinity intracellular receptors in target cells, forming **hormone-receptor complex.**
- These receptors can be located in the **nucleus** or in the **cytoplasm** (then the hormone-receptor complex traverses the nuclear membrane) of target cells.



- The activated **hormone receptor complex** binds with high affinity to a specific DNA sequence called the **hormone response element (HRE).**
- This results in recruitment of RNA polymerase II and the GTFs and activation of gene transcription.
- Transcription of DNA into mRNA→ mRNA leaves the nucleus→ attaches to a ribosome in cytoplasm → directs the synthesis of a specific protein product (translation).

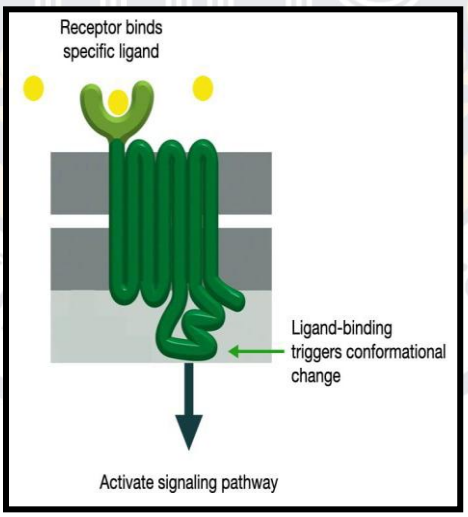



Uterine cell membrane
Hormone (e.g., oestrogen)
Nucleus
Genome
mRNA
Receptor-hormone complex
Proteins
Physiological responses (Tissue growth and differentiation)


CYTOPLASM
NUCLEUS
steroid receptor
Cellular response
Steroid hormone
Hormone-receptor complex
Complex binds to sites on chromatin, activating mRNA transcription

Mechanism of action of Group II Hormones

- The water soluble hormones (hydrophilic) have no transport proteins and can not freely cross the plasma membrane.
- They initiate a response by binding to a receptor located in **the plasma membrane**.
- The receptor complex activates series of intracellular molecules called **second messengers**, which initiate cell a ctivity.
- This process is called signal transduction, because the external signal (hormone) is transduced via internal intermediates.



- **The second messenger** is the signal produced as a result of hormone binding to its cell membrane receptor, mediating the effects of the hydrophilic hormones.

Q who is the first messenger??

- It is the Hormone.

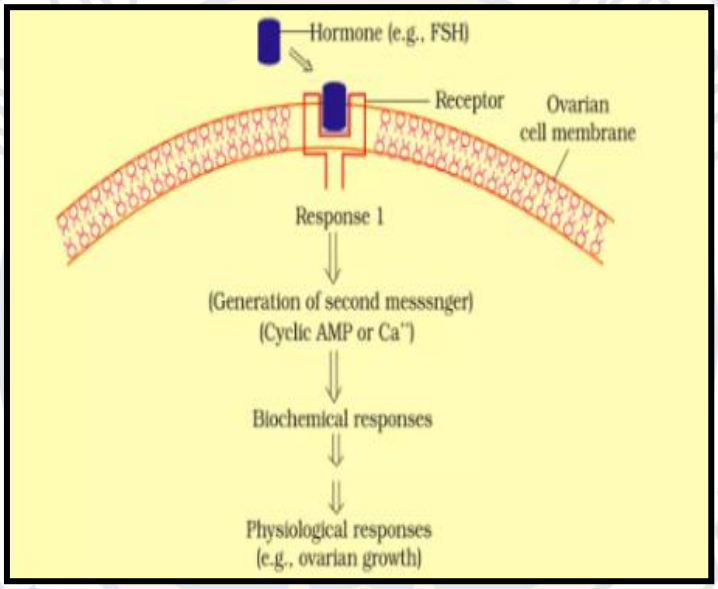
- **Second messengers may be:**

1) Cyclic Adenosine Monophosphate **(cAMP)**.

2) Cyclic Guanosine Monophosphate **(cGMP)**.

3) **Calcium or phosphatidyl inositides (PIs) or both**.

4) **Protein kinase** cascade.



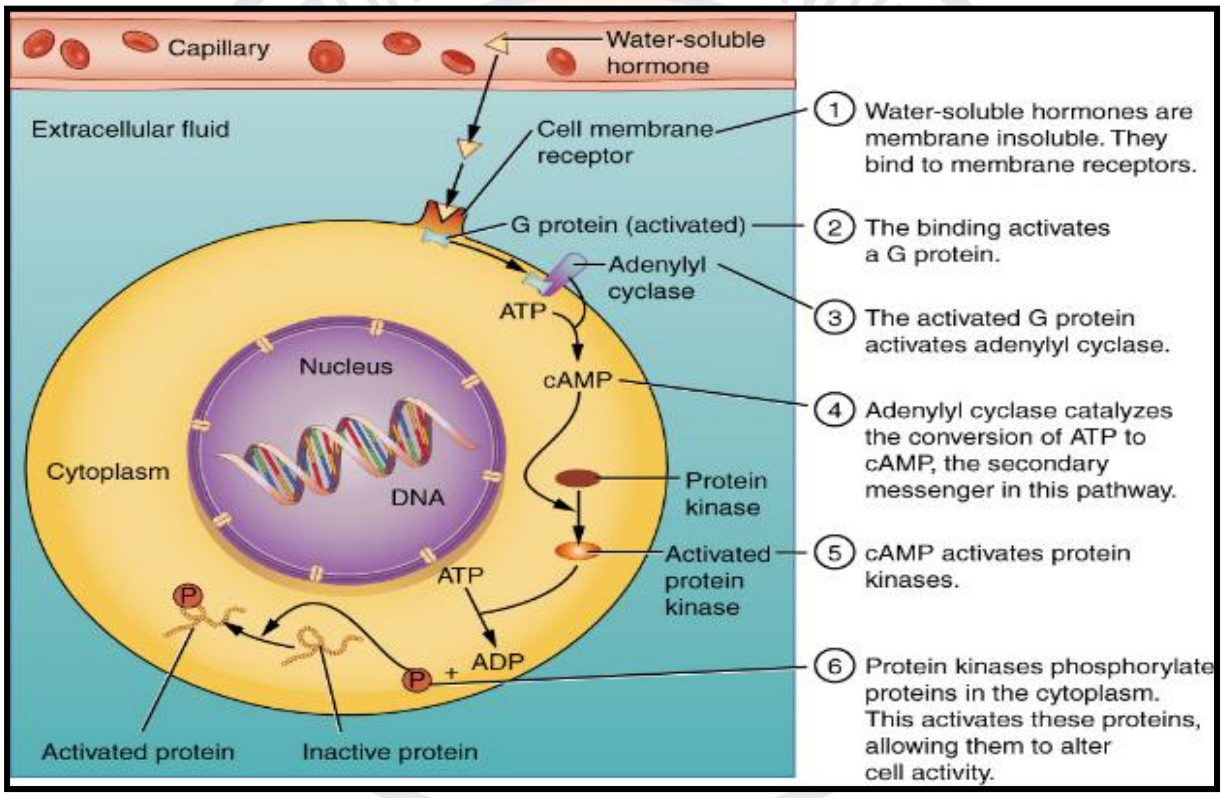
Cyclic AMP as a 2nd messenger

- Examples of hormones use cAMP as a second messengers:

✓ **Catecholamines.**

✓ **Calcitonin.**

✓ **FSH, ACTH, TSH, PTH.**

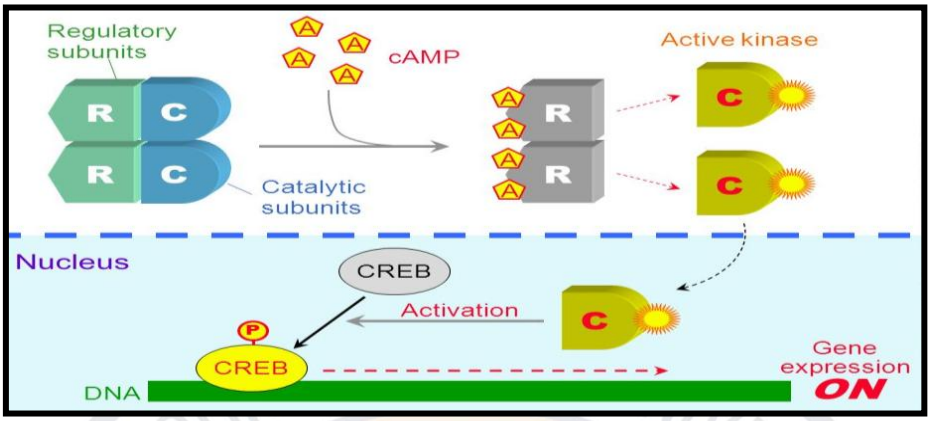


- Binding of the hormone (ligand) to cell membrane receptor→ activates a regulatory G protein (Gs)→ activates adenylate cyclase enzyme→ catalyzes the formation of cAMP from ATP.

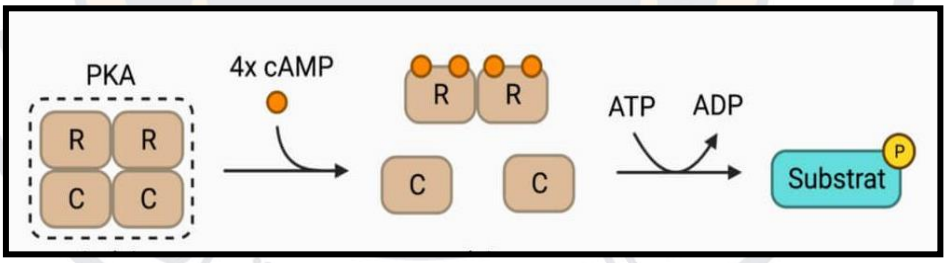
- Then cAMP:

activates protein kinase A (PKA) →Phosphorylation of certain enzymes

Or bind to DNA sequence →Control Gene Expression.



- PKA exists in an inactive form as an R2C2 heterotetramer consisting of two regulatory (R) and two catalytic (C) subunits.
- The cAMP binds to the regulatory subunit of PKA. This results in dissociation of the regulatory and catalytic subunits and activation of the catalytic subunits.



- Termination of hormone action:

  → phosphodiesterase enzyme (PDE) hydrolyses cAMP to AMP, and stop its action.

- NB. Some hormones act via inhibition (not activation) of adenyl cyclase.

G-regulatory protein

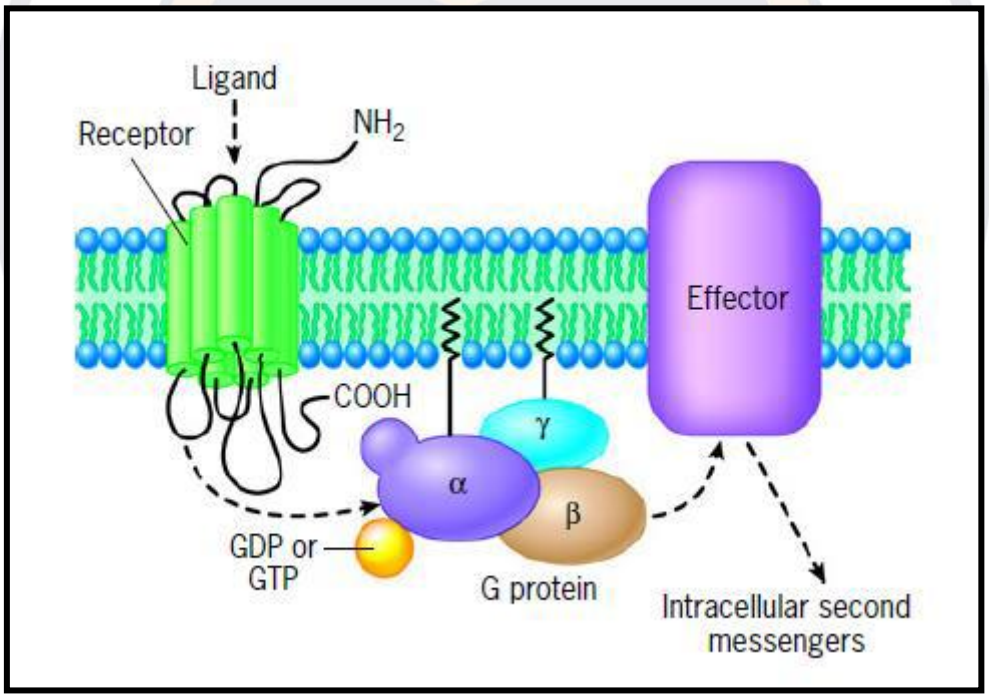
- A GTP-binding protein is a regulatory protein, consists of 3 polypeptide subunits (trimeric):

  → α subunit.

  → β subunit.

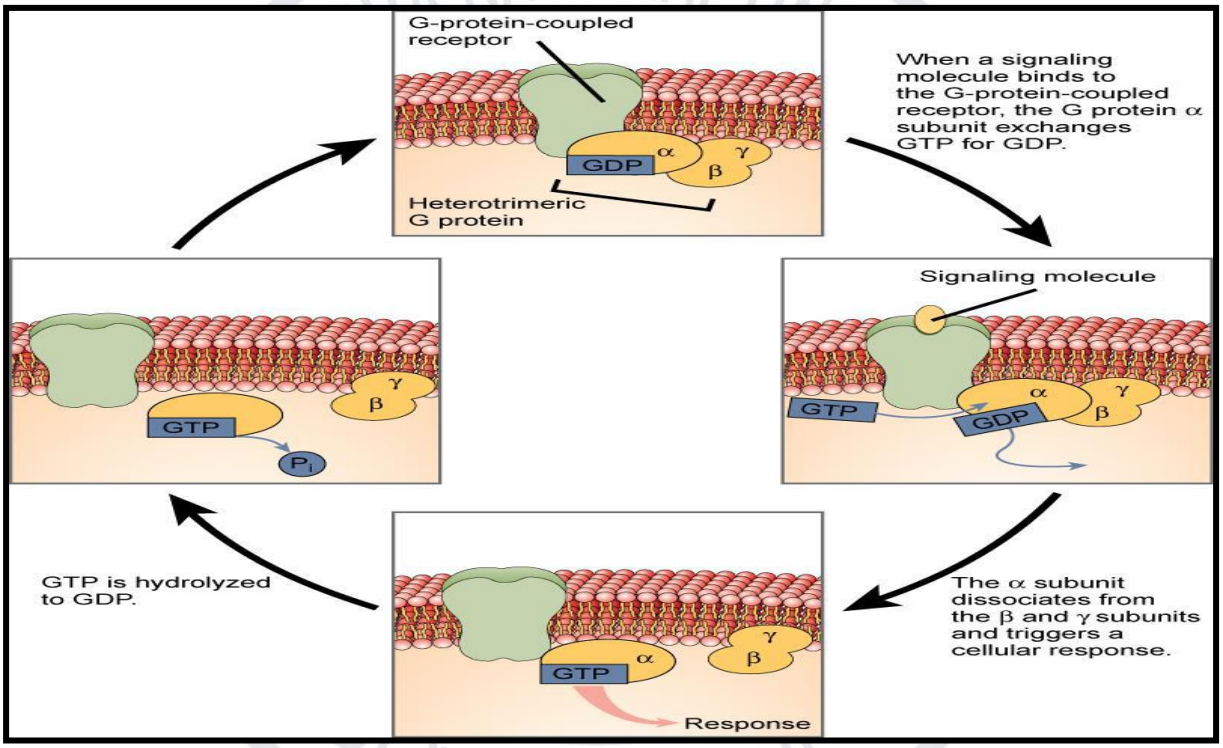
  → γ subunit.

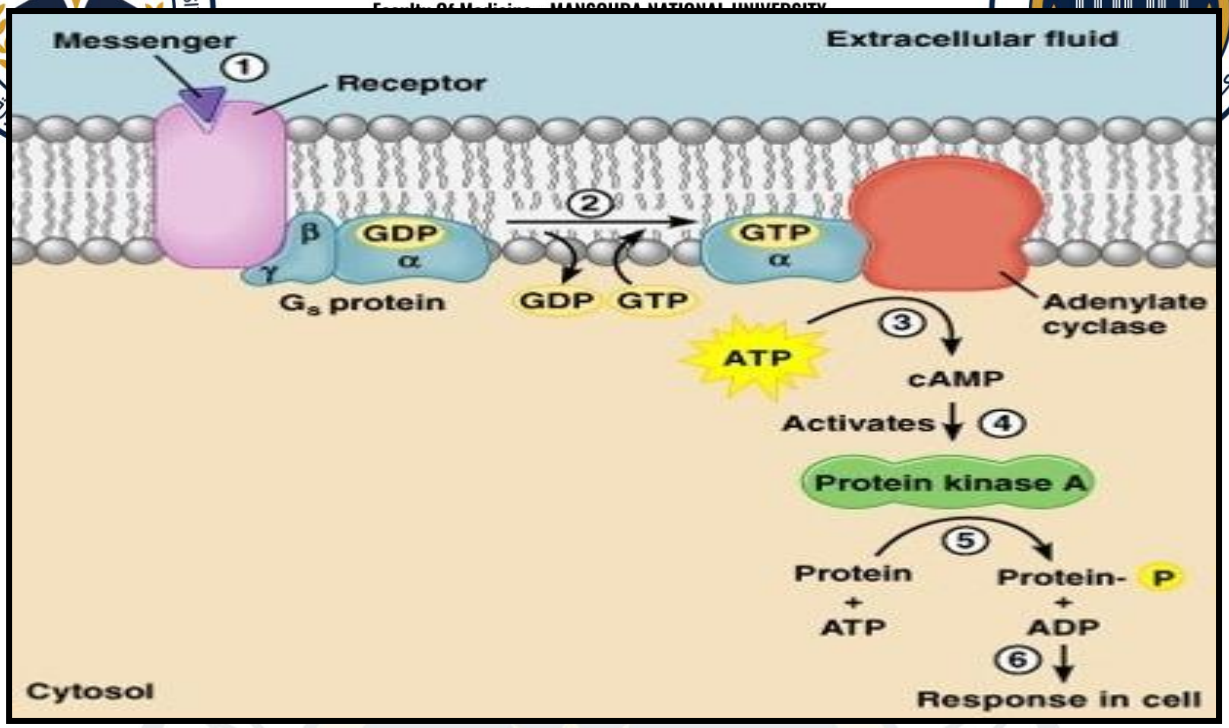
NB. The α subunit is responsible for the activity of the G protein, binds GDP and GTP, hydrolyzes GTP, and activates adenylate cyclase.

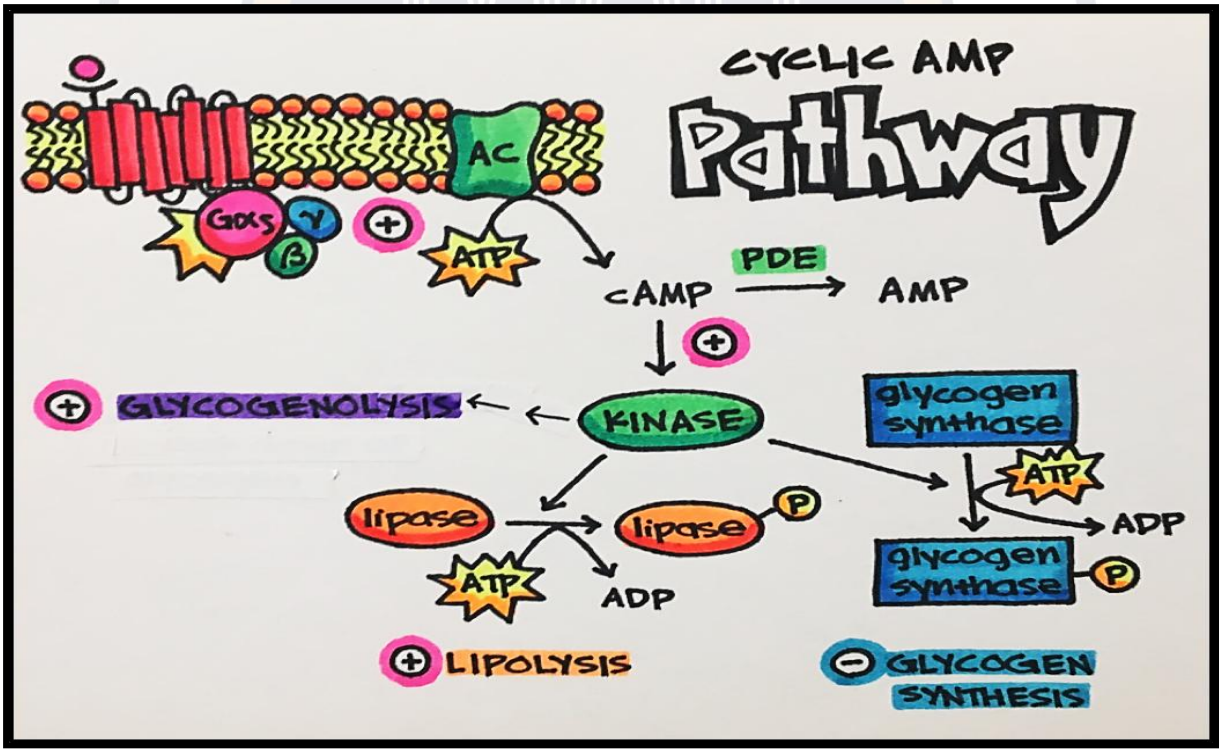


- Binding of the hormone to its receptor activates G protein.
- G α subunit releases its GDP and binds GTP.

- There are several types of G proteins:
  - Gs: Stimulates adenylate cyclase.
  - Gi: Inhibits adenylate cyclase.
  - Gq: Stimulates phospholipase C.
  - Other types affect Ca channels and K channels.



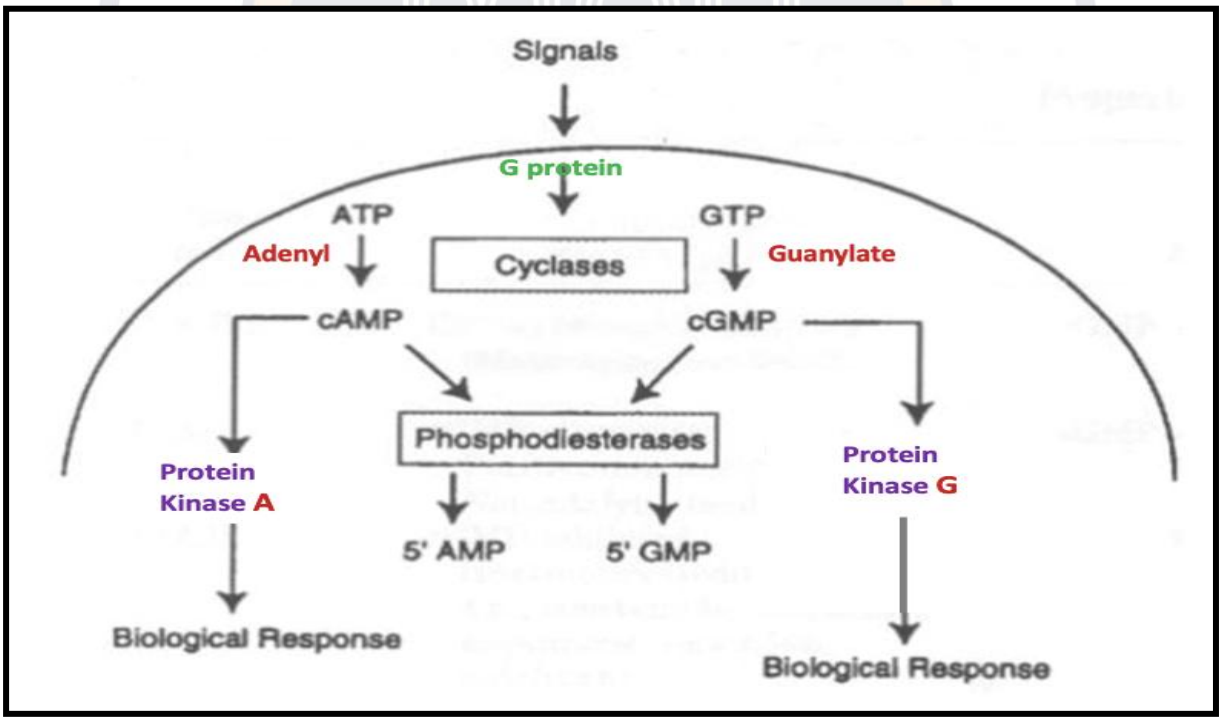

Messenger
1
Receptor
Extracellular fluid
β
γ
GDP
α
2
GTP
α
Gs protein
GDP GTP
Adenylate cyclase
3
ATP
cAMP
Activates
4
Protein kinase A
5
Protein + ATP
Protein- P + ADP
6
Cytosol
Response in cell


CYCLIC AMP
Pathway
AC
Gαs
γ
β
ATP
cAMP
PDE
AMP
GLYCOGENOLYSIS
KINASE
glycogen synthase
ATP
ADP
lipase
lipase
P
ATP
ADP
glycogen synthase
P
LIPOLYSIS
GLYCOGEN SYNTHESIS

Cyclic GMP as a 2nd messenger

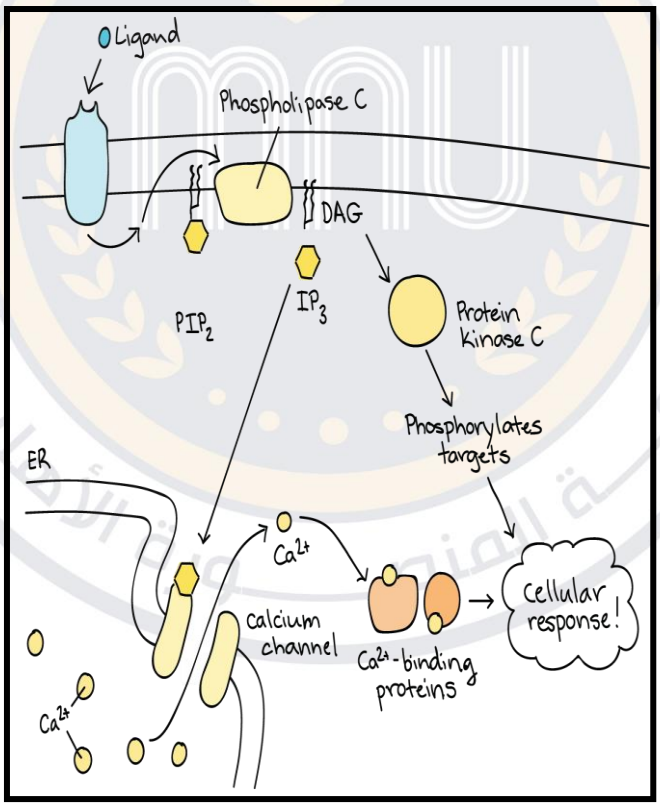
- Examples of hormones use cGMP as a second messengers:
  - ✓ **Atrial natriuretic factor (ANF).**
- Binding of hormone to its specific receptor→ activates the membrane bound form of guanylate cyclase → catalyzes the transformation of GTP to cGMP→ cGMP activates protein kinase G (PKG) → protein phosphorylation→ mediate the effects of the hormone (ANF: smooth muscle relaxation, vasodilatation).
- After mediating its effects, cGMP is hydrolyzed by cGMP dependent PDE enzyme to 5' GMP.

cAMP and cGMP as a 2nd messenger

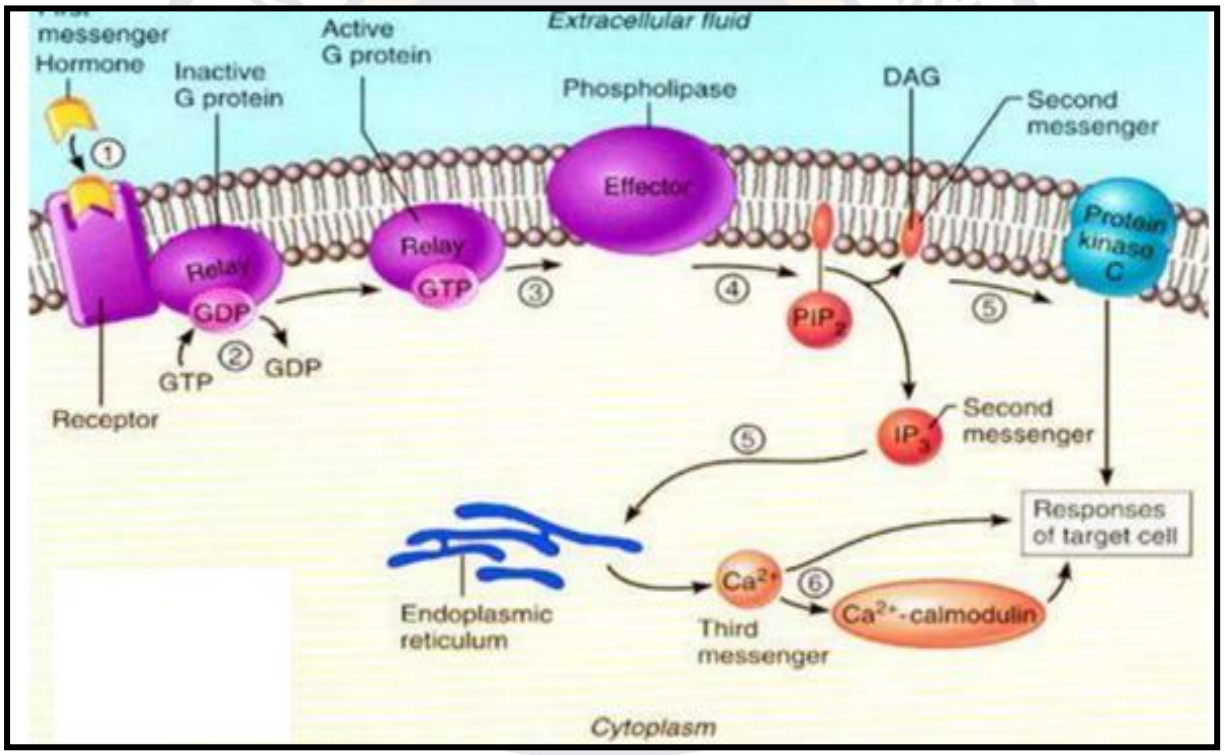


Calcium or phosphatidyl inositides (PIs) as a 2nd messenger

- Examples of hormones use Ca or PIs as second messengers:
  - ✓ **Angiotensin II, ADH, TRH.**
- Binding of the hormone (ligand) to its specific receptor → activates G protein (Gq) → activates the phospholipase C (PLC) enzyme → The active PLC hydrolyses phosphatidyl inositol biphosphate (PIP2) to: DAG and IP3.



- Diacyl glycerol (DAG)→ activates protein kinase C (PKC)→ phosphorylates of enzymes/protein → mediate the effects of the hormone.
- Inositol Triphosphate (IP3)→ bind to Ca Channel→ releases Ca2+ from intracellular storage sites (ER , Mitochondria) → Ca2+ binds to Ca binding protein (calmodulin) to form Ca2+/ calmodulin complex→ phosphorylation of enzymes → mediate the effects of the hormone.

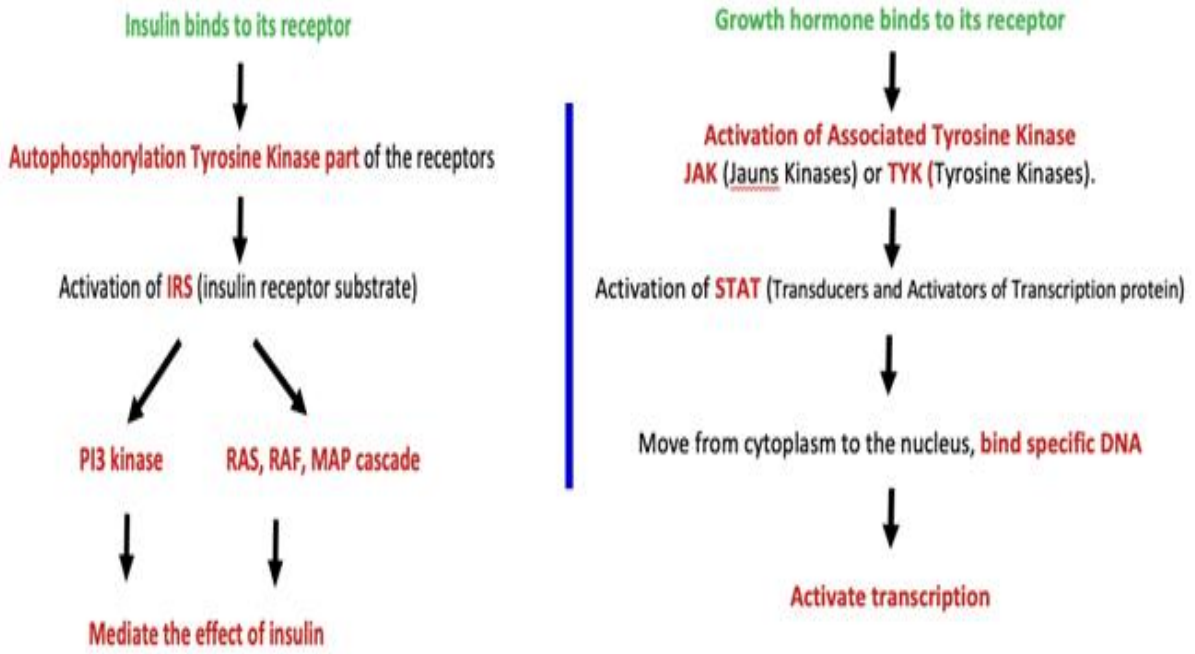


Tyrosine (Protein) kinase as a 2nd messenger

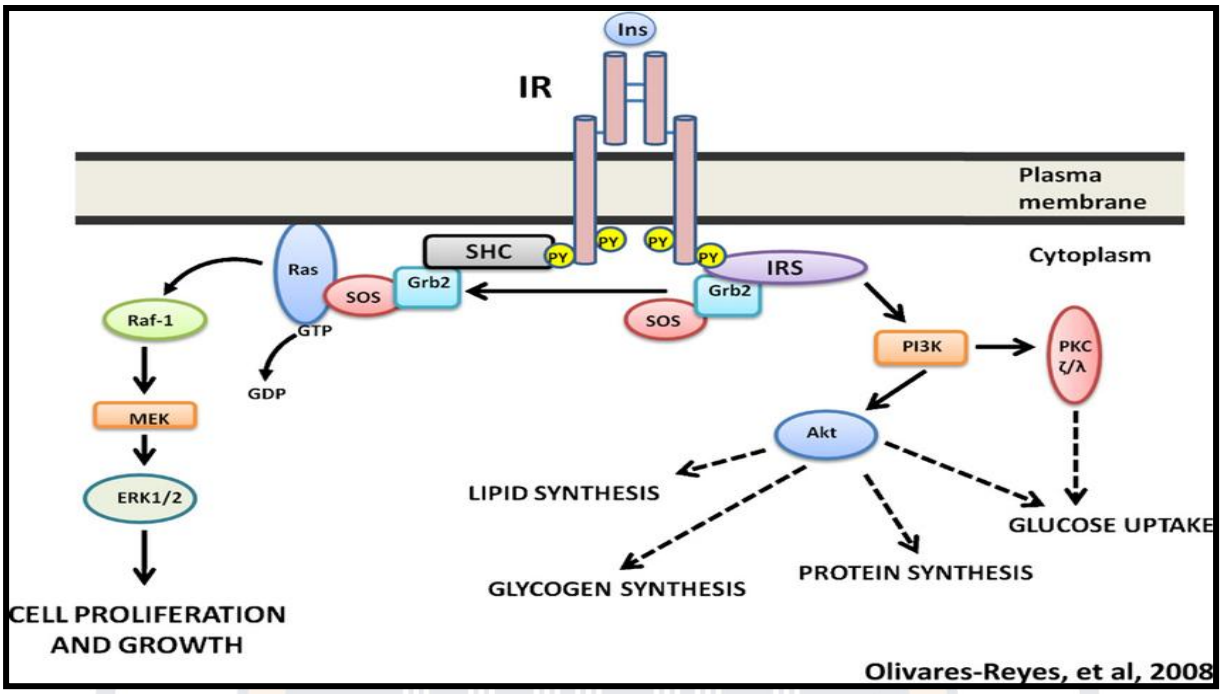
- Examples of hormones use tyrosine kinase as a second messengers:
  - ✓ **GH, Insulin.**
- Tyrosine kinases may be:

a) Intrinsic part of the receptor (ex. Insulin).

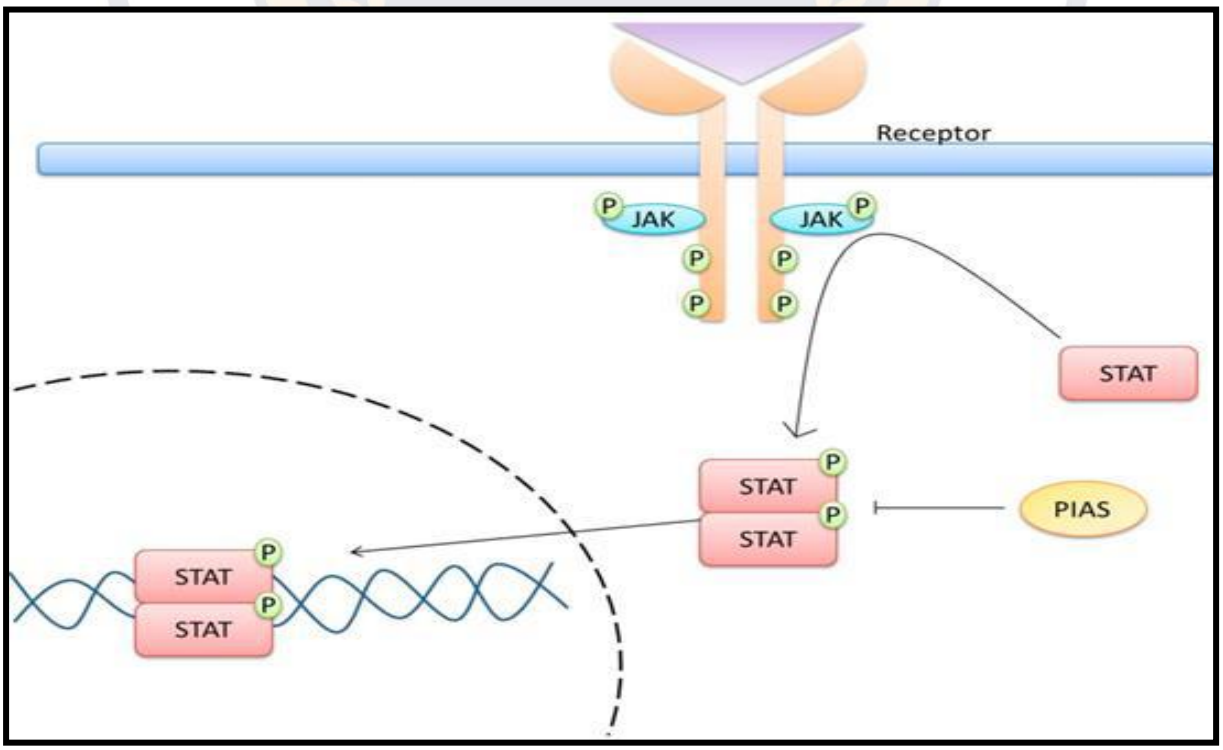
b) Intracellular associated with the receptor but not an intrinsic part of it (ex. GH).



Insulin

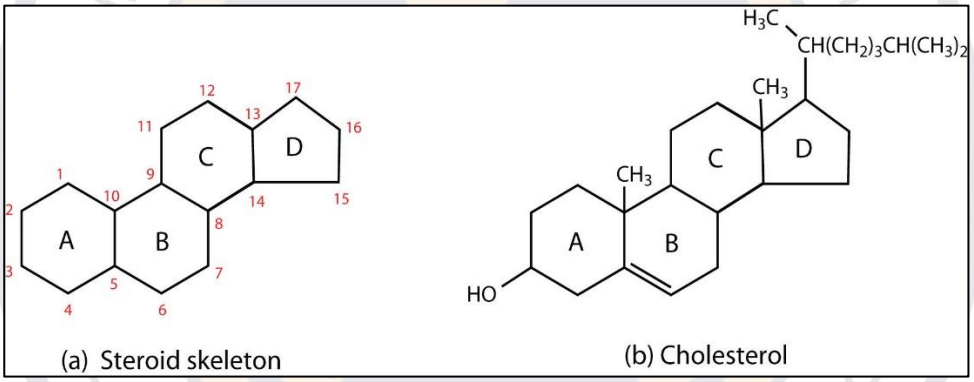

Ins
IR
Plasma membrane
Cytoplasm
Ras
SHC
PY
PY
PY
PY
IRS
SOS
Grb2
Grb2
SOS
Raf-1
GTP
GDP
PI3K
PKC ζ/λ
MEK
Akt
ERK1/2
LIPID SYNTHESIS
GLUCOSE UPTAKE
GLYCOGEN SYNTHESIS
PROTEIN SYNTHESIS
CELL PROLIFERATION AND GROWTH
Olivares-Reyes, et al, 2008

GH


Receptor
JAK
JAK
P
STAT
STAT
STAT
PIAS
STAT
STAT

Biochemistry of sex hormones

- They are steroid hormones (containing steroid nucleus).
- They are derived from cholesterol.
- They are produced by the adrenal glands and gonads (the reproductive glands which include ovaries in females and testes in males).
- They include androgens, estrogens, and progesterone.
- They are responsible for the development of sex organs and 2ry sex characteristics during puberty and play an essential role in reproduction.



- **Classification of sex hormones:**

1. **Male sex hormones (androgens):**
   a) **Weak androgens:**
      1: Dehydroepiandrosterone (DHEA) (**The major androgen produced by the adrenal cortex**).
      2: Androstenedione
   b) **Strong androgens:**
      1: Testosterone can be considered a **prohormone** since it is converted **outside the testes** into a much more potent compound (DHT).
      2: Dihydrotestosterone [DHT] (**more potent than testosterone**).

2. Female sex hormones:

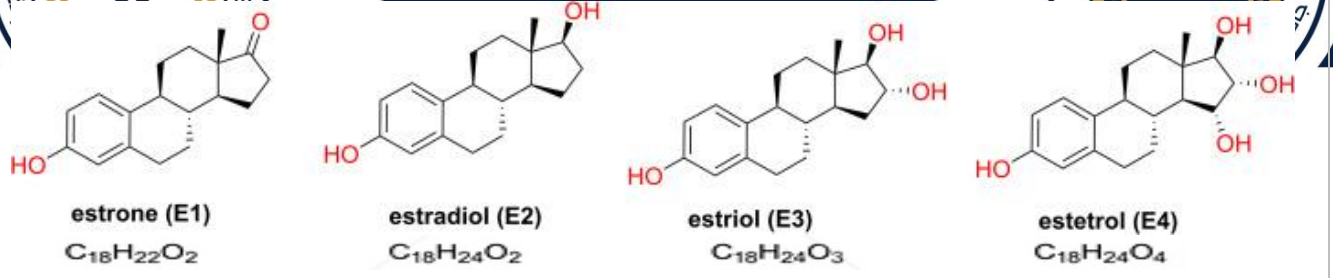
a) Progesterone

b) Estrogens: include Estrone (E1), Estradiol(E2), Estriol (E3), Estetrol (E4)

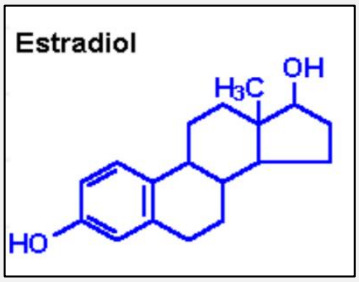
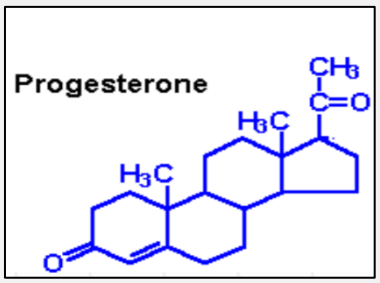
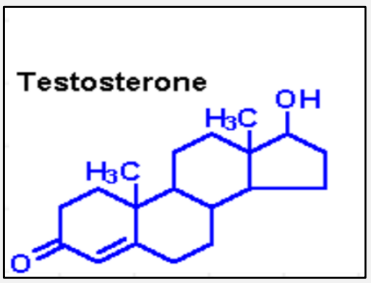
Site of production:

Androgens	Estrogens	Progesterone
1. Leydig cells of Testes (majority) 2. Adrenal cortex (lesser amount) 3. Ovaries (in female)	1. Ovaries (majority) 2. Adrenal cortex (lesser amount) 3. Adipose cells (lesser amount)	1. Ovaries (majority) 2. Adrenal cortex (lesser amount) 3. Placenta (during pregnancy).

Estrone (E1)	Estradiol (E2)	Estriol (E3)	Estetrol (E4)
1. produced by women after menopause. (postmenopausal women) 2. produced by ovaries, adrenal gland, and adipose tissue.	1. produced by women before menopause. 2. produced by ovaries. 3. The **most potent** and the **most prevalent** estrogen in **females**. 4. present in **lower amount** in **males**.	1. produced during pregnancy. 2. produced by the placenta.	1. produced during pregnancy. 2. produced by the liver in both male & female fetuses.



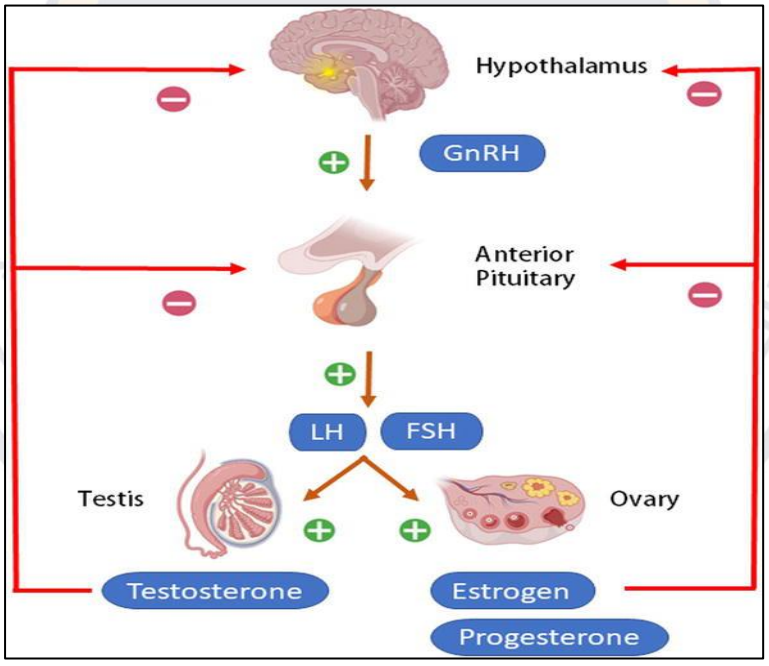
Structure of sex hormone:

Estradiol	Progesterone	Testosterone
18C Steroid nucleus Aromatic A ring Hydroxyl (OH) group at C3 Methyl group (CH3) at C13 Hydroxyl (OH) group at C17	21C Steroid nucleus Double bond between C4 and C5 Ketone group at C3 Methyl group (CH3) at C10 and C13 Acetyl group (CH3CO) at C17	19C Steroid nucleus Double bond between C4 and C5 Ketone group at C3 Methyl group (CH3) at C10 and C13 Hydroxyl (OH) group at C17
		

Biosynthesis of sex hormones:

☒ Synthesis of sex hormones by gonads is controlled by **Hypothalamic-Pituitary-Gonadal axis.**

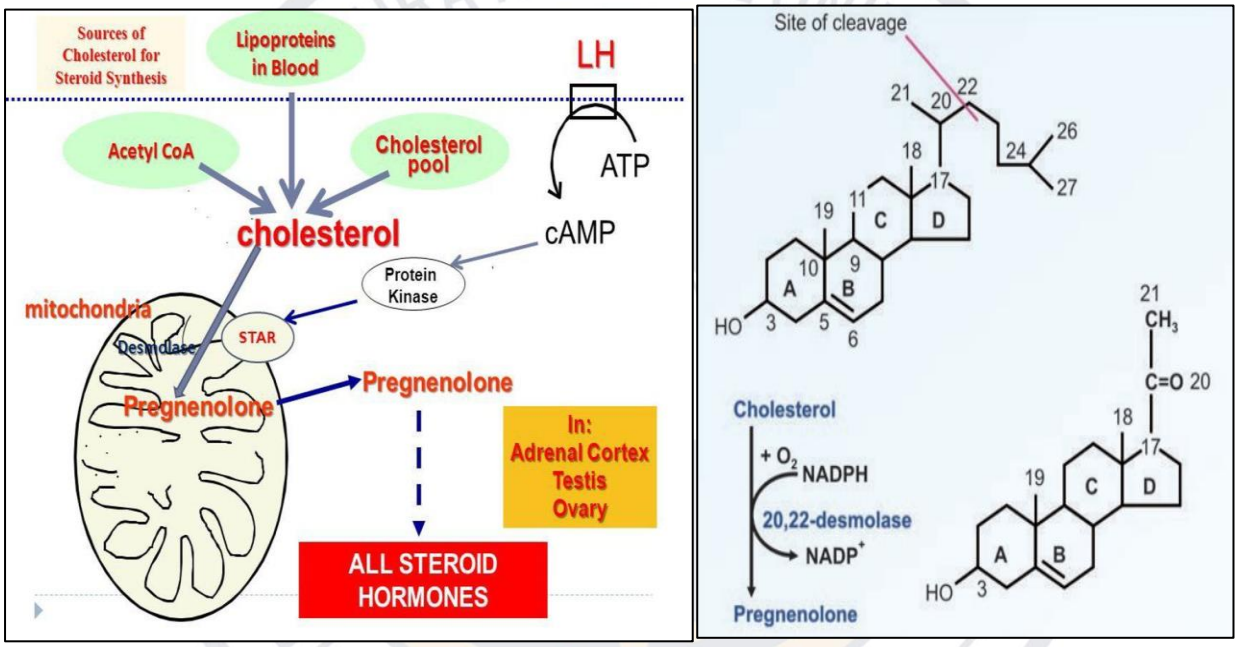
1. **At hypothalamus:** it produces gonadotropin-releasing hormone (GnRH) which travels via the hypophyseal portal system to anterior pituitary.
2. **At anterior pituitary gland:** GnRH stimulates the gonadotropic cells to release **gonadotropins** [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] which travel via the bloodstream to the target organs (testes and ovaries).



3. **At testes and ovaries**

- LH binds to its target cells and increases the expression of **steroidogenic acute regulatory protein** (StAR).
- StAR promotes the delivery of cholesterol to the inner mitochondrial membrane and initiates steroidogenesis.

- At the inner mitochondrial membrane, cholesterol is converted into **pregnenolone** by the action of **20, 22-desmolase enzyme [a cytochrome P450 side chain cleavage enzyme complex (P450scc)]**. Cleavage of the side chain involves two sequential hydroxylations, first at C22 and then at C20, followed by side chain cleavage (removal of the 6-carbon fragment) to give **the 21-carbon steroid pregnenolone**. [**This is the rate-limiting step for synthesis of all steroid hormones**]



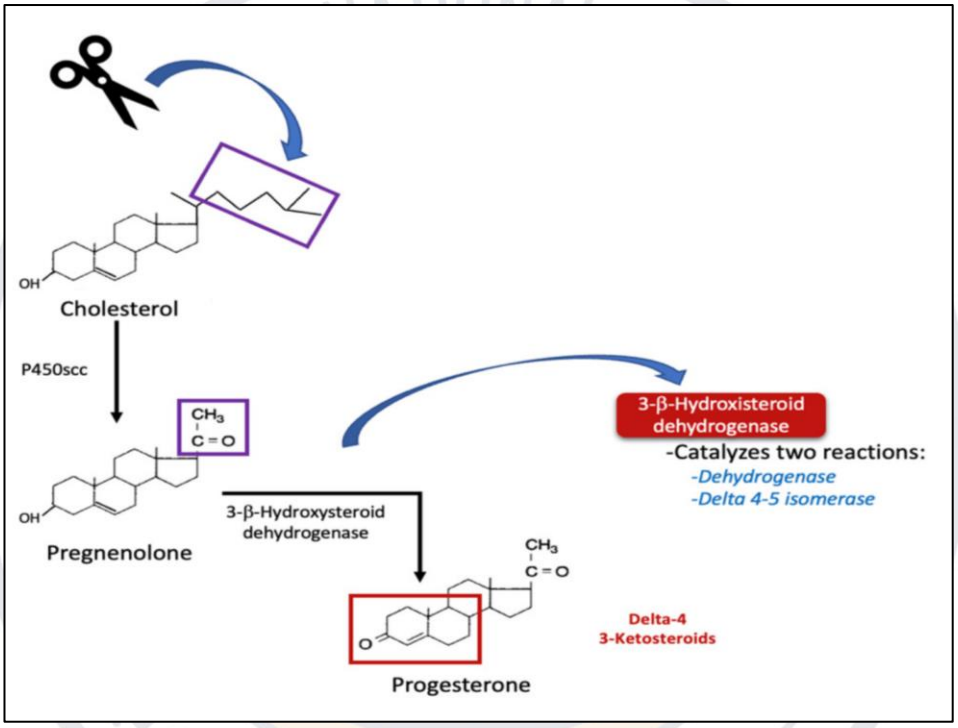
Important Notes:

- GnRH is a decapeptide.
- FSH and LH are glycoproteins hormones of αβ heterodimeric structure. They have a common α subunit, but unique β subunits.
- Conversion of cholesterol to pregnenolone is identical in the adrenal, testis and ovary, but in **adrenal**, the reaction is promoted by **ACTH** rather than LH.
- Pregnenolone is a common precursor for all the steroid hormones.

Synthesis of Progesterone:

☒ **Site:** in the corpus luteum cells, the placenta during pregnancy and the adrenals.

☒ Progesterone is the first steroid hormone formed from pregnenolone in two steps by action of 3β-hydroxy steroid dehydrogenase (3β-HSD).

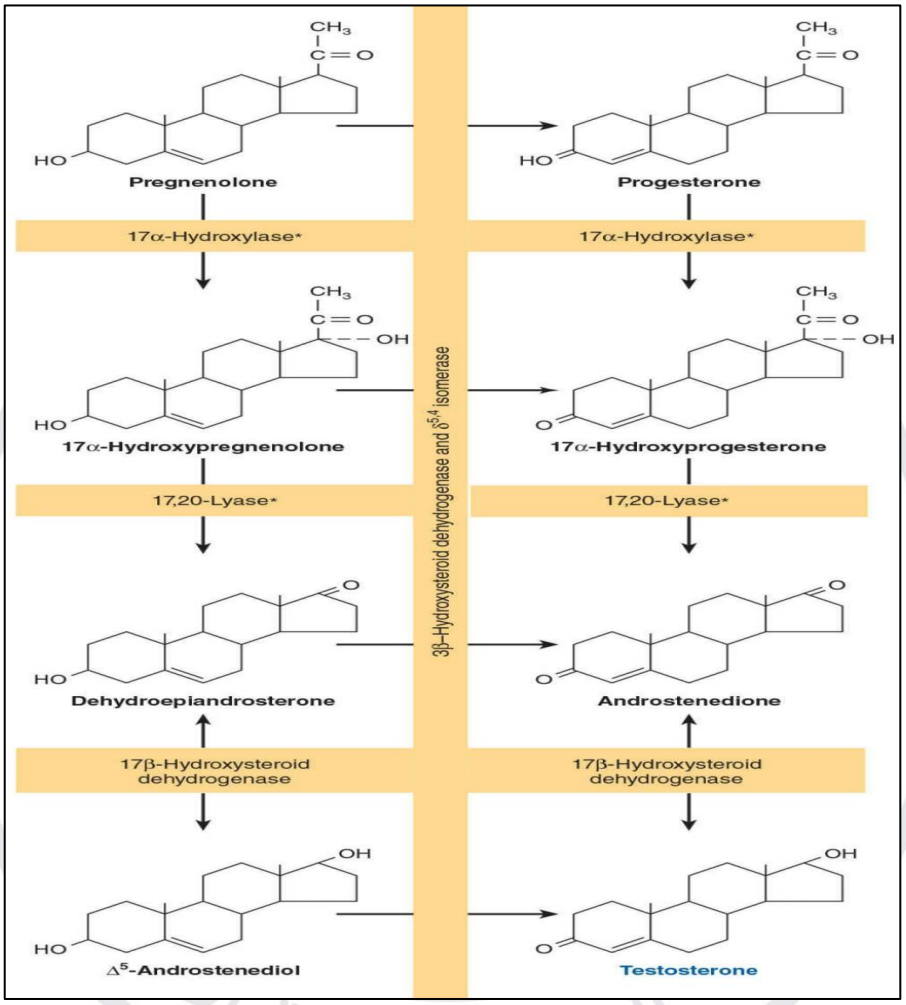


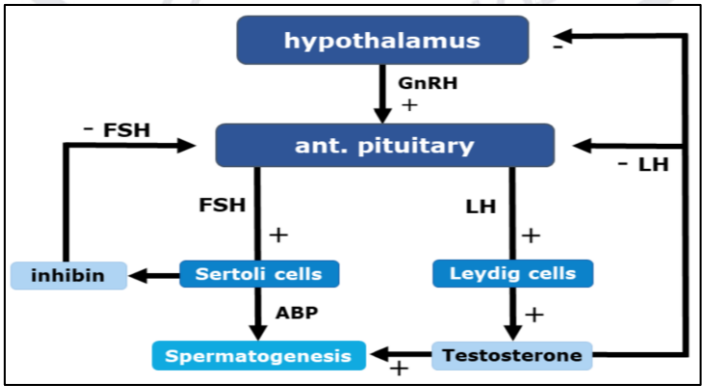
Synthesis of androgens:

1. In Leydig cells in testes:

- The LH initiates the production of pregnenolone.
- Pregnenolone is then converted to DHEA in a two-step process mediated by 17α-hydroxylase and 17,20-lyase.
- DHEA is converted to testosterone via an intermediate androstenedione by the action of 3β-HSD and 17β-HSD. This sequence, referred to as dehydroepiandrosterone (or Δ5) pathway.

- Pregnenolone can also be converted to testosterone by the progesterone (or Δ4) pathway.





Notes:

- **LH** stimulates the interstitial **Leydig cells** to produce **testosterone**.
- **FSH** stimulates **Sertoli cells** located within the seminiferous tubules resulting in spermatogenesis.

2. **In the peripheral tissues:** testosterone is converted to
   a. DHT by the **NADPH-dependent 5α-reductase**.
   b. Estradiol by **aromatase**.
   c. 17-ketosteroids (e.g., androstenedione) via oxidation by **17β-HSD**.

Estrogen synthesis in females:

☒ **Site:** occurs in the theca and granulosa cells of the ovaries

☒ **Steps:**

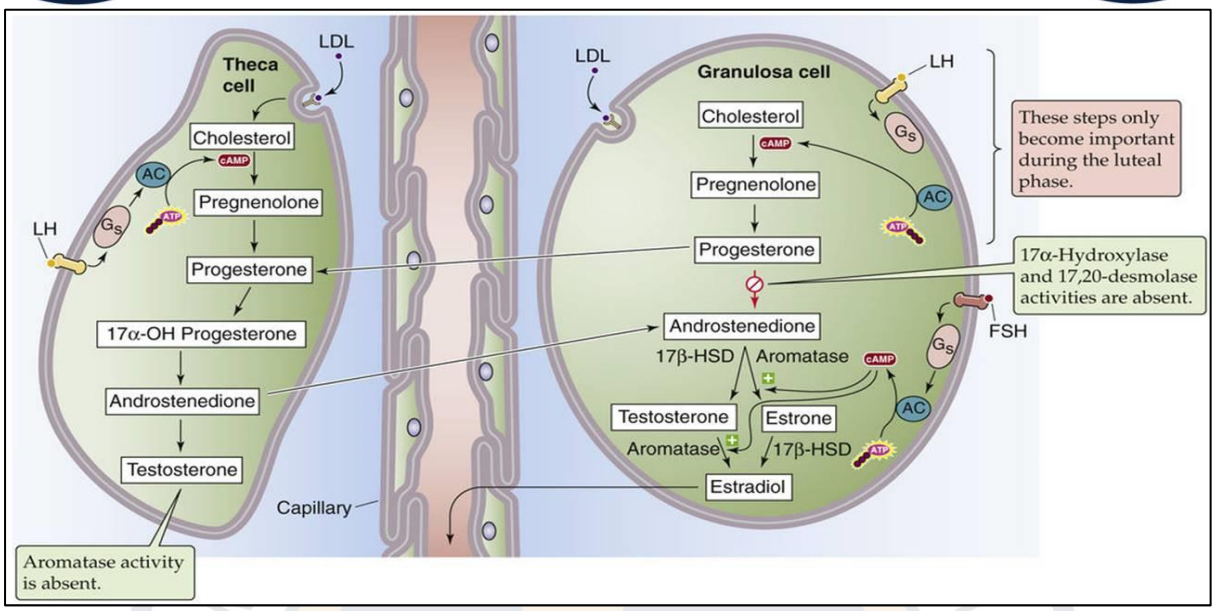
1. In the follicular phase, **LH** primes the **ovarian theca cells** to convert cholesterol to androstenedione.

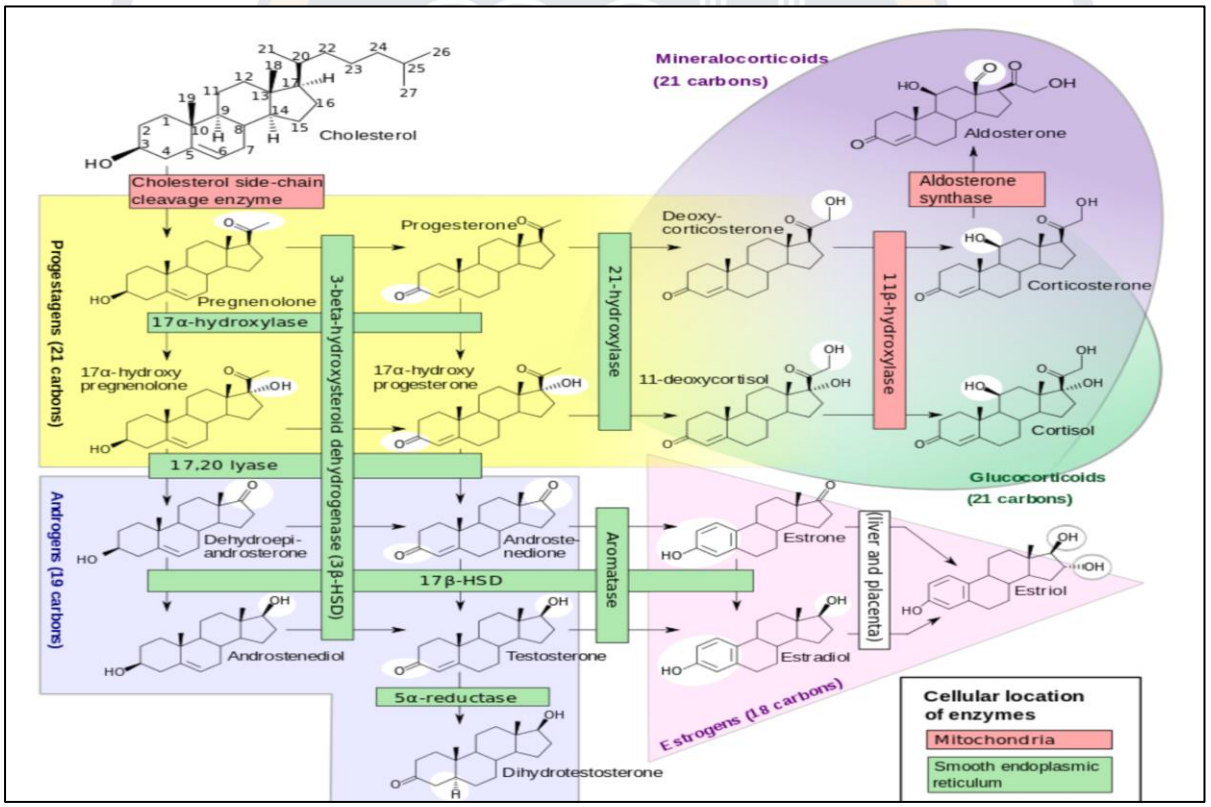
Cholesterol →Pregnenolone →DHEA →Androstenedione

2. Then, **androstenedione** diffuses to **the granulosa cells** and is converted to **estrone** by **aromatase**, which is then converted to **estradiol** by 17β-HSD. The activity of aromatase and 17β-HSD has been stimulated by **FSH**.

Androstenedione→ estrone → 17β estradiol

In **peripheral tissues** such as bone, aromatase enzyme converts testosterone to estrogen to help mature the epiphyses.





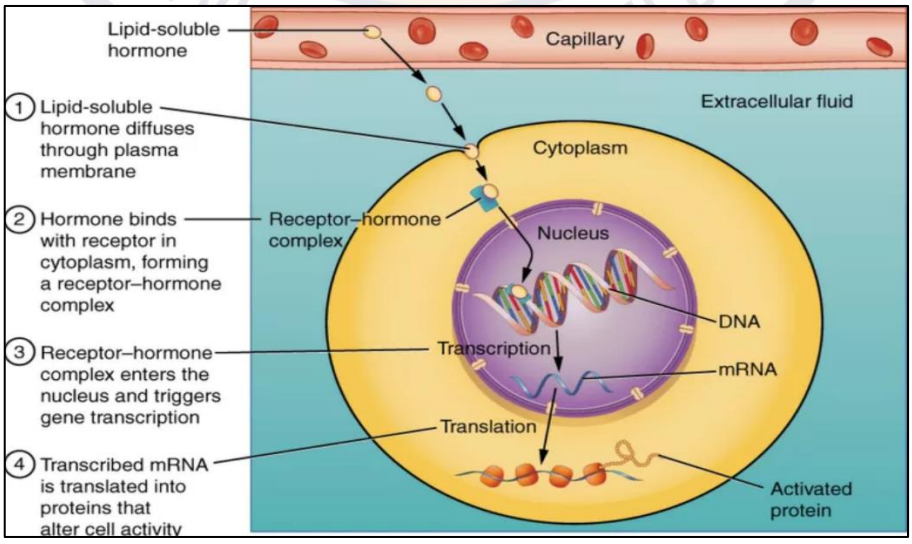
☒ **Notes:**

- Aromatase can convert androstenedione to estrone and testosterone to estradiol.

- The products of hormone synthesis vary with the menstrual cycle; in the follicular phase, **estradiol** is the **main product** during follicular maturation whereas in the luteal phase, **progesterone** is the **main product** following the ovulation, and the follicle becomes the corpus luteum.

Molecular mechanism of action of sex hormones:

1. Sex hormones are small **lipophilic** molecules that are transported in blood bound to a serum globulin known as **sex steroid binding globulin** (SSBG).
2. In the target cells, they can cross cell membrane freely to bind to their receptors in the cytoplasm forming hormone-receptor complex.
3. Then, the hormone-receptor complex enters nucleus and binds to specific DNA sequence called steroid response elements (SREs) located in the promoter of genes.
4. The hormone-receptor complex regulates gene transcription, which leads to formation of messenger RNA. The mRNA interacts with ribosomes to produce specific proteins that express the effect of sex hormones upon the target cell.



Physiological effects of Estrogens:

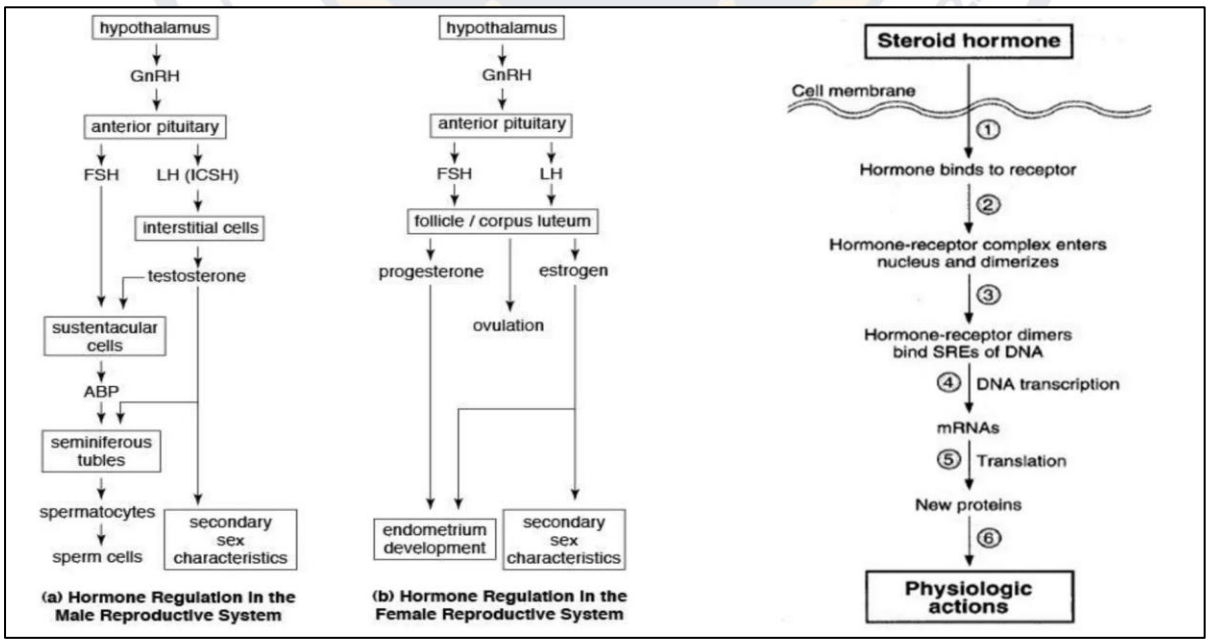
1. Development of female sex organs and secondary sex characteristics.
2. Role in ovulation (follicular phase in the first half of menstrual cycle).
3. Role in bone density modulation (male + female).
4. Role in mineral, carbohydrate, protein, and lipid metabolism.

Physiological effects of Progesterone:

1. Maintenance of Pregnancy (The name progestogens are given because of their function in maintaining a pregnancy).
2. Ovulation (luteal phase in the second half menstrual cycle).
3. Prevention of spontaneous uterine contractions.

Physiological effects of Androgens:

1. Development of the male sex organs and secondary sex characteristics.
2. Spermatogenesis.
3. Androgens also have an anabolic effect producing hypertrophy of prostate, seminal vesicles, skeletal muscles, bone and kidney cells.



FACULTY OF MEDICINE
MANSOURA NATIONAL UNIVERSITY

PARASITOLOGY

Parasites Affecting the Reproductive System.

1. **Toxoplasma gondii.**
2. **Trichomonas vaginalis.**
3. **Schistosoma spp.**
4. **Wuchereria bancrofti**

Toxoplasma gondii

- **Geographical distribution**: Worldwide.
- **Morphology:**

Toxoplasma gondii occurs in 4 forms:

I. Trophozoite (Tachyzoite):

- ☒ It is crescent, 3x6 µ with pointed anterior end and rounded posterior end.
- ☒ It has an ovoid posterior nucleus and anterior paranuclear granules.
- ☒ It is the active multiplying stage, seen intracellular in various tissues.
- ☒ It multiplies within cytoplasmic vacuoles of any nucleated cell.
- ☒ It is found in the acute stage of infection.

II. Pseudocyst:

- ☒ It is full of rapidly multiplying tachyzoites.
- ☒ It has no cyst wall.
- ☒ It is localized inside the RECs.
- ☒ It is found in the acute stage of infection.

III. True tissue cyst:

- ☒ The cyst is round or oval, 5-50 µ and contains slowly multiplying bradyzoites.
- ☒ It has cyst wall.
- ☒ It is found in the brain (most common site), skeletal and cardiac muscles and various organs.

☒ It is found in the chronic stage of infection.

☒ It remains viable for years, and immunosuppression causes reactivation of cysts.

IV. Oocyst:

☒ This stage is only present in cats and other felines.

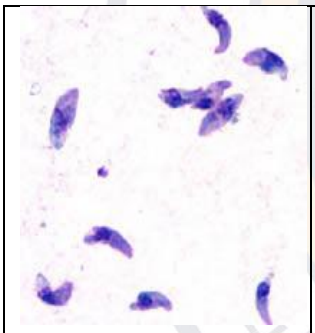
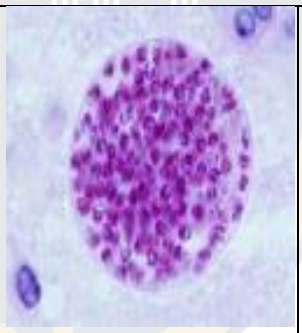
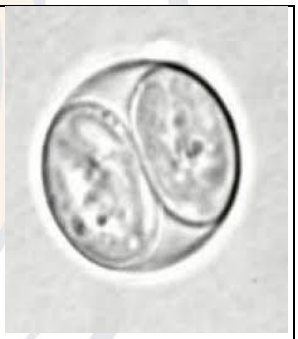
☒ It is oval, 10x12 µ and surrounded by a thick resistant wall.

☒ Non-infectious when excreted in unsporulated or immature stage in cat feces.

☒ It sporulates, by sporogony, within 1-5 days and becomes infectious.

☒ The mature or sporulated oocyst contains 2 sporocysts, each containing 4 sporozoites (disporocystic tetrazoic oocyst).

☒ It may remain viable in moist shaded soil for a year or more.

			
Tachyzoites	**Pseudocyst**	**True tissue cyst**	**Oocyst**

Morphological forms of *Toxoplasma gondii*

Life cycle:

☒ **Habitat:** T. gondii is an obligate intracellular parasite, which is found inside the RECs, brain, skeletal and cardiac muscles, and any other nucleated cells.

☒ **Definitive host:** Cats and other felines.

☒ **Intermediate host**: Man and other mammals (mice, rabbits, goat, sheep, cattle, and pigs), reptiles and birds.

☒ **Infective stage:** All stages are infectious to humans; tachyzoites, pseudocysts, true tissue cysts and sporulated oocysts.

☒ **Mode of infection:**

1. Oral route via ingestion of:
   - Mature oocysts in food and drinks contaminated with cat feces.
   - Pseudocysts or true cysts in raw or undercooked contaminated meat.
   - Tachyzoites in unpasteurized goat's and cow´s milk.
2. Inhalation of mature oocysts.
3. Blood transfusion.
4. Organ transplantation.
5. Contamination of mucous membrane, skin abrasions by:
   - Handling and preparation of fresh infected meat.
   - Handling of infected blood by laboratory workers.
6. Transplacental route: the tachyzoites can be transmitted from infected pregnant woman to the fetus via the blood stream (placenta).
7. Sexually transmitted or by artificial insemination with semen from infected male.

Life cycle:

☒ The life cycle of *T. gondii* is **heteroxenous** (alternation of generations between two hosts), where an asexual cycle occurs in the intermediate host, and sexual cycle occurs in the definitive host.

I. Exoenteric cycle (Asexual cycle):

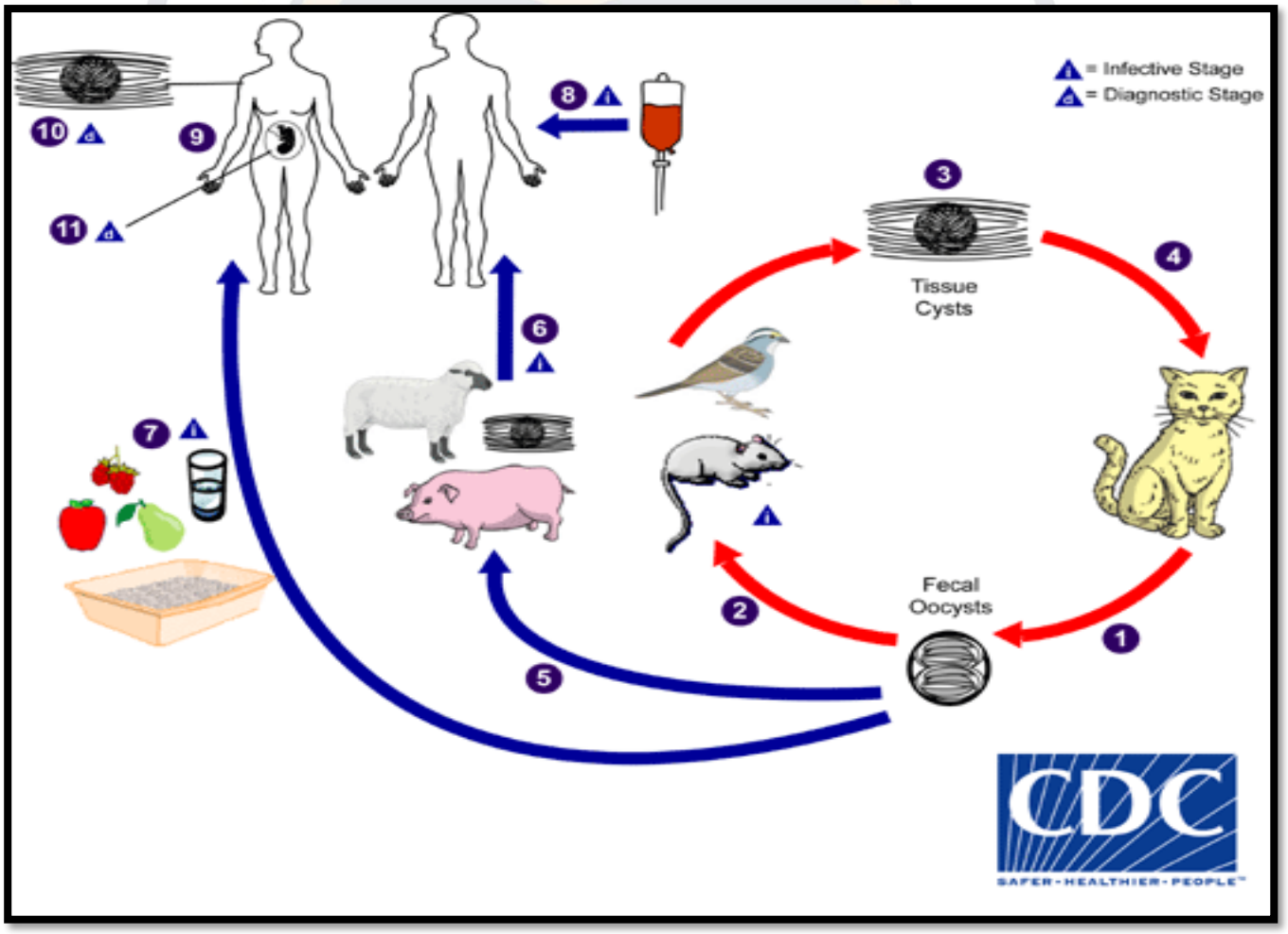
- It occurs in intermediate hosts (man, and other mammals, reptiles and birds).
- Sporozoites from sporulated oocysts and trophozoites from tissue cysts, enter the epithelial cells of intestinal mucosa, and proliferate as tachyzoites.
- Tachyzoites continue to multiply and may spread locally to invade new cells.

- Some tachyzoites also spread to distant extra-intestinal organs (e.g. brain, heart, skeletal muscles, eye, liver, spleen and placenta) by invading lymphatic and blood, forming tissue cysts.
- Tachyzoites invade and multiply inside the RECs to form pseudocysts.
- When the pseudocyst ruptures, the tachyzoites will invade either new macrophages or any other cells and multiply, forming true tissue cysts full of bradyzoites.
- The dormant bradyzoites inside the cyst can be reactivated in immunosuppression causing renewed infection in the host.
- The released trophozoites can enter the blood and the cycle is repeated.
- Man acts as blind or final host or dead end for T. gondii.

II. Enteric cycle (Sexual cycle):

- It occurs in cats and other felines, definitive hosts.
- Both sexual reproduction (gametogony) and asexual reproduction (schizogony) occur within the mucosal epithelial cells of the small intestine of cat.
- Cats acquire infection by their predatory habit of feeding on muscles, brain and other tissues of infected mice, harboring tissue cysts, or by eating raw infected meat of domestic animals, or by ingestion of mature oocysts passed in their feces.
- The sporozoites and trophozoites are released in the small intestine, penetrate its mucosal epithelial cells and multiply inside by several asexual cycles of schizogony, leading to formation of merozoites.
- Some merozoites (from rupture of schizont) may enter extraintestinal tissues resulting in formation of tissue cysts in other organs of the body as in man.

- Other merozoites invade the intestinal mucosa again and transform into micro- and macrogametocytes, and sexual cycle (gametogony) begins, with formation of microgamete and macrogamete.
- A macrogamete is fertilized by microgamete with production of zygote which develops into an oocyst.
- Unsporulated oocysts are shed in the cat feces for 1-2 weeks and take 1-5 days to sporulate in the environment and become infective.
- Man and other intermediate hosts acquire infection by ingesting the sporulating oocysts and the cycle is repeated.



Life cycle of *Toxoplasma gondii*.

Pathogenicity:

☒ proliferation of tachyzoites in the host cells causes cellular death with focal necrosis and surrounding inflammatory cells.

A. In acute infection: the outcome of the disease depends on host immune status.

- **In immunocompetent individuals:** tachyzoites disappear from various organs.
- **In immunocompromised patients:** the parasites disseminate through the bloodstream to various organs (as the brain, eyes, lungs, heart, liver, etc.), where they form pseudocysts causing severe necrotizing lesions.

B. In chronic infection: true tissue cysts remain viable in tissues for years in resting form. In immunodeficient status, their reactivation causes clinical disease.

Clinical picture:

A. Congenital toxoplasmosis:

☒ This occurs when the mother gets infected for the first time during pregnancy. But, in some woman with chronic infection, reactivation of tissue cysts leads to liberation of trophozoites, which may infect the fetus.

☒ The risk of fetal infection rises with progress of pregnancy.

☒ In contrast, the severity of fetal damage is high, when infection is transmitted in early pregnancy.

☒ **Clinical manifestations of congenital infections may be:**

- **Early manifestations:**
  - Still birth, abortion, hydrocephalus, microcephaly and microphthalmia.
  - The most common sequelae are retinochoroiditis that affects vision and results in blindness, cerebral calcification, convulsions (clinical triad).

- In some cases, fever, lymphadenopathy, hepatosplenomegaly (HSM), anemia, thrombocytopenia, petechial rash, jaundice, and myocarditis may present at birth.

- **Late manifestations:**
  - Mental retardation, visual affection and psychomotor disturbance in adolescence and adulthood.

B. Acquired toxoplasmosis:

☒ It is asymptomatic in 80-90% of healthy hosts.

☒ The classical clinical sign of acute acquired toxoplasmosis is lymphadenopathy and the deep cervical lymph nodes are the most commonly affected. The infected lymph nodes are discrete and non-tender.

☒ Mild fever, headache, myalgia (Flu-like syndrome), and HSM are often present.

C. Toxoplasmosis in immunocompromised patients:

☒ In these patients, affection of brain is more common, with meningoencephalitis, and neuropsychiatric manifestations.

☒ Pneumonia, myocarditis, chorioretinitis and HSM may occur.

Diagnosis:

A. Clinical diagnosis:

☒ A combination of signs such as hydrocephalus or microcephaly, chorioretinitis, and signs of intracerebral calcification make diagnosis of congenital toxoplasmosis probable.

☒ Acquired toxoplasmosis is diagnosed by exclusion from other diseases of the reticuloendothelial and lymphatic systems.

B. Laboratory diagnosis:

I. Direct:

1. Microscopy:

☒ Detection of trophozoites and tissue cysts in lymph node, bone marrow, spleen, placenta, blood, CSF, and amniotic fluid smears stained by Giemsa, or PAS stain.

2. Animal inoculation:

☒ Toxoplasma can be detected by intraperitoneal inoculation of infective material in mice.

☒ After 7-10 days, peritoneal fluid is examined for trophozoites.

☒ Mice are sacrificed after 3 weeks and examined for tissue cysts.

II. Indirect:

A. Serodiagnosis:

1. **Sabin-Feldman dye test:** It detects a circulating cytoplasm modifying antibody. Patient's serum is mixed with a *Toxoplasma* trophozoites suspension and methylene blue is added. If the parasite fails to take the stain, the test is considered positive. The test gives false positive results in *Sarcocytis* and *Trichomonas vaginalis* infections.

2. **Antibody detection:**

☒ For detection of IgM, IgG, and IgA antibodies.

☒ Tests used include ELISA, IFA, and IHA.

☒ Detection of specific IgM antibodies indicates acute infection.

☒ Detection of specific IgG titer indicates latent infection.

☒ Detection of IgM in babies' blood is fetal in origin as maternal IgM doesn't cross the placenta.

☒ IgA is also used for detecting congenital infection in newborns.

3. **Antigen detection:**

☒ Detection of antigen by ELISA indicates recent Toxoplasma infection.

☒ It is useful in diagnosis of congenital toxoplasmosis and toxoplasmosis in immunocompromised patients.

B. Molecular diagnosis:

☒ Can be used for diagnosis of T. gondii DNA in blood, CSF, urine, amniotic fluid, and different tissues.

☒ It is useful in diagnosis of congenital toxoplasmosis and toxoplasmosis in immunocompromised patients (antibody titers are low or absent).

C. Imaging:

☒ MRI and CT scan: to diagnose CNS involvement.

☒ US of fetus: to diagnose congenital toxoplasmosis.

Treatment:

1. **Pregnant women:**

Spiramycin (Rovamycin) should be taken for 4 weeks, to treat the infected pregnant women to reduce the risk of transplacental transmission.

2. **Congenital toxoplasmosis:**

Neonates with congenital infection:

- Pyrimethamine and sulfadiazine with folinic acid for one year.
- Systemic corticosteroids may be given to alleviate chorioretinitis.

3. **Immunocompetent individuals:**

- Most healthy people recover from toxoplasmosis without treatment.
- Persons who develop persistent, severe symptoms can be treated with a combination of drugs (such as pyrimethamine and sulfadiazine or clindamycin, plus folinic acid).

4. **Immunocompromised individuals:**
   - Immunosuppressed patients who are positive for T. gondii and have a CD4+ T-lymphocyte count less than 100/ µl should receive prophylactic treatment against Toxoplasma encephalitis.
   - Prophylaxis should be discontinued in patients whose CD4+ T-lymphocyte becomes more than 200/µl for 3 months after successful treatment.
   - Drugs used in prophylaxis:
     - Trimethoprim-sulfamethoxazole (the drug of choice).
     - Dapsone- pyrimethamine.

Prevention and control:

1. Women who are or may become pregnant should avoid contacts with cats or cleaning the litter box and undergo routine serological screening.
2. Individuals at risk, mainly children and immunocompromised individuals, should avoid contacts with cats and their feces.
3. Proper washing of hands, vegetables and fruits before eating.
4. Proper washing of hands and utensils after handling raw meat.
5. Proper freezing and cooking of meat before eating.
6. Never fed raw meat to cats; only dry, cooked or canned meat should be fed.
7. Cats should be kept indoors, and litter boxes changed daily. Cats' feces should be flushed down the toilet or burned. Litter pans should be cleaned by immersing them in boiling water.
8. Screening for T. gondii antibody should be done in all blood banks.

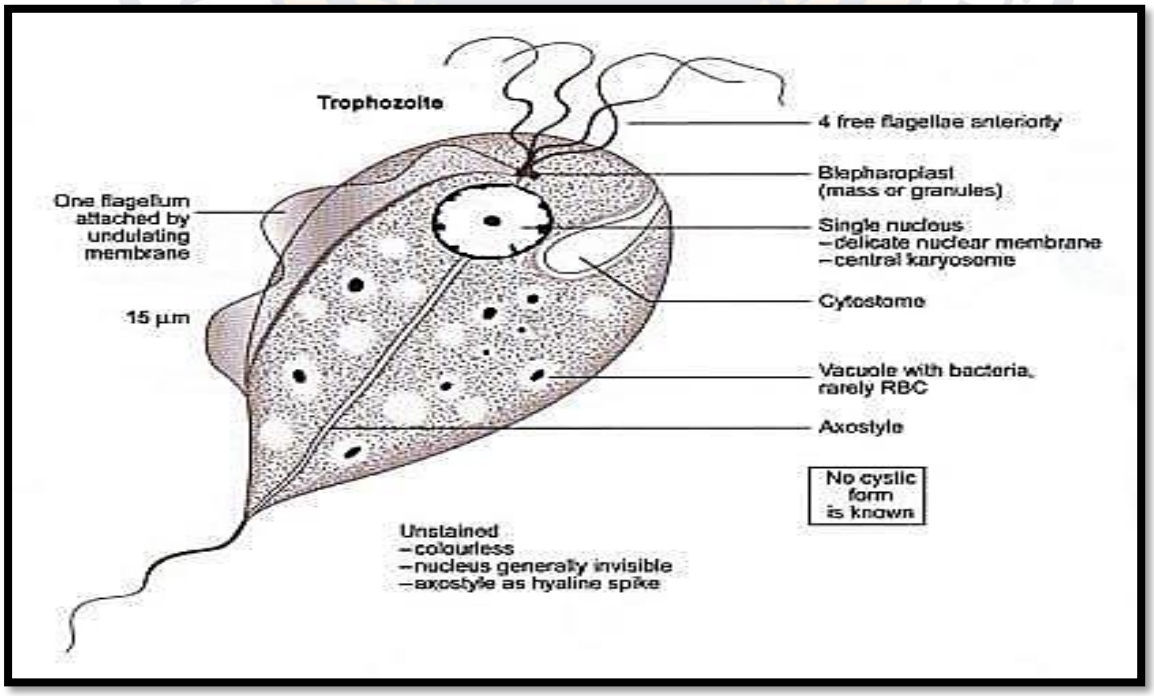
Sexually Transmitted Parasites

Trichomonas vaginalis

- **Geographical distribution:** Worldwide.
- **Morphology:**

☒ **Trophozoite:**

- It is pear-shaped, 17x10 µ, with a rapid jerky movement.
- It has an antero-lateral cytostome.
- The cytoplasm is granular with a single anterior nucleus.
- It has 4 flagella anteriorly, another flagellum attached to the body by undulating membrane, presents at the anterior 1/3 of body with no free end. The 6th flagellum passes through the body as axostyle which projects out of the body.
- A thick marked rod called the parabasal body is present between the axostyle and the undulating membrane.
- It has no cyst stage.



Morphology of *Trichomonas vaginalis* trophozoite.

Life cycle:

☒ **Habitat:**

1. **Females:** Posterior fornix of the vagina, cervix, and urethra.
2. **Males:** Urethra, epididymis, seminal vesicles and prostate.

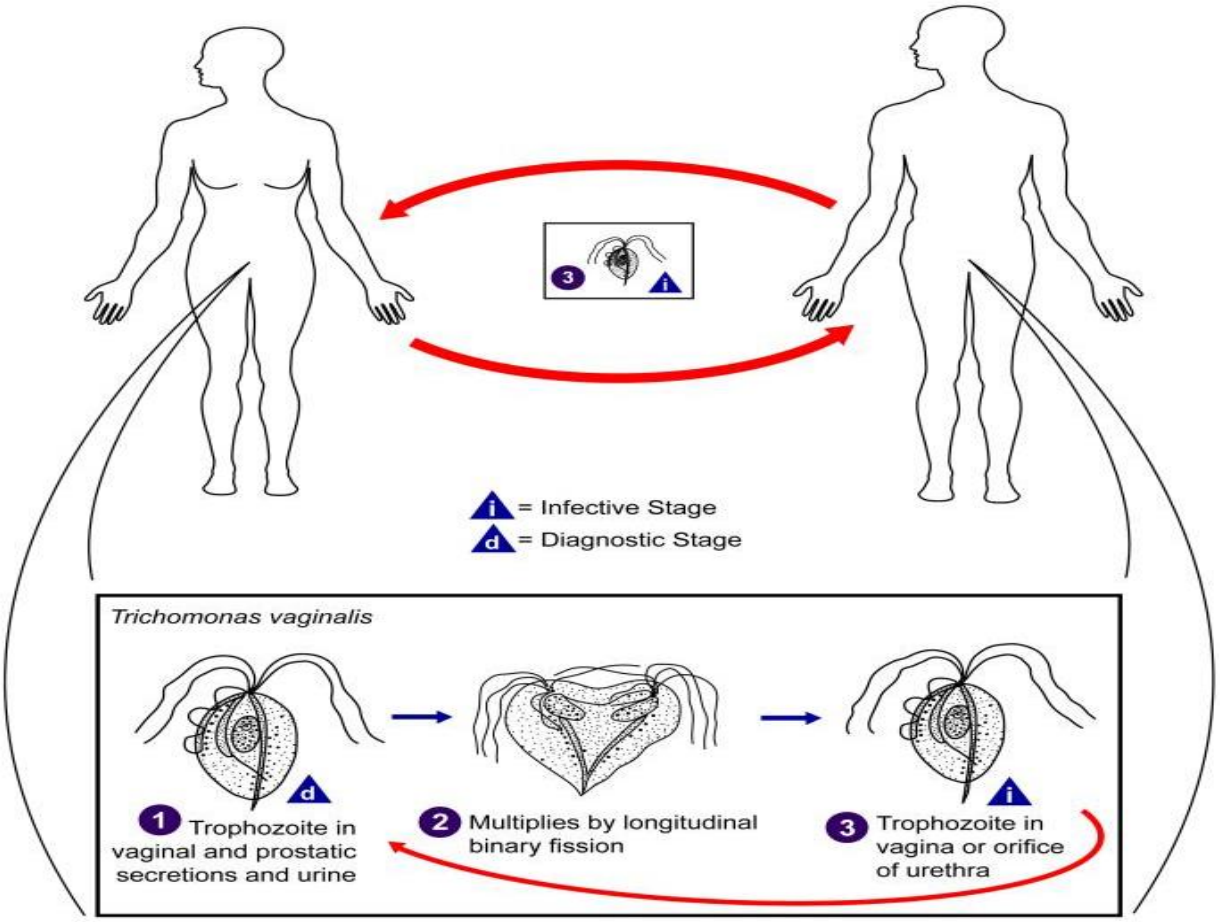
☒ **Definitive host:** Man.

☒ **Infective stage:** Trophozoite.

☒ **Mode of infection:**

1. Sexual transmission or by contaminated toilet seats and towels.
2. From infected mothers to babies during birth.

☒ **Multiplication:** By longitudinal binary fission.



Life cycle of *Trichomonas vaginalis*

Pathogenesis:

☒ Trichomonas vaginalis causes trichomoniasis, trichomonad vaginitis, urethritis, epididymitis, vesiculitis and prostatitis.

☒ The parasite can kill target cells by:

- Direct contact without phagocytosis (dependent cytopathic effect).
- a cell detaching factor: produced by the parasite, and its amount correlates with the severity of the clinical infection.

☒ **In female:**

- The vaginal wall is red, showing oedma, petechial hemorrhages (strawberry mucosa), mucosal erosion and necrosis.
- The mucosa is infiltrated with lymphocytes, plasma cells and polymorphonuclear leucocytes.
- A relationship between trichomoniasis and cervical carcinoma is suggested.

☒ **In male:** urethritis, vesiculitis, epididymitis and prostatitis may occur.

☒ **Predisposing factors for pathogenicity:**

1. Change of the normal vaginal bacterial flora and pH.
2. Decrease in the secretory IgA.

Clinical picture:

☒ Trichomoniasis may be asymptomatic in infected males (95%) and females (50%).

☒ Symptoms may be in the form of:

A. Females:

- Vaginal itching and burning with an offensive, frothy, profuse leucorrheic discharge forming a pool in the posterior fornix.

- Dyspareunia (painful sexual intercourse), frequency of micturition and dysuria, also cystitis may occur.

B. Males:

- Dysuria, and prostate may be enlarged and tender.

C. Newborn:

- Trichomonas respiratory tract infection and conjunctivitis may affect infants during vaginal delivery of an infected mother.

Diagnosis:

A. Clinical diagnosis.

B. Laboratory diagnosis:

1. Microscopy:

☒ **In females:**

- Specimens: are obtained through a vaginal speculum by using cotton–tipped applicator stick, and then the applicator is placed in glucose–saline before examination of the precipitate for the organisms.
- Direct wet smear examination for characteristic jerky motility and shape of trichomonad trophozoites.
- Fixed smears may be stained with Giemsa, Leishman and Papanicolaou stain.

☒ **In males:** Examination of prostatic fluid.

☒ **In both sexes:** Urine examination may beneficial.

2. **Culture:** On modified Diamond's medium.

3. Immunodiagnosis: For detection of T.vaginalis antigens.

- Direct fluorescent antibody test using labeled monoclonal antibodies.
- ELISA.

4. Molecular diagnosis.

Treatment:

1. Both partners must be treated at the same time.
2. Metronidazole is the most effective drug.
3. Restoration of normal vaginal acidity by vaginal douching with lactic acid or vinegar seems beneficial in mild vaginal trichomoniasis.

Prevention and control:

1. Good personal hygiene.
2. Avoidance of sexual contact with infected partners and use of condoms.
3. Treatment of diagnosed cases, and simultaneous treatment of sexual partners.