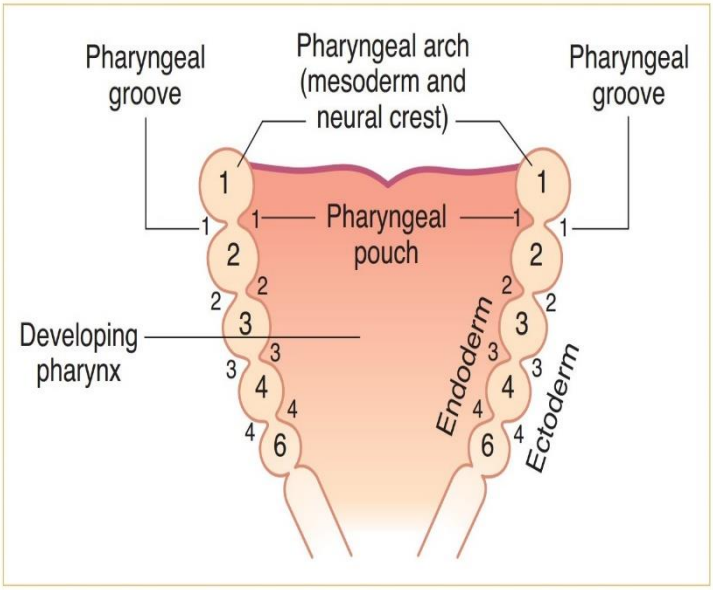
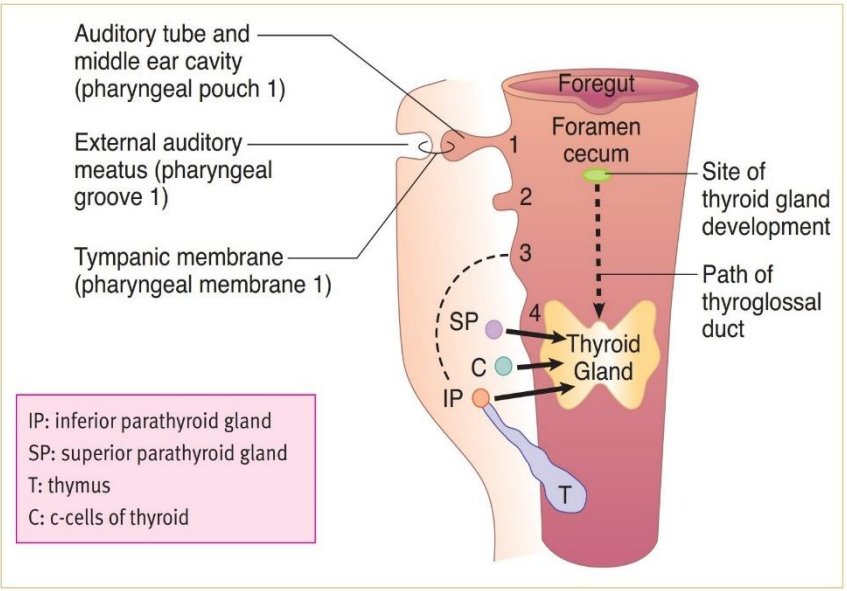
CHAPTER 1

Embryology

Pharyngeal apparatus





- <u>When we take a cut section through the pharynx of developing embryo we will find that:</u>

- The pharynx inside is covered with endoderm, the surface of the embryo's body is covered with ectoderm, between the endoderm inside and the ectoderm outside, it is filled with mesoderm but also lots of neural crest cells migrate to this region.
- The indentations in the outside are called grooves or clefts.
- The indentations in the inside are called pouches.
- The bulges between them are called arches.

- <u>So, the pharyngeal apparatus is composed of:</u>

- Pharyngeal pouches lined with endoderm (in the inner surface).
- Pharyngeal grooves or clefts lined with ectoderm (in the outer surface).
- Pharyngeal arches composed of mesoderm and neuroectoderm.

- <u>CAP covers outside to inside:</u>

- Clefts = ectoderm.
- Arches = mesoderm.
- Pouches = endoderm.

- We have five pharyngeal arches (1, 2, 3, 4, 6), the fifth pharyngeal arch degenerates during development, and four pharyngeal pouches and grooves (1, 2, 3, 4).

- The 1st groove and pouch only where they get deep, the endoderm and the ectoderm fuse together to form a membrane.

- This membrane is what makes the tympanic membrane (ear drum), so:

- The 1st groove must be the external ear canal.
- The 1st pouch must be the middle ear cavity.

- The pouch is directly continuous with the pharynx, which tells us that the middle ear cavity is continuous with the pharynx and this what actually happens through Eustachian tube.

- Mesoderm in pharyngeal arches gives rise to the Muscle, while neural crest cells give rise to bones and cartilage.

- In the middle ear, there are some bones (ossicles), the neural crest cells of the 1st arch give rise to the malleus and incus. The neural crest cells of the 2nd arch give rise to the stapes.

- There are also 2 muscles in the middle ear:

- The tensor tympani muscle comes from the mesoderm of the 1st arch.
- The stapedius muscle comes from the mesoderm of the 2nd arch.

- Each one of the arches has a nerve that goes into it and innervates whatever develops in this arch. Mandibular division of the trigeminal nerve innervate the 1st arch, so every muscle you know that is supplied by mandibular nerve must be a derivative of the 1st arch.

- Why we see only the 1st groove but not the others?

- 2nd through 4th grooves form temporary cervical sinuses but the 2nd arch get really big and grows to cover the 2nd, 3rd and 4th grooves (fill them in).

- However, it sometimes doesn't cover them completely, so you could have a little remnant of the 2nd, or 3rd, or 4th groove that didn't get filled in forming a cyst (ectoderm lined cyst) which is called lateral cervical cyst (pharyngeal cyst).

- Lateral cervical cyst (pharyngeal cyst) is a cyst found in the lateral part of the neck in a child along the anterior border of sternomastoid.

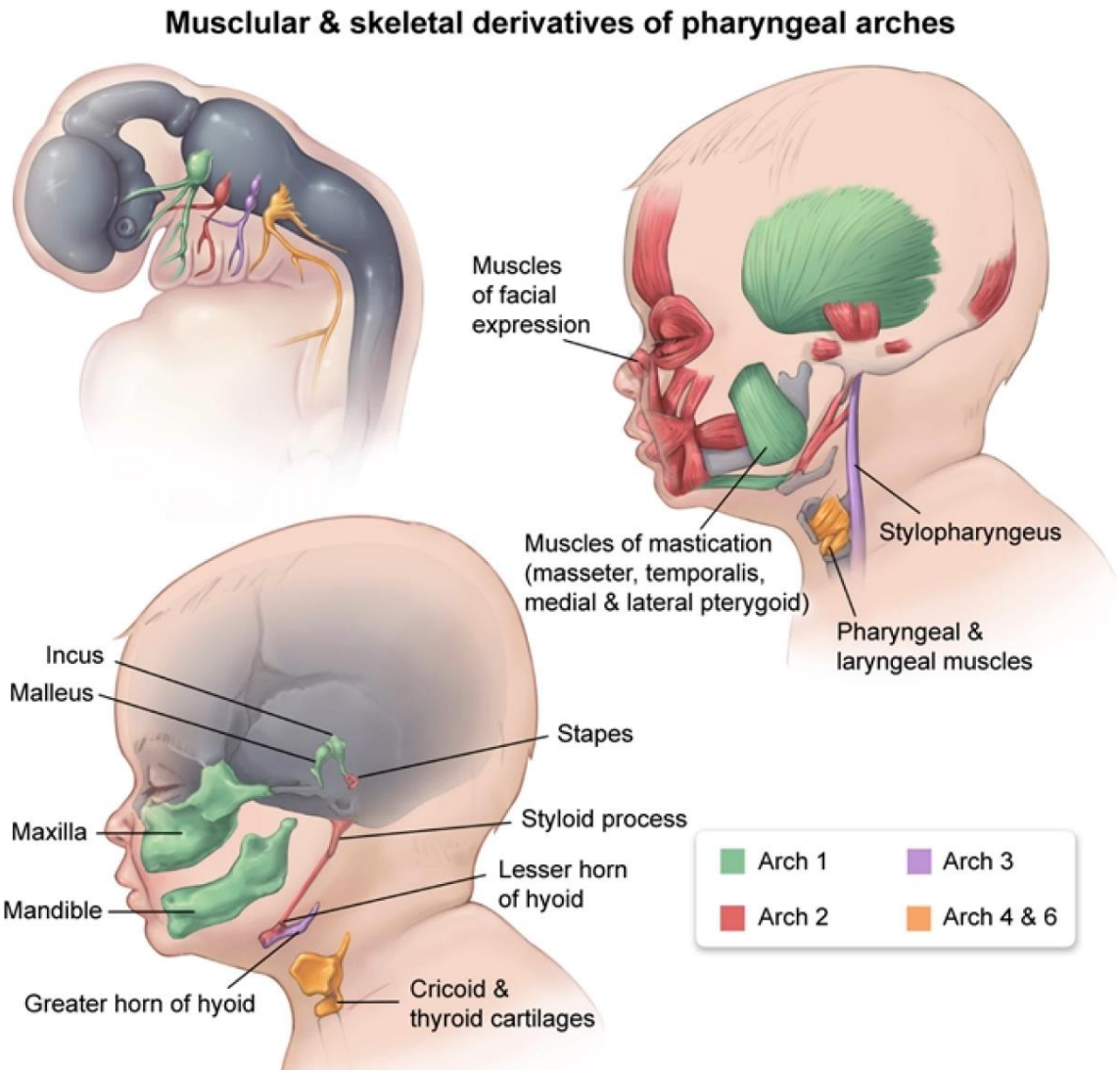
- In lateral cervical sinus, there is no movement of the cyst with swallowing or with protrusion of the tongue.

- The 3rd and 4th pouches cells tend to migrate.

- The cells of the 3rd pouch tend to migrate downward then medially and become the inferior parathyroid gland and others migrate and keep going downward to the thorax to form the thymus, that's why we can find some of the ectopic parathyroid tissue in the chest behind the thymus.

- The cells of the 4th pouch migrate medially to form the superior parathyroid gland and others also migrate medially to form the C cells of the thyroid gland.

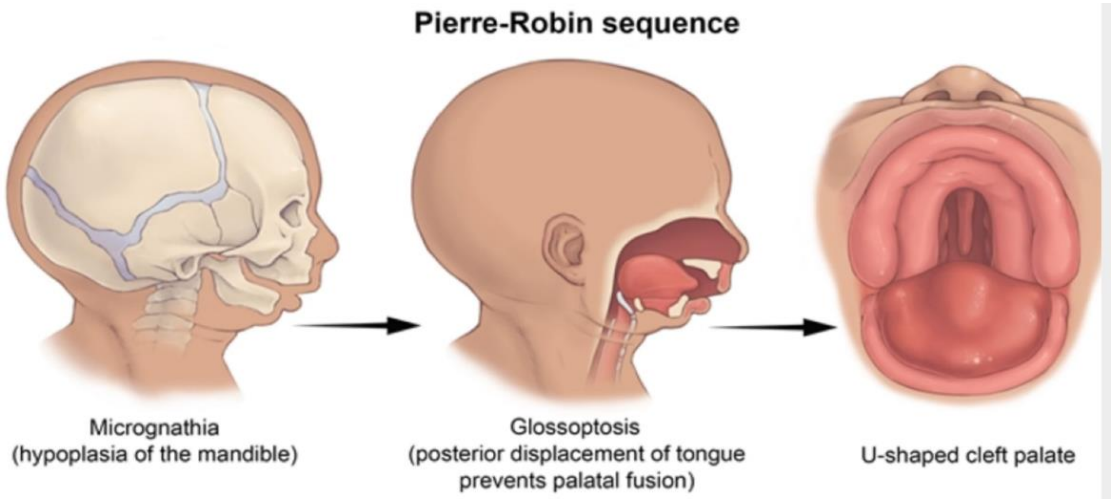
- Ectopic inferior parathyroid gland is more common than the ectopic superior parathyroid gland because inferior parathyroid gland migrates downward.

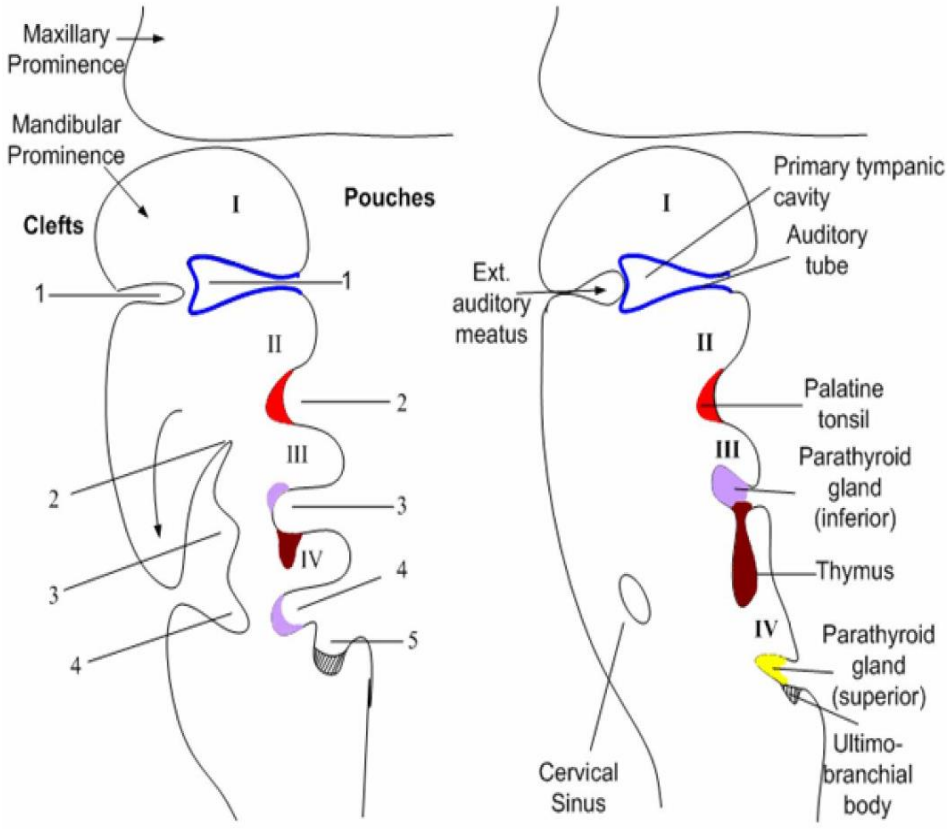


- Branchial arch derivatives:

Arch	Bones & Cartilage	Muscles	Nerves	Abnormalities/comments
1st arch	Maxillary process → Maxilla, zygoMatic bone. Mandibular process → Meckel cartilage → Mandible, Malleus and incus, sphenoMandibular ligament.	Muscles of Mastication (teMporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, tensor veli palatini, anterior 2/3 of tongue	CN V3 Chew	Pierre Robin sequence: micrognathia, glossoptosis, U shaped cleft palate, airway obstruction due to abnormally located tongue Treacher Collins syndrome: Autosomal dominant neural crest failure to migrate of the 1st and 2nd pharyngeal arches → craniofacial abnormalities (zygomatic bone and mandibular hypoplasia) often result in airway compromise and feeding difficulties, hearing loss due to absent or abnormal ossicles
2nd arch	Reichert cartilage: Stapes, Styloid process, leSSer horn of hyoid, Stylohyoid ligament	Muscles of facial expression, Stapedius, Stylohyoid, platySma, posterior belly of digastric	CN VII (facial expression) smile	Congenital pharyngo-cutaneous fistula: persistence of cleft and pouch → fistula between tonsillar area and lateral neck.
3rd arch	Cartilage: greater horn of hyoid	Stylopharyngeus (think of stylopharyngeus innervated by glossopharyngeal nerve)	CN IX (stylo-pharyngeus) swallow stylishly	
4th–6th arches	Cartilages: thyroid, cricoid, arytenoids, corniculate, cuneiform.	4th arch: most pharyngeal constrictors; cricothyroid, levator veli palatini. 6th arch: all intrinsic muscles of larynx except cricothyroid.	4th arch: CN X (superior laryngeal branch) simply swallow. 6th arch: CN X (recurrent laryngeal branch) speak	Arches 3 and 4 form posterior 1/3 of tongue. Arch 5 makes no major developmental contributions.

- Mnemonic: When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).


Pierre-Robin sequence
Micrognathia
(hypoplasia of the mandible)
Glossoptosis
(posterior displacement of tongue
prevents palatal fusion)
U-shaped cleft palate


Maxillary Prominence
Mandibular Prominence
Clefts
Pouches
I
II
III
IV
1
2
3
4
5
Primary tympanic cavity
Auditory tube
Ext. auditory meatus
Palatine tonsil
Parathyroid gland (inferior)
Thymus
Parathyroid gland (superior)
Ultimo-branchial body
Cervical Sinus

- Branchial pouch derivatives:

Pouch	Derivatives	Notes	Mnemonic
1st pouch	Develops into middle ear cavity, eustachian tube, mastoid air cells.	1st pouch contributes to endoderm-lined structures of ear.	Ear, tonsils, bottom-to-top: 1 (ear), 2 (tonsils), 3 dorsal (bottom for inferiorparathyroids), 3 ventral (to = thymus), 4 (top = superiorparathyroids).
2nd puch	Develops into epithelial lining of palatine tonsil.		
3rd pouch	Dorsal wings: develop into inferior parathyroids. Ventral wings: develop into thymus.	3rd pouch contributes to 3 structures (thymus, left and right inferior parathyroids). 3rd-pouch structures end up below 4th-pouch structures.	
4th pouch	Dorsal wings: develop into superior parathyroids. Ventral wings: ultimopharyngeal body → parafollicular (C) cells of Thyroid		

- Pharyngeal grooves (clefts):

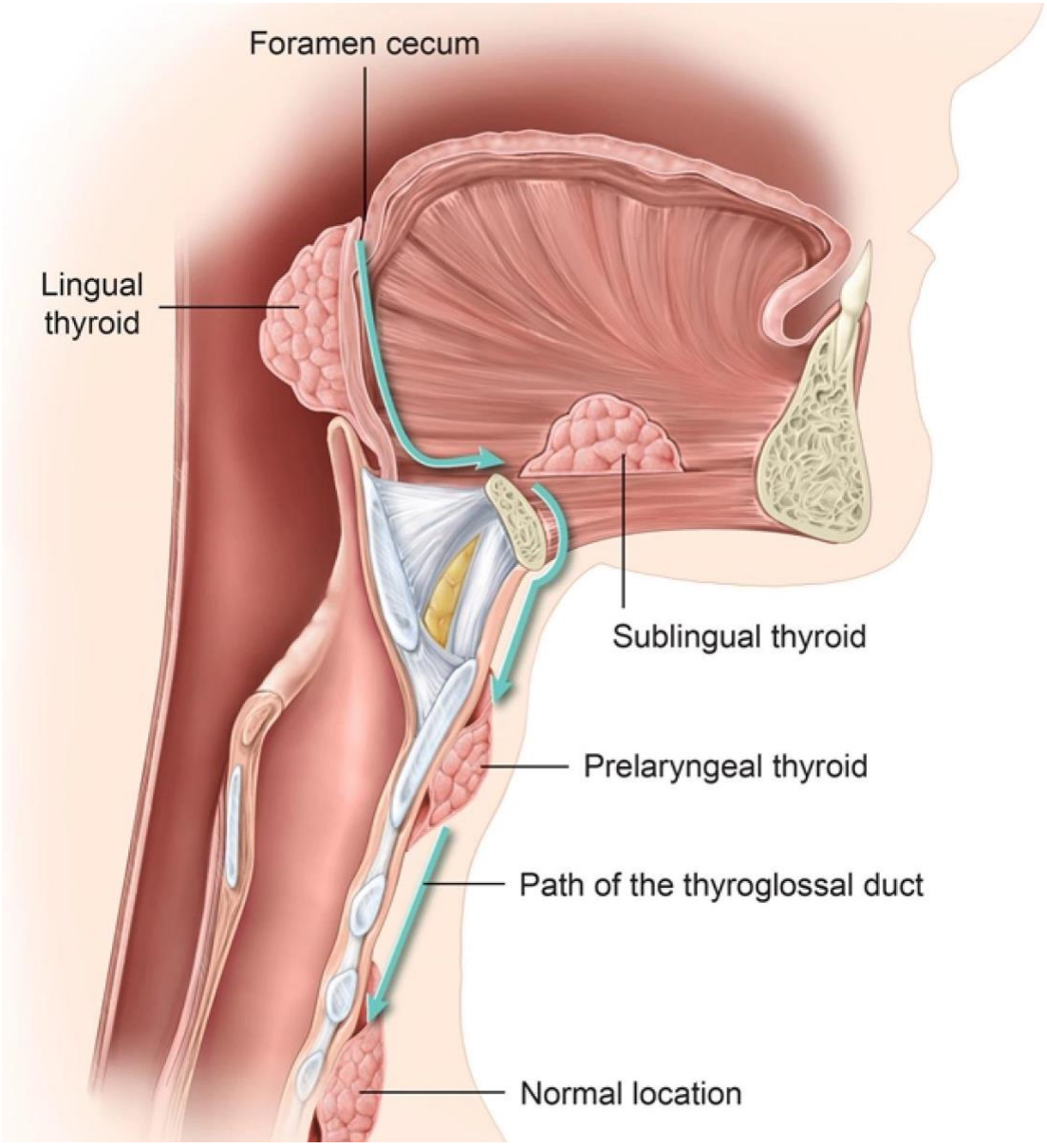
- Pharyngeal groove 1 give rise to the epithelial lining of external auditory meatus.

- Normally, the second, third, and fourth pharyngeal grooves are obliterated by overgrowth of the second pharyngeal arch.

- Failure of a groove to be completely obliterated results in a branchial cyst or lateral cervical cyst.

Thyroid gland

- The thyroglossal duct that develops from the midline of the pharynx goes downward infront of the pharynx then the distal end of this diverticulum enlarges and becomes the thyroid gland.
- The thyroid gland migrates caudally to its adult anatomic position in the neck but remains connected to the tongue via the thyroglossal duct, which is later obliterated.
- Foramen cecum is normal remnant of thyroglossal duct.



Lingual thyroid

- The normal thyroid gland is situated in the lower anterior neck, in front of the upper trachea and larynx.
- The thyroid gland is an outpouching, or evagination, of the pharyngeal epithelium that descends to the lower anterior neck. The thyroid gland develops at the lower end of this pharyngeal evagination.
- The remaining portion of the evagination forms the thyroglossal duct, which extends from the foramen cecum on the dorsal surface of the tongue to the superior border of thyroid isthmus.
- Due to failure of migration, the thyroid can form at any part along the thyroglossal duct's usual path (Ectopic thyroid). If the thyroid fails to migrate downward, it can form within the tongue and is called a "lingual thyroid". Sometimes, this lingual thyroid is the only thyroid tissue in the body. If it is removed, significant hypothyroidism occurs.
- Enlargement of a lingual thyroid can lead to obstructive symptoms (dysphagia, dysphonia, dyspnea), typically during times of heightened thyroid stimulation (puberty, pregnancy).
- Surgeons should be careful when removing any mass along the thyroglossal duct's usual path, as the mass could be the only thyroid tissue present in a patient.
- Defective migration is also responsible for other endocrinological disorders. Failure of GnRH-secreting neurons to migrate from the olfactory lobes to the hypothalamus describes Kallmann's syndrome. Failure of the testes to migrate from their intra-abdominal location to scrotum is called cryptorchidism.

Thyroglossal cyst

- Since the thyroglossal duct is supposed to fuse, it is sometimes doesn't fuse completely. Incomplete fusion of thyroglossal duct leads to → endodermal lined cyst called thyroglossal cyst (median cervical cyst) which moves with swallowing and with protrusion of the tongue.
- It occurs due to unobliterated portion of thyroglossal duct at any point of its course.
- It presents as anterior midline neck mass that moves with swallowing or protrusion of the tongue due to its relation to hyoid bone (branchial cleft cyst in lateral neck which doesn't move with swallowing).

Thyroglossal fistula

- It is an acquired fistula (never congenital) due to:

- Infection of thyroglossal cyst leading to rupture.
- Inadequate excision of the cyst.

DiGeorge syndrome (22q11 deletion)

- 3rd and 4th pouches fail to differentiate into thymus and parathyroid glands.

- Symptoms:

- Parathyroid aplasia → ↓ PTH → hypocalcemia → tetany.

- Thymic aplasia → T cell deficiency → recurrent viral and fungal infections, but cell mediated immunity still functional and can fight bacterial infection.

- Absent thymic shadow in CXR.

- Congenital heart and great vessel defects.

- Patients with DGS may have abnormal facial feature: short palpebral fissures, micrognathia, bifid uvula, and cleft palate.

CHAPTER 2

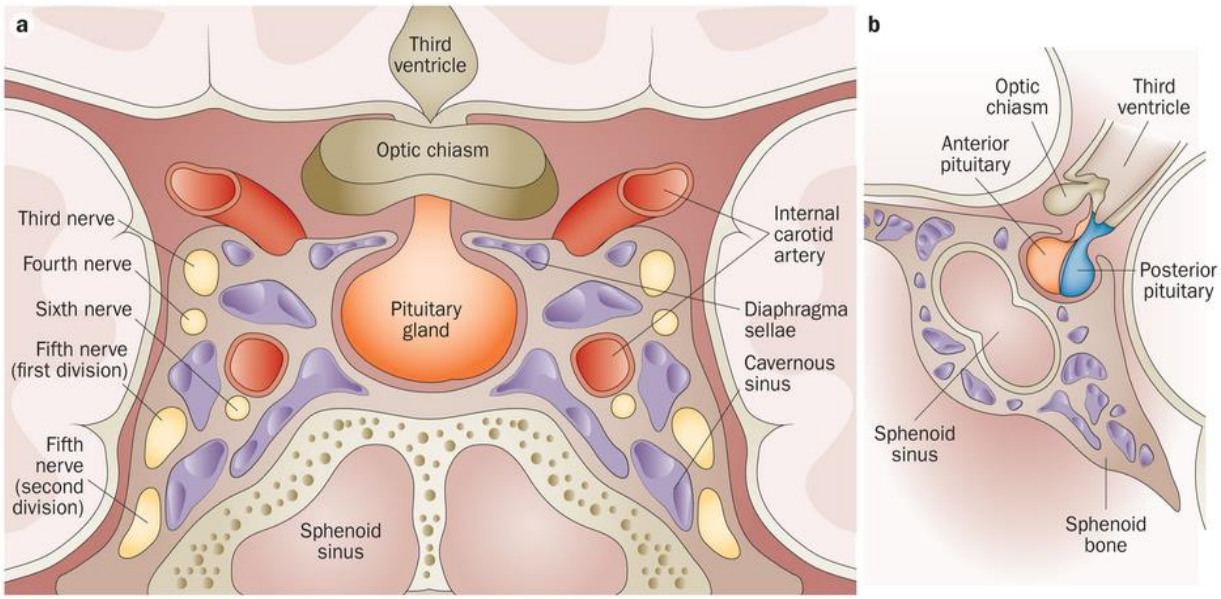
Anatomy & Pathophysiology

Hypothalamic – Anterior Pituitary System

- The hypothalamic hormones are synthesized in the neuron cell body, packaged in vesicles, and transported down the axons to be stored and released from the nerve terminals.
- The hormones are then secreted into the hypophyseal-portal system and transported to the anterior pituitary.
- The hypophyseal-portal system allows delivery of releasing and inhibitory hormones from the hypothalamus directly to anterior pituitary gland, where they control the production and release of trophic hormones into systemic circulation.
- Hypothalamic hormones bind to receptors on cells of the anterior pituitary and modify the secretion of its hormones.

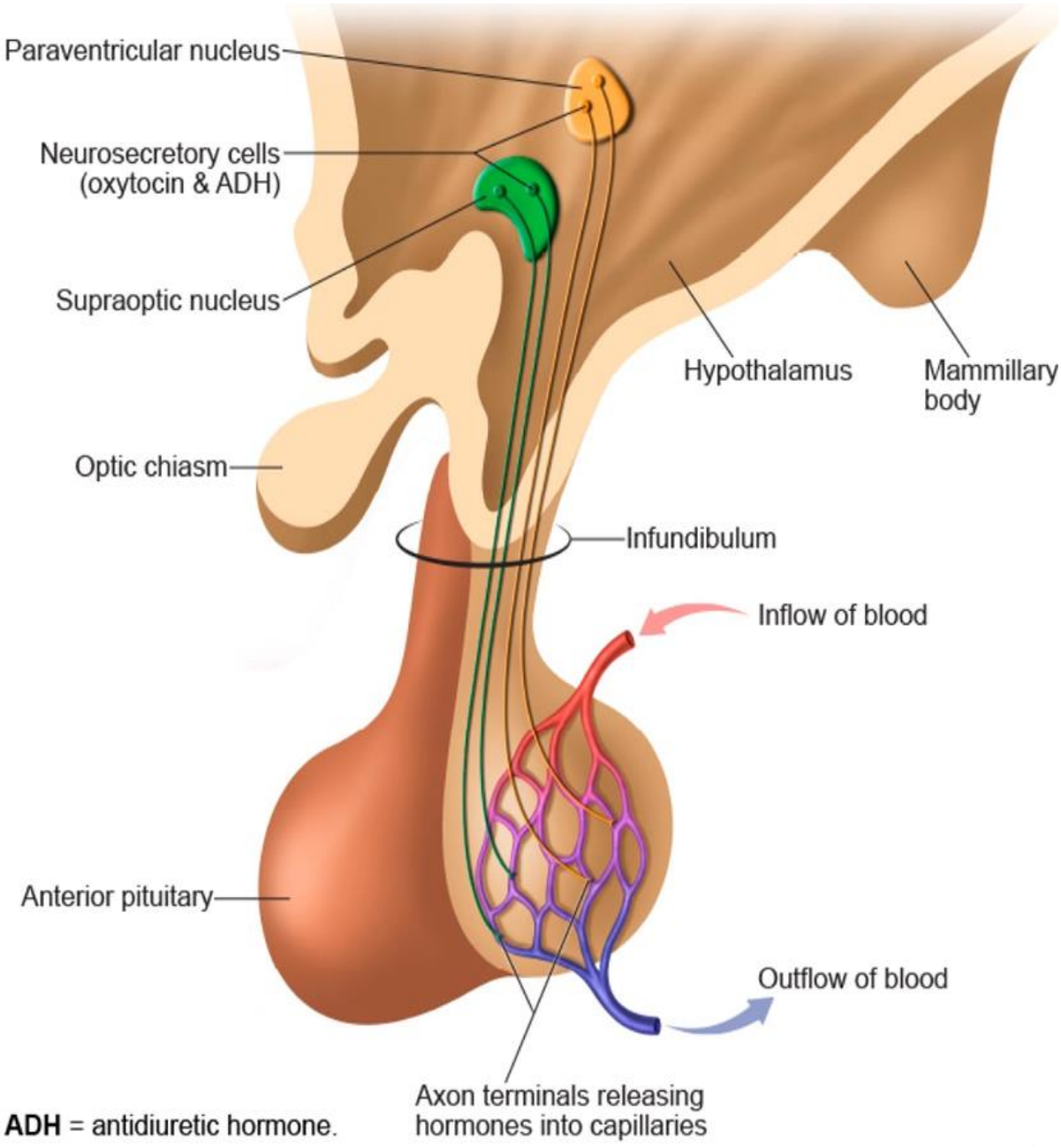
Pituitary gland

- The pituitary gland also called the hypophysis, is a small gland that lies in the Sella turica, a bony cavity at the base of the brain, the arachnoid membrane (diaphragma sellae) separates it from and prevents cerebrospinal fluid from entering the Sella turcica.
- Optic chiasm is 5-10 mm above this diaphragm.
- The pituitary gland is connected to the hypothalamus by the pituitary (hypophyseal) stalk.
- Compression of the pituitary stalk by suprasellar tumor causes a decrease in all anterior pituitary hormones except prolactin which increases leading to prolactinemia.



❖ N.B:

- Although sarcoidosis classically causes noncaseating granulomas involving the lungs, lymph nodes, and skin, granulomas can form in any tissue.
- Sarcoidosis can also involve the hypothalamus (neurosarcoidosis).
- Mass lesions in the hypothalamus or pituitary stalk can disrupt the hypothalamic-pituitary axis by obstructing the hypophyseal portal system.
- Unlike other pituitary hormones, prolactin release is negatively regulated by dopamine produced in the hypothalamus. Dopamine acts on the dopamine D_2 receptors of lactotrophs, the prolactin-producing cells of the pituitary.
- Disruption of dopaminergic pathways (by an infiltrating sarcoid lesion) in the pituitary stalk leads to loss of inhibition and a subsequent increase in prolactin.



- Physiologically, the pituitary gland is divisible into two distinct portions:

A. Anterior pituitary:

- Also known as adenohypophysis originates from the Rathke's pouch, which is an embryonic invagination of the pharyngeal epithelium.

- Secretes FSH, LH, ACTH, TSH, prolactin, GH.

- α subunit hormone subunit common to TSH, LH, FSH, and hCG.

- β subunit determines hormone specificity.

B. Posterior pituitary:

- Also known as the neurohypophysis.

- Derived from neuroectoderm.

- Secretes vasopressin (antidiuretic hormone, or ADH) and oxytocin, made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins).

- Anterior pituitary hormones:

- There is one cell type of each major hormone formed in the anterior pituitary gland. At least five cell types can be differentiated:

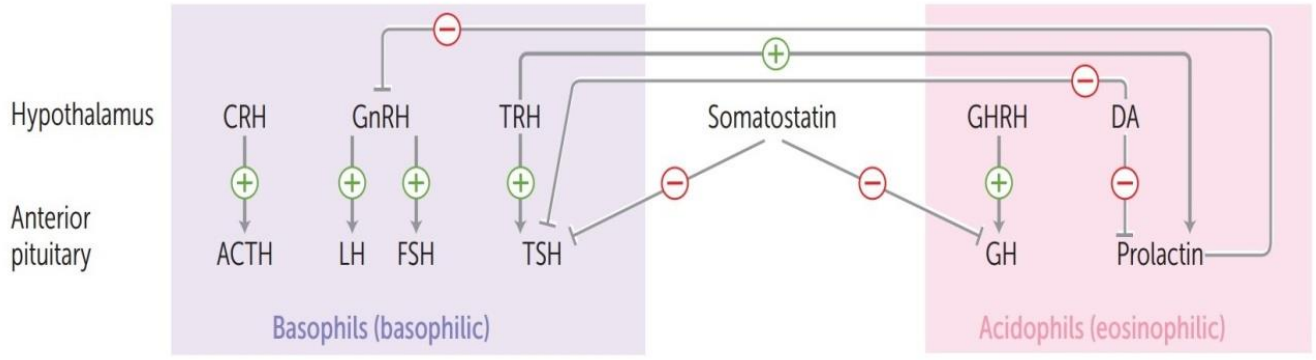
1. Somatotropes: for human growth hormone (GH).
2. Corticotropes: for adrenocorticotropic hormone (ACTH).
3. Thyrotropes: for thyroid stimulating hormone (TSH).
4. Gonadotropes: for gonadotropic hormones which include both lutenizing-hormone (LH) and follicle-stimulating hormone (FSH).
5. Lactotropes: for prolactin (PRL).

- FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH.
- B-FLAT: Basophils → FSH, LH, ACTH, TSH.
- Acid PiG: Acidophils → PRL, GH.

- Hypothalamic pituitary hormones:

- The hypothalamus secretes many substances which affect the secretion of anterior pituitary by secreting releasing or inhibiting hormones.

Hormone	Function	Clinical notes
ADH	↑ water permeability of distal convoluted tubule and collecting duct cells in kidney to ↑ water reabsorption	Stimulus for secretion is ↑ plasma osmolality, except in SIADH, in which ADH is elevated despite ↓ plasma osmolality
CRH	↑ACTH, MSH, B-endorphin	↓in chronic exogenous steroid use.
Dopamine (Also called prolactin-inhibiting factor)	↓Prolactin, ↓ TSH	Dopamine antagonists (antipsychotics) can cause galactorrhea due to hyperprolactinemia.
GHRH	↑GH	Analog (tesamorelin) used to treat HIV associated lipodystrophy.
GnRH	↑FSH, LH	Suppressed by hyperprolactinemia Pulsatile GnRH leads to puberty, fertility. Tonic GnRH analog (leuprolide) suppresses Hypothalamic-pituitary-gonadal axis.
MSH	↑ melanogenesis by melanocytes	Causes hyperpigmentation in Cushing disease, as MSH and ACTH share the same precursor molecule, proopiomelanocortin
Oxytocin	Causes uterine contractions during labor. Responsible for milk letdown reflex in response to suckling.	Modulates fear, anxiety, social bonding, mood, and depression
Prolactin	↓GnRH Stimulates lactogenesis.	Pituitary prolactioma → amenorrhea, osteoporosis, hypogonadism, galactorrhea. Breastfeeding → ↑ prolactin → ↓ GnRH → delayed postpartum ovulation (natural contraception)
Somatostatin (Also called growth hormone inhibiting hormone)	↓GH, ↓ TSH	Analogs used to treat acromegaly.
TRH	↑TSH, ↑ Prolactin	↑ TRH (in 1°/2° hypothyroidism) may increase prolactin secretion → galactorrhea



Growth Hormone

- Also called somatotropin.

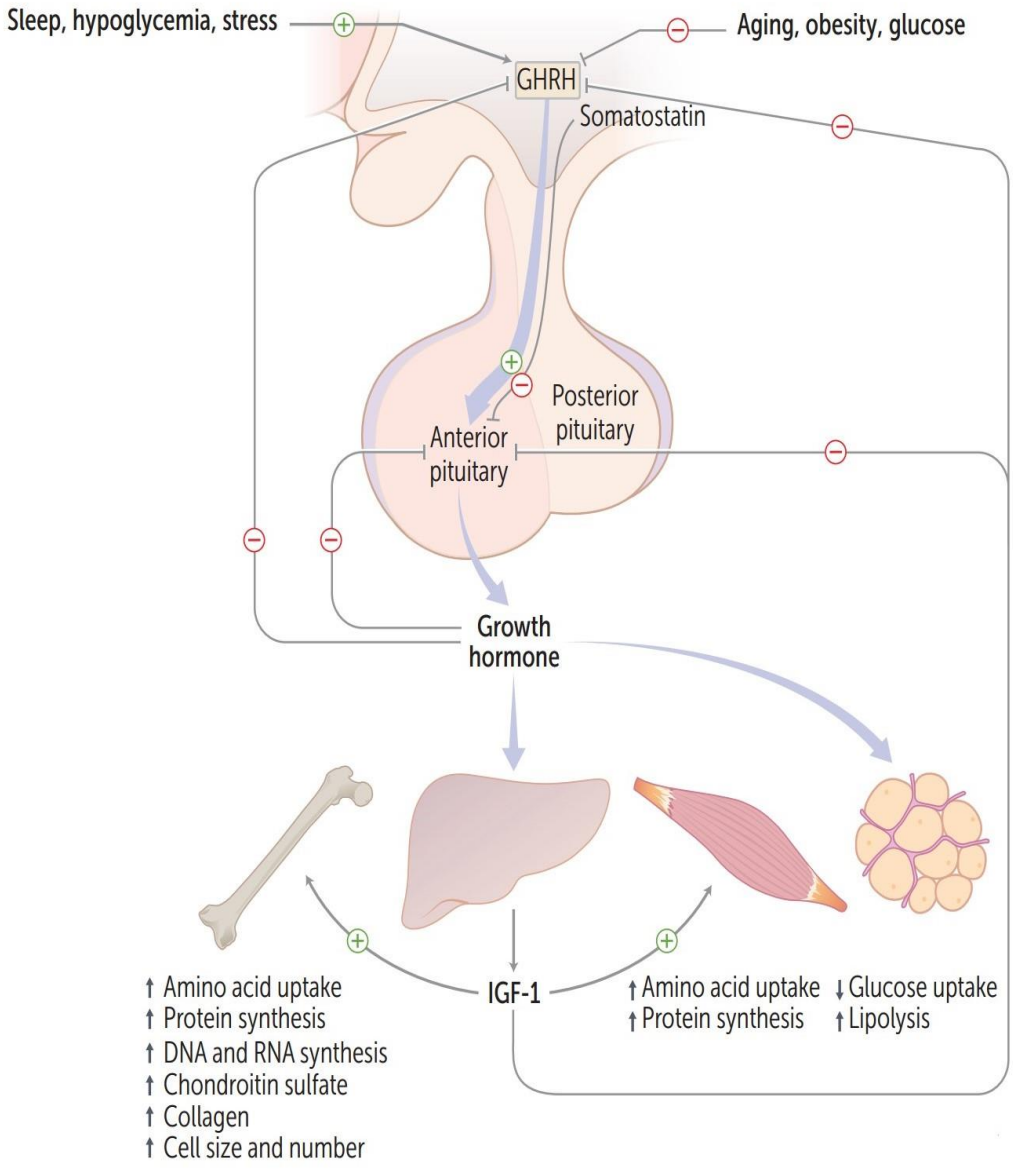
- Source:

- Secreted by the anterior pituitary.

- Released in pulses in response to growth hormone-releasing hormone (GHRH).

- Secretion ↑ during exercise, deep sleep, puberty, hypoglycemia, CKD.

- Secretion ↓ by glucose, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).



- Function:

- Growth hormone is a major anabolic growth-promoting hormone and a stress hormone.

- All anabolic hormones (growth hormone, insulin, thyroid hormones, and androgens) are required for normal growth.

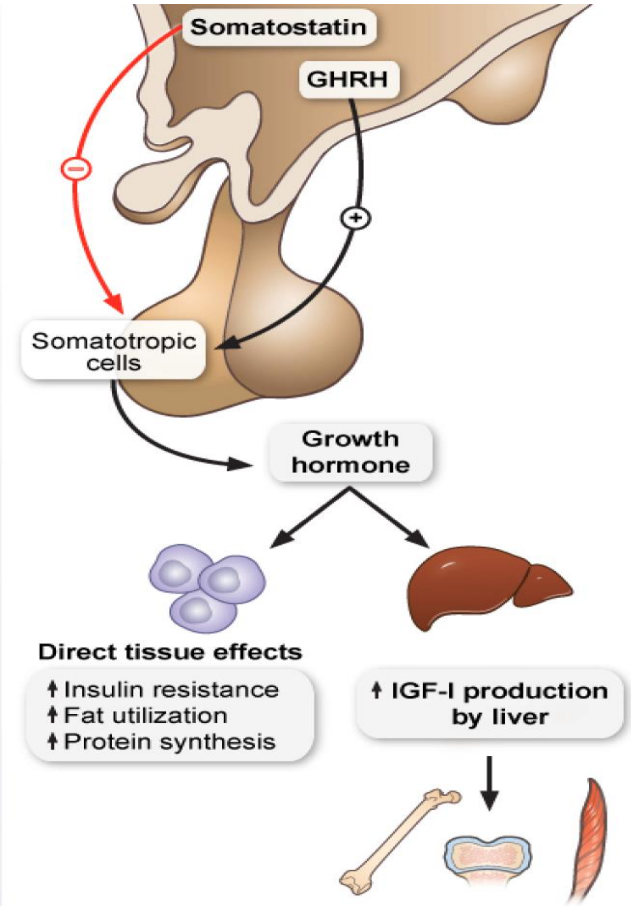
- Direct catabolic effect which is consistent with its actions as a stress hormone:
  - Decreases uptake of glucose in adipose tissue and muscles → raises blood glucose.
  - Mobilizes fats by increasing the activity of hormone sensitive lipase → ↑ free fatty acids.
  - ↑ insulin resistance (diabetogenic).

- Direct anabolic effect consistent with its action as a growth hormone: Increases uptake of amino acids into cells.

- Indirect anabolic effects: Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver.

- Most of the anabolic actions of growth hormone are an indirect result of increased production of growth factors, which are called somatomedin C, or insulin-like growth factor I (IGF- I).

- The major known anabolic effect of IGF-I is that it increases the synthesis of cartilage (chondrogenesis) in the epiphyseal plates of long bones, thereby increasing bone length.



- Disturbance of GH function:

- These disturbances may be either hypofunction or hyperfunction.

A. Effects of hyperfunction:

- Excess secretion of GH (pituitary adenoma) may cause acromegaly (adults) or gigantism (children).

- If there is excess growth hormone before closure of the epiphysis, it is called → gigantism a condition characterized by a tall stature and long limbs.

- After closure of the epiphysis, the condition is called → acromegaly.

- Although gigantism and acromegaly are caused by the same excess hormone, the symptoms not alike.

Gigantism

- Cause: Due to increase in growth hormone before adolescence and before the union of epiphysis with the shaft as a result of acidophilic adenoma (pituitary adenoma).

- Characters:

- Because it occurs before the union of epiphysis with the shaft, there is symmetrical overgrowth of all bones, so that the patient become taller than normal but with normal proportions (span = height, and vertex to symphysis = symphysis to heel).

- Symmetrical overgrowth of all soft tissues, splenomegaly and muscles at first strong while later on very weak due to over stretch.

- Hyperglycemia, glycosuria and in about 10 percent diabetes mellitus eventually develops.

- Treatment: Somatostatin analogs (octreotide) or surgery.

Acromegaly

- Cause:

- It occurs when hyperfunction develops after the ossification and union of the epiphyses of long bones (after puberty).

- It is almost always due to macroadenoma (> 1 cm) of the anterior pituitary and second in frequency to prolactinomas.

- Characters:

- Increased IGF-I causes most of the deleterious effects of acromegaly, but growth hormone excess directly causes the hyperglycemia and insulin resistance.

- There is no linear growth of long bones.

- All bones of the body (flat & long) increase in thickness, which is clearer in the terminal portions of the skeleton (increased hat, ring, shoe size).

- The limbs (hands, feet, fingers, digits) became large & broad (acro = periphery, megaly = enlarged).

- Growth of the skull flat bones produces a characteristic acromegalic facies. It is box shaped with prominent cheeks, nasal bones, super ciliary ridges, and a protruded lower jaw (proganthism) with widely separated teeth.

- The joints are also frequently involved in acromegaly, as excessive GH causes hyperplasia of articular chondrocytes and synovial hypertrophy, leading to wear and degeneration of articular cartilage and periarticular bone (hypertrophic arthropathy).

- In the heart, chronic GH elevation stimulates cardiac growth, causing left ventricular hypertrophy, diastolic dysfunction, and possible heart failure.

- Soft tissue involvement is also common and manifests as macroglossia, deepening of the voice (due to laryngeal soft tissue growth), carpal tunnel syndrome, and peripheral neuropathy.

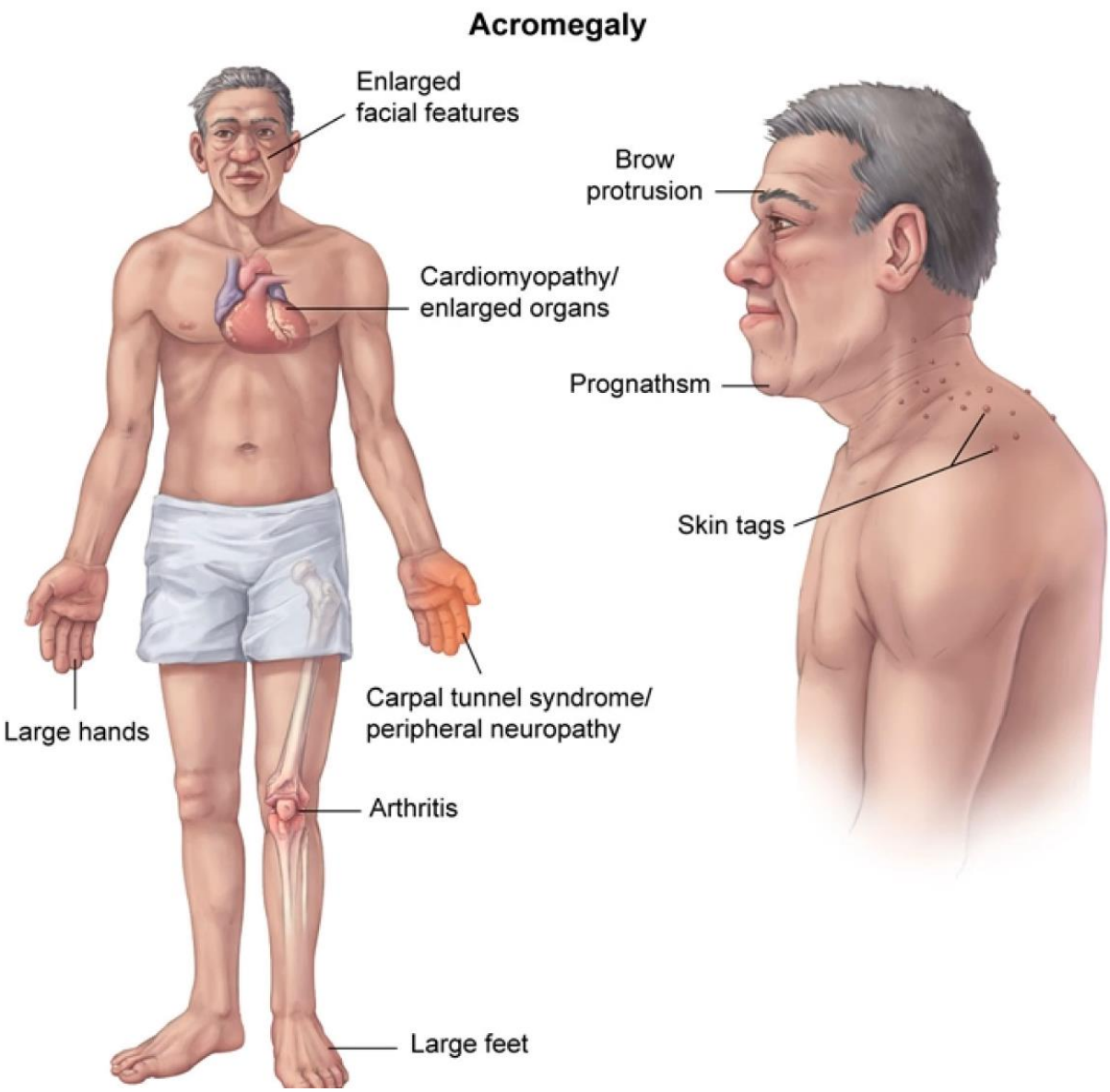
- Pituitary enlargement may press on the optic chiasma → bitemporal hemianopia.

- Hyperglycemia, glycosuria and secondary diabetes due to exhaustion of beta cells occur late in the disease.

- A structural chemical similarity between GH and prolactin molecule produces in male → hypogonadism and galactorrhea.

- Diagnosis: Measurement of IGF-I is a useful screening measure and confirms diagnosis with the lack of growth hormone suppression by oral glucose (not somatostatin).

- Treatment: somatostatin analogs (octreotide) or surgery.



B. Effects of hypofunction:

Pituitary dwarfism

- Short stature (100-120 cm) due to pituitary hypofunction may be due to:

- GHRH (growth hormone releasing hormone deficiency) deficiency.

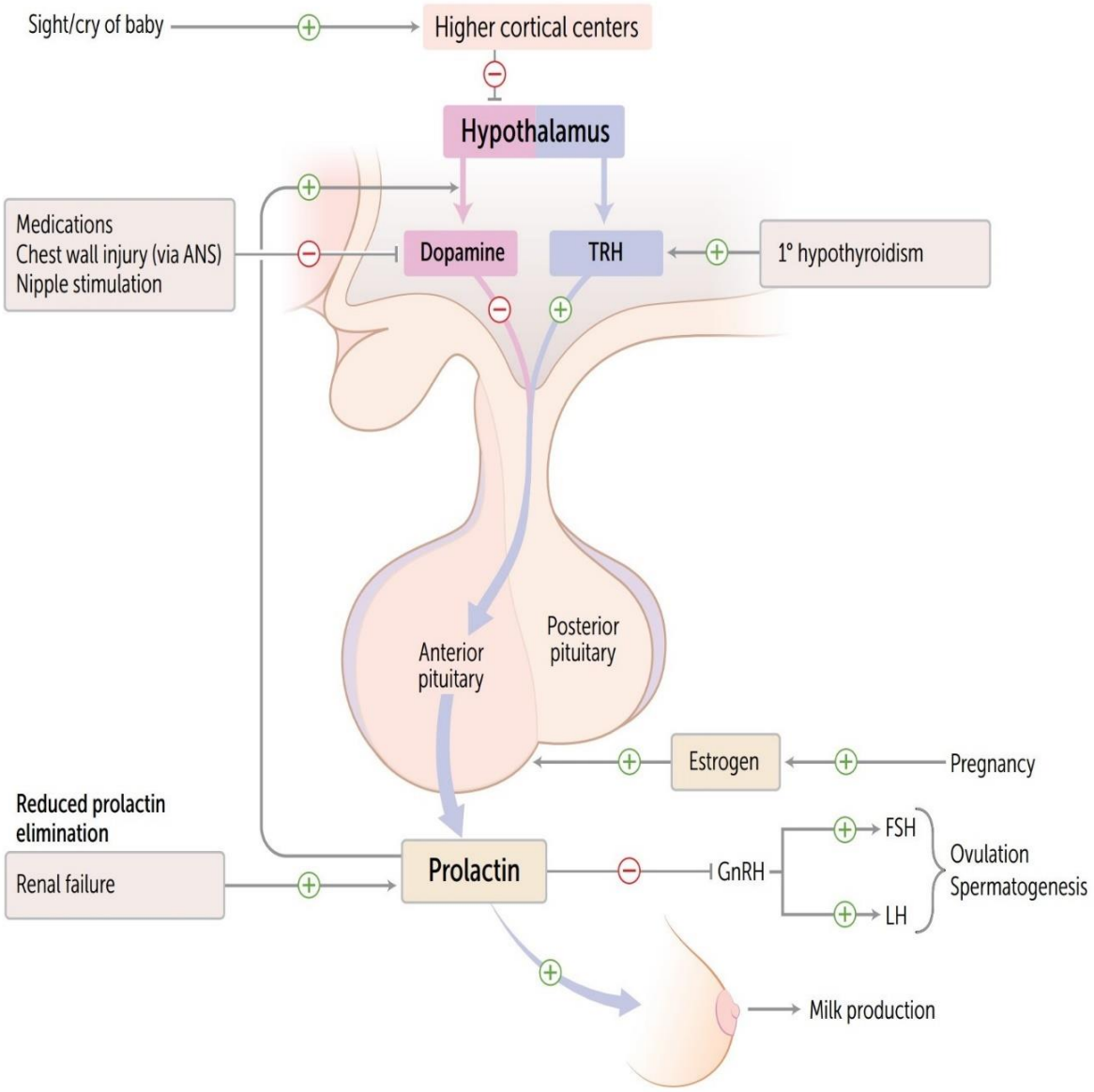
- GH deficiency.

- GH insensitivity: mutation of GH receptor gene leading to defective growth hormone receptors which will lead to decrease in linear growth and is called Laron dwarfism. It is characterized by high serum levels of growth hormone in the presence of low IGF-1 levels.

- There is a decrease in the size of the trunk and all extremities, but they are well proportioned (span = height, vertex to symphysis = symphysis to heel).
- They are mentally and sexually normal.
- Treatment: Human growth hormone synthesized by E. Coli bacteria by recombinant DNA technology.

Prolactin

- Source:
  - Secreted from lactotrophs of the anterior pituitary gland.
  - Structurally homologous to growth hormone.
- Function:
  - The primary physiologic action of prolactin is preparation of the breasts for milk production/lactation in the postpartum period.
  - Prolactin also suppresses gonadotrophin-releasing hormone (GnRH) production from the hypothalamus, which causes inhibition of ovulation in females → amenorrhea, and inhibition of spermatogenesis in males.
- Regulation:
  - Prolactin secretion from anterior pituitary is tonically inhibited by dopamine from hypothalamus.
  - Prolactin in turn inhibits its own secretion by ↑ dopamine synthesis and secretion from hypothalamus.
  - TRH ↑ prolactin secretion (in 1° or 2° hypothyroidism).
  - Dopamine agonists (bromocriptine) inhibit prolactin secretion and can be used in treatment of prolactinoma.
  - Dopamine antagonists (most antipsychotics) and estrogens (OCPs, pregnancy) stimulate prolactin secretion.



Pituitary adenoma

- Hyperplasia of only one type of endocrine cells found in pituitary.
- May be nonfunctioning (silent) or hyperfunctioning (hormone-producing).
- Most commonly from lactotrophs (prolactin) → hyperprolactinemia (Approximately 60%).
- Less commonly, from somatotrophs (GH) → acromegaly, gigantism; corticotrophs (ACTH) → Cushing disease.
- Rarely, from thyrotrophs (TSH), gonadotrophs (FSH, LH).
- Pituitary tumors can grow beyond the limits of the sella turcica, causing compression and erosion of surrounding structures.

- If the pituitary tumor grows superiorly, it erodes the optic chiasm; laterally, it invades the cavernous sinus; inferiorly, it grows into the sphenoid sinus. A growing pituitary tumor can also compress normal pituitary cells, causing hypopituitarism.

- Compression of the optic chiasm by suprasellar extension of pituitary tumors causes the characteristic bitemporal hemianopsia. Headache may also present due to an increase in intracranial pressure, caused by mass effect of the tumor.

Hyperprolactinemia

- Unlike secretion of other pituitary hormones, prolactin is under tonic (constant) inhibition by dopamine secretion from the hypothalamus.

- Causes of hyperprolactinemia:

A. Hypothalamic destruction causes hyperprolactinemia by loss of this tonic inhibition.

B. The secretion of prolactin is unique in that it is regulated by the inhibitory effect of hypothalamic dopamine. Dopamine acts on the D_2 receptors of lactotrophs, causing the release and synthesis of prolactin to decrease. Medications such as phenothiazines also act on this receptor and cause hyperprolactinemia at certain doses. Risperidone is a very effective anti-psychotic drug often used in the management of schizophrenia. Because risperidone has anti-dopaminergic action, it decreases dopaminergic D_2 receptor activity, causing a loss of feedback inhibition on prolactin-producing lactotrophs, which can cause amenorrhea and galactorrhea.

C. Prolactinoma (the most common hyperfunctioning pituitary adenoma):

- Prolactinomas stimulate inappropriate milk production in nonpostpartum females (galactorrhea). Prolactin also suppresses gonadotrophin-releasing hormone (GnRH) production from the hypothalamus, which causes decreased libido, amenorrhea, and infertility.

- Prolactinomas in males generally have a delayed diagnosis because men are often reluctant to report erectile dysfunction. Hence, prolactinomas in men are typically much larger at the time of presentation than in women.

- Postmenopausal women with prolactinomas are already amenorrheic and infertile, so they present mainly with headaches and visual field defects.

- As hyperprolactinemia causes hypogonadism → low estrogen in females, affected patients are at risk for accelerated bone loss. Estrogens maintain bone mass in females, so any loss of estrogen-whether from menopause, hormone imbalances, or surgical removal of the ovaries-leads to loss of bone density. Severe loss of bone density is described by the word "osteoporosis".

- If hyperprolactinemia is not treated, prolonged hypogonadism (low estrogen) causes accelerated bone loss exactly as it occurs with postmenopausal osteopenia/osteoporosis. Low bone density puts patients

at high risk for fragility fractures (fractures sustained with minimal trauma such as a fall from standing height, also called pathological fractures).

- Vaginal dryness is another very common manifestation of estrogen deficiency.

- Treatment: dopamine agonists (bromocriptine, cabergoline), transsphenoidal resection.

Causes of hypopituitarism

- Undersecretion of pituitary hormones due to:

- Nonsecreting pituitary adenoma, craniopharyngioma.
- Sheehan syndrome.
- Empty sella syndrome
- Pituitary apoplexy.
- Brain injury.
- Radiation.

- Treatment: Hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone).

Craniopharyngioma

- Most common childhood supratentorial brain tumor.

- Craniopharyngiomas are usually tumors of childhood, being most frequently discovered between the ages of 5 and 10 years of age.

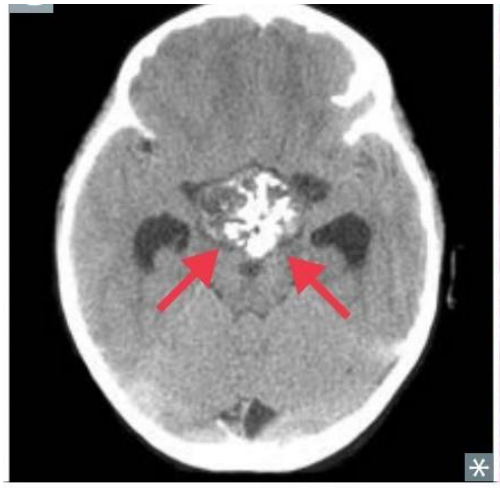
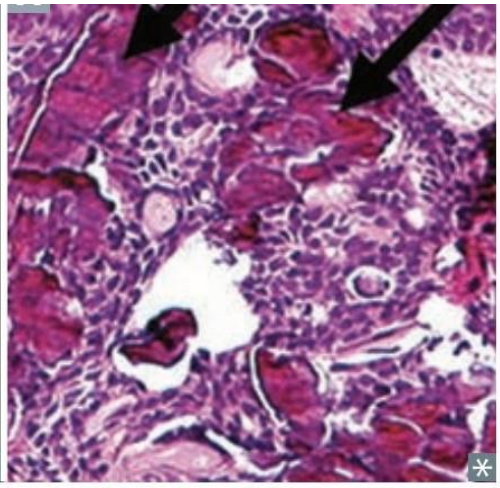
- Craniopharyngiomas are tumors arising from remnants of Rathke's pouch (an embryonic precursor of the anterior pituitary).

- During the time of pituitary development, remnants of Rathke's pouch cells can remain in the diencephalon (the posterior region of the forebrain). Neoplastic transformation of these "pouch cells" is called a craniopharyngioma.

- Typically, craniopharyngiomas have three components: solid (comprised of the actual tumor cells), cystic (filled with "machinery oil" liquid), and a calcified component. Any suprasellar mass with three components is highly suggestive of craniopharyngioma.

- By gross inspection: it shows cystic spaces filled with thick brownish fluid that is rich in cholesterol.

- Craniopharyngioma symptoms include headaches, visual field defects, and hypopituitarism.

Sheehan's Syndrome

- During pregnancy, the pituitary enlarges due to estrogen-induced hyperplasia of the lactotrophs. However, the blood supply to the pituitary does not increase proportionally.
- As a result, the enlarged pituitary is vulnerable to ischemia in case of systemic hypotension due to peripartum hemorrhage.
- The most common manifestation of Sheehan syndrome is failure of lactation due to prolactin deficiency.
- Cortisol deficiency manifests rapidly, however, with nausea, postural hypotension, fatigue, and weight loss.
- It also commonly causes hypocortisolism and hypothyroidism. Manifestations of thyroid deficiency may take a few weeks to develop due to the long circulating half-life of thyroxine (5-7 days) and peripheral conversion of thyroxine (T_4) to T_3.

Pituitary Apoplexy

- Pituitary apoplexy (acute hemorrhage into the pituitary gland), which occurs most often in patients with preexisting pituitary adenomas.
- Typically, chronic symptoms related to the pituitary tumor (headaches, decreased libido) are present for months before the actual hemorrhage event.
- The bleeding often presents acutely with severe headache and bitemporal hemianopsia (due to compression of the optic chiasm), and ophthalmoplegia (due to compression of the oculomotor nerve [CN III]).

- Signs of meningeal irritation can also be seen and mimic subarachnoid hemorrhage. However, subarachnoid hemorrhage can be differentiated from a sellar mass with suprasellar extension by the presence of bitemporal hemianopsia, which is present only in the latter.

- Patients with pituitary apoplexy can develop cardiovascular collapse due to ACTH deficiency and subsequent adrenocortical insufficiency.

- Pituitary apoplexy is a medical emergency that requires urgent neurosurgical consultation and treatment with glucocorticoid.

Features of pituitary apoplexy	
Pathogenesis	• Caused by acute **intrapituitary hemorrhage** • Occurs most often in **preexisting adenoma**
Presentation	• Severe headache • Bitemporal hemianopsia • Ophthalmoplegia • Panhypopituitarism
Diagnosis	• Neuroimaging shows pituitary enlargement & signs of hemorrhage
Treatment	• **Glucocorticoid replacement** (critical to prevent life-threatening hypotension) • Surgical decompression for persistent visual symptoms

Empty Sella syndrome

- The pituitary gland shrinks or becomes flattened, creating a void in the sella turcica wherein it resides.

- When the pituitary gland shrinks or becomes flattened, it cannot be seen on an MRI scan. This makes the pituitary gland look like an "empty sella".

- Often idiopathic.

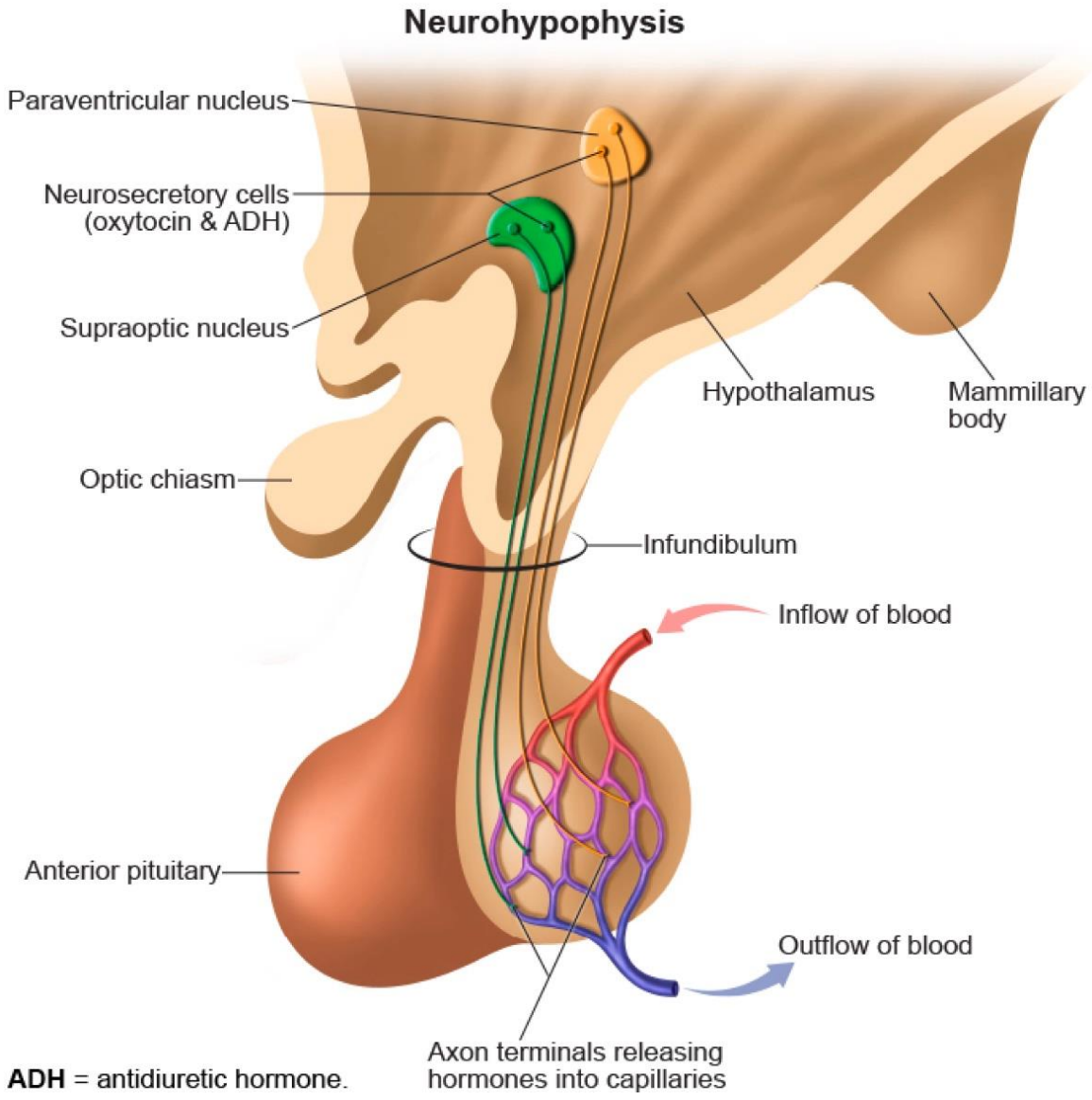
- Common in obese women.

- Associated with idiopathic intracranial hypertension.

Posterior Pituitary

- <u>The posterior pituitary gland releases 2 hormones:</u>

- Anti-diuretic hormone (Vasopressin).
- Oxytocin.



- Antidiuretic hormone formation begins in the supraoptic nuclei, while oxytocin production starts in the paraventricular nuclei.

- Once translated, these hormones are packaged into neurosecretory vesicles and travel via anterograde axonal transport to the posterior pituitary in association with intra-vesicular proteins known as neurophysins.

- Neurophysins are proteins involved in the posttranslational processing of oxytocin and vasopressin. Neurophysin II has a binding site specific for vasopressin and is thought to be involved in the transport and packaging of vasopressin through the endoplasmic reticulum (ER) and Golgi apparatus into neurosecretory granules.

- A point mutation in neurophysin II could result in abnormal protein folding and removal from the ER along with bound vasopressin, thereby decreasing availability of vasopressin for neurosecretory release.

- Such a mechanism may be responsible for some cases of autosomal dominant hereditary hypothalamic diabetes insipidus, a disorder resulting from insufficient ADH release into the systemic circulation.

Antidiuretic Hormone (vasopressin)

- Source: ADH is synthesized in the hypothalamus, mainly in the supraoptic nucleus (SO), but also in the paraventricular nucleus (PVN), it is stored and released from the posterior pituitary.

- Function:

- ADH is a major controller of water excretion and ECF volume. ADH also controls osmolarity.

- Antidiuretic hormone (ADH) is responsible for the maintenance of water balance by regulating water absorption in the kidney.

- Without ADH, the kidney's collecting duct cells are impermeable to water, causing water to be lost to the body via urine. When ADH is present, however, water is free to osmotically move across the collecting duct cells.

- Secretion of ADH is most sensitive to plasma osmolarity, however, if blood volume decreases as in hemorrhage or cardiac output fails, high levels of ADH are secreted even if it causes abnormal plasma osmolarity.

- Osmoreceptors are neurons that respond to increased plasma osmolarity, principally sodium concentration. They synapse with neurons of the SO and PVN and stimulate them to secrete ADH from the posterior pituitary. They also stimulate consumption of water through hypothalamic centers that regulate thirst.

- The SO and PVN also receive input from atrial and other volume receptors as well as arterial receptors. High blood volume or blood pressure tends to inhibit secretion of ADH.

- ADH activates G protein coupled V_2 receptors, which allow the transposition of aquaporin 2 from their intracellular locations to the luminal cell membrane. At the cell membrane aquaporin lives up to its name by serving as a water channel, a "pore" that water passes through.

- In severe hemorrhage, high levels of ADH via V_1 receptors on vascular smooth muscle cause a vasoconstriction. Activation of the V_1 receptors increases intracellular Ca, which induces intense vasoconstriction that raises the dropped arterial blood pressure in cases of hemorrhage (vasopressor effect). This effect is minor, since renin-angiotensin & sympathetic nervous systems are the primary regulators of arterial BP.

- Regulation of ECF volume and osmolarity:

1. Volume regulation (↓ Volume → ↑ ADH, ↑ Volume → ↓ ADH):

- Stimuli arising from stretch receptors act to chronically inhibit ADH secretion.

- Decrease in blood volume cause venous and arterial stretch receptors to send fewer signals to the CNS, decreasing chronic inhibition of ADH secretion.

- This mechanism is especially important for restoring ECF volume following a hemorrhage.

2. Osmoregulation (↑ Osmolarity → ↑ ADH, ↓ Osmolarity → ↓ ADH):

- An increase of only 1% in the osmolarity of the ECF bathing the hypothalamic osmoreceptors will evoke an increased rate of ADH secretion.

- A similarly sized decrease in osmolality will decrease ADH secretion.

- In this manner, ECF osmolality is kept very close to 285 mOsm/L.

Diabetes Insipidus

- Definition: Diabetes insipidus (DI) is a decrease in either the amount of ADH from the pituitary (central DI) or its effect on the kidney (nephrogenic DI).

- Etiology:

A. Central DI (CDI):

- It is a disorder of the neurohypophyseal system, caused by partial or total deficiency of ADH.

- Any destruction of the brain from stroke, tumor, trauma, hypoxia, or infiltration of the gland from sarcoidosis or infection can cause CDI.

B. Nephrogenic DI (NDI):

- Hereditary (ADH receptor mutation).

- A few kidney diseases such as chronic pyelonephritis, amyloidosis, myeloma, or sickle cell disease will damage the kidney enough to inhibit the effect of ADH.

- Hypercalcemia and hypokalemia also inhibit ADH's effect on the kidney.

- Drugs: lithium and demeclocycline (ADH Antagonist).

- The differential diagnosis of DI includes primary disorders of water intake (psychogenic polydipsia, drug-induced polydipsia from chlorpromazine, anticholinergic drugs, or thioridazine).

- Presentation:

- Diabetes insipidus (DI) is a disease characterized by polyuria (excessive urination) and polydipsia (excessive thirst) despite normal blood glucose levels (in contrast to diabetes mellitus).

- DI presents with extremely high-volume urine resulting in volume depletion. Urine osmolality and urine sodium are decreased.

- Central DI patients usually do not have an intact thirst mechanism → high serum sodium.

- Nephrogenic DI patients usually have an intact thirst mechanism → normal serum sodium.

- Serum sodium is elevated when oral replacement is insufficient. Urine osmolality and urine sodium are decreased. Serum osmolality, which is largely a function of serum sodium, is elevated.

- When hypernatremia is severe, there will be neurological symptoms such as confusion, disorientation, lethargy, and eventually seizures and coma. Neurological symptoms occur only when volume losses are not matched with drinking enough fluid.

- Primary polydipsia is due to increased water intake that surpasses the kidney's ability to excrete it. The increased water leads to hyponatremia, a very dilute urine, and urine osmolality < serum osmolality.

ADH-related causes of polyuria & polydipsia

	Primary polydipsia	Central DI	Nephrogenic DI
Defect	↑ Water intake	↓ ADH release from pituitary	ADH resistance in kidney
Etiology	• Antipsychotics • Anxious, middle-age women	• Idiopathic • Trauma • Pituitary surgery • Ischemic encephalopathy	• Chronic lithium use • Hypercalcemia • Hereditary (*AVPR2* mutations)
Clinical features	Low serum Na	High serum Na	Normal serum Na

ADH = antidiuretic hormone; **DI** = diabetes insipidus.

- Diagnostic Tests:

- A water deprivation test can distinguish between central and nephrogenic DI and also definitively exclude primary polydipsia. Restriction of water intake normalizes urine output in patients with primary polydipsia.

- The patient must first abstain from water for at least 2-3 hours. The serum and urine osmolality are measured periodically:
  - Urine osmolality >600 mOsm/kg suggests primary polydipsia due to intact ADH and ability to concentrate urine in the absence of water intake.
  - Patients with continued dilute urine likely have DI.

- These patients then receive desmopressin to distinguish between central and nephrogenic DI:
  - Central DI typically has >50% (sometimes up to 200%-400%) increase in urine osmolality with desmopressin.
  - Nephrogenic DI has minimal change in urine osmolality with desmopressin.

▪ Treatment:

- Central DI is treated with long-term vasopressin (desmopressin) use.

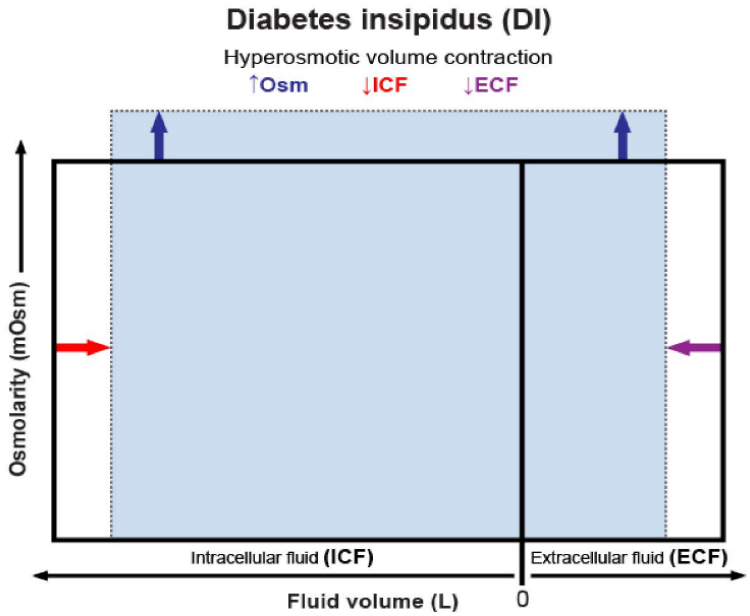
- Nephrogenic DI is managed by trying to correct the underlying cause (hypokalemia or hypercalcemia).

- Nephrogenic DI also responds to hydrochlorothiazide (Thiazide diuretics lead to sodium depletion in distal convoluted tubules, which causes compensatory sodium and water reabsorption in the proximal tubules. As a result, less water reaches the distal tubules and volume of urine decreases), amiloride (Indicated in patients with lithium-induced NDI; amiloride blocks lithium entry through the sodium channel), and prostaglandin inhibitors such as NSAIDs (experimental studies have shown that prostaglandins can inhibit the integration of aquaporin 2 water channels into the collective ducts).

❖ N.B:

▪ The graph below illustrates the volume within the extracellular fluid (ECF) and intracellular fluid (ICF) compartments as well as the osmolarity of the fluid in those compartments.

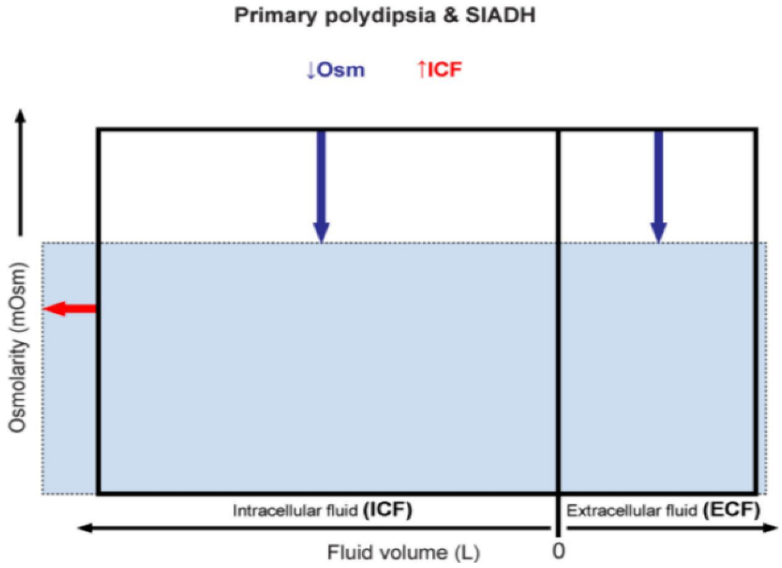
▪ Hyperosmotic volume contraction occurs when the loss of free water exceeds the loss of electrolytes resulting in increased osmolarity and decreased volumes in the ICF and ECF spaces. This occurs in the setting of diabetes insipidus most classically but can also occur with profuse sweating due to the hypotonic nature of sweat.



Primary (Psychogenic) Polydipsia

- Primary polydipsia, called psychogenic polydipsia in older literature, is simply excessive (pathologic) water drinking.

- It is a psychologic disorder more commonly found in women and children and cannot be diagnosed if there is an underlying etiology causing excessive thirst, such as a medication side effect giving patients "dry mouth" and making them thirsty.



Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

- SIADH is characterized by excessive release of antidiuretic hormone from the posterior pituitary gland or another source.

- Etiology:

- Syndrome of inappropriate antidiuretic hormone has many causes:
  - Malignancy such as small cell carcinoma due to ectopic ADH secretion.
  - Nonmalignant pulmonary disease such as tuberculosis, pneumonia, and lung abscess.
  - CNS disorder such as head injury, cerebral vascular accident, and encephalitis.
  - Drugs (cyclophosphamide, Carbamazepine, SSRI).

- Presentation:

- In general, increased ADH causes water retention and extracellular fluid volume expansion without edema or hypertension, owing to natriuresis.

- The water retention and sodium loss both cause hyponatremia, which is a key feature in SIADH.

- Hyponatremia and concentrated urine, as well as no signs of edema or dehydration.

- When hyponatremia is severe (sodium <120 mOsm), or acute in onset, symptoms of cerebral edema become prominent (irritability, confusion, seizures, and coma).

▪ Diagnostic Tests:

- Lab findings in SIADH include:
  - Hyponatremia <130 mEq/L.
  - Posm <270 mOsm/kg.
  - Uosm > 300 mOsm.
  - Urine sodium concentration >20 mEq/L (inappropriate natriuresis).

▪ Management:

- Treat underlying causes.

- Restrict fluid to 800-1,000 mL/d to increase serum sodium. In chronic situations when fluid restriction is difficult to maintain, use demeclocycline which inhibits ADH action at the collecting duct [V_2].

- Conivaptan and tolvaptan are V_2 receptor blockers indicated for moderate to severe SIADH.

- For very symptomatic patients (severe confusion, convulsions, or coma), use IV hypertonic saline (3%) 200-300 mL in 3-4 h. Correct slowly to prevent osmotic demyelination syndrome (formerly called central pontine myelinolysis).

❖ N.B:

1. The combination of hyponatremia and a lung mass is suggestive of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

▪ Small cell carcinoma of the lung commonly presents with symptoms related to ectopic hormone production (paraneoplastic effects). These neoplastic cells contain dense neurosecretory granules and can produce hormones such as antidiuretic hormone (ADH).

▪ Production of ADH by small cell carcinoma is constitutive and therefore not regulated by feedback inhibition.

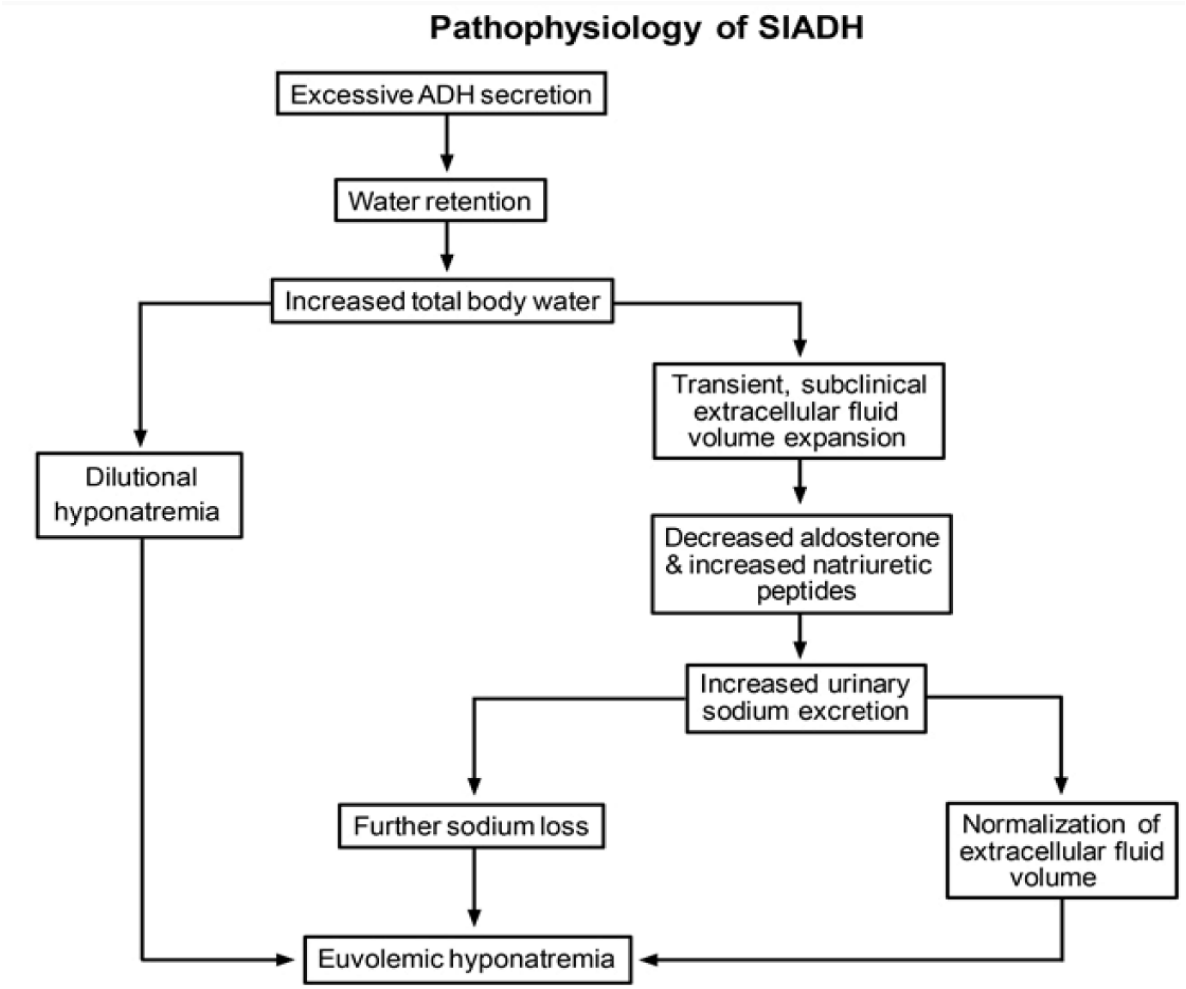
▪ Low serum sodium levels, depressed plasma osmolality, and elevated urine osmolality (which normally should be < 100 mOsm/kg given the degree of hyponatremia) are typical of an ADH-secreting small cell carcinoma.

2. In SIADH, the extra ADH leads to excessive water absorption by the kidneys, causing a transient, subclinical hypervolemia.

▪ The mild increase in extracellular fluid volume suppresses the renin-aldosterone axis and stimulates the production of natriuretic peptides, leading to excretion of sodium in the urine (natriuresis).

▪ Therefore, patients with SIADH present with a clinically normal body fluid volume and low plasma osmolality (euvolemic hyponatremia).

▪ SIADH can cause a variety of consequences secondary to profound hyponatremia, including headache, weakness, altered mental status, and seizures.



SIADH = syndrome of inappropriate antidiuretic hormone.

Oxytocin

- It is a nonapeptide that circulates in blood and reaches its target organs to bind to its receptors in the breast myoepithelial cells, the uterine myometrium and the plain muscles in the vas deferens.

- The secretion of oxytocin is very characteristic; it is through a neurohormonal reflex. The components of the reflex are:

A. Stimulus:
- Genital stimulation of the male and the female.
- Massage of the nipple by suckling or sexual playing.
- Dilatation of the cervix: during labor by the head of the fetus.

B. Afferent: each of the previous stimuli sends impulses through the spinal cord to reach the hypothalamic nuclei.

C. Efferent: it is hormonal; the hypothalamus nuclei release the already present oxytocin from the posterior pituitary into the systemic circulation to reach their target organ.

- This reflex is termed "milk ejection reflex".

- Function of oxytocin:
- During sexual intercourse: it is responsible for orgasm.
- In males: contraction of smooth muscle in vas deferens to ejaculate semen.
- In females: the contraction of myometrium followed by relaxation decreases the intrauterine pressure to help semen transport into the uterus after intercourse.
- During labor: it causes strong contractions of the uterus to expel the baby and placenta.
- During suckling: it causes squeezing of milk from the breast alveoli into the large ducts and then the nipple.

Adrenal Gland

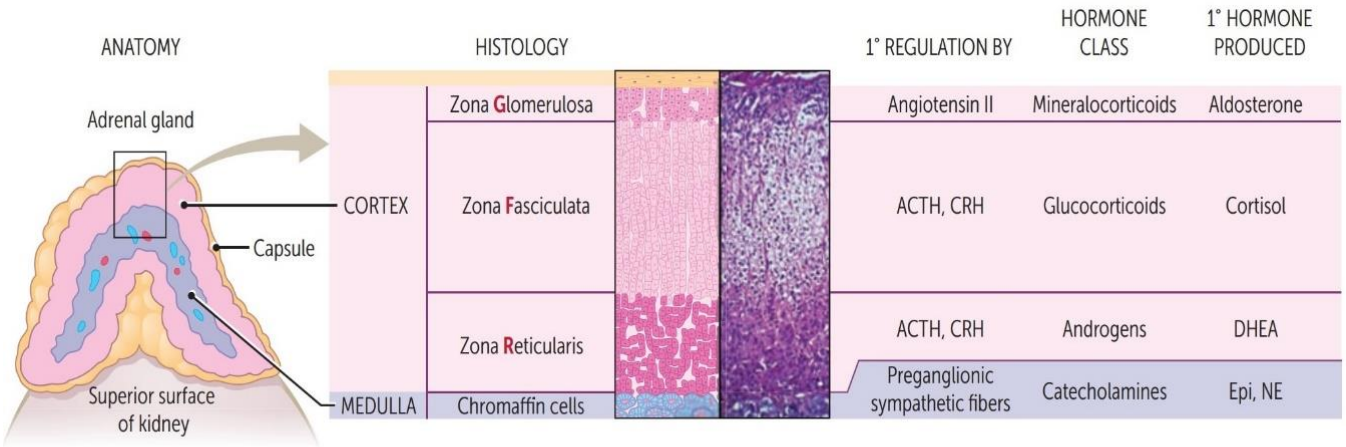
- The adrenal glands are situated above the kidneys and consist of an outer cortex and an inner medulla.
- The adrenal cortex develops and functions independently from the adrenal medulla.
- Adrenal cortex is derived from mesoderm, but adrenal medulla is derived from neural crest.
- <u>The mature adrenal cortex consists of three distinct zones (GFR):</u>

- The outer zona Glomerulosa → synthesizes mineralocorticoids.
- The middle zona Fasciculata → produces cortisol.
- The inner zona Reticularis → produces androgens.

- GFR corresponds with Salt (Na), Sugar (glucocorticoids), and Sex (androgens). The deeper you go, the sweeter it gets.

	Anatomy	Primary regulatory control	Secretory products
CORTEX	Zona Glomerulosa	Renin – angiotensin	Aldosterone
	Zona Fasciculata	ACTH, CRH	Cortisol
	Zona Reticularis	ACTH, CRH	Sex hormones (androgen)
MEDULLA	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines (epinephrine, norepinephrine)

- ACTH from the anterior pituitary increases the secretion of cortisol and adrenal androgens from the zona fasciculata and zona reticularis, respectively, but there is no substantial effect of ACTH on aldosterone secretion. Secretion of aldosterone from the zona glomerulosa is regulated by the renin-angiotensin system.



GFR corresponds with Salt (mineralocorticoids), Sugar (glucocorticoids), and Sex (androgens).
"The deeper you go, the sweeter it gets."

- Anterior pituitary corticotrophes synthesize pro-opiomelanocortin which is cleaved to give rise to multiple peptide hormones:

1. ACTH:

- Stimulates the secretion of cortisol and adrenal androgens of adrenal cortex.
- Cortisol suppresses the release of ACTH by acting on the hypothalamus and anterior pituitary.

2. β-Lipotropin:

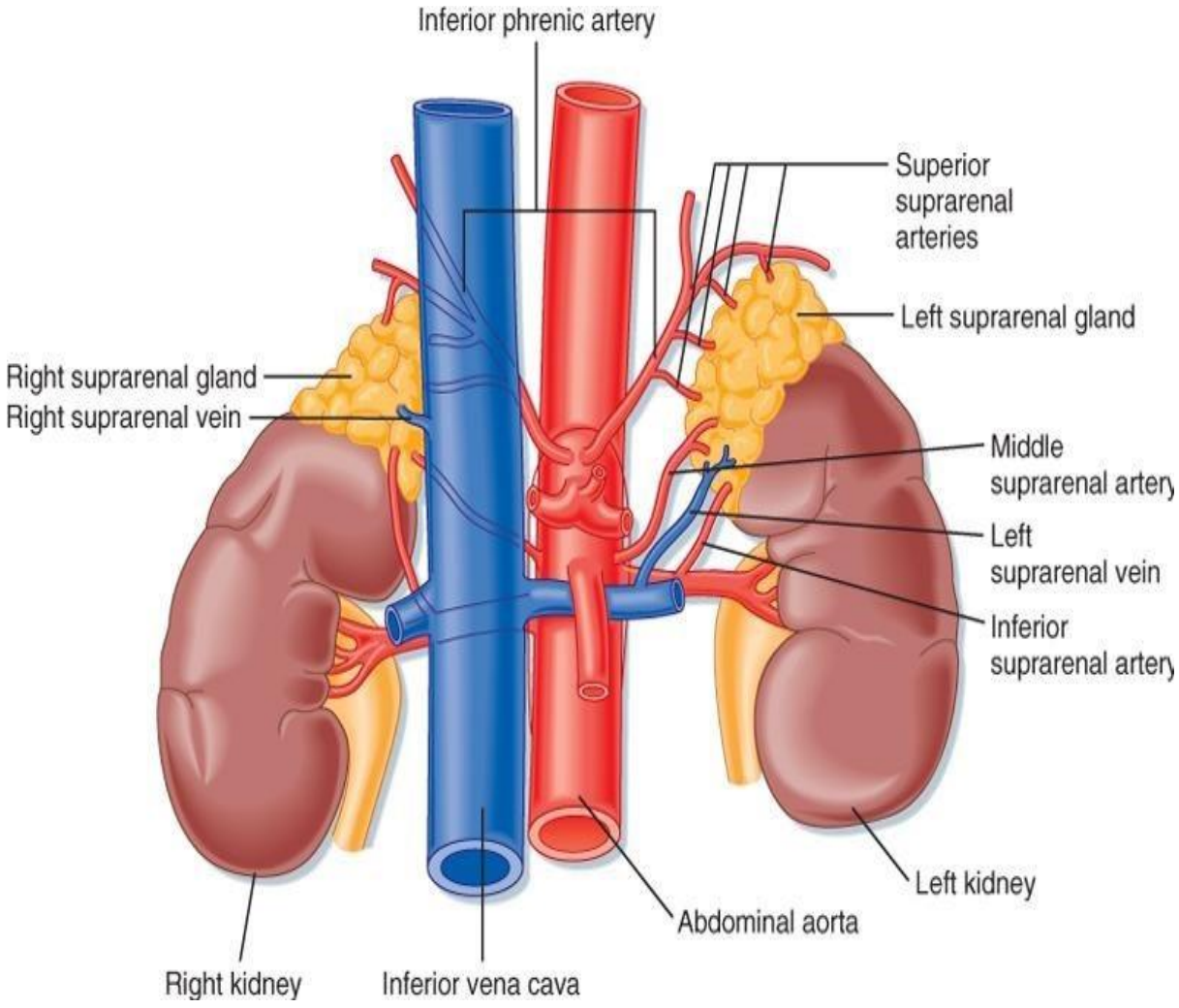
- Role not well understood.
- Precursor to MSH and endorphins.
- Endorphins may modulate the perception of pain.

- Excessive secretion of ACTH (primary adrenal insufficiency) causes darkening of the skin due to associated increase of melanocyte-stimulating hormone.

- Adrenal gland drainage:

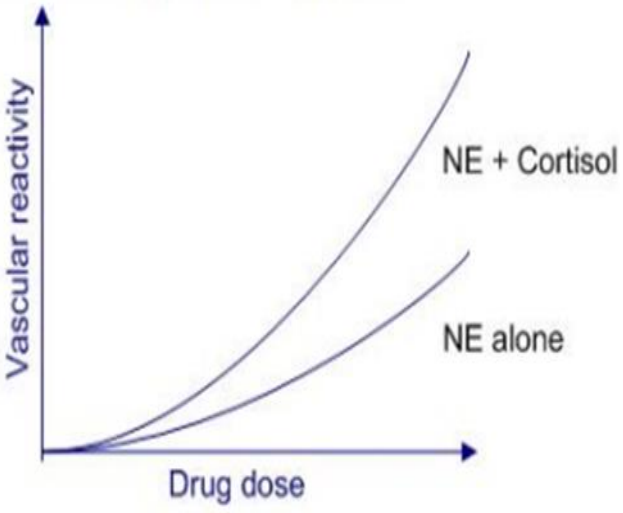
- Left adrenal → left adrenal vein → left renal vein → IVC.

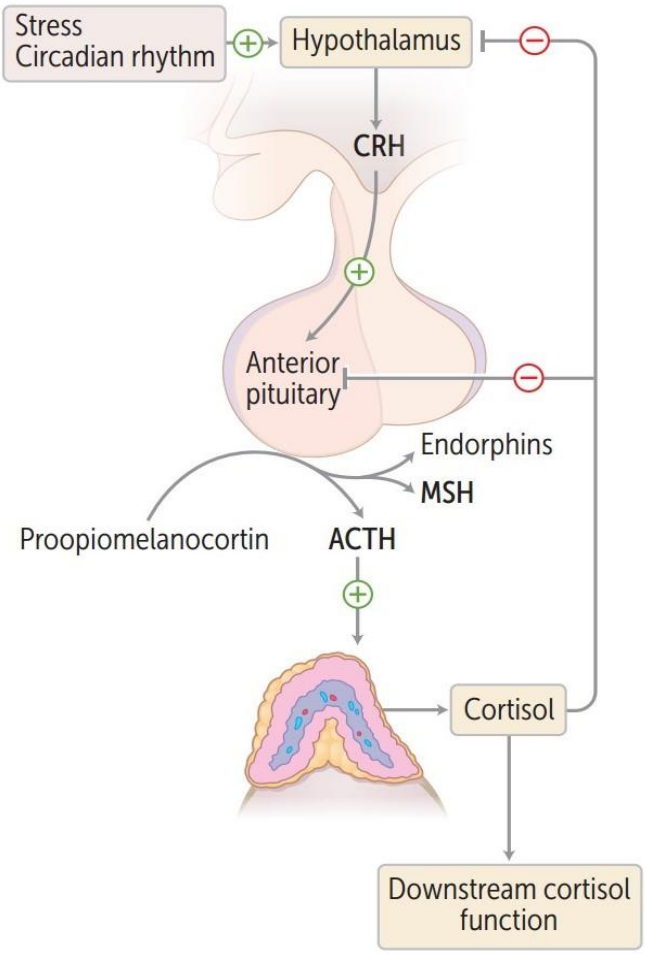
- Right adrenal → right adrenal vein → IVC.



Physiological effect of cortisol (glucocorticoid)

- Source: Adrenal zona fasciculata.





- Function:

- ↑ Appetite.

- ↑ Blood pressure:
  - Upregulates α1-receptors on arterioles → ↑ sensitivity to norepinephrine and epinephrine (permissive action). It increases vascular reactivity to catecholamines. Without cortisol, blood pressure decreases.
  - At high concentrations, can bind to mineralocorticoid (aldosterone) receptors.

- ↑ Insulin resistance (diabetogenic).

- ↑ Gluconeogenesis, lipolysis, and proteolysis (↓ glucose utilization).

- ↓ Fibroblast activity (poor wound healing, ↓ collagen synthesis, ↑ striae).

- Inflammatory and Immune responses:
  - Inhibits production of leukotrienes and prostaglandins.
  - Inhibits WBC adhesion → neutrophilia.
  - Blocks histamine release from mast cells.
  - Eosinopenia, lymphopenia.
  - Blocks IL-2 production. Exogenous corticosteroids can cause reactivation of TB and candidiasis by blocks IL-2 production.

- ↓ Bone formation (↓ osteoblast activity and collagen synthesis).

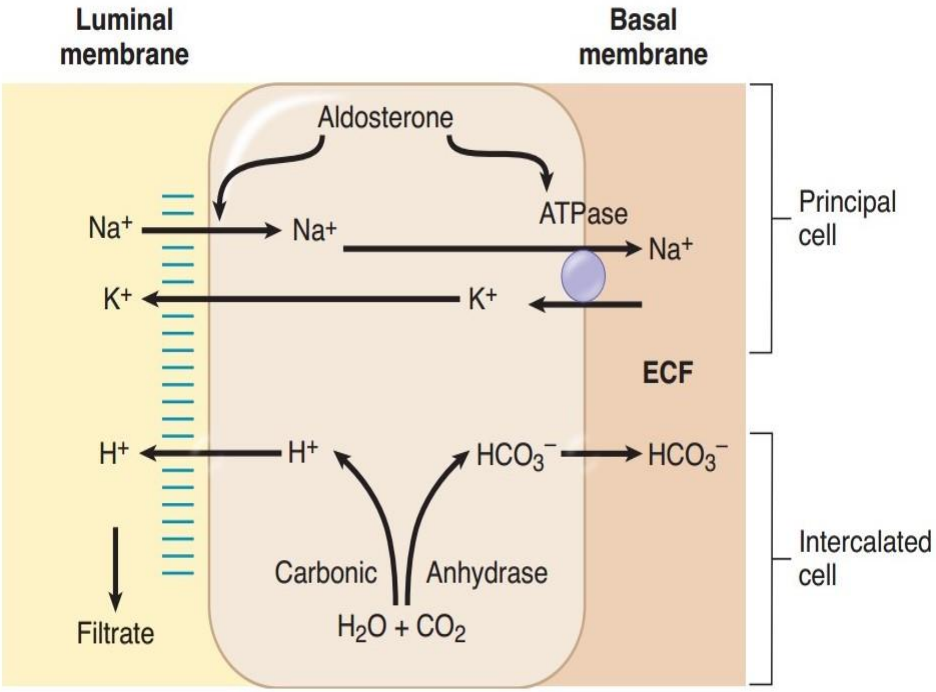
- Regulation:
- CRH (hypothalamus) stimulates ACTH release (pituitary) → cortisol production in adrenal zona fasciculata.

- Excess cortisol ↓ CRH, ACTH, and cortisol secretion.

Physiologic action of aldosterone

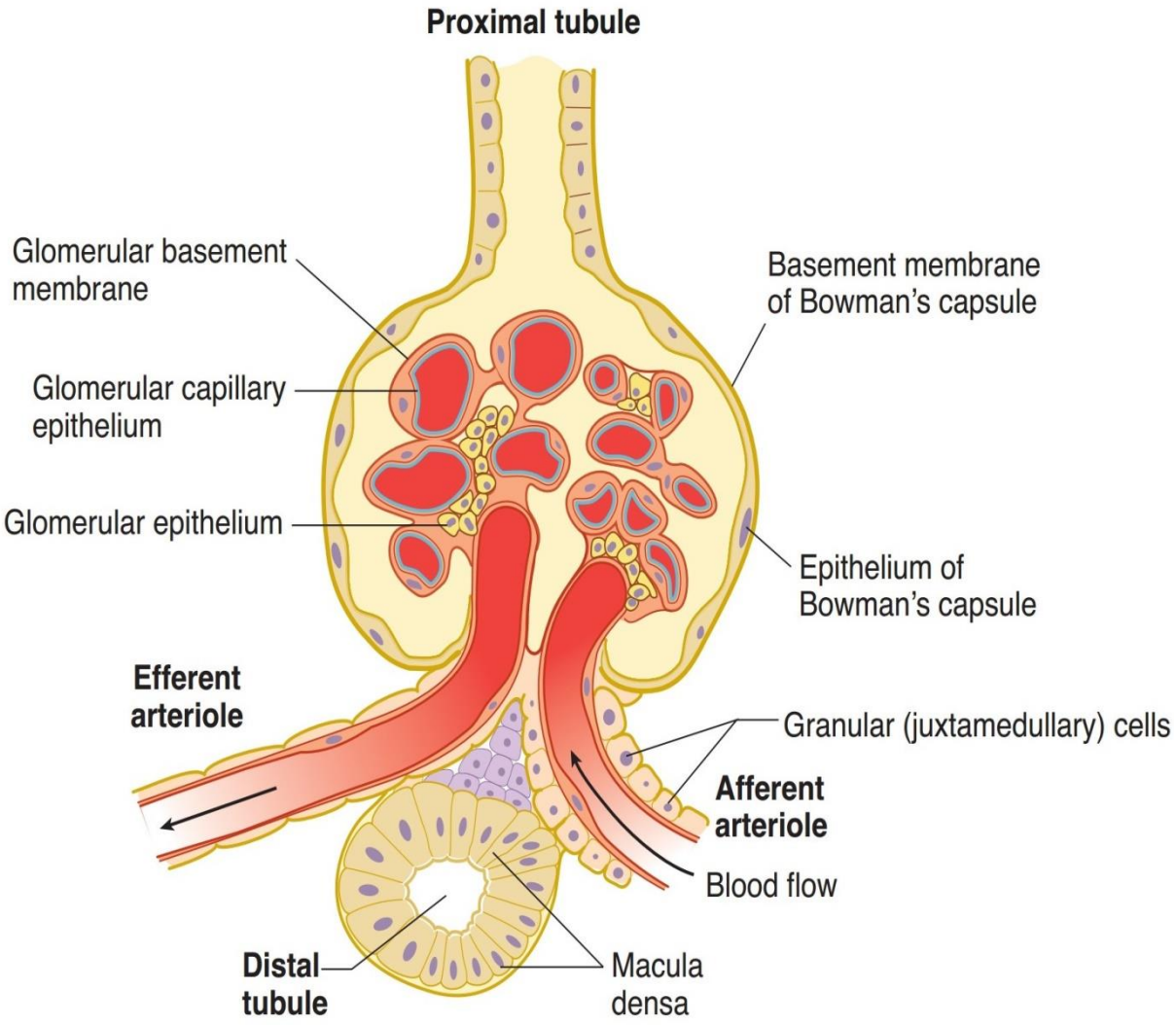
1. The primary target tissue for aldosterone is the kidney, where its most important action is to increase Na reabsorption by the principal cells of the kidney's collecting ducts. Because water is reabsorbed along with the Na, aldosterone can be considered to control the amount of Na rather than the concentration of Na in the ECF.

2. Aldosterone also promotes the secretion of H by the intercalated cells of the collecting duct, and K secretion by the principal cells.



Juxtaglomerular Apparatus

- The main sensory input that controls secretion of aldosterone is the juxtaglomerular cells.
- They are modified smooth muscle cells which surround and directly monitor the pressure in the afferent arteriole. This signal in many cases is in response to a reduction in circulating fluid volume.
- These cells are also innervated and stimulated by sympathetic neurons via norepinephrine and beta receptors. Thus, the release of renin induced by hypovolemia is enhanced by increased sympathetic neural activity.
- Additional sensory input is from the macula densa cells of the distal tubule. They perceive sodium delivery to the distal nephron and communicate with the juxta-glomerular cells.



Long-term Regulation of Blood Pressure and Cardiac Output by the Renin-Angiotensin-Aldosterone System

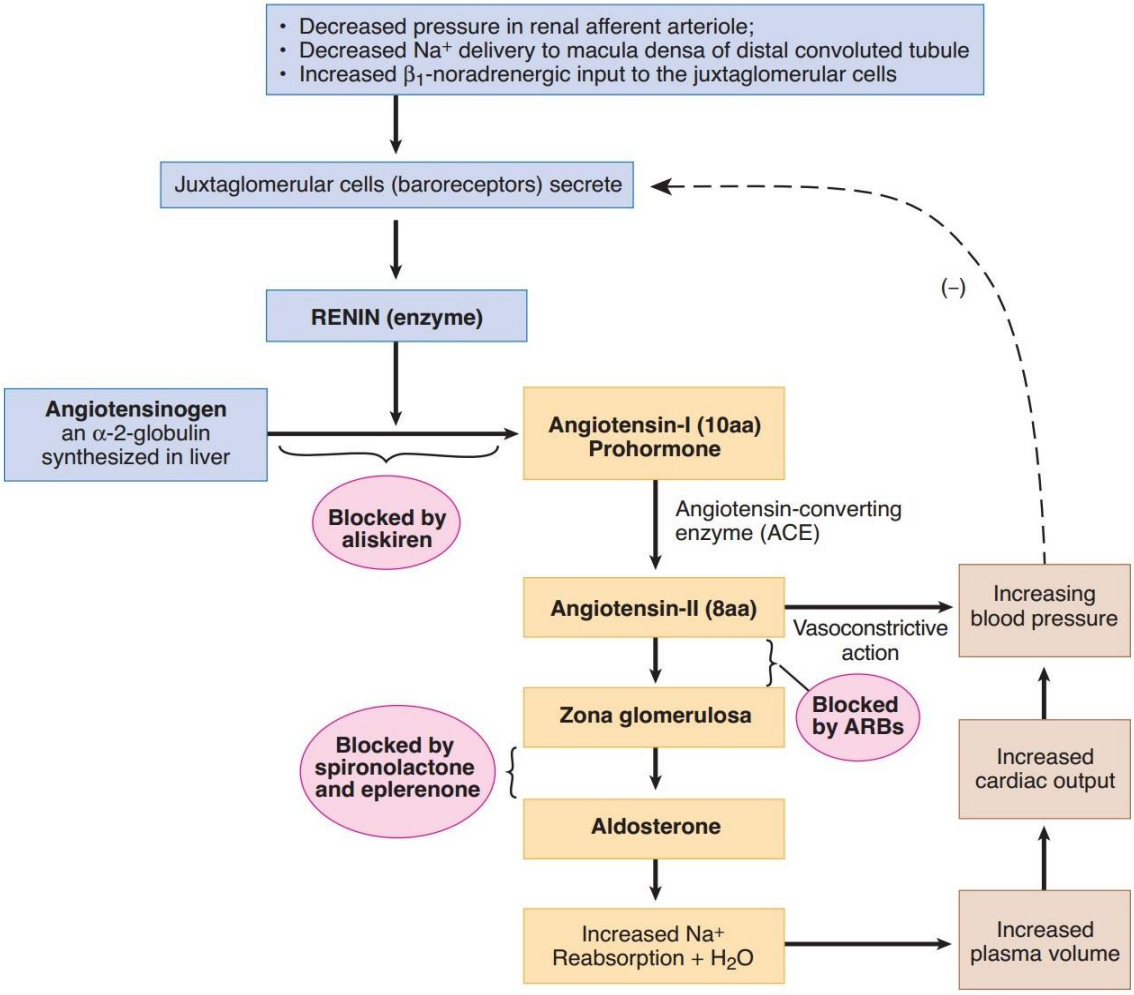
- Blood pressure is monitored by the juxtaglomerular apparatus.
- When renal perfusion pressure decreases, secretion of renin increases; conversely, when pressure increases, renin secretion is suppressed.
- Renin is an enzyme that converts a circulating protein produced in the liver, angiotensinogen, also called renin substrate, into angiotensin I.
- Angiotensin converting enzyme (ACE) is found mainly in endothelial cells of pulmonary vessels and converts angiotensin I into angiotensin II.
- Angiotensin II has potent effects to stimulate secretion of aldosterone and to cause arteriolar vasoconstriction. It also directly stimulates reabsorption of sodium in the proximal tubule.

$$MAP = CO \times TPR$$

- This system regulates both resistance, via vasoconstriction, and cardiac output, via preload.
- Angiotensin II raises blood pressure by 2 independent actions:

- The direct vasoconstrictive effects of angiotensin II increase total peripheral resistance.
- It stimulates the adrenal cortex to secrete aldosterone, resulting in increased reabsorption of Na.

- As Na reabsorption is increased, so is water. This increases the volume of the ECF, the plasma, and the blood, thus raising cardiac output and blood pressure.



Physiologic action of androgens and estrogens

- Adrenal androgen:

- Adrenal androgens DHEA & Androstendione are under ACTH control.

- Their physiological function is due to their peripheral conversion to the potent androgen testosterone.

- In females, they maintain normal pubic hair and axillary hair, and stimulate red cell production with no masculinizing effect in their normal amounts.

- In males, adrenal androgens have no physiological importance because the amount of testosterone produced by the testes is greater than that produced by adrenal glands.

- Adrenal estrogens:

- Are either secreted directly from adrenal cortex or result from the conversion of adrenal androgens to estrogens.

- They are an important source of estrogen in both men and postmenopausal women.

Glucocorticoid disorders

Cushing syndrome

- Cushing syndrome: hypercortisolism regardless of origin, including chronic glucocorticoid therapy.

- Cushing disease: hypercortisolism due to an adenoma of the anterior pituitary.

- Causes:

1. Exogenous corticosteroids (most common cause):

- Excess glucocorticoids suppress the hypothalamic-pituitary-adrenal axis → ↓ ACTH → Bilateral adrenal atrophy.

2. Endogenous corticosteroids:

A. Primary hypercortisolism:

- Primary adrenal adenoma, hyperplasia, or carcinoma → ↑ endogenous corticosteroids → ↓ ACTH with atrophy of the uninvolved adrenal gland.

- ACTH independent.

B. Secondary hypercortisolism:

- Hypersecretion of ACTH results in bilateral adrenal hyperplasia.

- ACTH dependent.

- Two main subcategories:

1. Cushing disease:
   - Cause is a pituitary adenoma usually a microadenoma (< 1 cm diameter).
   - Most common pathological cause of Cushing syndrome.
2. Ectopic ACTH syndrome: Most frequently in patients with small cell carcinoma of the lung or bronchial carcinoids.

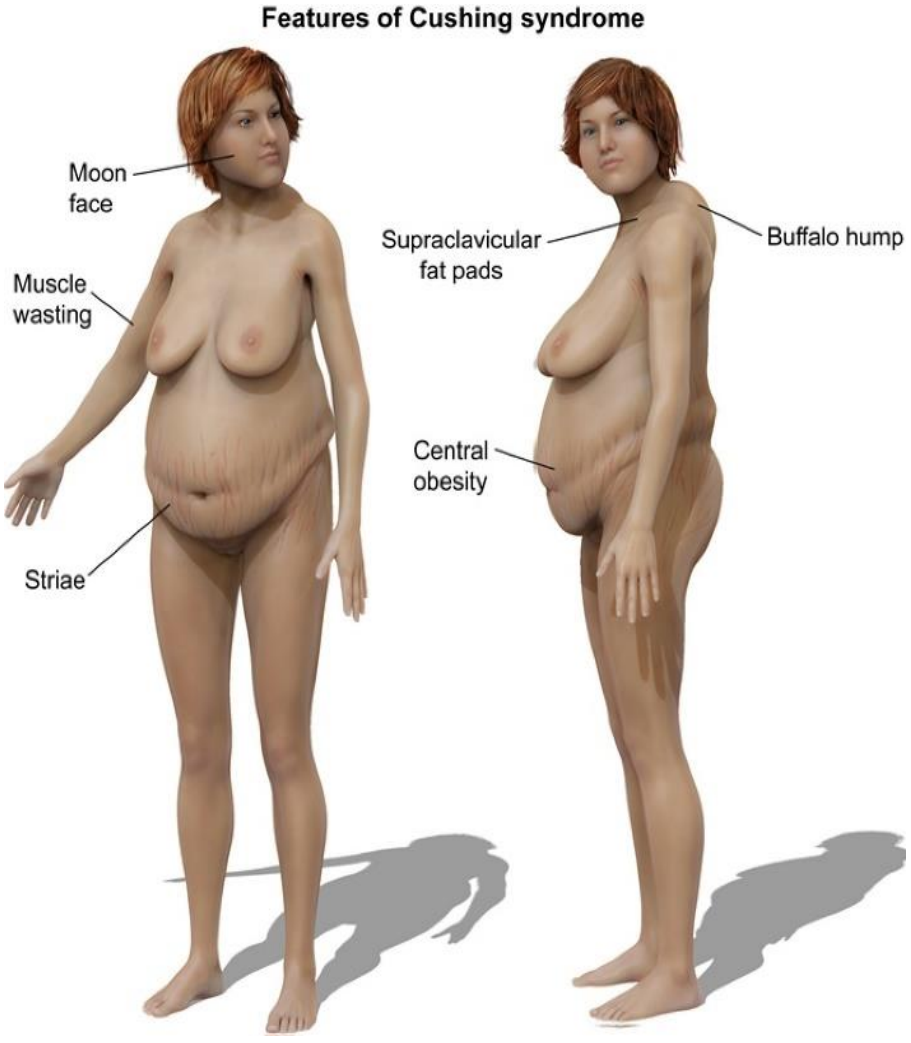
- Findings:

- Fat redistribution: Moon face, truncal obesity, buffalo hump, thin extremities, increased abdominal fat.

- Skin: striae, easy bruising, decreased wound healing, and thinning of skin.

- Osteoporosis.

- Hypertension: from increased sodium reabsorption in the kidney and increased vascular reactivity.
- Hyperglycemia is common (due to peripheral insulin resistance and hypercortisolism-induced gluconeogenesis).
- Menstrual disorders in women due to co-secretion of adrenal androgens with cortisol.
- Erectile dysfunction in men.
- Cognitive disturbance: from decreased concentration to psychosis.
- Polyuria: from hyperglycemia and increased free water clearance.
- Myopathy in Cushing syndrome is characterized by progressive painless muscle weakness predominantly involving the proximal muscles. It is due to the direct catabolic effects of cortisol on skeletal muscle, leading to muscle atrophy.
- Hypokalemia and alkalosis may be present (due to the partial mineralocorticoid effects of cortisol) if cortisol levels are very high. Clinically significant hypokalemia is uncommon.



- Diagnosis:

A. Establish the Presence of Hypercortisolism:

- Screening tests include:
  - ↑ free cortisol on 24-hr urinalysis. The best initial test for the presence of hypercortisolism.
  - ↑ late night salivary cortisol. In normal patients, cortisol is at its lowest at midnight. In Cushing patients, cortisol is abnormally elevated at midnight.
  - No suppression with overnight low-dose (1 mg) dexamethasone test. The 1 mg overnight dexamethasone suppression test should normally suppress the morning cortisol level. If this suppression occurs, hypercortisolism can be excluded.

B. Establish the Cause of Hypercortisolism:

- ACTH testing is the best initial test to determine the cause (source) or location of hypercortisolism.

- Following are indicators of the source of the hypercortisolism:

A. ACTH level low:

- This means the origin is in the adrenal gland.
- Scan the gland with a CT or MRI and remove the adenoma that you find.

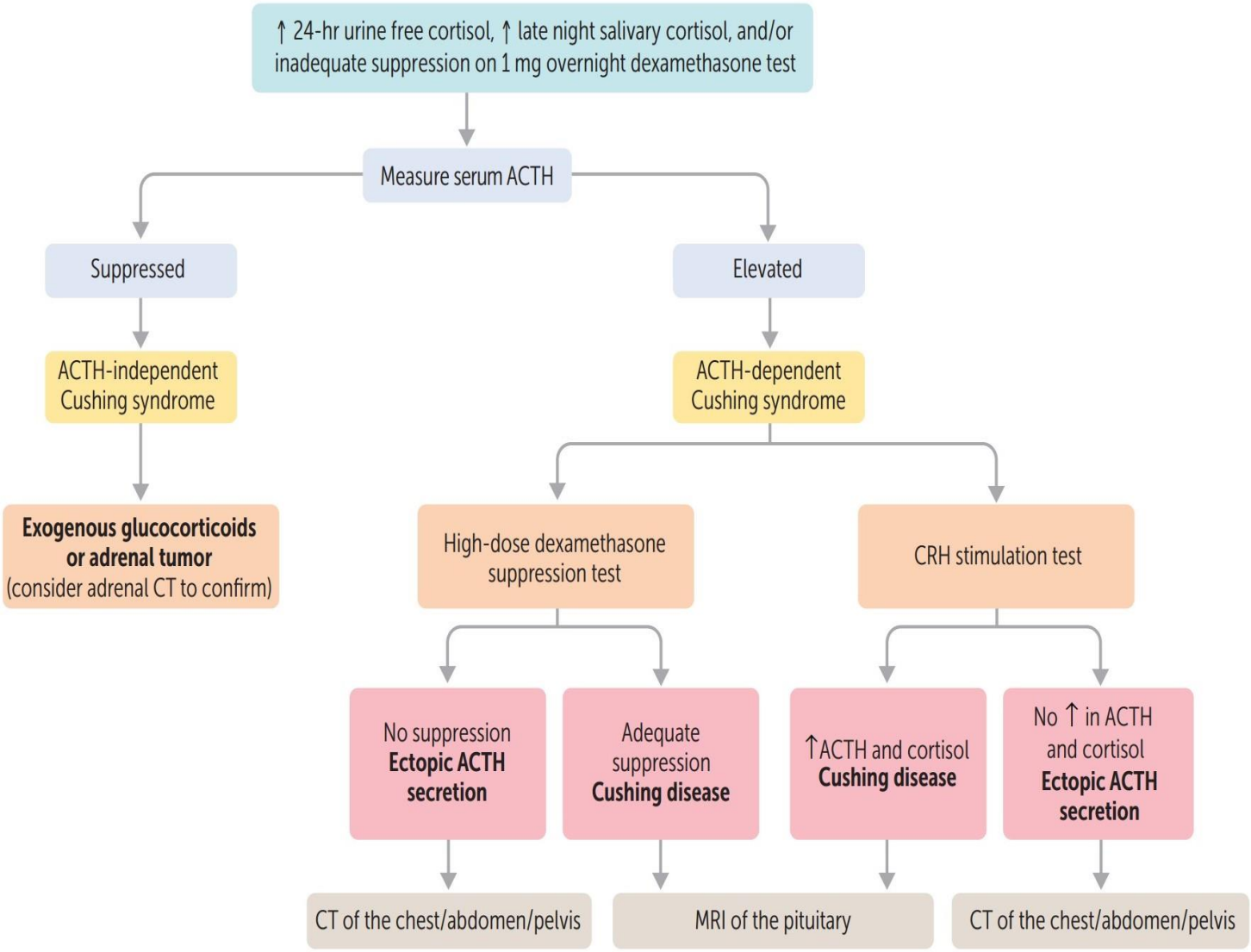
Decreased ACTH level = adrenal source

B. ACTH level high: This means the origin is either in the pituitary gland or from the ectopic production of ACTH.

- The next step is a high-dose dexamethasone suppression test:
  - If high-dose dexamethasone suppresses the ACTH, the origin is the pituitary. Scan the pituitary. Remove the adenoma if it is visible.
  - If high-dose dexamethasone does not suppress the ACTH, the origin is an ectopic production of ACTH or a cancer that is making ACTH. Scan the chest for lung cancer or carcinoid. Remove the cancer if possible.

- CRH stimulation test:
  - ACTH and cortisol levels increase further: Cushing's disease.
  - No increase in ACTH or cortisol levels: ectopic ACTH production.

- Ectopic secretion will not increase with CRH because pituitary ACTH is suppressed.



Biochemical findings in Cushing syndrome			
Etiology	**ACTH**	**Cortisol**	**High-dose dexamethasone suppression test**
Pituitary adenoma	↑	↑	↓ Cortisol
Ectopic ACTH secretion	↑	↑	Cortisol remains elevated
Adrenal adenoma/carcinoma	↓	↑	

Adrenal insufficiency

- Adrenal insufficiency means inability of adrenal gland to generate enough glucocorticoid +/- mineralocorticoids for the body needs.

- Types:

1. Primary adrenal insufficiency:

- Patients with primary AI have loss of glucocorticoid, mineralocorticoid, and adrenal androgen secretion.

- Symptoms are often severe, and patients may develop significant hypotension, hyperkalemia, and hyperchloremic acidosis.

- Primary AI is also frequently associated with hyperpigmentation due to increased pituitary secretion of ACTH and melanocyte-stimulating hormone.

- Primary Pigments the skin/mucosa.

- It may be acute or chronic:

A. Acute (Adrenal crisis):

- Sudden onset (due to massive hemorrhage).

- Waterhouse-Friderichsen syndrome: acute 1° adrenal insufficiency due to adrenal hemorrhage associated with septicemia (usually Neisseria meningitidis), DIC, endotoxic shock.

- May present with shock in acute adrenal crisis.

B. Chronic (Addison disease):

- Due to adrenal atrophy or destruction by disease.

- Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency, and results from autoantibody production against all 3 zones of the adrenal cortex. Associated with autoimmune polyglandular syndromes.

- Tuberculosis is the most common cause of primary adrenal insufficiency in developing countries.

2. Secondary adrenal insufficiency:

- Seen with ↓ pituitary ACTH production.

- In contrast to primary AI, patients with secondary AI have only glucocorticoid and adrenal androgen deficiency with preservation of mineralocorticoid production (regulated primarily by the renin-angiotensin system, not the pituitary). Therefore, hyperkalemia, significant hypotension, and hyperchloremic acidosis are not seen.

- No skin/mucosal hyperpigmentation (ACTH is not elevated), no hyperkalemia (aldosterone synthesis preserved due to functioning adrenal gland, intact RAAS).

- Secondary Spares the Skin/mucosa.

3. Tertiary adrenal insufficiency:

- Seen in patients with chronic exogenous steroid use, precipitated by abrupt withdrawal.

- Aldosterone synthesis unaffected.

- Tertiary from Treatment.

▪ Diagnosis:

- Diagnosis involves measurement of serum electrolytes, morning/random serum cortisol, and response to ACTH stimulation test.

- Adrenal insufficiency: ↓ AM or random cortisol, or ACTH stimulation test with ↓ peak cortisol.

- Then measure random serum ACTH:

  - ↑ ACTH: Primary adrenal insufficiency.
  - ↓ ACTH: 2°/3° adrenal insufficiency.

- Alternatively, as we are talking about hypofunction, we can use metyrapone stimulation test.

- Metyrapone stimulation test:

  - Metyrapone blocks cortisol synthesis by inhibiting the enzyme 11-β-hydroxylase, which is responsible for the conversion of 11-β-deoxycortisol to cortisol (see enzymatic pathway).

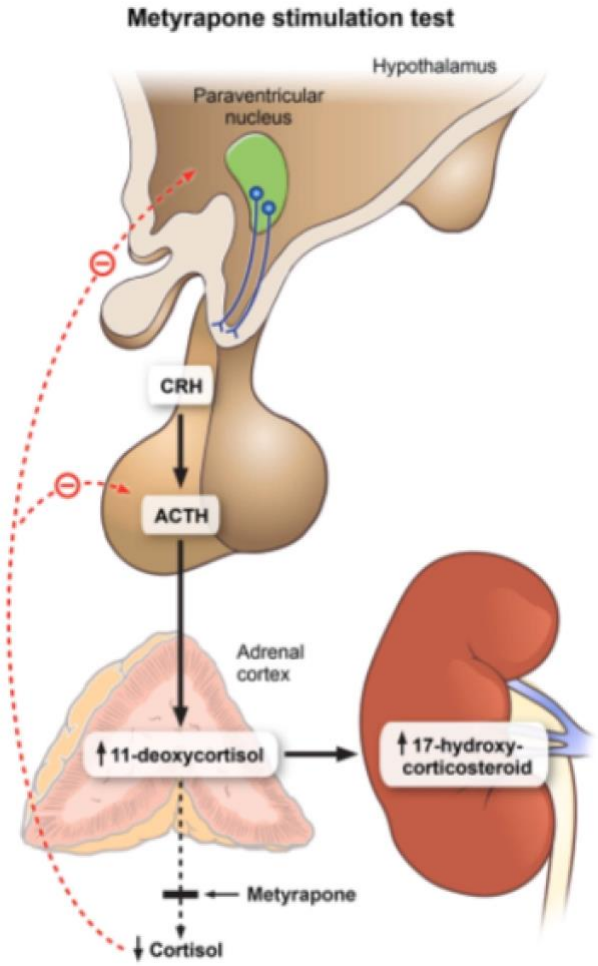
  - Thus, with metyrapone administration, serum cortisol levels are reduced, stimulating pituitary secretion of ACTH. In this setting, the high ACTH level stimulates the adrenal gland to produce more deoxycortisol (since cortisol cannot be produced due to inhibition of 11-β-hydroxylase).

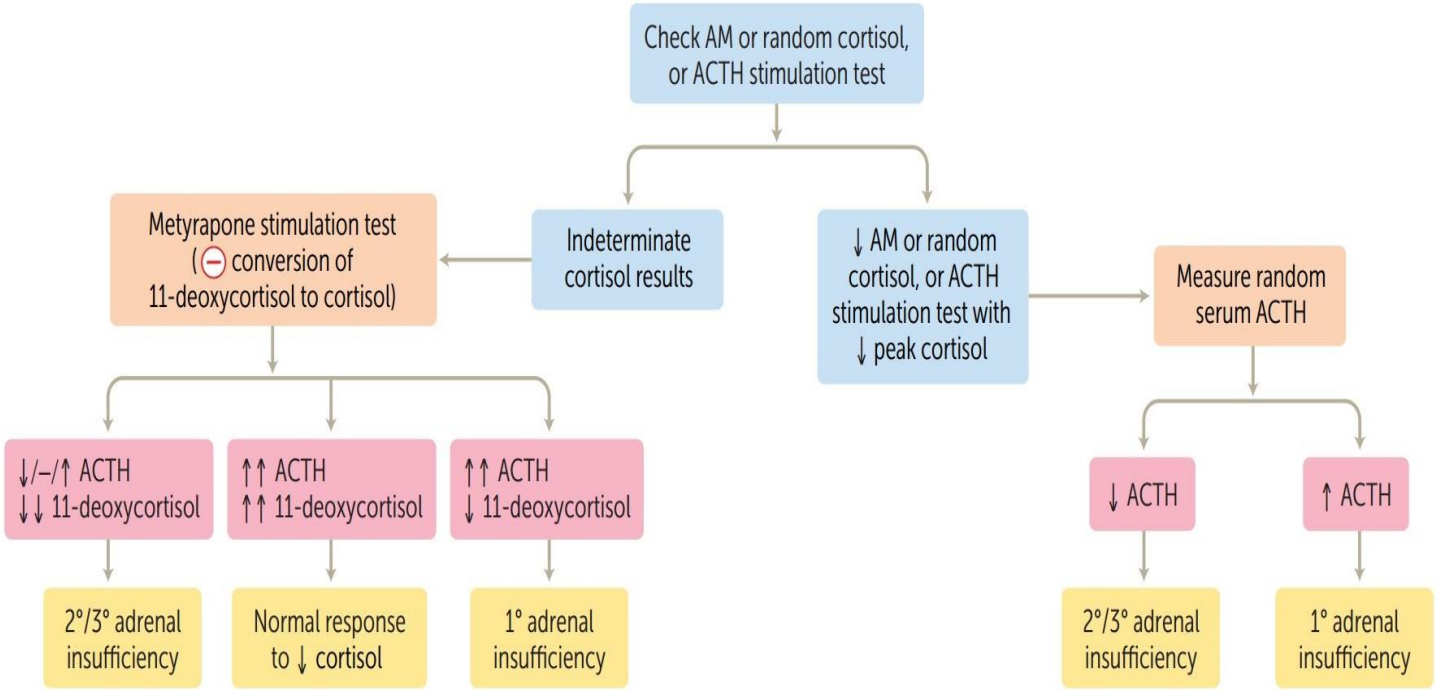
  - Unlike cortisol, 11-deoxycortisol does not cause feedback inhibition of pituitary ACTH production. 11-deoxycortisol metabolites are measurable in the urine as 17- hydroxy-corticosteroids.

A. If the HPA axis is normal: administration of metyrapone will cause a significant increase in 11-deoxycortisol in serum and ↑↑ ACTH production.

B. In primary adrenal insufficiency: there is increased ACTH but 11 deoxycortisol level doesn't increase because the problem is in the adrenal gland (although the high ACTH level, adrenal gland has failed to produce the deoxycortisol).

C. In secondary and tertiary adrenal insufficiency: there is a defect in hypothalamic pituitary axis there is no increase in ACTH or 11 deoxycortisol level because the decreased cortisol level has failed to stimulate the affected pituitary to increase the amount of ACTH.





❖ N.B:

1. When pharmacological doses of glucocorticoid therapy are used for more than three weeks duration, treatment cessation should be gradual (steroid taper) to prevent development of adrenal insufficiency.

2. Type 1 diabetes mellitus (due to autoimmune destruction of pancreatic B-cells) increases the risk of developing other autoimmune disorders such as Hashimoto thyroiditis and autoimmune adrenalitis.

Adrenal crisis

- This may occur in:

1. Bilateral adrenal infarction or hemorrhage:

- Meningococcal septicemia can cause adrenal hemorrhage leading to acute adrenal crisis (Waterhouse-Friderichsen syndrome).
- In addition to features of adrenal crisis, the patient also presents with fever, vomiting, nuchal rigidity and petechial rash, these clinical signs strongly suggestive of meningococcal meningitis.

2. Acute illness/injury/surgery in patient with chronic adrenal insufficiency or long-term glucocorticoid therapy:

A. Previously undiagnosed patient with adrenal insufficiency who has undergone surgery, serious infection, and/or major stress. Cortisol plays an important cardiovascular role during stress; and during stressful situations (infections or surgery), normal individuals experience a 3- to 9-fold increase in the level of endogenous glucocorticoids.

B. Patient who is abruptly withdrawn from chronic glucocorticoid therapy:

- Long-term use of supraphysiological doses of glucocorticoids causes suppression of the hypothalamic-pituitary-adrenal axis, which in turn leads to bilateral adrenocortical atrophy. If the patient then suddenly stops taking the doses of exogenous corticosteroids for whatever reason, adrenal crisis can result.

- Acute adrenal crisis presents with fever, profound hypotension, confusion, and coma.

- Treatment with hydrocortisone or dexamethasone is more important than testing in acute adrenal crisis.

- In a patient with suspected acute adrenal insufficiency, it is critical to administer hydrocortisone. This is more important than diagnosing the etiology. Hydrocortisone possesses sufficient mineralocorticoid activity to be life-saving. In addition, hydrocortisone will increase the blood pressure because there is a permissive effect of glucocorticoids on the vascular reactivity effect of catecholamines. BP will come up fast with steroids because norepinephrine will be more effective on constricting blood vessels.

Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Acute illness/injury/surgery in patient with chronic adrenal insufficiency or long-term glucocorticoid use
Clinical features	• **Hypotension/shock** • Nausea, vomiting, abdominal pain • Weakness • Fever
Treatment	• **Hydrocortisone** or **dexamethasone** • High-flow intravenous fluids

❖ N.B:

- In a patient with a suppressed HPA axis, stress response during stressful situations is lacking and an adrenal crisis can develop even when the patient's baseline glucocorticoid regimen is maintained. In such cases, a higher "stress dose" is usually given to compensate for the normal physiologic increase and minimize the risk of adrenal insufficiency.

Mineralocorticoid disorders

Primary hyperaldosteronism (Conn's syndrome)

- Etiology:

- Primary hyperaldosteronism is the autonomous overproduction of aldosterone despite a high pressure with a low renin activity.

- The most common causes of primary hyperaldosteronism include unilateral adrenal adenoma and bilateral adrenal hyperplasia. It is rarely malignant.

- Presentation/"What Is the Most Likely Diagnosis?"

- Aldosterone's main effect is to stimulate sodium absorption and potassium and hydrogen ion excretion at the distal renal tubule.

- Thus, overproduction of aldosterone by tumors or hyperplastic zona glomerulosa cells can result in sodium retention, hypertension, hypokalemia, and metabolic alkalosis.

- In the case of primary hyperaldosteronism, there is high blood pressure in association with a low potassium level. The low potassium level is either found on routine lab testing or because of symptoms of muscular weakness or paresthesias.

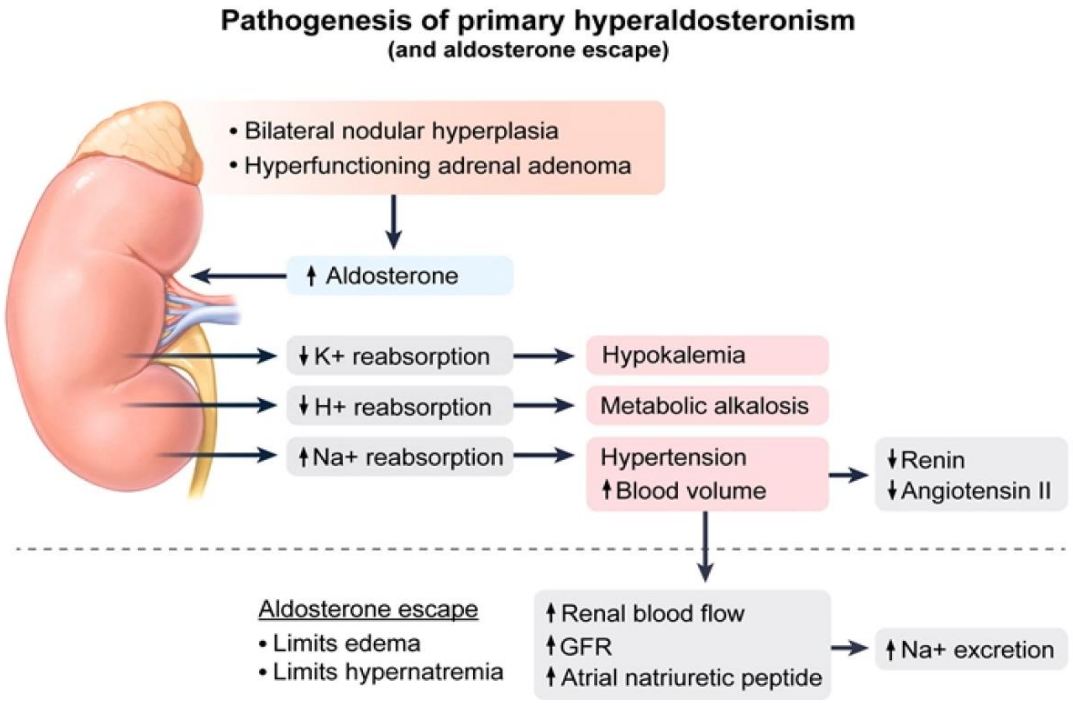
- Metabolic alkalosis occurs because aldosterone increases hydrogen ion (H) excretion.

- Although aldosterone causes increased renal reabsorption of sodium, most patients do not have edema or clinically significant hypernatremia due to aldosterone escape phenomenon.

- Aldosterone escape phenomenon:
  - The high aldosterone levels cause increased renal sodium and water absorption, thus increasing renal blood flow and GFR, which in turn increase the rate of sodium excretion from the renal tubules.

  - Furthermore, the increase in intravascular volume stimulates the release of atrial natriuretic peptide, which causes natriuresis.

  - This counteracts the increase in Na reabsorption induced by aldosterone, leading to only a mild increase in extracellular fluid volume that manifests clinically as hypertension without significant edema or hypernatremia.



- Renin levels are typically very low, due to the hypervolemia.

- SO, hypertension, mild hypernatremia, hypokalemia, metabolic alkalosis, suppressed plasma renin, weakness and paresthesias are highly suggestive of primary mineralocorticoid excess (Conn's syndrome).

- The question may ask you about the electrolyte pattern most likely be seen in conn's syndrome?
- Normal Na, ↓ k, ↑ Bicarbonate.

- Treatment:
- Surgery to remove the tumor and spironolactone (a K sparing diuretic that works by acting as an aldosterone antagonist).

Primary hyperaldosteronism	
Etiology	• Bilateral adrenal hyperplasia (60%) • Unilateral adrenal adenoma
Clinical features	• **Hypertension** • **Hypokalemic alkalosis**: Muscle weakness & paresthesias
Diagnosis	• **Elevated plasma aldosterone** • **Low plasma renin activity** • Aldosterone remains elevated following oral saline load

Secondary hyperaldosteronism

- It is an overactive renin-angiotensin system due to kidney perception of low intravascular volume.
- Causes: Seen in patients with renovascular hypertension, juxtaglomerular cell tumors (renin-producing), and edema (cirrhosis, heart failure, nephrotic syndrome).
- Modest to highly elevated renin.
- Hypokalemia and metabolic alkalosis.
- So, in a nutshell:

- Symptoms of hyperaldosteronism + ↓ renin → primary hyperaldosteronism (Conn's syndrome).
- Symptoms of hyperaldosteronism + ↑ renin → secondary hyperaldosteronism.

Congenital adrenal hyperplasia

- Congenital adrenal hyperplasia (CAH) is a group of disorders due to enzyme deficiencies for cortisol synthesis in the adrenal cortex that has 3 forms:

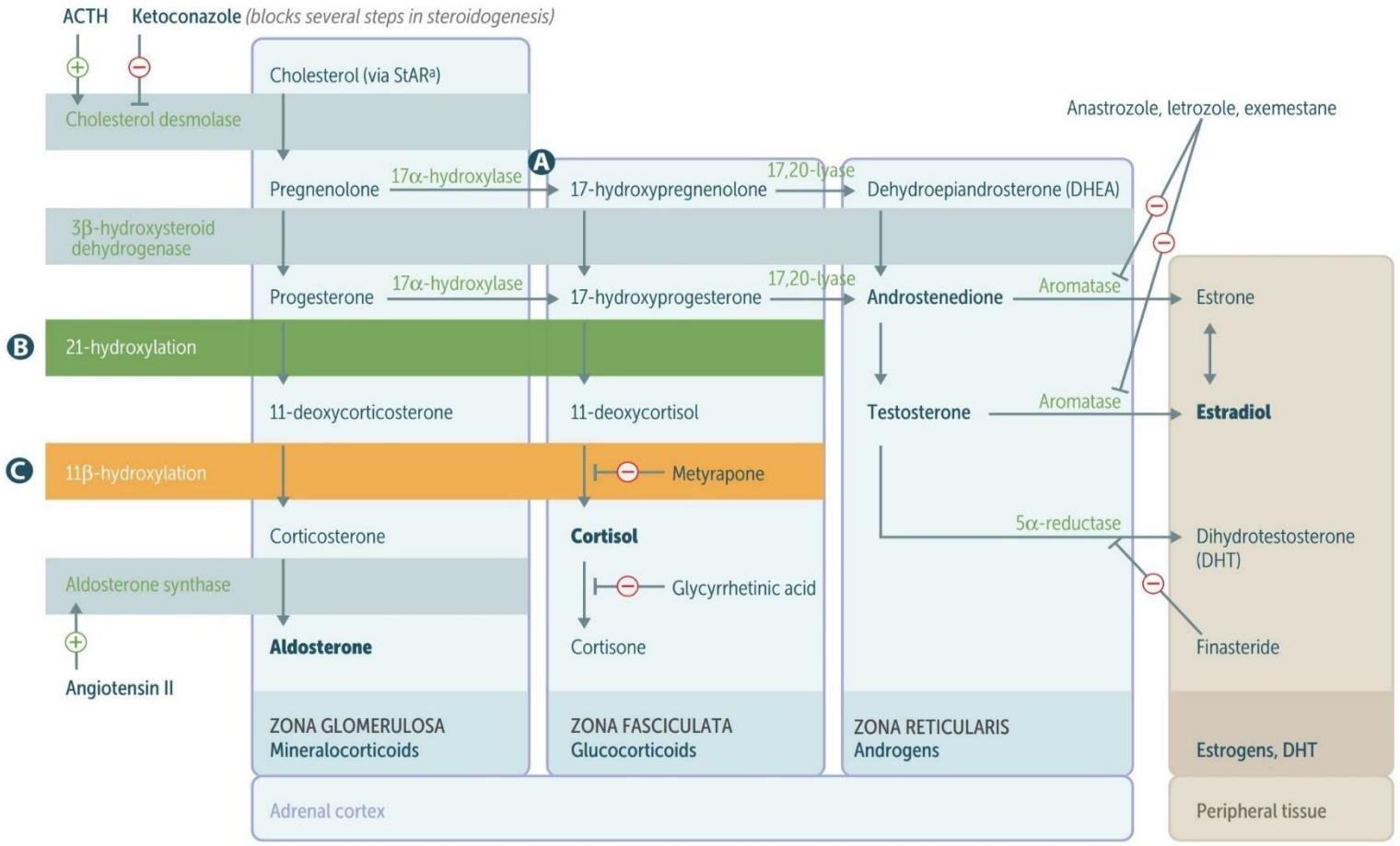
- 21-hydroxylase (the most common).
- 17 hydroxylase.
- 11 -beta-hydroxylase.

- Approximately 90% of cases are due to 21- hydroxylase deficiency, which is involved in the cortisol and aldosterone pathways.

- The low plasma cortisol stimulates the pituitary to increase ACTH production, which leads to adrenal hyperplasia.

- All congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to ↑ MSH production, which is coproduced and secreted with ACTH).

- If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.



[a]Rate-limiting step.

A. 21-hydroxylase deficiency:

- Defect:

- Deficiency of 21-hydroxylase is the most common cause of CAH, accounting for 90% of all cases.

- This enzyme catalyzes the conversion of 17-hydroxyprogesterone to 11-deoxycortisol in the zona fasciculata and the conversion of progesterone to 11-deoxycorticosterone in the zona glomerulosa. 11-deoxycorticosterone is a precursor of aldosterone, and 11-deoxycortisol is a precursor of cortisol.

- In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. This causes increased production of adrenal androgens because the accumulating cortisol and aldosterone precursors are diverted toward adrenal androgen biosynthesis.

- The resulting low cortisol levels stimulate pituitary production of ACTH, which further increases the production of adrenal androgens.

- Presentation:

- Increased androgen levels lead to ambiguous genitalia in females (virilization), but males will have normal genitalia. Boys may present at 2-4 years with signs of early virilization (pubic and axillary hair).

- Salt-wasting occurs with more severe enzymatic deficiencies due to lack of sufficient amounts of mineralocorticoids and presents with vomiting, hypotension, hyponatremia, and hyperkalemia, and increased renin activity.

- Severe enzymatic defects can also result in significant cortisol deficiency, which can cause hypoglycemia and further impair blood pressure maintenance (leading to circulatory collapse).

- Diagnosis:

- A high serum level of 17-hydroxyprogesterone is diagnostic for 21-hydroxylase deficiency (as its conversion to 11-deoxycortisol is impaired by the enzymatic defect) and testing is often performed during routine newborn screening.

- Treatment:

- Treatment of congenital adrenal hyperplasia involves administering low (physiologic} doses of exogenous corticosteroids to suppress ACTH secretion. By removing excessive ACTH stimulation, exogenous corticosteroids can decrease androgen production by the adrenal cortex.

B. 11 β-hydroxylase deficiency:

- Defect:

- 11 β-hydroxylase deficiency is the second most common cause of congenital adrenal hyperplasia (CAH).

- 11 β-hydroxylase converts 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol.

- Deficiency of this enzyme prevents the adrenal gland from synthesizing cortisol and aldosterone efficiently. This causes increased production of adrenal androgens due to cortisol and aldosterone precursors being diverted toward adrenal androgen biosynthesis.

- The resulting low cortisol levels stimulate pituitary production of ACTH, which further increases the production of adrenal androgens.

▪ Presentation:

- Females with 11 β-hydroxylase deficiency are born with ambiguous genitalia.

- Impaired metabolism of 11-deoxycorticosterone allows this weak mineralocorticoid to accumulate, leading to the development of low-renin hypertension and hypokalemia even in the setting of impaired aldosterone synthesis.

- This is in contrast to 21-hydroxylase deficiency, in which the symptoms of mineralocorticoid deficiency predominate since 11-deoxycorticosterone cannot be synthesized.

C. 17 α-hydroxylase deficiency:

▪ Defect:

- 17 α-hydroxylase deficiency is a rare cause of congenital adrenal hyperplasia (CAH) accounting for < 1 % of all cases.

- The 17 α-hydroxylase enzyme is active in both the adrenal gland and gonads, where it converts pregnenolone to 17- hydroxypregnenolone and progesterone to 17-hydroxyprogesterone.

- 17 α-hydroxylase deficiency impairs the synthesis of androgens, estrogens, and cortisol but does not inhibit mineralocorticoid production. In fact, the high ACTH levels that result from decreased cortisol production overstimulate the mineralocorticoid pathway, leading to excessive formation of 11-deoxycorticosterone and corticosterone.

▪ Presentation:

- Males appear phenotypically female at birth (but lack internal female genitalia) due to the absence of virializing androgens in utero. However, females develop normal internal and external genitalia.

- At puberty, impaired synthesis of sex hormones prevents the development of secondary sexual characteristics in both sexes and prevents menarche in females.

- Excessive production of mineralocorticoids by the adrenals also results in hypertension, hypokalemia, and low renin levels that are usually detected around the time of expected puberty.

Enzyme deficiency	Hormonal abnormalities	Symptoms
21-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 17-hydroxyprogesterone	• Ambiguous genitalia in girls • Salt wasting (vomiting, hypotension, $\downarrow Na^+$, $\uparrow K^+$)
11β-hydroxylase	• ↓ Cortisol & aldosterone • ↑ Testosterone • ↑ 11-deoxycorticosterone (weak mineralocorticoid) & 11- deoxycortisol	• Ambiguous genitalia in girls • Fluid & salt retention, hypertension
17α-hydroxylase	• ↓ Cortisol & testosterone • ↑ Mineralocorticoids • ↑ Corticosterone (weak glucocorticoid)	• All patients phenotypically female • Fluid & salt retention, hypertension

Adrenal medulla

- The adrenal medulla forms about 20% of the adrenal gland.

- It secretes catecholamines: epinephrine (80%), norepinephrine (20%), and dopamine.

Pheochromocytoma

- Etiology:

- It is a tumor of the chromaffin tissue of the adrenal medulla (arise from neural crest) that causes increased production of catecholamines (norepinephrine, epinephrine and dopamine).

- Most common adrenal medulla tumor in the adults.

- Usually unilateral benign tumors.

- May be associated with germline mutations (NF-1, VHL, RET [MEN 2A, 2B]).

- Symptoms:

- Fluctuating catecholamine release results in increased vascular tone and hypertension, which cause episodic hypertension. Often associated with episodic headache, diaphoresis, and palpitations.

- Episodic hyperadrenergic symptoms (5Ps):
  - Pressure (↑ BP).
  - Pain (headache).
  - Perspiration.
  - Palpitation (tachycardia).
  - Pallor.

- Rule of 10's:
  - 10% malignant.
  - 10% bilateral.
  - 10% extra-adrenal.
  - 10% calcify.
  - 10% kids.

- Paragangliomas are extraradrenal pheochromocytomas of sympathetic ganglia located primarily within the abdomen and that secrete norepinephrine.

- Findings: ↑ catecholamines and metanephrines (homovanillic acid, vanillylmandelic acid) in urine and plasma.

- Treatment:

- Irreversible alpha antagonist (phenoxybenzamine) followed by B-blockers prior to tumor resection. Phenoxybenzamine for pheochromocytoma.

- Alpha blockade must be achieved before giving B-blockers to avoid a hypertensive crisis (unopposed alpha agonist).

Pheochromocytoma	
Pathogenesis	• Arises from neuroendocrine cells in **adrenal medulla** • 25% inherited: ◦ *VHL* gene (von Hippel-Lindau) ◦ *RET* gene (multiple endocrine neoplasia type 2) ◦ *NF1* gene (neurofibromatosis) • Symptoms result from **increased catecholamine secretion**
Symptoms	• Headache • Tachycardia/palpitations • Sweating • Hypertension
Rule of 10s	• 10% bilateral • 10% extraadrenal (paragangliomas) • 10% malignant
Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

Neuroblastoma

- Etiology:

- Most common tumor of the adrenal medulla in children, usually < 4 years old.

- Originates from neural crest cells.

- Occur anyway along the sympathetic chain.

- Symptoms:

- Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs. Wilms tumor, which presents with smooth and unilateral abdominal mass).

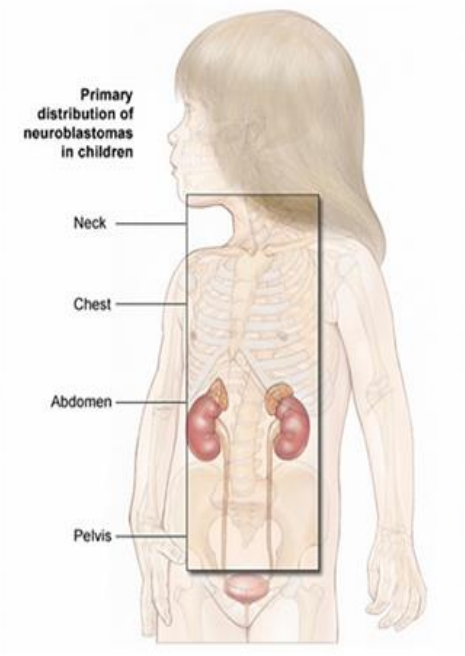
- Bone marrow infiltration can cause anemia or pancytopenia, and orbital metastases may result in proptosis and/or periorbital ecchymoses. Although rare, opsoclonus-myoclonus (dancing eyes, dancing feet) is a paraneoplastic syndrome highly associated with neuroblastoma and is believed to be an autoantibody response to central nervous system antigens.

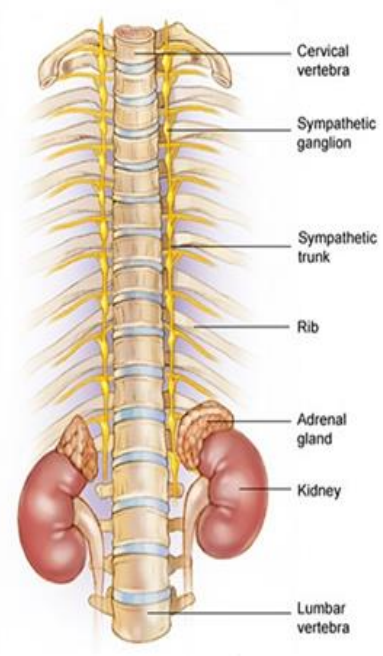
- Less likely to develop hypertension (Neuroblastoma is Normotensive). Associate with overexpression of N-myc oncogenes.

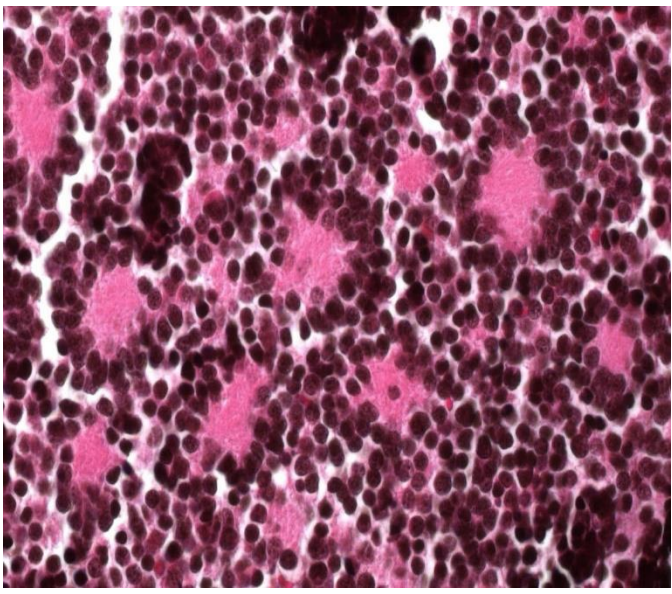
- Findings:

- Homovanilic acid (HVA, a breakdown product of dopamine) and vanillylmandelic acid (VMA, a breakdown product of norepinephrine) increase in urine.

- Homer-Wright rosettes is characteristic (neuroblasts surrounding a central lumen). Bombesin and neuron-specific enolase positive.

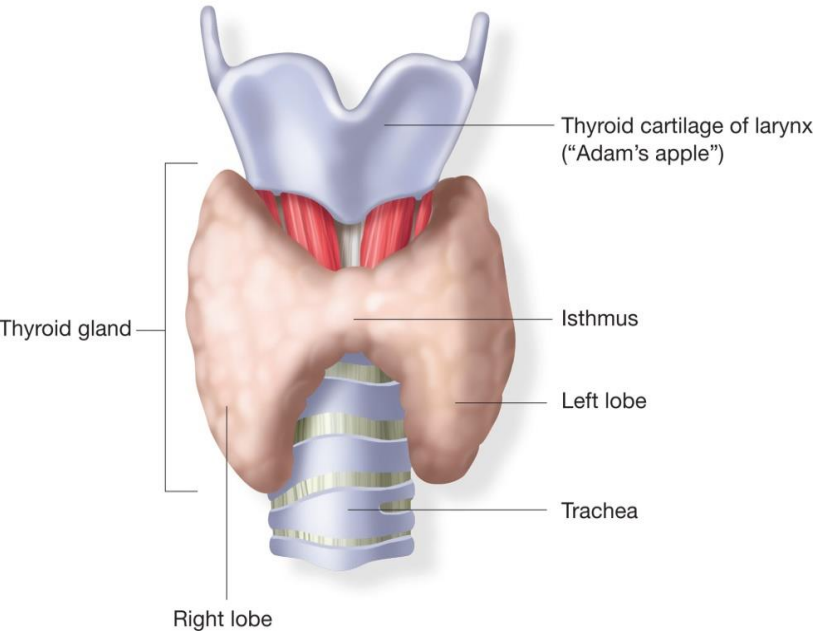


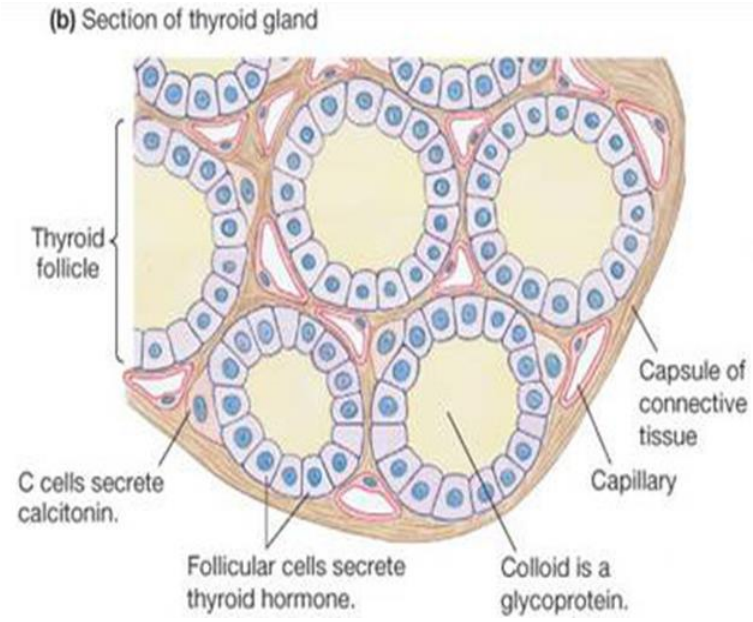




Thyroid gland

- The thyroid is a butterfly shaped gland, composed of 2 lobes connected by an isthmus.
- It is present in front and on either side of the upper part of the trachea.
- It possesses one of the highest rates of blood flow in the body.
- It is composed of follicles; each follicle surrounds a cavity full of colloid material (thyroglobulin).
- Parafollicular cells, lie in between the follicles.





Thyroid hormones

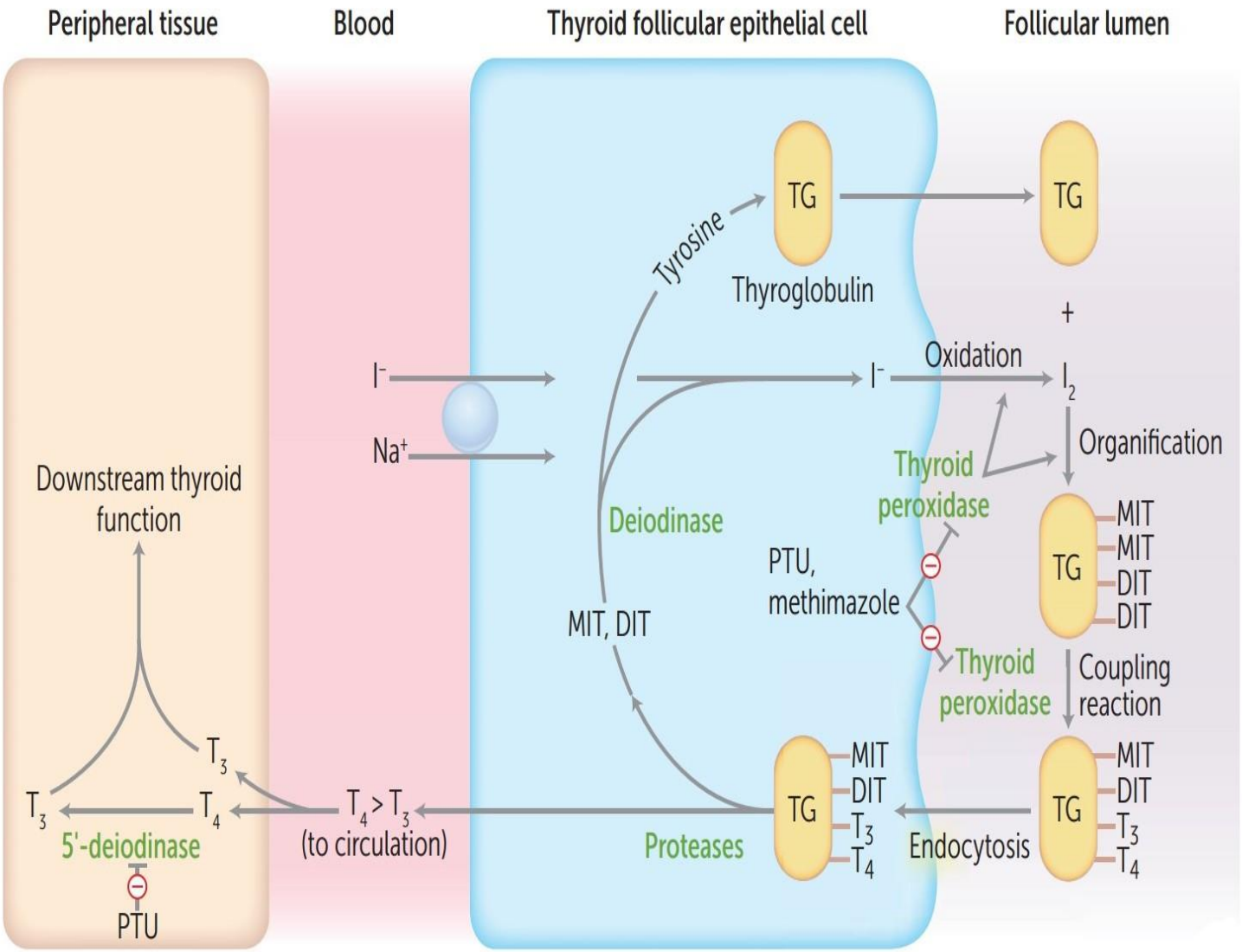
- The normal thyroid gland takes up iodine against a concentration gradient using a sodium iodine symporter (NIS) in an energy-dependent process, called "iodine trapping".
- After dietary, inorganic iodine enters the thyroid follicular cells, it is oxidized to organic iodide by the enzyme thyroid peroxidase.
- Following oxidation, Iodide binds to tyrosine residues in the thyroglobulin to form monoiodotyrosine. Several combinations are then possible.

- Either two monoiodotyrosines can combine to form diiodotyrosine, which can then unite with another diiodotyrosine to form thyroxine (T_4) or a monoiodotyrosine can link with a diiodotyrosine to make triiodothyronine (T_3).

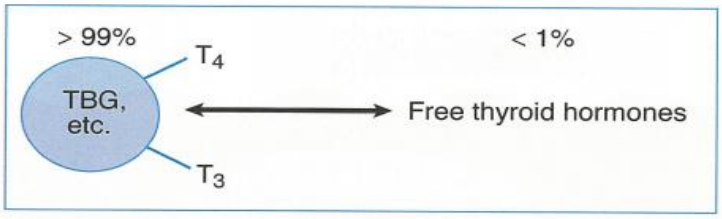
- The thyroid follicular cells then engulf thyroglobulin, which contains any and all of the iodinated tyrosine compounds (mono and diiodo tyrosine, triiodothyronine, and thyroxine) by endocytosis.

- In the thyroid cytoplasm, the iodinated tyrosine residues are removed from the rest of the thyroglobulin, then secreted from the basolateral border of the thyroid follicular cells.

- Thyroid peroxidase is responsible for the oxidation of inorganic iodine, the formation of mono and diiodotyrosine (organification), and the coupling that forms T_3 and T_4.



- More than 99% of circulating thyroid hormones are bound to plasma proteins. The main protein responsible for binding circulating thyroid hormone is thyroid binding globulin (TBG).

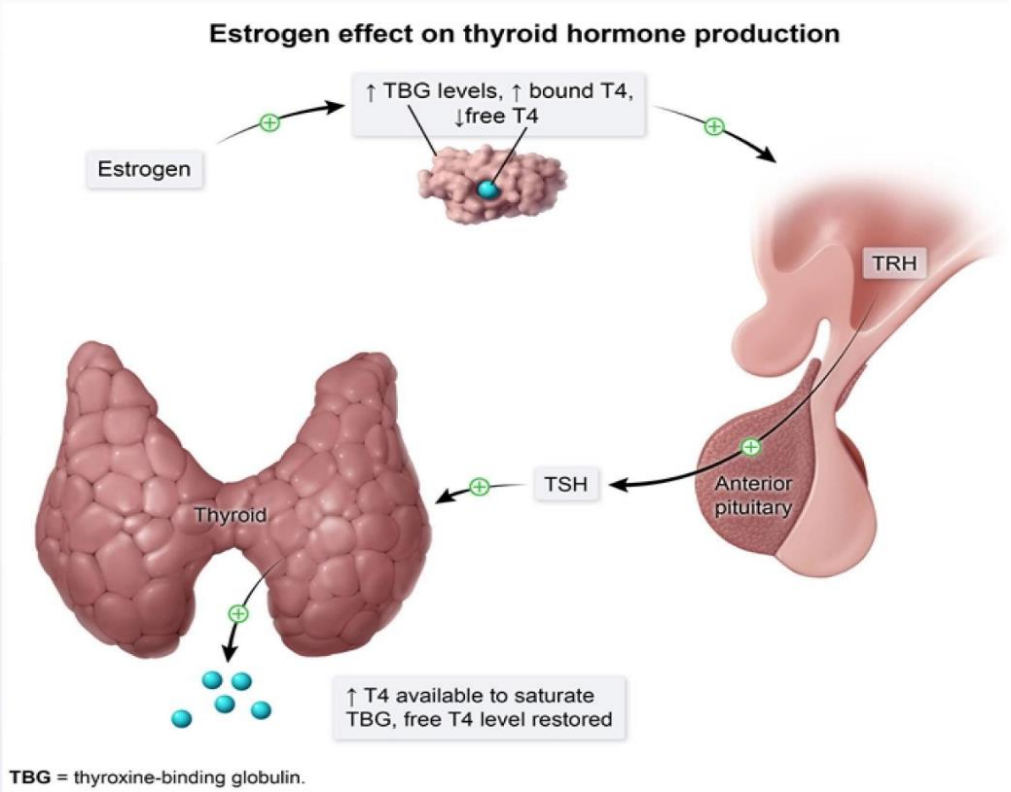


- TBG ↓ in hepatic failure and nephrotic syndrome due to decrease of globulin synthesis by the liver or loss of plasma proteins in nephrotic syndrome, ↑ TBG in pregnancy or OCP use (estrogen ↑ TBG).

- High levels of estrogen (pregnancy, oral contraceptive pills, hormone replacement therapy) increase the level of TBG by decreasing its catabolism and increasing its synthesis in the liver.

- As the additional TBG binds more thyroid hormone, thyroid hormone production increases to maintain a euthyroid state; this most likely explains slight elevation in total T_4 level but free T_4 level would be expected to be normal.

- Most patients with hypothyroidism have an increased requirement for levothyroxine after starting oral estrogen (estrogen replacement therapy or oral contraceptives). Patients with normal thyroid function can readily increase thyroxine production to saturate the increased number of TBG binding sites, but hypothyroid patients are dependent on exogenous thyroid replacement and cannot compensate. This results in decreased free thyroxine and increased thyroid-stimulating hormone. As a result, higher dosing of levothyroxine may be required.



- Thyroid hormone exists in three forms:

- T_4 is the thyroid hormone that is produced in the greatest quantity by the thyroid gland.

- T_3 is the most active form, having four times the activity of T_4.

- Reverse T_3 (rT_3) is an inactive form of thyroid hormone.

- In the peripheral tissues, T_4 is converted to T_3 and to rT_3 by the action of deiodinase enzymes (distinct isoforms preferentially convert T_4 into T_3 or rT_3). However, T_3 cannot be converted into T_4 or rT_3.

- Peripheral conversion is inhibited by glucocorticoids, β-blockers, and propylthiouracil (PTU).

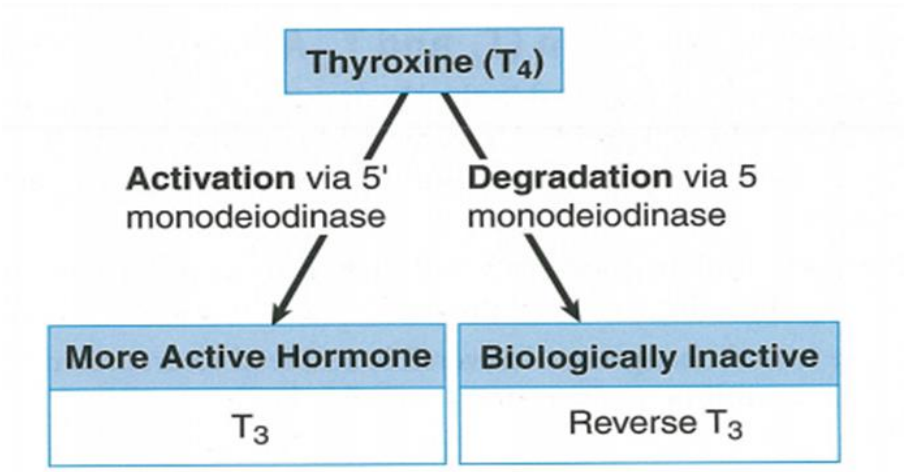
- Also, T_4 has the higher affinity for binding proteins; therefore, it binds more tightly to protein than does T_3, and consequently has a greater half-life than T_3. Most circulating thyroid hormone is T_4. Normally, there is 50 times more T_4 than T_3.

- T_4, T_3, and rT_3 have plasma half-lives of 7 days, 1 day, and less than one day, respectively; and they are cleared from circulation by glucuronidation in the liver.

- Synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it has a short half-life and patients can experience wide fluctuations in plasma T3 levels. T4 (levothyroxine) supplementation provides a more physiologic effect and is preferred.

- T3 is primarily produced by conversion from T4 in peripheral tissues; serum levels widely fluctuate due to its short half life, and can often be within the normal range in patients with hypothyroidism.

- T_3 and T_4 bind to the same nuclear receptor but T_3 binds with 10 times more affinity than T_4. Thus, because it has greater affinity for the receptor, T_3 is the more active form of thyroid hormone.



Physiologic action of thyroid hormones

- A multitude of processes function properly only when optimal amounts of thyroid hormones are present. This underscores the permissive nature of thyroid hormones.

1. Metabolic rate:

- Thyroid hormones increase basal metabolic rate via ↑ Na/K ATPase activity, as evidenced by increased O_2 consumption, increased respiratory rate and heat production.

2. Growth and Maturation:

- Without adequate thyroid hormones during the perinatal period, abnormalities rapidly develop in nervous system maturation because:
  - Synapses develop abnormally and there is decreased dendritic branching and myelination. These abnormalities lead to mental retardation.
  - These neural changes are irreversible and lead to cretinism unless replacement therapy is started soon after birth.

3. Lipid Metabolism:

- Break down lipids (↑ lipolysis).

- Thyroid hormone accelerates cholesterol clearance from the plasma.

4. Cardiovascular Effects:

- Thyroid hormones in the normal range are required for optimum cardiac performance.

- Thyroid hormones have positive inotropic and chronotropic effects on the heart. The increased contractility is partly direct and partly indirect:
  - They increase the number and affinity of β-adrenergic receptors in the heart, thereby increasing the sensitivity to catecholamines.
  - Acting on the SA node they directly increase heart rate.

- Cardiac output is increased, and both heart rate and stroke volume are elevated. Systolic pressure increases are due to increased stroke volume, and diastolic pressure decreases are due to decreased peripheral resistance.

- Many symptoms suggest a state of excess catecholamines but circulating catecholamines are usually normal.

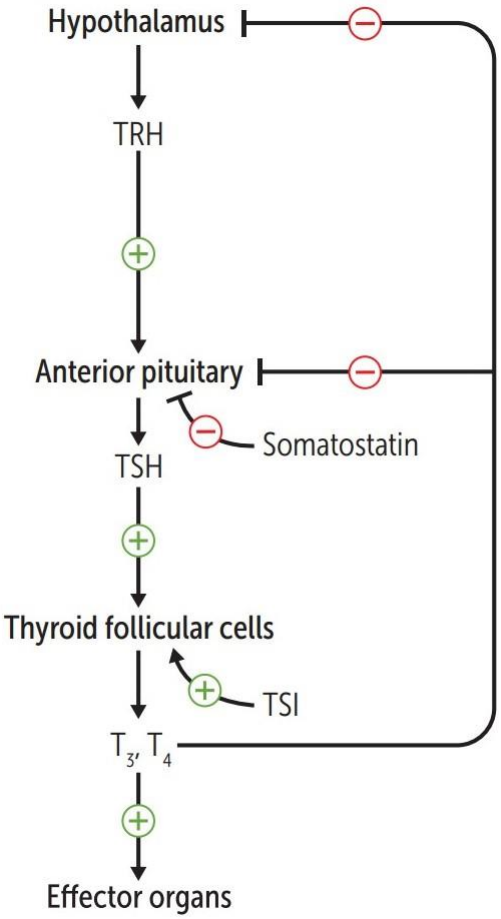
5. Bone growth (synergism with GH).

Regulation of thyroid hormones

- TRH from hypothalamus stimulates thyrotophs of pituitary gland to secrete TSH, which stimulates follicular cells to secrete thyroid hormones.

- The release of thyroid hormone is regulated through negative feedback inhibition by free T_3, T_4 on hypothalamic TRH-secreting neurons and thyrotrophs cells of the anterior pituitary:

- Anterior pituitary → ↓ sensitivity to TRH.
- Hypothalamus → ↓ TRH secretion.



❖ N.B:

- Exogenous T_3 thyroid supplementation would reduce circulating levels of TSH, and thus cause decreased secretion of T_4 from the thyroid gland (which would also lead to decreased peripheral rT_3 conversion).

Hypothyroidism vs hyperthyroidism

FINDINGS	Hypothyroidism	Hyperthyroidism
METABOLIC	Cold intolerance, ↓ sweating, weight gain (↓ basal metabolic rate → ↓ calorigenesis), hyponatremia (↓ free water clearance)	Heat intolerance, ↑ sweating, weight loss (↑ synthesis of Na^+-K^+ ATPase → ↑ basal metabolic rate → ↑ calorigenesis)
SKIN/HAIR 	Dry, cool skin (due to ↓ blood flow); coarse, brittle hair; diffuse alopecia; brittle nails; puffy facies and generalized nonpitting edema (myxedema) due to ↑ GAGs in interstitial spaces → ↑ osmotic pressure → water retention	Warm, moist skin (due to vasodilation); fine hair; onycholysis (A); pretibial myxedema in Graves disease
OCULAR	Periorbital edema	Ophthalmopathy in Graves disease (including periorbital edema, exophthalmos), lid lag/retraction (↑ sympathetic stimulation of levator palpebrae superioris and superior tarsal muscle)
GASTROINTESTINAL	Constipation (↓ GI motility), ↓ appetite	Hyperdefecation/diarrhea (↑ GI motility), ↑ appetite
MUSCULOSKELETAL	Hypothyroid myopathy (proximal weakness, ↑ CK), carpal tunnel syndrome, myoedema (small lump rising on the surface of a muscle when struck with a hammer)	Thyrotoxic myopathy (proximal weakness, normal CK), osteoporosis/↑ fracture rate (T_3 directly stimulates bone resorption)
REPRODUCTIVE	Abnormal uterine bleeding, ↓ libido, infertility	Abnormal uterine bleeding, gynecomastia, ↓ libido, infertility
NEUROPSYCHIATRIC	Hypoactivity, lethargy, fatigue, weakness, depressed mood, ↓ reflexes (delayed/slow relaxing)	Hyperactivity, restlessness, anxiety, insomnia, fine tremors (due to ↑ β-adrenergic activity), ↑ reflexes (brisk)
CARDIOVASCULAR	Bradycardia, dyspnea on exertion (↓ cardiac output)	Tachycardia, palpitations, dyspnea, arrhythmias (eg, atrial fibrillation), chest pain and systolic HTN due to ↑ number and sensitivity of β-adrenergic receptors, ↑ expression of cardiac sarcolemmal ATPase and ↓ expression of phospholamban
LABS	↑ TSH (if 1°) ↓ free T_3 and T_4 Hypercholesterolemia (due to ↓ LDL receptor expression)	↓ TSH (if 1°) ↑ free T_3 and T_4 ↓ LDL, HDL, and total cholesterol

❖ N.B:

1. Small changes in thyroid hormone levels lead to marked changes in serum TSH level.

- In hypothyroidism, the TSH rise occurs well before a low thyroid hormone level is seen. Thus, serum TSH is the most sensitive marker for diagnosis of hypothyroidism.
- Serum TSH level is the single most important screening test in diagnosing primary hypothyroidism.
- In primary hypothyroidism, there is ↑ TSH and ↓ free T4.

2. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting hyperadrenergic state can lead to significant cardiovascular complications.

- Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity.
- Atrial fibrillation is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis.
- Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can precipitate angina in patients with underlying coronary disease.
- It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to high-output heart failure.

3. Increased TRH in hypothyroidism may stimulate prolactin secretion → hyperprolactinemia.

- In women, it may result in amenorrhea with galactorrhea; more often anovulatory cycles with menorrhagia.
- In men infertility and gynecomastia.

Cardiovascular effects of hyperthyroidism	
Increased rate	• Tachycardia/palpitations • Atrial fibrillation
Increased contractility	• ↑ Ejection fraction & cardiac output • ↑ Myocardial oxygen demand & angina • ↑ Pulmonary artery pressure
Decreased afterload	• ↓ Systemic vascular resistance
Additional effects	• ↓ Diastolic pressure • ↑ Systolic pressure • ↑ Pulse pressure • High-output heart failure

4. Involvement of the musculoskeletal system causes hypothyroid myopathy, which is characterized by myalgia, proximal muscle weakness, and cramping.
- Elevation of serum creatine kinase (CK), is common in hypothyroidism and can occur even in asymptomatic patients.
- Hypothyroidism should be excluded with measurement of thyroid-stimulating hormone levels in patients with unexplained CK elevation.

5. Hypothyroidism should be excluded in patients with unexplained hypercholesterolemia and unexplained menorrhagia.

6. Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and low/undetectable thyroglobulin.
- Excess T4 supplementation suppresses TSH, which decreases iodine organification and colloid formation resulting in atrophy of thyroid follicles.

7. Thyrotoxicosis by definition is the clinical syndrome whereby tissues are exposed to high levels of thyroid hormone (hyperthyroidism).
- The most common cause of thyrotoxicosis is Grave's disease.

8. Goiter is simply an enlarged thyroid and does not designate functional status.
- A goiter can be present in hypo-, hyper-, and euthyroid states.
- There is no correlation between thyroid size and function.
- A generalized enlargement of the thyroid is considered a "diffuse goiter". Examples: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma.
- An irregular or lumpy enlargement of the thyroid is considered a "nodular goiter". Examples: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

Hypothyroidism

Hashimoto's thyroiditis

- In the United States, the most common etiology of hypothyroidism in areas where iodine is sufficient is Hashimoto's thyroiditis, an autoimmune process that destroys the cells of the thyroid and affects women more than men.

- Histology:

- The thyroid has intense mononuclear infiltration consisting of lymphocytes and plasma cells.

- There are several germinal centers also present.

- The thyroid follicular epithelial cells undergo a metaplastic change, leading to the formation of large, oxyphilic cells with granular cytoplasm, called "Hurthle cells".

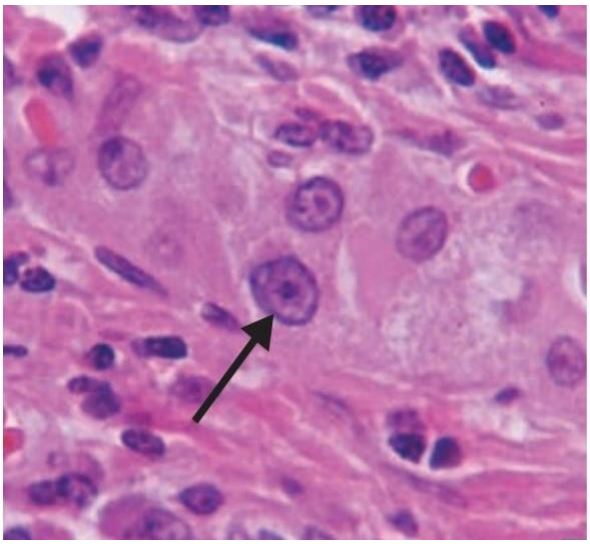
- Finding:

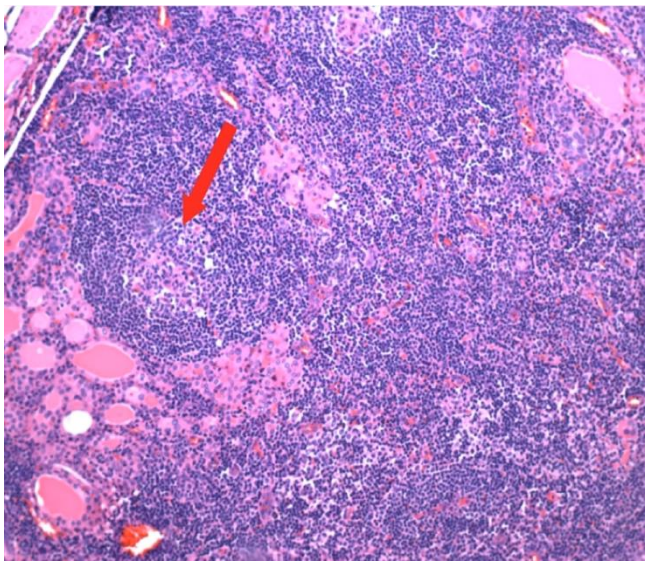
- In most patients, the diagnosis of Hashimoto's thyroiditis is based on clinical examination, presence of hypothyroidism (elevated TSH and low T4/T3) and elevated antithyroid peroxidase (antimicrosomal) antibody, and antithyroglobulin antibodies.

- May be hyperthyroid early in course due to thyrotoxicosis during follicular rupture.

- Early stages have a diffusely enlarged thyroid due to thyrotoxicosis during follicular rupture progressing in the later stages to a smaller atrophic and fibrotic gland.

- Associated with HLA-DR3, HLA-DR5, ↑ risk of non-Hodgkin lymphoma (typically of B-cell origin).





Subacute thyroiditis (de Quervain's thyroiditis)

- Subacute (de Quervain, granulomatous) thyroiditis is thought to be due to a post-viral inflammatory process and is often preceded by an upper respiratory illness.
- Subacute (de Quervain) thyroiditis is characterized by fever, ↑ ESR, neck and jaw pain, and a tender goiter following an upper respiratory illness.
- Thyrotoxicosis in subacute thyroiditis resolves spontaneously within a few weeks and may be followed by a hypothyroid phase lasting a few months (permanent in ~15% of cases). Most patients eventually recover to a euthyroid state.
- Thyrotoxicosis in subacute thyroiditis is caused by release of stored thyroid hormones secondary to thyroid inflammation; subacute thyroiditis does not cause excessive production of thyroid hormone, which is why iodine uptake is decreased.
- Histology:

- Granulomatous inflammation.
- The involvement of thyroid gland in subacute thyroiditis can be patchy. Initial neutrophil infiltration predominance is followed by infiltration of lymphocytes, histiocytes, and multinucleated giant cells. The thyroid follicles become disrupted, and multinucleated giant cells surround the fragmented colloid.
- Mixed, cellular infiltration with occasional multinucleate giant cells are characteristic histologic findings.

- Most patients respond to non-steroidal anti-inflammatory drugs for thyroid pain and inflammation.
- De Quervain is associated with pain.

Riedel thyroiditis

- Thyroid replaced by fibrous tissue and inflammatory infiltrate.
- Results from intense fibrosis of the thyroid and surrounding structures (including mediastinal and retroperitoneal fibrosis).
- Fibrosis may extend to local structures (trachea, esophagus), mimicking anaplastic carcinoma.
- Considered a manifestation of IgG4-related systemic disease (autoimmune pancreatitis, retroperitoneal fibrosis, noninfectious aortitis).
- Findings: fixed, hard (rock-like), painless goiter.

Congenital Hypothyroidism (cretinism)

- Severe fetal hypothyroidism due to thyroid dysgenesis (The most common cause; aplasia, hypoplasia, or ectopic gland), which has been incriminated in 85% of cases. Other causes include inborn errors of thyroxin synthesis (10%), and transplacental maternal thyrotropin-receptor blocking antibodies (5%).

- Findings:

- Pot-bellied, Pale, Puffy-faced child with Protruding umbilicus, Protuberant tongue, and Poor brain development (the 6 P's).

- Untreated postnatal hypothyroidism results in cretinism, a form of dwarfism with mental retardation.

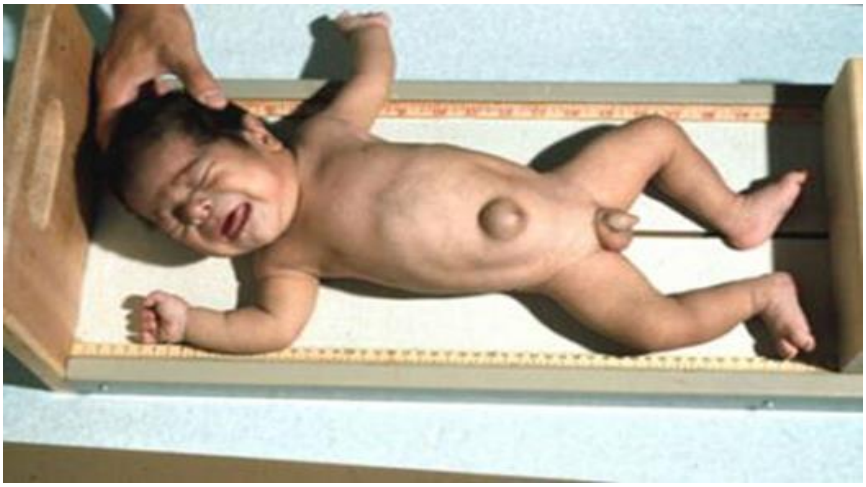
- Individuals often appear normal following delivery but may display some respiratory difficulty, jaundice, feeding problems, and hypotonia.

- Abnormalities rapidly develop in nervous system maturation, which are irreversible and result in mental retardation.

- Prepubertal growth, including bone ossification, is retarded in the absence of thyroid hormones.

- There is no evidence that thyroid hormones act directly on growth or bone formation. Rather, thyroid hormone appears to be permissive or act synergistically with growth hormone or growth factors acting directly on bone. Thyroid hormone is required for normal synthesis and secretion of growth hormone.

- Acquired hypothyroidism during childhood results in dwarfism but there is no mental retardation.



Postpartum thyroiditis

- Self-limited thyroiditis arising up to 1 year after delivery.
- Presents as transient hyperthyroidism, hypothyroidism, or hyperthyroidism followed by hypothyroidism.
- Majority of women are euthyroid following resolution.
- Thyroid usually painless and normal in size.
- Histology:

- Lymphocytic infiltrate with occasional germinal center formation.

Other causes

A. Secondary hypothyroidism generally associated with panhypopituitarism. Secondary hypothyroidism characterized by ↓ TSH and ↓ Free T_4.

B. Severe iodine deficiency (not in the United States).

C. Drug induced (lithium, amiodarone).

D. Wolff-Chaikoff effect:

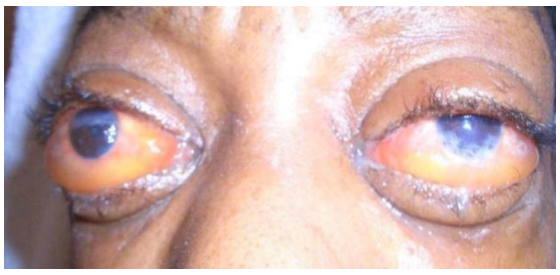
- Following excessive iodine intake → excess iodine temporarily inhibits thyroid peroxidase → ↓ iodine organifcation → ↓ T_3/T_4 production.

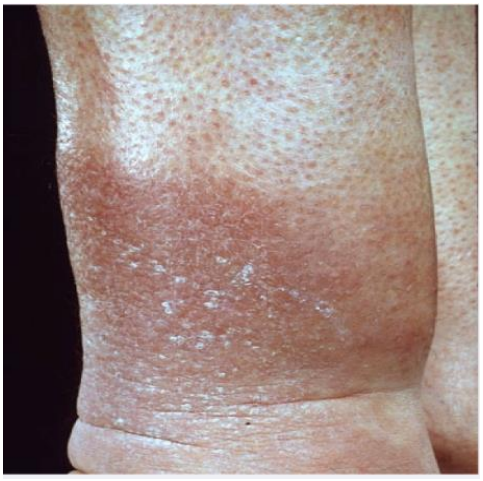
Hyperthyroidism

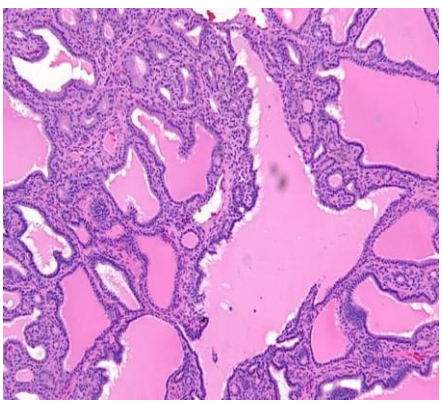
Grave's disease

- Grave's disease (toxic diffuse goiter) is an autoimmune problem in which autoantibody (IgG) is directed against the thyroid receptor. It is referred to as the thyroid stimulating antibody (TSI).
- Women > men.
- Associated with HLA-DR3 and HLA-B8.
- Finding:

- In Grave's disease, the thyroid is symmetrically enlarged.
- Patients with Graves' disease develop lymphocytic infiltration of the orbital and pretibial connective tissue because of increased TSH receptor expression in these regions.
- Cytokines released by activated T-cells increase fibroblast proliferation and secretion of glycosaminoglycans, resulting in mucinous edema and tissue expansion. Progressive infiltration eventually leads to the development of Graves' ophthalmopathy and pretibial myxedema.
- Pretibial myxedema manifests as nonpitting edema that is sometimes scaly in appearance (classically described as resembling an orange peel). This leads to induration and thickening of the skin over the shins.
- Graves ophthalmopathy occurs in a similar manner, with expansion of the retro-orbital tissues displacing the globe forward (proptosis).
- Onycholysis: Occurring in only 10 percent of cases, this is separation of the nail from the nailbed.





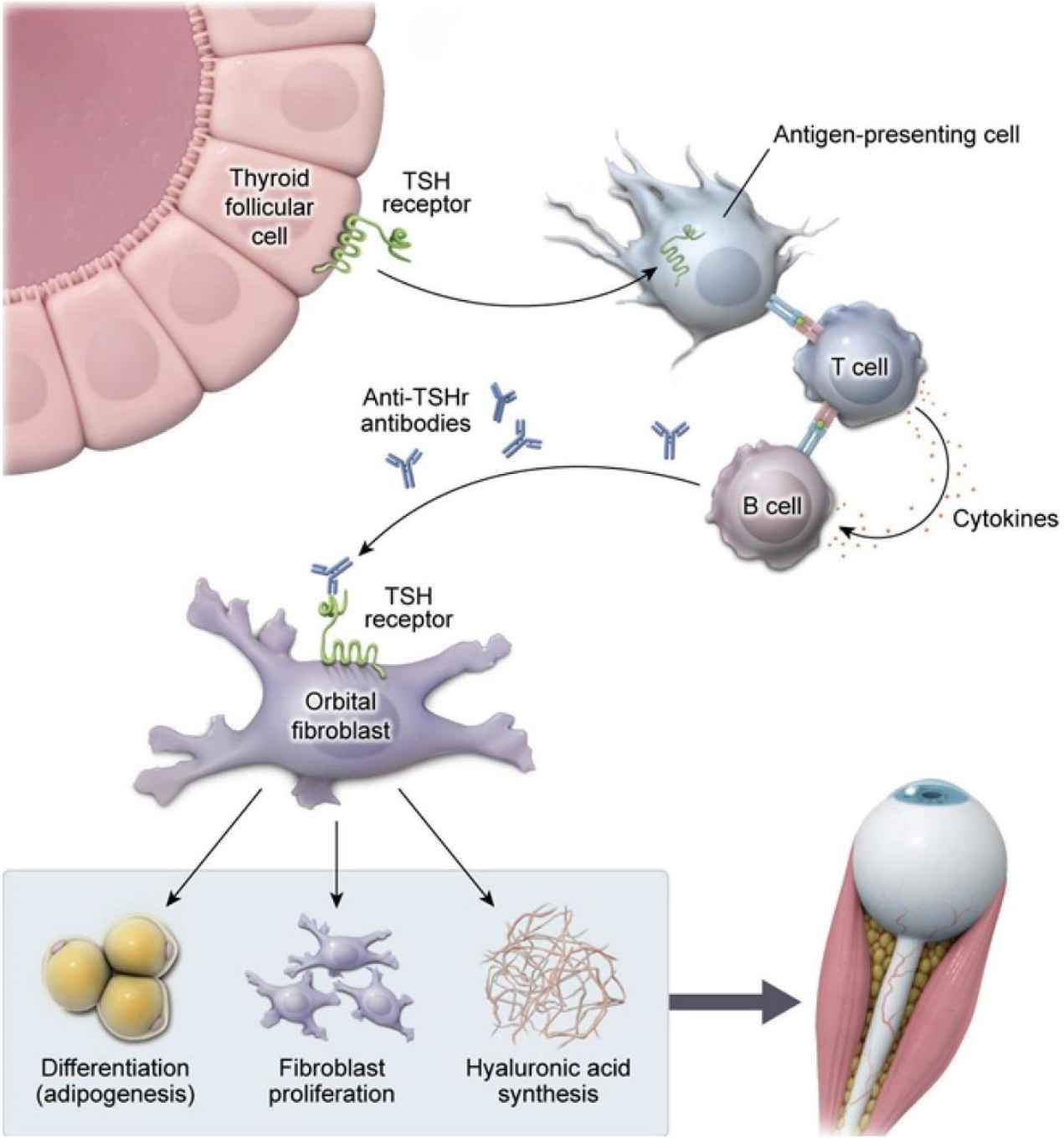


- Laboratory:

- ↑ Free T4, ↓ TSH; it is the TSI stimulating the TSH receptor on the thyroid that is driving the hyperthyroidism.

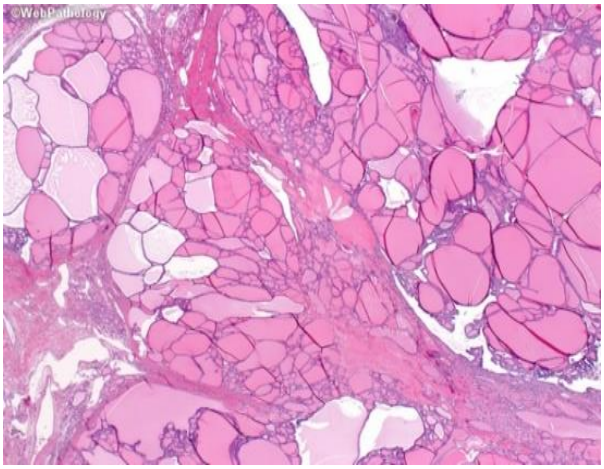
- Additional laboratory findings would be increased radioiodine uptake by the thyroid. A high RAIU suggests de novo hormone synthesis due to Graves' disease (diffusely increased uptake) or toxic nodular disease (nodular uptake).

- Histology: tall, crowded follicular epithelial cells; scalloped colloid.



Toxic multinodular goiter

- Focal patches of hyperfunctioning follicular cells distended with colloid working independently of TSH due to mutation in TSH receptor.
- ↑ release of T_3 and T_4.
- Hot nodules (hyperfunctioning nodules) are rarely malignant.



Thyroid storm

- Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery.
- Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death).
- May see increased ALP due to ↑ bone turnover.
- Treat with the 4 P's: β-blockers (Propranolol), Propylthiouracil, corticosteroids (Prednisolone), Potassium iodide (Lugol iodine):

- Beta blockers (propranolol) for symptom control and decrease the rate of peripheral conversion of T4 to T3.
- Thionamides (propylthiouracil) to block new hormone synthesis.
- Iodine solution to block thyroid hormone release (given at least an hour after propylthiouracil to prevent excess iodine incorporation into thyroid hormone).
- Glucocorticoids (Prednisolone) to decrease peripheral conversion of T4 to T3.

Jod-Basedow phenomenon

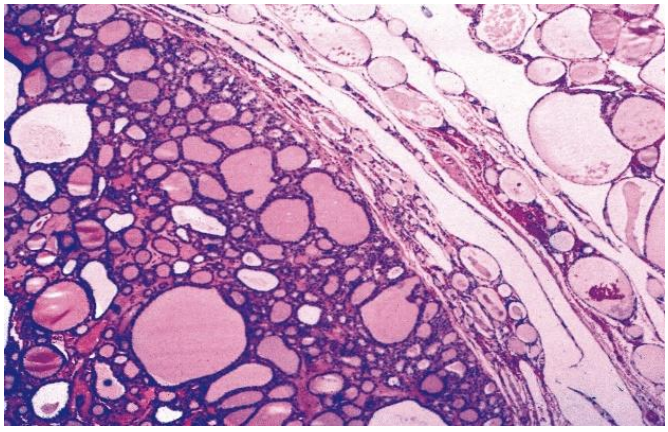
- Iodine-induced hyperthyroidism.
- Occurs when a patient with iodine deficiency and partially autonomous thyroid tissue (autonomous nodule) is made iodine replete.
- Can happen after iodine IV contrast or amiodarone use.
- Opposite to Wolff-Chaikoff effect.

❖ N.B:

- Amiodarone is a class Ill anti-arrhythmic agent used to suppress life-threatening cardiac conduction abnormalities.
- Amiodarone causes thyroid dysfunction because it is 40% iodine by weight.
- Amiodarone-induced hypothyroidism is due to excessive iodine and occurs in 5 - 20% of the amiodarone-treated patients in iodine-sufficient regions. Patients with preexisting autoimmune thyroid disease are at a greater risk for hypothyroidism, which is why thyroid functions are routinely measured before and during treatment with amiodarone. Amiodarone-induced hypothyroidism is treated with levothyroxine, and amiodarone is typically continued.
- Amiodarone can also induce thyrotoxicosis due to excessive production of thyroid hormone and primarily seen with patients living in iodine-deficient areas.

Thyroid adenoma

- Benign solitary growth of the thyroid.
- Most are nonfunctional (cold), can rarely cause hyperthyroidism via autonomous thyroid hormone production (“hot” or “toxic”).
- Most common histology is follicular; absence of capsular or vascular invasion (unlike follicular carcinoma).



Thyroid cancer

- Usually presents as a distinct, solitary nodule.

- Thyroid nodules are more likely to be benign than malignant, radioactive uptake studies are useful to further characterize nodules:

- Increased uptake (hot nodule) is seen in Graves' disease or nodular goiter.
- Decreased uptake (cold nodule) is seen in adenoma and carcinoma; often warrants biopsy.

- Biopsy is performed by fine needle aspiration (FNA).

- Treated with thyroidectomy.

- Complications of surgery include:

- Hypocalcemia due to removal of parathyroid glands.

- Transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]).

- Injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

Papillary carcinoma

- The two most common malignancies arising from the thyroid follicular epithelium are papillary thyroid cancer (PTC, the most common type) and follicular thyroid cancer (FTC).

- The prognosis for patients with papillary thyroid cancer is generally good.

- Lymphatic invasion common.

- ↑ risk with RET and BRAF mutations, childhood irradiation.

- Histology:

- Microscopically, PTC consists of branching papillae with a fibrovascular stalk lined by single or multiple layers of cuboidal epithelium.

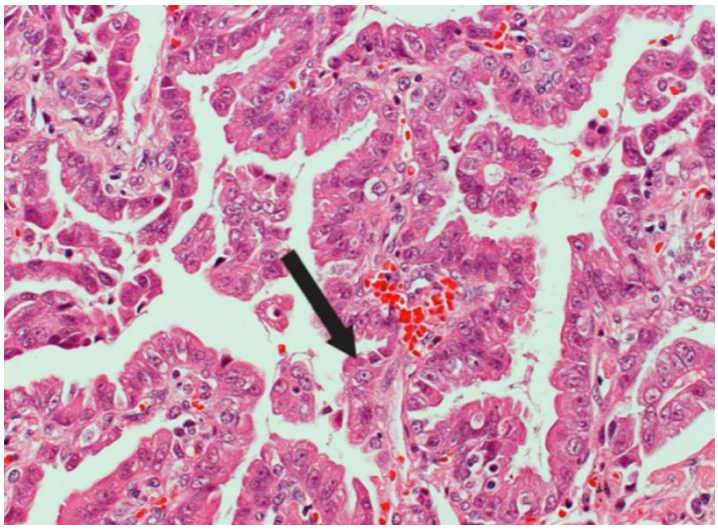
- Papillary carcinoma cells are characteristically large with overlapping nuclei containing finely dispersed chromatin, giving them an empty or ground-glass appearance (sometimes termed Orphan Annie eye nuclei after a cartoon character whose eyes were drawn without pupils or irises).

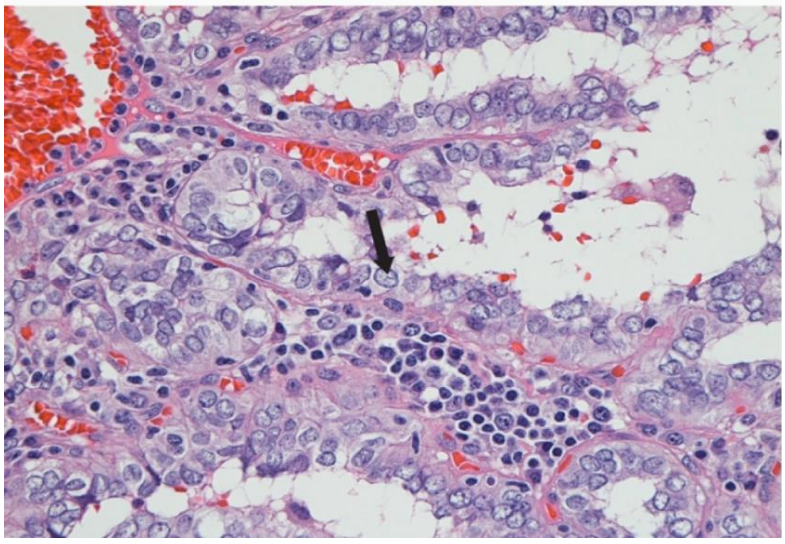
- Numerous intranuclear inclusions and grooves (arrow) can be seen due to invagination of the nuclear membrane.

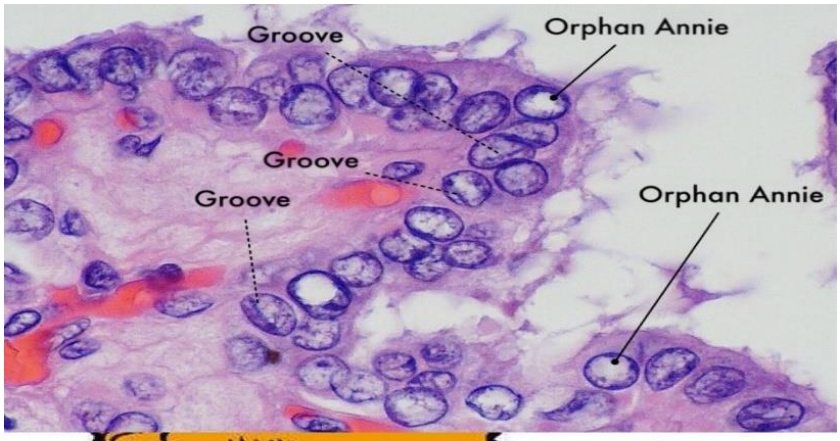
- Concentrically calcified structures (psammoma bodies) are usually present and are also characteristic. Psammoma bodies are not seen in any thyroid malignancy other than PTC.

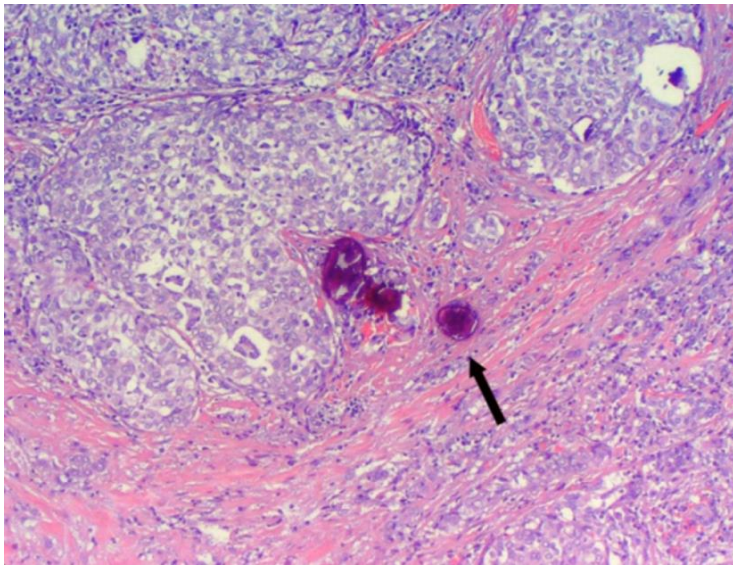
- Psammoma bodies and ground glass, grooved nuclei, Empty-appearing nuclei with central clearing ("Orphan Annie" eyes) are characteristic microscopic features of papillary cancer of the thyroid gland.

▪ Papillary carcinoma: most Prevalent, Palpable lymph nodes. Good prognosis.





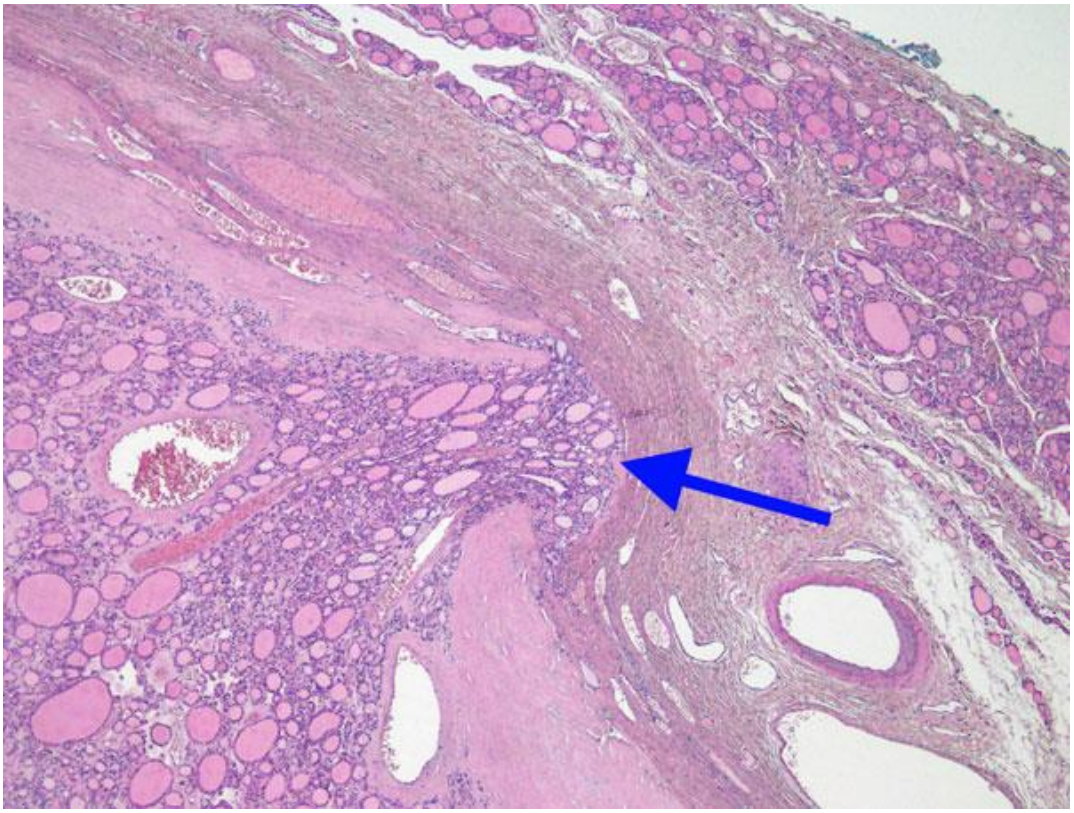




Follicular carcinoma

- Follicular thyroid cancer (FTC) is the second most common thyroid cancer.
- FTC is distinguished from benign follicular adenomas by its capsular and vascular invasion.
- More malignant than papillary carcinoma.
- Good prognosis.
- Spreads hematogenously (unlike carcinoma) with distant metastasis to the lung and bone.
- Associated with RAS mutation and PAX8-PPAR-γ translocations.
- Histology:

- Histologically, FTC may be well-differentiated, simulating normal thyroid morphology, or less well-differentiated, consisting of sheets of follicular cells or large cells with eosonophilic cytoplasm.
- FTC and PTC are differentiated based on the presence of ground glass nuclei and psammoma bodies in PTC.

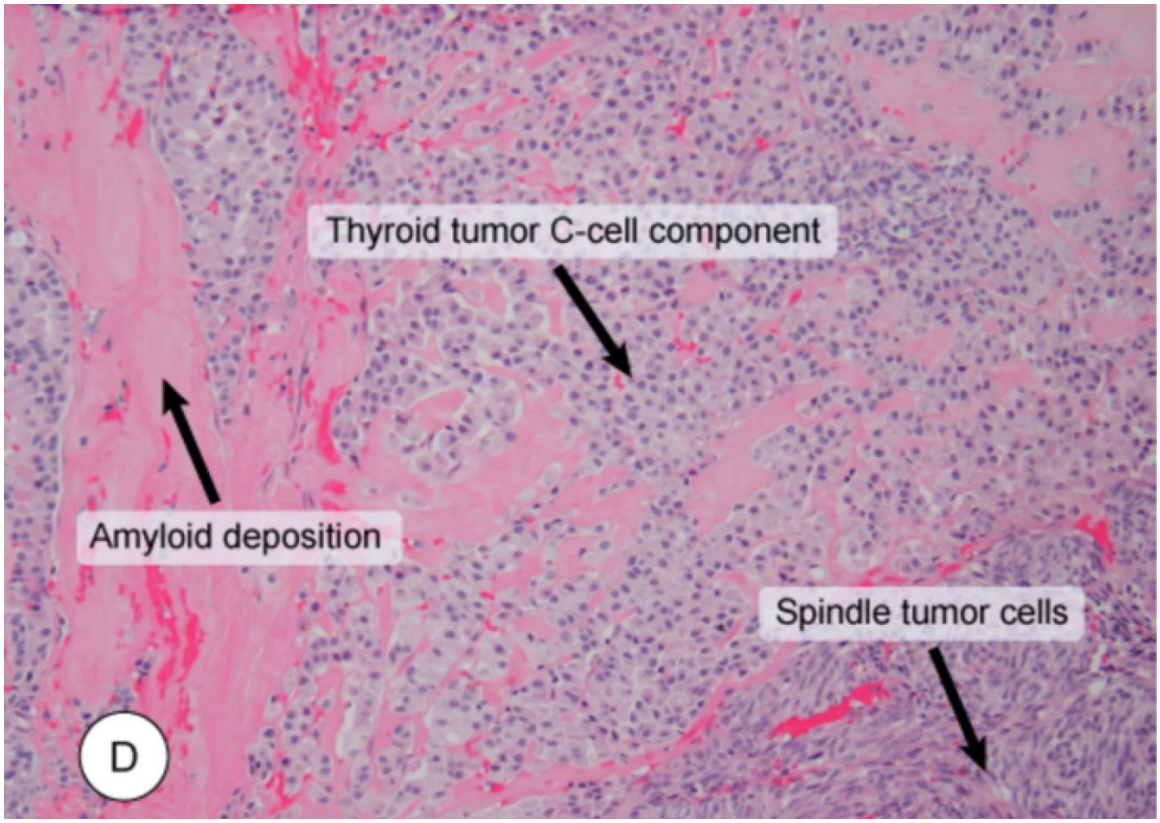


Medullary carcinoma

- Medullary thyroid cancers are tumors of parafollicular calcitonin-secreting C-cells.
- 80% of medullary thyroid cancers are sporadic and 20% are familial (as in the MEN type 2 syndrome).
- Activating mutations of the RET proto-oncogene are strongly associated with medullary thyroid cancer.
- Germline mutations of the RET proto-oncogene are present in more than 95% of patients with familial medullary thyroid cancer. RET proto-oncogene mutations are also commonly found in sporadic medullary thyroid cancers.
- Histology:

- Microscopically, there are uniform polygonal or spindle-shaped cells with extracellular amyloid deposits derived from secreted calcitonin. Amyloid stains with Congo red.

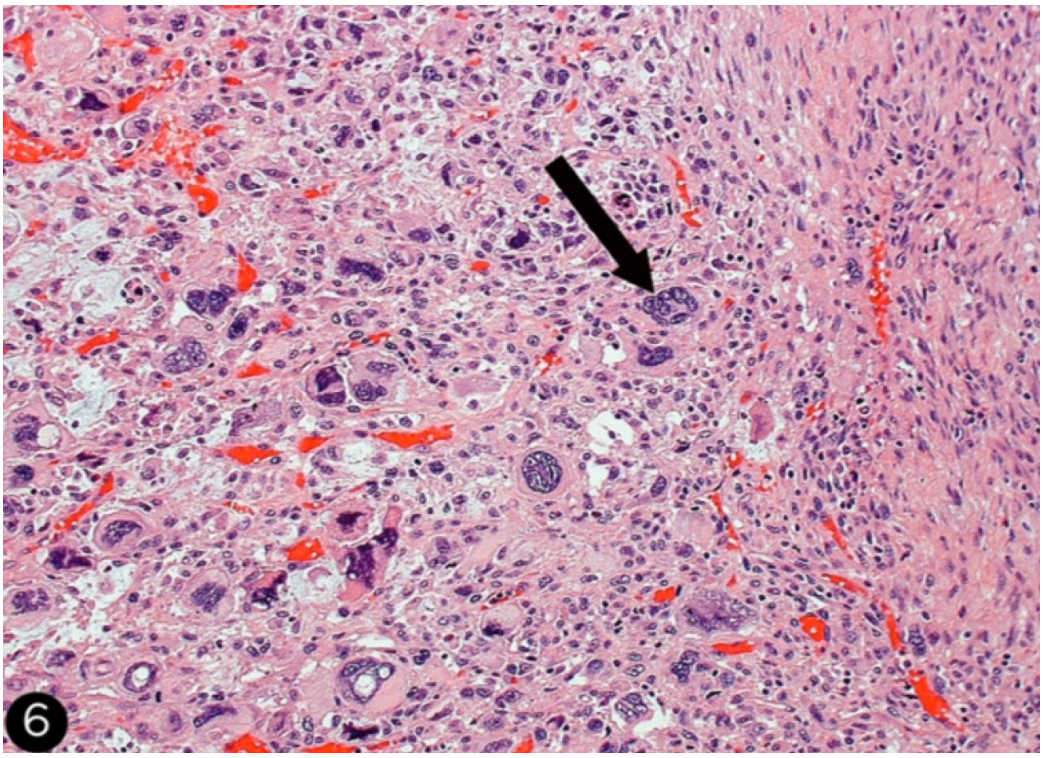
- From parafollicular "C cells"; produces Calcitonin. Amyloid stains with Congo red.



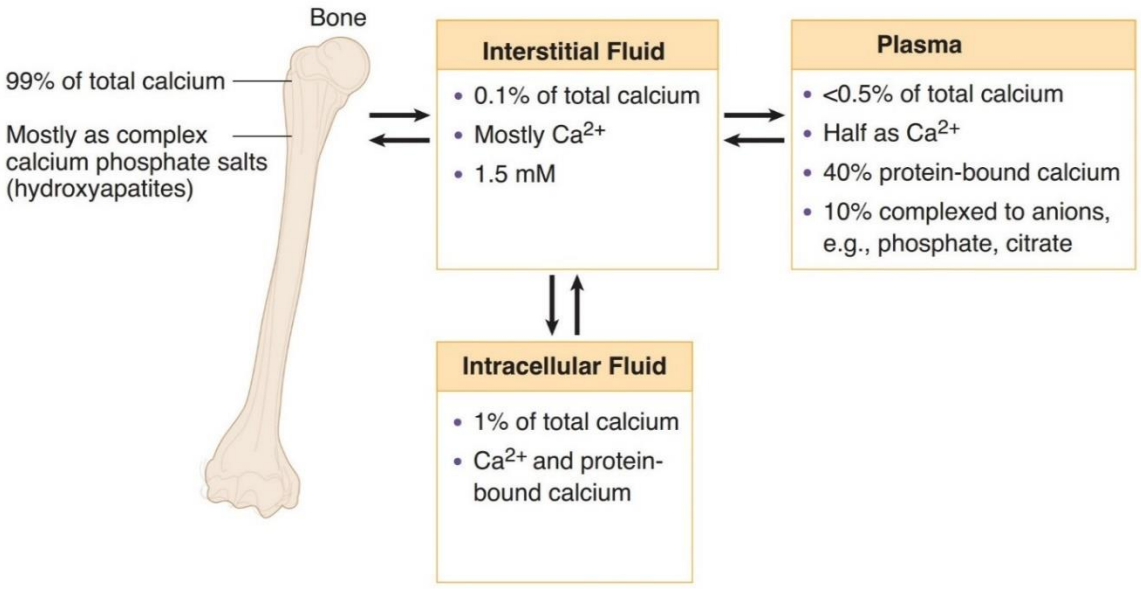
Undifferentiated/anaplastic carcinoma

- Anaplastic thyroid carcinoma is a very aggressive tumor with a poor prognosis.
- Presents with rapidly enlarging neck mass → compressive symptoms (dyspnea, dysphagia, hoarseness).
- The 1-2-year mortality approaches 100% given the tendency of this tumor to invade nearby structures and metastasize to distant sites.
- Histology:

- Microscopically, this tumor consists of large pleomorphic cells and large multinucleated osteoclast-like cells.
- Occasionally small cells mixed with spindle cells are seen as well.
- The psammoma bodies and ground glass nuclei of PTC are not seen with anaplastic cancer.



Calcium hemostasis



- <u>Plasma Ca exists in three forms:</u>

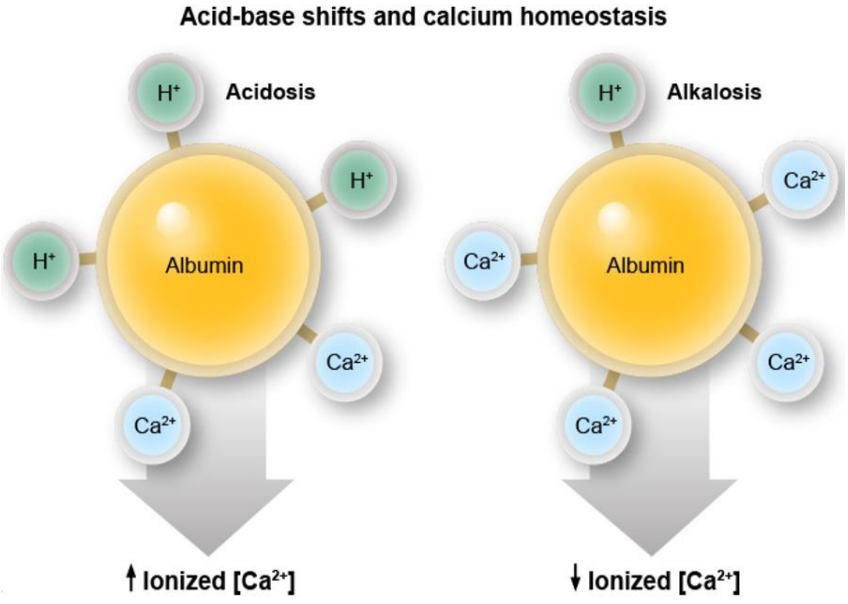
- Ionized/free (50%, active form).
- Bound to albumin (40%).
- Bound to anions such as phosphate and citrate (10%).

- The free calcium is the physiologically active and precisely regulated form.

- <u>Free H displaces free Ca from proteins:</u>

- ↑ H in acidosis will ↓ bound form of Ca → ↑ free Ca → ↓ Excitability of neurons.

- ↓ H in alkalosis will ↑bound form of Ca → ↓ free Ca → ↑ Excitability of neurons → tetany.



Parathyroid hormone

- Source: PTH is a peptide hormone released from the chief cells of parathyroid gland.

- Function:

- ↑ bone resorption with release of Ca and PO_4.

- ↑ kidney reabsorption of Ca in distal convoluted tubule.

- ↓ reabsorption of PO_4 in proximal convoluted tubule (PTH = Phosphate Trashing Hormone).

- ↑1,25-$(OH)_2$ D_3 (calcitriol) production by stimulating kidney 1α-hydroxylase in proximal convoluted tubule.

- ↑ absorption of calcium in the intestine by increasing the production of activated vitamin D.

- So, PTH ↑ serum Ca, ↓ serum (PO_4), ↑ urine (PO_4), ↑ urine cAMP (second messenger for PTH in the kidney).

- PTH ↑ production of macrophage colony-stimulating factor and RANK-L (receptor activator of NF-κB ligand). RANK-L (ligand) secreted by osteoblasts and binds RANK (receptor) on osteoclasts precursors to stimulate its differentiation to osteoclasts → bone resorption and ↑ Ca.

- Regulation:

- In fact, the only important physiologic signal regulating release of PTH is free Ca:

  - ↓ serum Ca, ↑ serum PO_4, ↓ vitamin D→ ↑ PTH secretion.

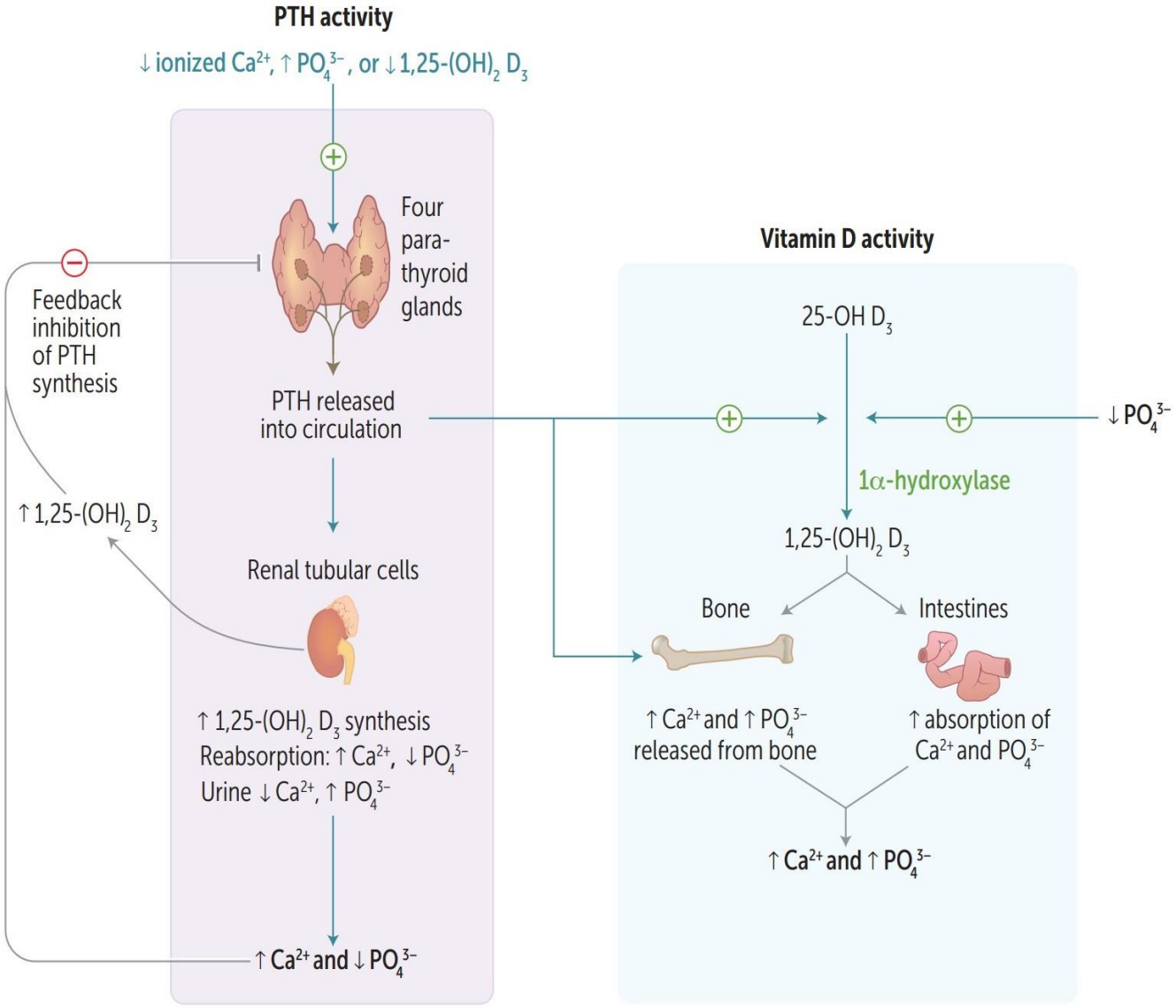
  - ↓serum Mg → ↑ PTH secretion.

  - ↓↓ serum Mg → ↓PTH secretion

  - Common causes of ↓ Mg include diarrhea, diuretics, aminoglycosides, alcohol abuse.

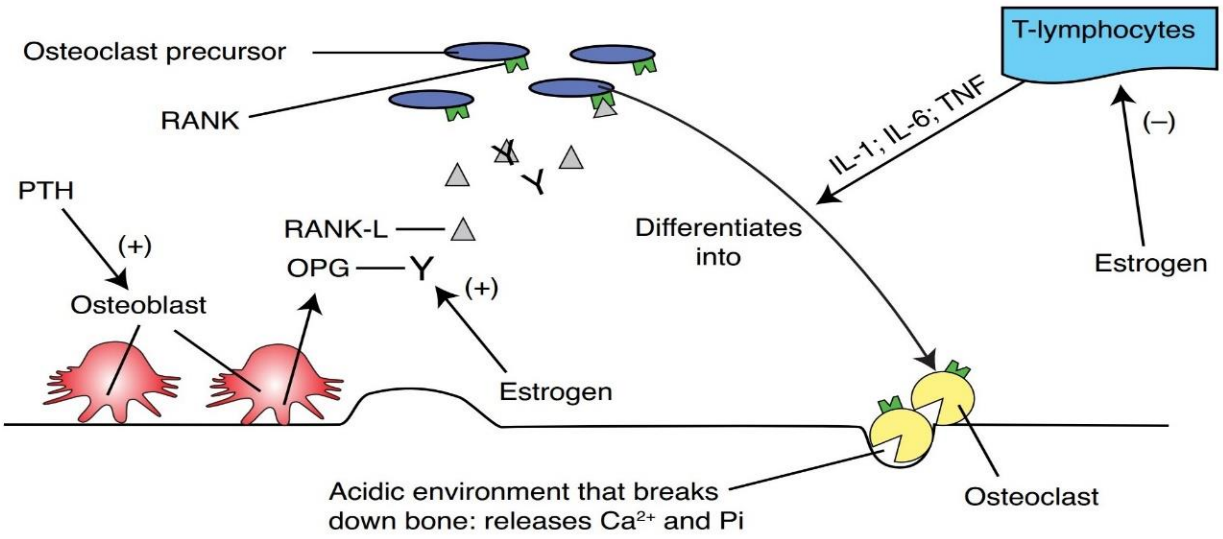
- PTH-related peptide (PTHrP) functions like PTH and is commonly increased in malignancies (squamous cell carcinoma of the lung, renal cell carcinoma).

- Osteoblasts build up bones, while osteoclasts turnover bones.



❖ N.B:

- Osteoblast secretes RANK L (Receptor Activator of Nuclear Factor Kappa Beta Ligand) and osteoprogetrin (endogenous blocker of RANK L).
- RANK L promotes resorption of bones by increasing osteoclast activity.
- When RANK L binds RANK receptors in osteoclast precursors it will induce its differentiation to osteoclast.
- High level of PTH stimulates osteoblast to secrete RANK L which increases the differentiation of osteoclast precursors to osteoclast.
- When T lymphocytes is activated in inflammatory conditions, it releases cytokines as IL1, IL6, TNF which also induce the differentiation of osteoclast precursor to osteoclast.
- Osteoprogetrin (OPG) reduces bone resorption by binding to RANK L preventing it from binding to its receptors → ↓ osteoclast and bone resorption.
- Estrogen protective effect on bones is mediated by increasing the production of OPG and reducing the cytokines released from activated T lymphocytes → ↓ osteoclast and bone resorption.
- High glucocorticoid increase RANK L and decrease OPG → ↑ Osteoclast and bone resorption.



RANK = receptor activator of nuclear factor kappaB

RANK-L = receptor activator of nuclear factor kappaB ligand

OPG = osteoprotegerin (endogenous blocker of RANK-L)

Pi = phosphate

Calcitonin

- Source: Calcitonin (CT) is a peptide hormone secreted by the parafollicular cells (C cells) of the thyroid gland.

- Function:

- Calcitonin lowers plasma calcium by decreasing the activity of osteoclasts, thus decreasing bone resorption.

- Calcitonin tones down Ca levels.

- Calcitonin is useful in the treatment of Paget's disease.

- Regulation: It is released in response to elevated free calcium.

- Calcitonin is not a major controller of Ca in humans. Removing the thyroid (with the C cells) or excess of calcitonin via a C cell tumor (medullary carcinoma of the thyroid) has little impact on plasma calcium.

Vitamin D (cholecalciferol)

- Source:

- On exposure to sunlight, 7-dehydrocholesterol-or provitamin D_3-present in the skin absorbs ultraviolet-B rays from the sun to form vitamin D_3 or cholecalciferol.

- At this point either physiologically-produced D_3 or plant-derived D_2 will undergo two hydroxylation steps to form 1,25-dihydroxy vitamin D, the active form of vitamin D.

- D_3 from sun exposure in skin. D_2 ingested from plants. Both converted to 25-OH in liver and to 1,25-$(OH)_2$ (active form) in kidney.

- 24,25-$(OH)_2$ D_3 is an inactive form of vitamin D

- Function:

- Under normal conditions, vitamin D acts to raise plasma Ca and phosphate.

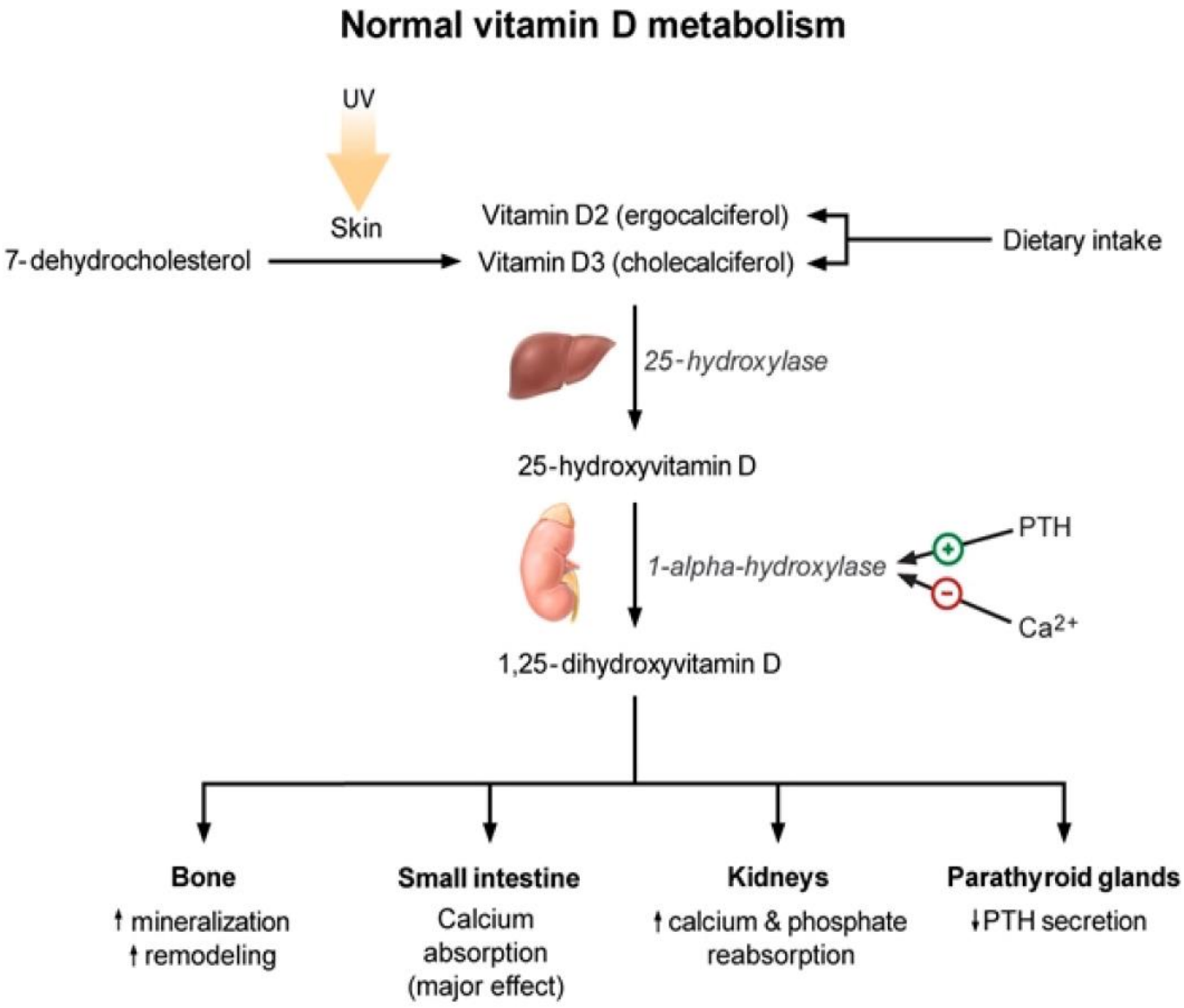
- ↑ absorption of dietary Ca and PO_4.

- ↑ bone resorption → ↑ Ca and PO_4.

- Regulation:

- ↑ PTH, ↓ [Ca], ↓ PO_4 → ↑ 1,25-$(OH)_2$ production.

- 1,25-$(OH)_2$ feedback inhibits its own production.



PTH = parathyroid hormone.

❖ N.B:

- Infusion of intravenous calcium directly raises serum calcium.
- As calcium and PTH are inversely related, PTH levels will decline; hence, the formation of 1,25-dihydroxy vitamin D will diminish.
- The increase in calcium levels will prompt the release of calcitonin, a calcium antagonist, as the body tries to reestablish homeostasis.

Disorders of calcium metabolism

Hypercalcemia

1. Primary hyperparathyroidism:

- Primary hyperparathyroidism is caused by a parathyroid adenoma in 80-85% of patients and by parathyroid hyperplasia in the remaining 10-15% (Parathyroid cancer is a very uncommon cause of primary hyperparathyroidism).

- The excess serum calcium found in hyperparathyroidism occurs by three mechanisms:

- An increase in the renal absorption of calcium.
- An increase in bone resorption by osteoclast activation.
- Indirectly, by 1,25-dihydroxy vitamin D formation (parathyroid hormone increases the formation of 1, 25 dihydroxy vitamin D in the kidneys).
- An increase in the gastrointestinal absorption of calcium by the ↑ activated vitamin D.

- The serum phosphorus in patients with hyperparathyroidism is usually low because parathyroid hormone decreases phosphate absorption in the proximal renal tubule.

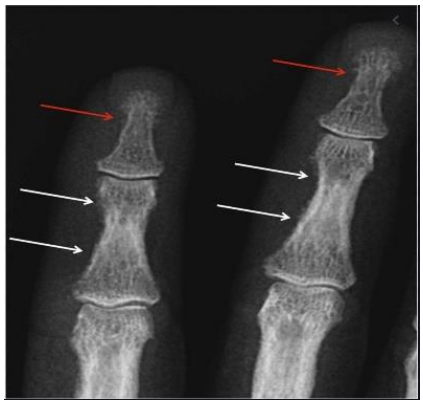
- Consequences include increased plasma calcium, decreased plasma phosphate, polyuria and calciuria, ↑ urinary cAMP, and decreased bone mass.

- Most patients asymptomatic.

- May present with bone pain (bones), weakness and constipation (groans), abdominal/flank pain (kidney stones, acute pancreatitis), depression (psychiatric overtones).

- "Stones, bones, groans, and psychiatric overtones".

- Subperiosteal thinning with cystic degeneration is a characteristic feature of Primary hyperparathyroidism. Radiologically, this thinning appears as subperiosteal erosions in the medial sides of the second and third phalanges of the hand, and as a granular, "salt-and-pepper" appearance of the calvarium.

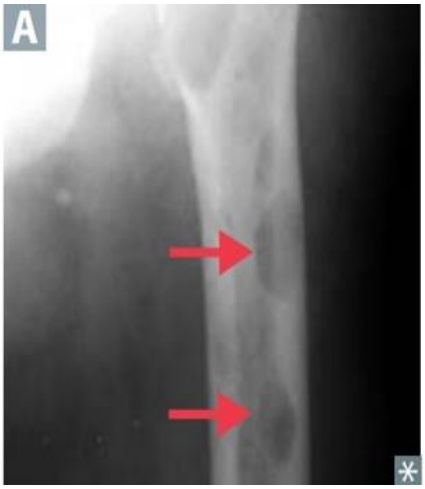


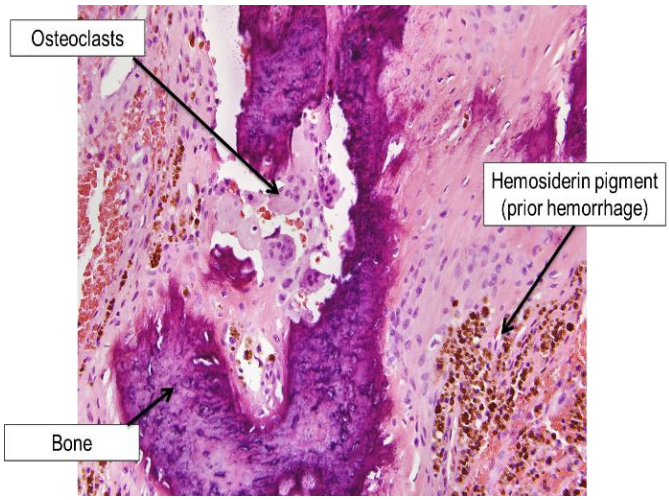
- Osteitis fbrosa cystica:

- Bone manifestation is osteitis fibrosa cystica in which there are increased osteoclasts in scalloped areas of the surface bone and replacement of marrow elements with fibrous tissue.

- Cystic bone spaces filled with brown fibrous tissue ("brown tumor" consisting of deposited hemosiderin from hemorrhages; causes bone pain).

- Increased plasma alkaline phosphatase due to high bone turnover, osteocalcin and increased excretion of cAMP (second messenger for PTH in the kidney), and hydroxyproline.





2. Secondary hyperparathyroidism:

- Secondary hyperparathyroidism due to ↓ Ca absorption and/or ↑ PO_4 as seen in patients with chronic renal failure.

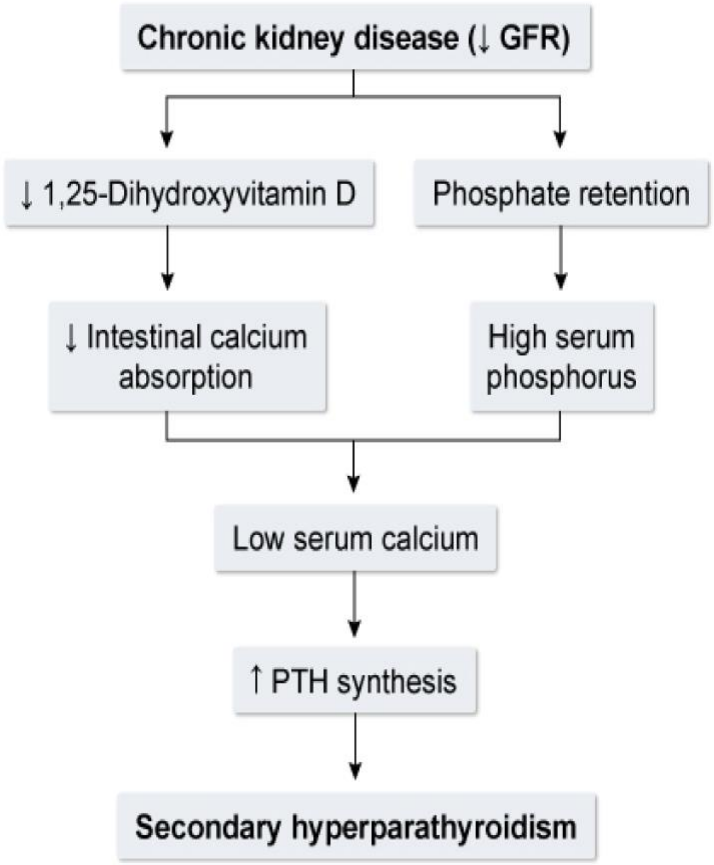
- The activity of renal alpha hydroxylase is decreased in chronic kidney disease, which causes the decreased formation of 1,25-dihyroxy vitamin D. The gastrointestinal absorption of calcium is consequently decreased; the ultimate result is a decrease in serum calcium.

- Another electrolyte change is the elevation of phosphorous because chronic renal disease impairs its excretion.

- The result of the decrease in 1,25-dihydroxy vitamin D, the decrease in serum calcium, and the increase in serum phosphorus is an increase in the secretion of parathyroid hormone, a state termed "secondary hyperparathyroidism".

- Despite excess PTH, calcium levels remain in the normal to only slightly low range; PTH is unable to increase the serum calcium because of the deficiency in 1-alpha hydroxylase.

- So, in secondary hyperthyroidism there is an elevated serum PTH, accompanied by normal to low serum calcium levels, and high serum phosphorus levels. Circulating 1,25-dihydroxy vitamin D levels are low due to the deficiency of 1-alpha hydroxylase, an enzyme that resides in the kidneys.



GFR = glomerular filtration rate; **PTH** = parathyroid hormone.

3. Tertiary hyperparathyroidism:

- Refractory (autonomous) hyperparathyroidism resulting from chronic renal disease.
- In a very small proportion of cases of secondary hyperparathyroidism continuous stimulation of the parathyroid may result in adenoma formation and autonomous PTH secretion.
- ↑↑PTH, ↑ Ca.
- Renal osteodystrophy: Renal disease → 2° and 3° hyperparathyroidism → bone lesions.

4. Other causes:

A. Sarcoidosis and other granulomatous disorders (10%) due to increased activity of vitamin D.

B. Hydrochlorothiazide (HCTZ) is one of the commonest agents used for the treatment of hypertension. HCTZ causes an increase in the distal tubular reabsorption of calcium, causing both relative hypercalcemia as well as hypocalciuria. The increased serum calcium levels seen with HCTZ therapy usually suppress PTH.

C. Familial hypocalciuric hypercalcemia (FHH):

- Defective G-coupled Ca sensing receptor on parathyroid cells and kidney tissue.

- PTH cannot be suppressed by an increase in Ca level → mild hypercalcemia with normal to ↑ PTH levels.

- FHH is indicated by the presence of hypercalcemia at the same time with hypocalciuria (In all other causes of hypercalcemia, elevated calcium levels in the blood are correlated with elevated calcium urine levels, as a properly sensing kidney works to excrete calcium).

- No treatment is generally required, since patients are most commonly asymptomatic.

D. Milk-alkali syndrome (MAS):

- It is caused by excessive intake of calcium and absorbable alkali (calcium carbonate preparations used in patients with osteoporosis).

- The resulting hypercalcemia causes renal vasoconstriction and decreased glomerular blood flow. In addition, inhibition of the Na-K-2CI cotransporter (due to activation of calcium-sensing receptors in the thick ascending loop) and impaired antidiuretic hormone activity lead to loss of sodium and free water.

- This results in hypovolemia and increased reabsorption of bicarbonate (augmented by the increased intake of alkali).

- In addition to hypercalcemia, metabolic findings in MAS include metabolic alkalosis, and acute kidney injury. Parathyroid hormone levels are suppressed.

Hypocalcemia

- Due to injury to parathyroid glands or their blood supply (usually during surgery), autoimmune destruction, or DiGeorge syndrome → primary hypoparathyroidism.

- Hypomagnesemia (from malnutrition of alcoholism): Magnesium is necessary for PTH to be released from the gland. Hypomagnesemia is very common in hospitalized alcoholics and can cause hypocalcemia by inducing resistance to parathyroid hormone (PTH) as well as by decreasing PTH secretion. Hypocalcemia due to hypomagnesemia is typically refractory to treatment with calcium unless magnesium is replaced as well.

- Findings:

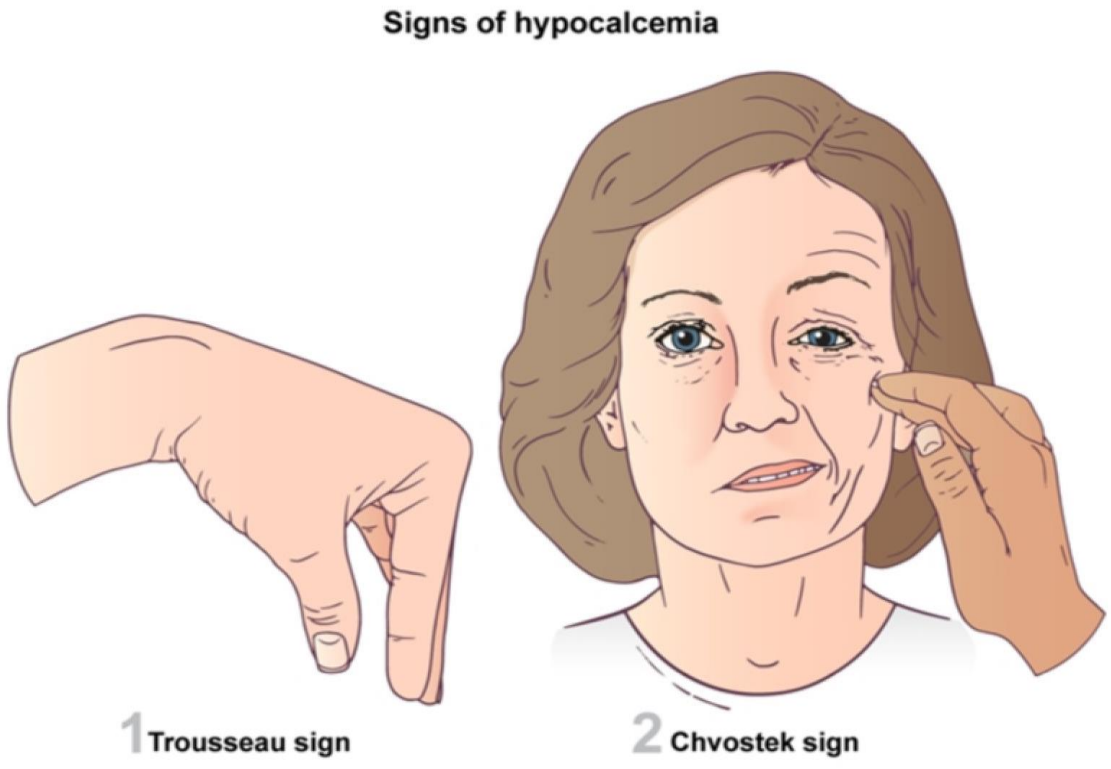
- Hypocalcemia, hyperphosphatemia.

- Symptoms focus on the hypocalcemia induced increased excitability of motor neurons creating muscular spasms and tetany.

- This sort of neuromuscular hyperexcitability becomes clinically apparent with serum calcium levels < 7.0 mg/dl.

- Chvostek sign: tapping of facial nerve (tap the Cheek) → contraction of facial muscles.

- Trousseau sign: occlusion of brachial artery with BP cuff (cuff the Triceps) → carpal spasm.

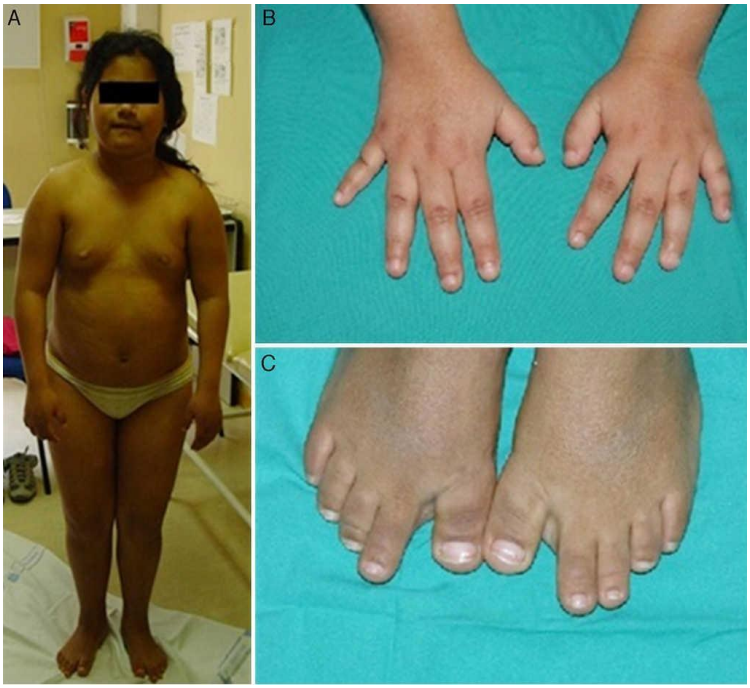


Pseudohypoparathyroidism type 1A

- Autosomal dominant, maternally transmitted mutations (imprinted GNAS gene).
- GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the Gs protein α subunit → inactivation of adenylate cyclase when PTH binds to its receptor → end-organ resistance (kidney and bone) to PTH.
- Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits, short stature, round face, subcutaneous calcifications, developmental delay).
- Labs: ↑ PTH, ↓ Ca, ↑ PO_4.

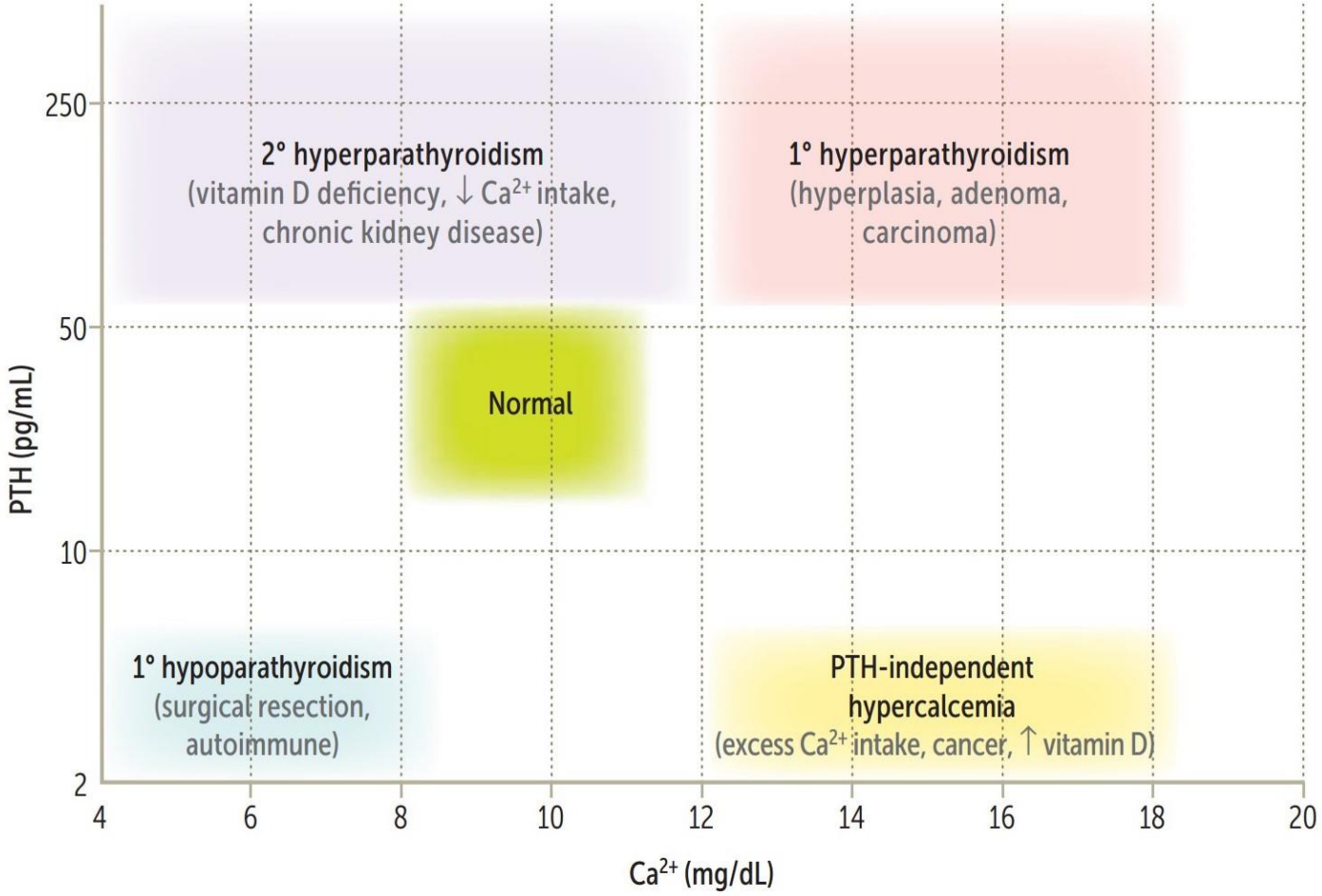
Pseudopseudohypoparathyroidism

- Autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.
- Physical findings: same as Albright hereditary osteodystrophy.
- Labs: Normal PTH, Ca, PO_4.



Lab values in hypocalcemia

DISORDER	Ca^{2+}	PO_4^{3-}	PTH
Vitamin D deficiency	↓	↓	↑
Hypoparathyroidism	↓	↑	↓
2° hyperparathyroidism (CKD)	↓	↑	↑
Pseudohypoparathyroidism	↓	↑	↑
Hyperphosphatemia	↓	↑	↑



Pancreas

- The location and proportion of each major hormone-secreting cell type of the islets of Langerhans are:

1. Alpha cells:

- Constitute about 20% of the islet cells.

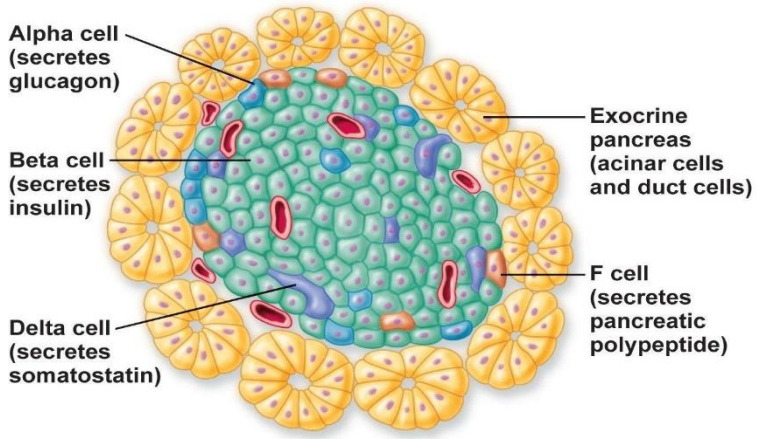
- Secrete glucagon and tend to be located near the periphery of the islet.

2. Beta cells:

- Constitute 60-75% of the islet cells and tend to be located near the center of the islet.

- The beta cells synthesize preproinsulin, which is cleaved to form proinsulin, which, in turn, splits into insulin and C peptide both of which are secreted in equimolar quantities.

3. Delta cells: Constitute about 5% of the islet cells, are interspersed between the alpha and beta cells and secrete somatostatin.



Insulin

- Synthesis:

- The insulin gene directs the synthesis of preproinsulin in the ribosomes.

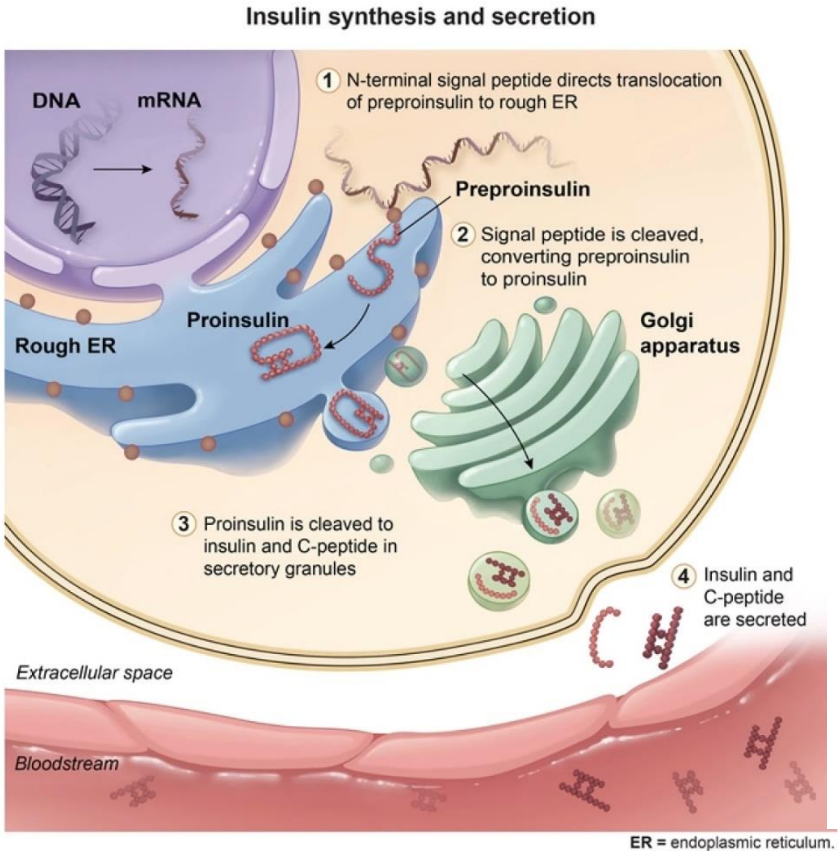
- Preproinsulin contains 4 peptides in sequence: Signal peptide, B chain of insulin, a connecting peptide (C Peptide), and A chain of insulin.

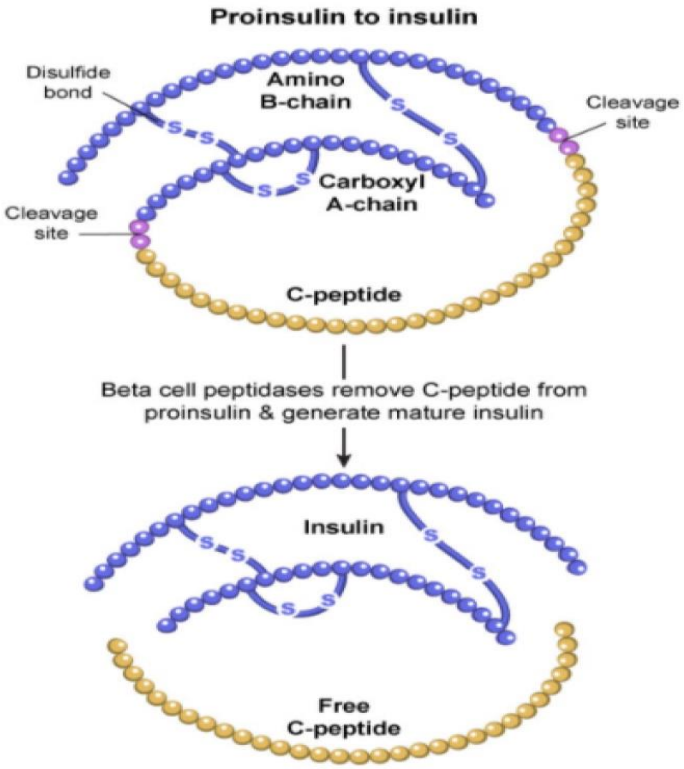
- As preproinsulin enters the endoplasmic reticulum, the signal peptide is splitted and the rest of the molecule forms proinsulin.

- During its packaging into granules by the Golgi apparatus, proinsulin is cleaved by converting enzymes to insulin and C-peptide inside the granules which are secreted in equimolar quantities.

- C peptide has no known function but serves as a marker of endogenous insulin secretion, particularly when exogenously administered insulin interferes with the measurement of endogenous insulin.

- Insulin and C-peptide are ↑ in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.





- <u>Function:</u>

- Binds insulin receptors (tyrosine kinase activity), inducing glucose uptake (carrier-mediated transport) into insulin-dependent tissue and gene transcription:
  - ↑ glucose transport in skeletal muscle and adipose tissue.
  - ↑ glycogen synthesis and storage.
  - ↑ triglyceride synthesis.
  - ↑ protein synthesis (muscles).
  - ↓ lipolysis in adipose tissue.
  - ↑ cellular uptake of K and amino acids.

- ↑ Na retention (kidneys).
- ↓ glucagon release.

❖ N.B:

- Insulin pumps K into cells. Although the overall process is not well understood, insulin increases the activity of Na/K-ATPase in most body tissues.
- This K-lowering action of insulin is used to treat acute, life-threatening hyperkalemia. For example, sometimes hyperkalemia of renal failure is successfully lowered by the simultaneous administration of insulin and glucose (The glucose is given to prevent severe insulin-induced hypoglycemia from developing).

- Glucose transporters:

- Glucose is the major source of energy for all cells of the body.
- In the majority of tissues, glucose transport occurs along its concentration gradient, from higher concentrations outside the cell toward lower concentrations inside the cell. However, glucose cannot passively diffuse across the cell membrane in any significant amount and requires carrier proteins to aid its crossing.
- Transport across the cell membrane by carrier proteins (which undergo conformational changes as the substrate is transported, unlike channel proteins) is termed carrier-mediated transport.
- Transport that is facilitated by transmembrane proteins without the expenditure of energy is called facilitated diffusion.

A. Insulin-dependent glucose transporters:

- GLUT4 is the insulin-sensitive transporter found in skeletal muscle cells and adipocytes. In these cells, the GLUT 4 protein is stored in cytoplasmic vesicles. Under the influence of insulin, the transporter protein is incorporated into the cell membrane. An increased number of transporters in the membrane lead to an increased rate of glucose uptake by the cells.
- In the absence of insulin, muscle cells and adipocytes are impermeable to glucose.
- In contrast to GLUT-4, the other glucose transporters are always present on the plasma membrane to constitutively transport glucose.

B. Insulin-independent transporters:

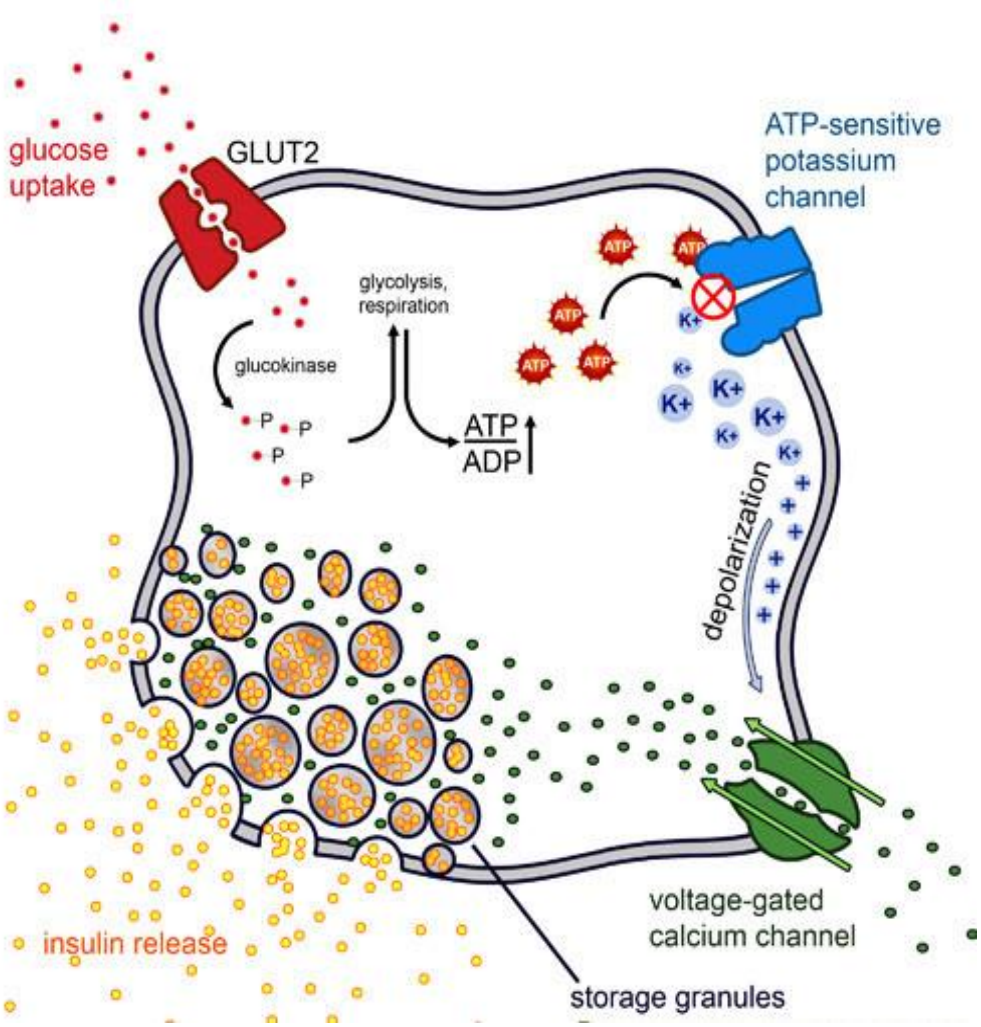
- GLUT1: RBCs, brain, cornea, placenta.
- GLUT2 (bidirectional): β islet cells, liver, kidney, GI tract (think 2-way street).
- GLUT3: brain, placenta.

- GLUT5 (Fructose): spermatocytes, GI tract.
- SGLT1/SGLT2 (Na glucose cotransporters): kidney, small intestine.

- Control of insulin secretion:

1. Plasma glucose level:

- The most important controller of insulin secretion is plasma glucose.
- Type 2 glucose transporters (GLUT2) mediate the entry of glucose into beta cells.
- Glucose is phosphorylated by the rate-limiting enzyme glucokinase. This modified glucose becomes effectively trapped within the beta cells and is further metabolized to create ATP, the central energy molecule.
- For glucose to promote insulin secretion, it must not only enter the β-cell but also be metabolized, so as to increase intracellular ATP concentration.
- The increased ATP: ADP ratio causes the ATP-gated potassium channels in the cellular membrane to close up, preventing potassium ions from being shunted across the cell membrane.
- The ensuing rise in positive charge inside the cell, due to the increased concentration of potassium ions, leads to depolarization of the cell. The net effect is the activation of voltage-gated calcium channels, which transport calcium ions into the cell.
- The brisk increase in intracellular calcium concentrations triggers export of the insulin-storing granules by a process known as exocytosis.
- The ultimate result is the export of insulin from beta cells and its diffusion into nearby blood vessels.
- Blockade of these potassium channels is a possible mechanism of some hypoglycemic drugs used for treatment of type 2 diabetes.



2. Amino acids:

- Insulin secretion is also stimulated by some amino acids as arginine and lysine that result from digestion of protein in meal.

- Amino acids strongly potentiate the glucose stimulus for insulin secretion.

- This is purposeful response because the secreted insulin in turn promotes transport of amino acids into tissue cells and formation of intracellular protein.

3. Gastrointestinal hormones:

- Oral glucose leads to an increase in insulin secretion more than when glucose in administered intravenously, this is due to:

1. Glucagon like Peptide-1 (GLP-1) and gastric inhibitory peptide (also known as glucose dependent insulinotropic polypeptide or GIP):

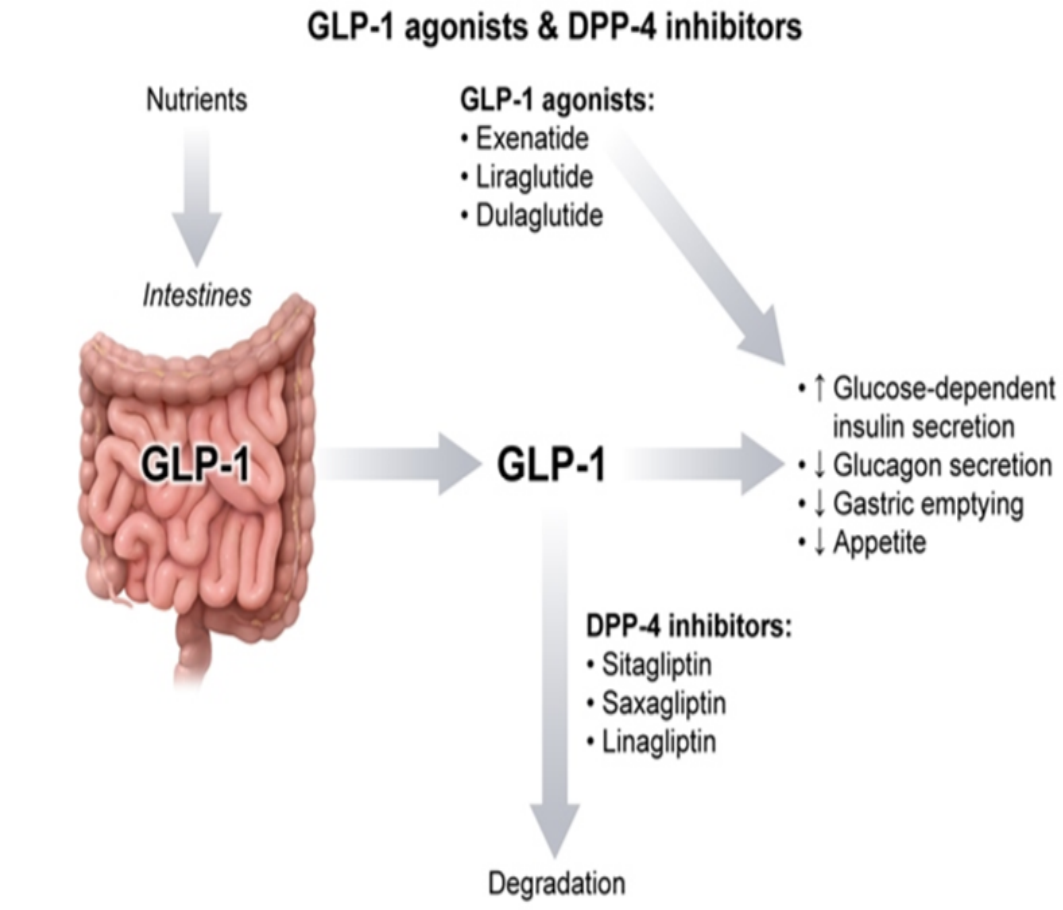
- Both of them are called incretins.

- Incretins, especially GLP-1 and GIP are secreted by K and L cells in the gut and stimulate a decrease in blood glucose level by causing an increase in the amount of insulin released from pancreatic beta cells after eating, before blood glucose level become elevated.

- They also inhibit the release of glucagon from alpha cells.

- Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

2. Amino acids potentiate the glucose stimulated insulin secretion.



DDP-4 = dipeptidyl peptidase-4; **GLP-1** = glucagon-like peptide-1.

4. Other hormones:

- Glucagon stimulates insulin release:

- The amino acid sequence of glucagon is similar to that of the duodenal hormone, secretin. Like secretin (and most other gut hormones), glucagon stimulates insulin secretion.

- Somatostatin inhibits insulin release.

5. Autonomic nervous system:

- Pancreatic beta cell insulin secretion is influenced by autonomic nervous system activity:

A. Parasympathetic stimulation of muscarinic M_3 receptors promotes insulin secretion and is induced by the smell and/or sight of food.

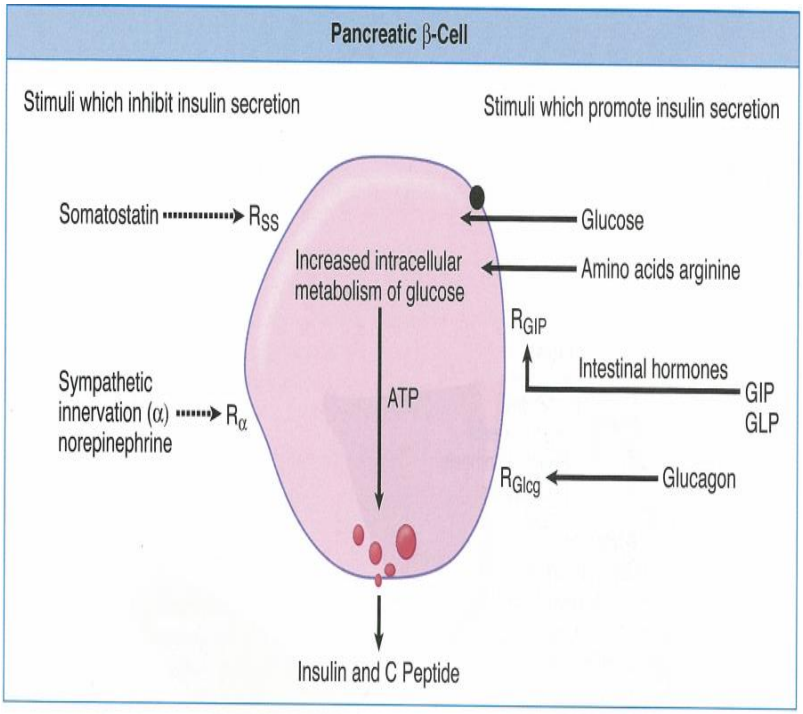
B. Sympathetic stimulation is more complex, since both alpha-2 and beta-2 adrenergic receptors are present on pancreatic beta cells and exert opposite effects:

- Stimulation of beta-2 receptors promotes insulin secretion while stimulation of alpha-2 receptors inhibits insulin release.

- However, the alpha-2-mediated inhibitory effect is predominant, causing sympathetic stimulation to lead to overall inhibition of insulin secretion.

G protein-coupled receptors on pancreatic beta cells

Receptor	G alpha subunit	Insulin secretion
Muscarinic M3	G_q	↑
Glucagon	G_s/ G_q	
• Beta-2 adrenergic • Glucagon-like peptide-1	G_s	
• Alpha-2 adrenergic • Somatostatin 2	G_i	↓



Glucagon

- Source: Made by α cells of pancreas.

- Function:

- Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (fasting state).

- The primary target for glucagon action is the liver hepatocyte.

- Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis.

- Regulation:

- Low plasma glucose (hypoglycemia) is the most important physiologic promoter for glucagon secretion, and elevated plasma glucose (hyperglycemia) the most important inhibitor.

- Inhibited by insulin, hyperglycemia, somatostatin.

Diabetes mellitus

- Definition/Etiology:

- Diabetes mellitus (DM) is a disorder of carbohydrate metabolism, caused by relative or absolute deficiency of insulin, hyperglycemia, and end-organ complications (nephropathy, retinopathy, neuropathy, accelerated atherosclerosis).

- Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

A. Type 1 DM (insulin-dependent or juvenile onset):

- Accounts for 5-10% of diabetes worldwide.
- The age of onset is usually age <30 (Onset in childhood).
- There is an increased prevalence of autoantibodies to islet cells (Insulin dependent from an early age).
- Not related to obesity. Patients usually have a lean body build and are prone to ketosis owing to absent insulin production.

B. Type 2 DM (non-insulin-dependent or maturity onset):

- It is the most common type of diabetes, accounting for 90% of cases.
- Age of onset is usually > 40 (Onset in adulthood).
- Directly related to obesity.
- Defined as insulin resistance.

- Presentation:

- Polyuria, polydipsia, and polyphagia are the most common presentation.

- The first event may be an acute metabolic decompensation, resulting in coma (ketoacidosis for IDDM and hyperosmolar coma for NIDDM).

- Occasionally the initial expression of DM is a degenerative complication like neuropathy.

- Diagnostic Tests:

- Diabetes is defined/diagnosed as:

1. Two fasting blood glucose measurements ≥ 126 mg/dL (Fasting for > 8 hours). In the United States, fasting blood sugar is the most preferred way to screen patients for diabetes mellitus.

2. Single glucose level ≥ 200 mg/dL in presence of symptoms.

3. Hemoglobin A1c ≥ 6.5% is a diagnostic criterion and is the best test to follow response to therapy over the last several months. HbA1c levels are affected by alterations in red blood cell survival; conditions that increase red blood cell turnover (hemolytic anemia) can cause falsely low HbA1c levels.

4. Plasma glucose ≥ (200 mg/dl) two hours after a 75-g oral glucose load as in a glucose tolerance test.

- Type 1 vs. type 2 diabetes mellitus:

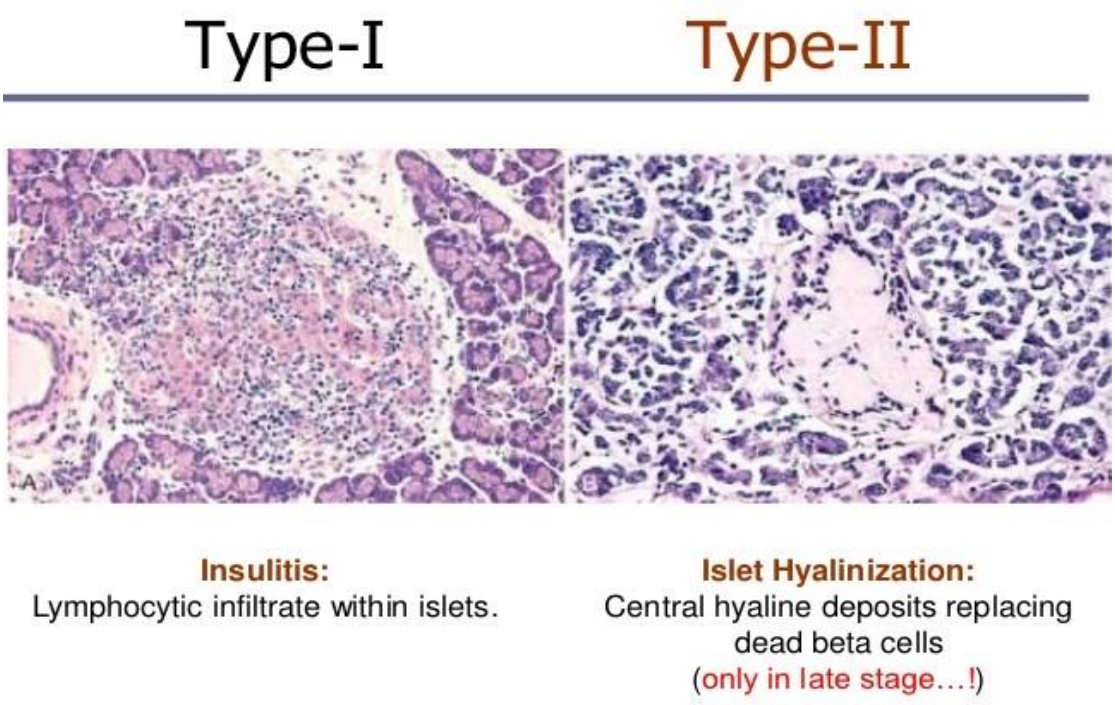
Variable	Type 1	Type 2
1° defect	Autoimmune T-cell mediated destruction of β cells (due to presence of glutamic acid decarboxylase antibodies)	↑ resistance to insulin, progressive pancreatic β-cell failure
Insulin necessary in treatment	Always	Sometimes
Age (exceptions commonly occur)	< 30 yr	> 40 yr
Association with obesity	No	Yes
Genetic predisposition	Relatively weak (50% concordance in identical twins), polygenic	Relatively strong (90% concordance in identical twins), polygenic
Association With HLA system	Yes, HLA-DR3 and -DR4 (4 - 3 = type 1)	No
Glucose intolerance	Severe	Mild to moderate
Insulin sensitivity	High	Low
Ketoacidosis	Common	Rare
β-cell numbers in the islets	↓	Variable (with amyloid deposits)
Serum insulin level	↓	↑ initially, but ↓ in advanced disease
Classic symptoms of polyuria, Polydipsia, Polyphagia, Weight loss	Common	Sometimes
Histology	Islet leukocytic infiltrate	Islet amyloid polypeptide (IAPP) deposits

❖ N.B:

1. The two cardinal defects involved in the pathophysiology of type 2 diabetes mellitus are increased insulin resistance and defective insulin secretion.

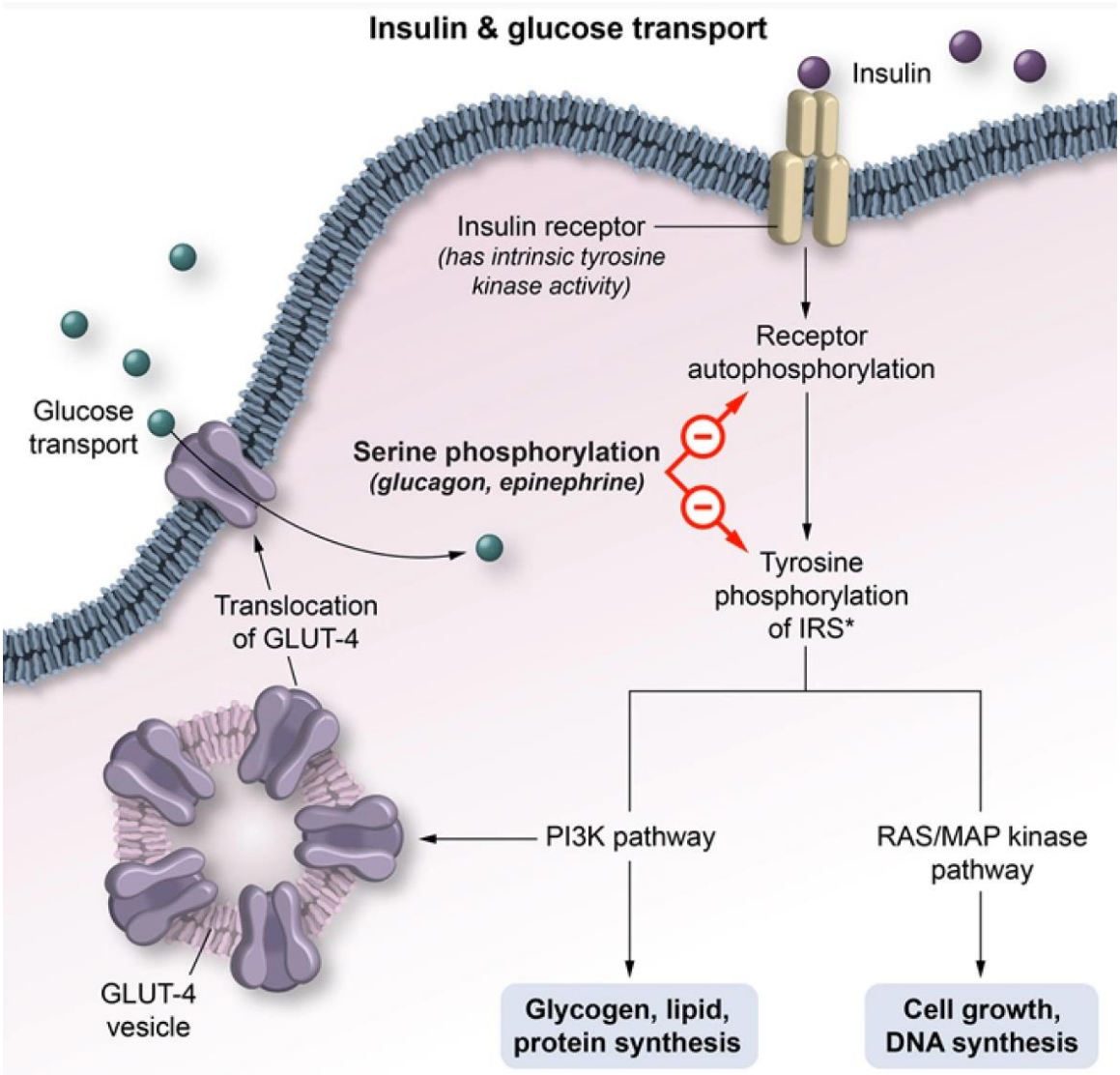
- Although still controversial, many researchers believe that increased insulin resistance is the primary abnormality in type 2 diabetes mellitus. Early in the pathogenesis of type 2 diabetes, glucose tolerance is thought to remain normal because of a compensatory increase in insulin secretion from beta cells. This compensatory insulin response by beta cells ultimately fails, causing poor glucose tolerance.
- Islet amyloid polypeptide (amylin) is one factor thought to be responsible for this beta cell dysfunction. Amylin is stored in insulin secretory granules and is co-secreted with insulin from pancreatic beta cells.

Deposits of amylin are universally seen in the pancreatic islets of patients with type 2 diabetes mellitus. Amylin may play a causative role in beta cell apoptosis and defective insulin secretion; however, this theory is still controversial.



2. Insulin resistance is a heterogenous disorder caused by number of genetic and environmental factors. Genetic defects include receptor and post-receptor mutations that result in faulty insulin signaling.

- Environmental factors that increase insulin resistance include lack of physical activity and obesity.
- There are two different types of fat in the body: visceral fat and subcutaneous fat.
- In general, the visceral deposition of fat (fat surrounding internal organs) has a much stronger correlation with insulin resistance than does subcutaneous fat.
- Measuring of the waist-to-hip ratio (WHR) indirectly measures the visceral fat to subcutaneous fat as the abdomen contains mainly viscera and hips have only subcutaneous fat.
- A high waist hip ratio is associated with metabolic syndrome, insulin resistance, and type 2 diabetes mellitus.
- The mechanism by which free fatty acid induces insulin resistance is unclear. Serine phosphorylation of the insulin receptor's beta subunit could be involved. This phosphorylation of serine interferes with down-stream signaling because serine kinase, instead of tyrosine kinase, becomes activated. Serine phosphorylation is a known mechanism of insulin resistance induced by TNF-alpha, glucagon, and glucocorticoids.
- Free fatty acids also act to decrease insulin secretion, which prevents the compensatory rise of insulin that is required to overcome insulin resistance. The induction of insulin resistance and beta cell dysfunction along with high free fatty acids is termed "lipotoxicity."


Insulin & glucose transport
Insulin
Insulin receptor
(has intrinsic tyrosine kinase activity)
Receptor autophosphorylation
Glucose transport
Serine phosphorylation
(glucagon, epinephrine)
Tyrosine phosphorylation of IRS*
Translocation of GLUT-4
PI3K pathway
RAS/MAP kinase pathway
GLUT-4 vesicle
Glycogen, lipid, protein synthesis
Cell growth, DNA synthesis

Complication of diabetes mellites

Chronic complications

- Complications of long-standing diabetes mellitus such as microangiopathy, retinopathy, nephropathy and peripheral neuropathy occur at least in part due to chronic hyperglycemia that induces several metabolic changes.

- The most important mechanisms involved in the development of complications are:

A. Non-enzymatic glycosylation (NEG) of the vascular basement membrane:

- Glycosylation refers to the attachment of glucose to amino acid residues in various proteins forming reversible glycosylation products that slowly stabilize to irreversible products.

- Glycosylation products accumulate and cross-links with collagen in blood vessel walls and interstitial tissues.

- NEG of large- and medium-sized vessels leads to atherosclerosis and its resultant complications:
  - Cardiovascular disease is the leading cause of death among diabetics.
  - Peripheral vascular disease in diabetics is the leading cause of nontraumatic amputations.

- NEG of small vessels (arterioles) leads to hyaline arteriolosclerosis. Involvement of renal arterioles leads to glomerulosclerosis.

B. Polyol pathway impairment:

- Occurs in tissues that do not depend on insulin for glucose transport (lens, peripheral nerves, blood vessels and kidneys).

- Hyperglycemia results in increased intracellular glucose concentrations in these tissues.

- Glucose undergoes conversion into sorbitol by aldose reductase, and sorbitol, in turn, is converted into fructose.

- Sorbitol and fructose increase the osmotic pressure in tissues and stimulate the influx of water leading to osmotic cellular injury.

- Increased water in lens fiber cells leads to rupture of these cells with resultant opacification of the lens and cataract formation.

- Osmotic injury of Schwann cells contributes to peripheral neuropathy in diabetes.

- Examples of chronic complications:

1. Microvascular disease (due to damage to small blood vessels):

- The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

A. Diabetic nephropathy:

- Damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis.
- Diabetes mellitus is the most common cause of adult kidney failure in the developed world.

B. Diabetic neuropathy:

- Abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands.
- When combined with damaged blood vessels this can lead to diabetic foot.
- Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy.

- Autonomic neuropathy can be devastating; patients will have orthostatic hypotension and syncope as main manifestations.

- Autonomic dysregulation can lead to decreased sweating and dry feet (susceptible to skin fissure formation) and further increase the risk for ulceration.

- After several years, DM decreases the ability of the gut to sense the stretch of the walls of the bowel. Stretch is the main stimulant to gastric motility.

- Diabetic gastroparesis (delayed gastric emptying) presents with symptoms of anorexia, nausea, vomiting, early satiety, postprandial fullness, and impaired glycemic control. Hypoglycemic episodes can occur with insulin administration prior to meals in patients with impaired gastric emptying or delayed absorption. Prokinetic agents (metoclopramide, erythromycin, cisapride) are useful in the management of symptoms.

- Impotence and retrograde ejaculation can occur; the prevalence of erectile dysfunction is as high as 50% in patients with 10 years of diabetes.

C. Diabetic retinopathy:

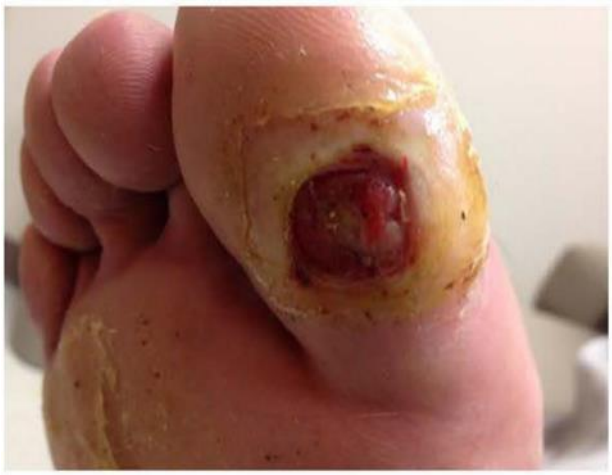
- Growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness.
- Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.

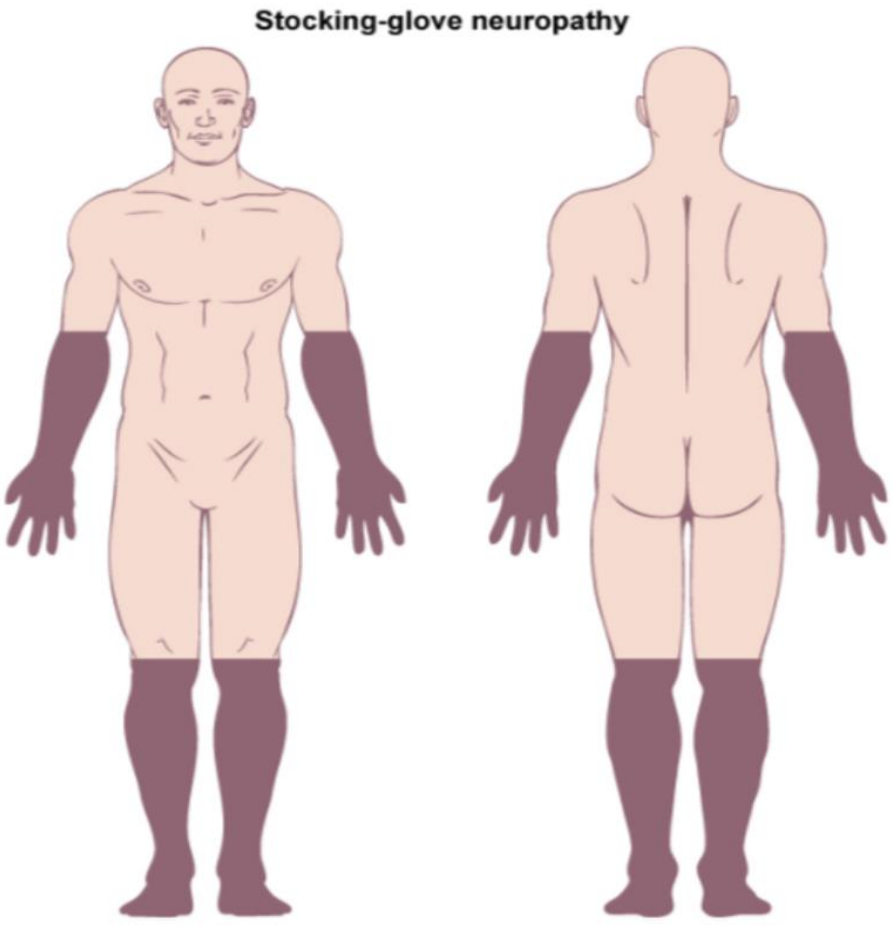
2. Macrovascular disease (due to damage to the arteries):

A. Coronary artery disease, leading to angina or myocardial infarction. Coronary heart disease is the most common cause of death in patients with diabetes mellitus.

B. Peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.

C. Stroke (mainly the ischemic type).





Acute complications

1. Diabetic Ketoacidosis:

- Although more common in those with Type 1 diabetes, diabetic ketoacidosis (DKA) can definitely present in those with Type 2 diabetes.

- DKA can be the initial presentation of DM, especially in patients lacking regular health follow-up.

- Presentation:

- DKA is often precipitated by infections, severe stress as myocardial infarction or omission of insulin.

- Insulin and glucagon normally act in opposition to one another, with insulin inhibiting glucagon release. Patients with DM (especially type I DM), however, are unable to synthesize sufficient insulin to prevent hyperglycemia and to inhibit glucagon's effects.

- Because glucose is inadequately transported into cells in patients with DM and DKA, the body perceives hypoglycemia and a starved state despite high serum glucose levels → Adrenergic nervous system activation and increased glucagon production result.

- Glucagon stimulates ketoacids synthesis in adipose tissue because during starvation ketoacids can be used by cells for energy in place of glucose.

- If ketones increase sufficiently in the blood, they can lead to ketoacidosis → metabolic acidosis.

- Increased alveolar ventilation partially compensates for the metabolic acidosis → ventilation becomes deep and rapid (Kussmaul breathing).

- Patients with DKA clinically exhibit nausea and vomiting, severe abdominal pain, dry mucous membranes and lethargy. There is classically a fruity odor on their breath (acetone odor).

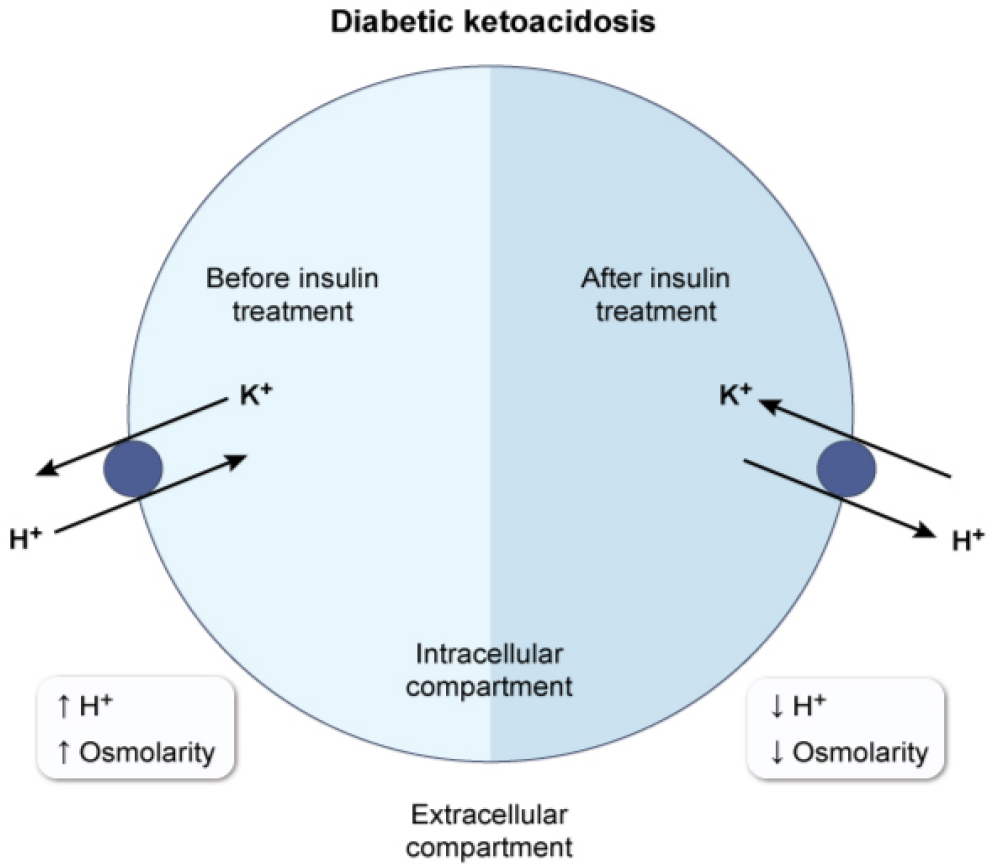
- DKA patient has both clinical (polyuria, polydipsia, volume depletion) and biochemical (hyperglycemia, low bicarbonate, high anion gap) signs. Hyperglycemia is associated with glycosuria that leads to obligatory water loss and subsequent marked dehydration.

- Metabolic acidosis during diabetic ketoacidosis (DKA) is typically accompanied by hyperkalemia.

- DKA is characterized by an osmotic diuresis that reduces total body K stores even though the serum K level may be elevated. This hyperkalemia is sometimes called paradoxical, because the body potassium reserves are actually depleted due to increased gastrointestinal losses and osmotic diuresis.

- The main causes of this paradoxical hyperkalemia are:
  - Extracellular shift of potassium in exchange to hydrogen ion, with resultant intracellular potassium deficit.

- Impaired insulin-dependent cell entry of the potassium ion.



- Diagnosis:

- For making a diagnosis of DKA, three things are necessary:

- Elevated blood glucose.

- Metabolic acidosis (low serum bicarbonate and low blood pH), and increased anion gap (sodium – [bicarbonate + chloride]).

- Detection of plasma ketones (increased serum levels of acetoacetate, acetone, and hydroxybutyrate).

- Treatment:

- IV fluids, IV insulin, K (to replete intracellular stores) +/– glucose to prevent hypoglycemia:

- Restoration of intravascular volume: using 0.9% saline (normal saline).
- Correction of hyperglycemia: using intravenous regular insulin.
- Correction of electrolyte abnormalities: Potassium correction is very crucial.

- Correct the underlying cause: noncompliance with medications, infection, or any serious illness.

- Complications: Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias, HF.

Diabetic ketoacidosis	
Patient characteristics	• Young age • Brittle type 1 diabetes • May be initial manifestation of diabetes
Clinical symptoms	• Acute to subacute onset ○ **Initial**: Polydipsia/polyuria, blurred vision, weight loss ○ **Later**: Altered mentation, hyperventilation, abdominal pain
Diagnosis	• **Glucose 250-500 mg/dL** • Bicarbonate <18 mEq/L • Elevated anion gap • Positive serum ketones
Treatment	• High-flow IV fluids • IV insulin • Follow & replace potassium

2. Hyperosmolar hyperglycemic state (HHS):

- Was previously known as hyperglycemic, hyperosmolar, nonketoic coma or (HONK).
- It is a syndrome that occurs predominantly in patients with type 2 diabetes and is characterized by severe hyperglycemia in the absence of significant ketosis.
- The pathophysiology involved is profound dehydration resulting from a sustained hyperglycemic diuresis.
- HHS is characterized by severe hyperglycemia (frequently >1000 mg/dL) and increased serum osmolality (>320 mOsm/kg). There is little or no ketonemia or acidosis present, and most patients have pH >7.3 and serum bicarbonate >20 mEq/L.
- Clinical findings are weakness, polyuria, polydipsia, lethargy, confusion, convulsions, and coma.
- Patients with HHS also frequently develop neurologic symptoms (focal signs, lethargy, blurry vision, and obtundation) due to severe hyperglycemia and elevated serum osmolality.
- Management of HHS involves high-volume fluid and electrolyte replacement, and insulin.
- Severe hyperglycemia induces an osmotic diuresis, which can lead to a deficit of 8-10 liters in total body water. Fluid replacement with normal saline is the most important initial step in management of hyperosmolar hyperglycemic state.

	Diabetic ketoacidosis	Hyperosmolar hyperglycemic state
Patient characteristics	• Type 1 diabetes usually • Younger age	• Type 2 diabetes usually • Older age
Clinical symptoms	• Less pronounced altered mentation • More rapid onset of hyperglycemic symptoms • Hyperventilation & abdominal pain common	• More pronounced altered mentation • Gradual onset of hyperglycemic symptoms • Hyperventilation & abdominal pain less common
Laboratory studies	• Glucose 250-500 mg/dL (13.9-27.8 mmol/L) • Bicarbonate <18 mEq/L (18 mmol/L) • Elevated anion gap • Positive serum ketones • Serum osmolality <320 mOsm/kg (320 mmol/kg)	• Glucose >600 mg/dL (33.3 mmol/L) • Bicarbonate >18 mEq/L (18 mmol/L) • Normal anion gap • Negative or small serum ketones • Serum osmolality >320 mOsm/kg (320 mmol/kg)

3. Hypoglycemia:

- Often occurs during exercise or fasting, these situations normally associated with low insulin and elevated counterregulatory hormones. This would tend to raise plasma glucose. However, in the diabetic, overdosing with insulin causes hypoglycemia.

- Exercise is an important cause of hypoglycemia in diabetics. Exercise is generally associated with lowering of blood sugar both in diabetic and non-diabetic individuals. Exercise increases glucose uptake by muscle cells through two main mechanisms:

- Sensitization of muscle cells to the action of insulin.
- Increased insulin-independent glucose uptake into the exercising muscles.

- In normal individuals, a drop in blood glucose will stop insulin release from beta cells, which prevents a further drop in blood glucose. However, diabetics do not have this feedback mechanism because they are treated with exogenous insulin or sulfonylurea agents (insulin secretogogue) which cause circulating insulin levels to remain elevated despite low blood glucose levels. Moreover, circulating insulin levels can jump even higher secondary to the rapid absorption of insulin injected into an exercising limb.

- There are two important causes of hypoglycemia in non-diabetic patients with elevated insulin level:

1. Insulinoma (beta cell tumor).
2. Surreptitious use of insulin or sulfonylurea.

- Helpful tests used in the evaluation of hypoglycemic patients are measurements of c-peptides, proinsulin and sulfonylurea levels. Elevated C-peptide levels and proinsulin levels are seen in patients with beta cell tumors.

Evaluation of hypoglycemia			
	Serum insulin	**C-peptide**	**Hypoglycemic drug assay**
Exogenous insulin	Normal/increased	**Low**	Negative
Oral hypoglycemic agents	Normal/increased	Normal/elevated	**Positive**
Insulinoma	Normal/increased	Normal/elevated	Negative

- The brain relies heavily on glucose as an energy source, and the level of glucose uptake by the brain is not regulated by insulin. If hypoglycemia persists despite this autonomic reaction, the activity of higher brain centers diminishes in order to reduce glucose requirements. Thus, there are two types of hypoglycemic symptoms:

- Adrenergic symptoms such as sweating, tremor, palpitations, hunger, and nervousness occur due to epinephrine and norepinephrine release. Adrenergic symptoms are the early signs of hypoglycemia.
- CNS symptoms develop later and at lower glucose levels. They include behavioral changes, confusion, visual disturbances, stupor, and seizures. Prolonged CNS hypoglycemia leads to irreversible neurological deficits and death.

- Non-selective B-blockers (propranolol, timolol and nadolol) inhibit the epinephrine and norepinephrine-mediated compensatory reactions to hypoglycemia. Thus, the adrenergic symptoms of hypoglycemia (tremor, palpitations) are blunted. Additionally, blockade of B_2 adrenergic receptors inhibits hepatic gluconeogenesis and peripheral glycogenolysis and lipolysis.

- Non-selective B-blockers exacerbate hypoglycemia and mask its adrenergic symptoms. For this reason, they should not be used in patients with diabetes mellitus. Selective B antagonists should be used instead if a B-blocker is necessary.

- Treatment:

- Blood glucose can be raised to normal within minutes by taking 10-20 grams of carbohydrates; it can be taken as food or drink if the person is conscious and able to swallow.

- If the patient is unconscious or has seizures, we can establish IV access and give intravenous dextrose.

- If IV access cannot be established, the patient can be given intramuscular glucagon injection.

Infant of diabetic mother

- Infants of diabetic mothers (IDMs) are at increased risk for a variety of complications:

- Premature delivery.
- Fetal macrosomia.
- Neural tube defects (caudal regression syndrome).
- Hypoglycemia.

- In women with poorly controlled diabetes mellitus during pregnancy, the fetus is subjected to high blood glucose levels since glucose crosses the placenta.

- However, since maternal insulin is not able to cross the placenta, fetal hyperglycemia leads to insulin hypersecretion by the fetus due to beta cell hyperplasia, which promotes abnormal growth and storage of excess calories as fat (macrosomia).

- After birth, the infant is no longer exposed to the mother's high blood glucose levels, but a transient hyperinsulinemic state will persist for several days, during which the infant is susceptible to developing hypoglycemia.

Metabolic Syndrome (Syndrome X)

- Metabolic syndrome includes hypertension, impaired fasting glucose, and dyslipidemia. Patients are also characteristically overweight, with predominantly central (abdominal) fat distribution that is reflected by an increased waist-to-hip ratio.

- Insulin resistance plays a central role in the pathogenesis of metabolic syndrome.

- Metabolic syndrome is diagnosed when at least 3 of the 5 following criteria are met:

- Abdominal obesity (Men: Waist circumference >40 inches; Women: Waist circumference >35 inches).
- Fasting glucose >100 -110 mg/dL.
- Blood pressure > 130/80 mm Hg.
- Triglycerides >150 mg/dL.
- HDL cholesterol (Men: <40 mg/dL; Women: <50 mg/dL).

Pancreatic endocrine-secreting tumors

Insulinoma

- Most common islet cell tumor.
- Tumor of pancreatic β cells → overproduction of insulin → hypoglycemia.
- Most common symptoms due to the hypoglycemia (confusion, disorientation, headache).
- May see Whipple triad:
  - Low blood glucose.
  - Symptoms of hypoglycemia (lethargy, syncope, diplopia).
  - Resolution of symptoms after normalization of glucose levels.
- Symptomatic patients have ↓ blood glucose and ↑ C-peptide levels (vs exogenous insulin use).
- Association with MEN 1.
- Treatment: surgical resection.

Zollinger-Ellison syndrome (gastrinoma)

- Gastrin-secreting tumor (gastrinoma) of pancreas or duodenum.
- Gastrinomas are neuroendocrine tumors that are most commonly located in the pancreas, the peripancreatic tissue around the head of the pancreas, or the duodenum.
- The gastrin produced by these tumors stimulates gastric acid production, resulting in recurrent gastrointestinal ulcerations resistant to treatment, oftentimes in unusual locations, such as the jejunum.
- In fact, the presence of jejunal ulcers is strongly suggestive of a diagnosis of gastrinoma.
- Patients with gastrinomas also often complain of diarrhea (malabsorption because the high gastric acidity inactivate pancreatic enzymes) and abdominal pain (peptic ulcer disease).
- The diagnosis of gastrinoma is made by measuring basal and stimulated gastrin levels (secretin stimulation test).

- Positive secretin stimulation test: Gastrin levels remain elevated after administration of secretin, which normally inhibits gastrin release.

- Workup of all patients with newly diagnosed gastrinoma should include measurement of serum calcium, PTH, and pituitary hormones, because of the association with MEN-I.

- Proton pump inhibitors are the first-line therapy for most gastrinomas.

Glucagonoma

- Glucagonoma is a rare tumor arising from the alpha-cells of the pancreatic islets of Langerhans.

- Glucagonomas characteristically present with necrolytic migratory erythema, an elevated painful and pruritic rash typically affecting the face, groin, and extremities.

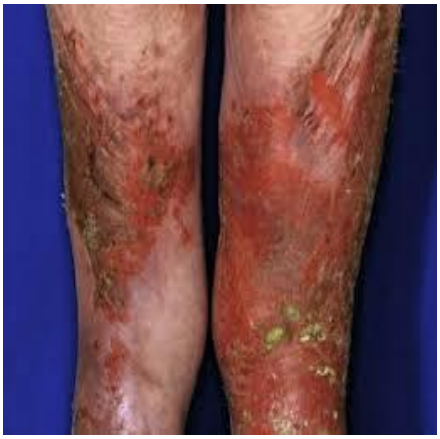
- Over time, small erythematous papules/plaques coalesce to form large lesions with central clearing of bronze-colored induration. The rash also commonly affects the mucus membranes, leading to glossitis, cheilitis, and blepharitis.

- Other features of glucagonomas include hyperglycemia (causing diabetes mellitus) and nonspecific gastrointestinal symptoms.

- Normocytic normochromic anemia resembling anemia of chronic disease is present in the majority of patients.

- Diagnosis is made by detecting elevated levels of glucagon in the serum.

Features of glucagonoma	
Clinical presentation	• **Necrolytic migratory erythema** • Erythematous papules/plaques on face, perineum & extremities • Lesions enlarge & coalesce, leaving a central indurated area with peripheral blistering & scaling • **Diabetes mellitus**/hyperglycemia • Gastrointestinal symptoms (diarrhea, anorexia, abdominal pain)
Diagnosis	• Markedly elevated glucagon levels



Somatostatinoma

- Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells.
- The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland.
- Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells.
- Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin.
- Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones.
- Gallbladder stones form because of poor gallbladder contractility, which is secondary to inhibition of cholecystokinin release.

Neuroendocrine tumors

- Heterogeneous group of neoplasms originating from neuroendocrine cells (which have traits similar to nerve cells and hormone-producing cells).
- Most neoplasms occur in the GI system (carcinoid, gastrinoma), pancreas (insulinoma, glucagonoma), and lungs (small cell carcinoma). Also in thyroid (medullary carcinoma) and adrenals (pheochromocytoma).
- Neuroendocrine cells (pancreatic β cells, enterochromaffin cells) share a common biologic function through amine precursor uptake decarboxylase (APUD) despite differences in embryologic origin, anatomic site, and secretory products (chromogranin A, neuron-specific enolase [NSE], synaptophysin, serotonin, histamine, calcitonin).
- Treatment: surgical resection, somatostatin analogs.

Multiple Endocrine Neoplasia

- All MEN syndromes have autosomal dominant inheritance.
- "All MEN are dominant" (or so they think).
- Multiple Endocrine Neoplasia (MEN) refers to a group of familial disorders characterized by specific clusters of endocrine abnormalities.

MEN 1

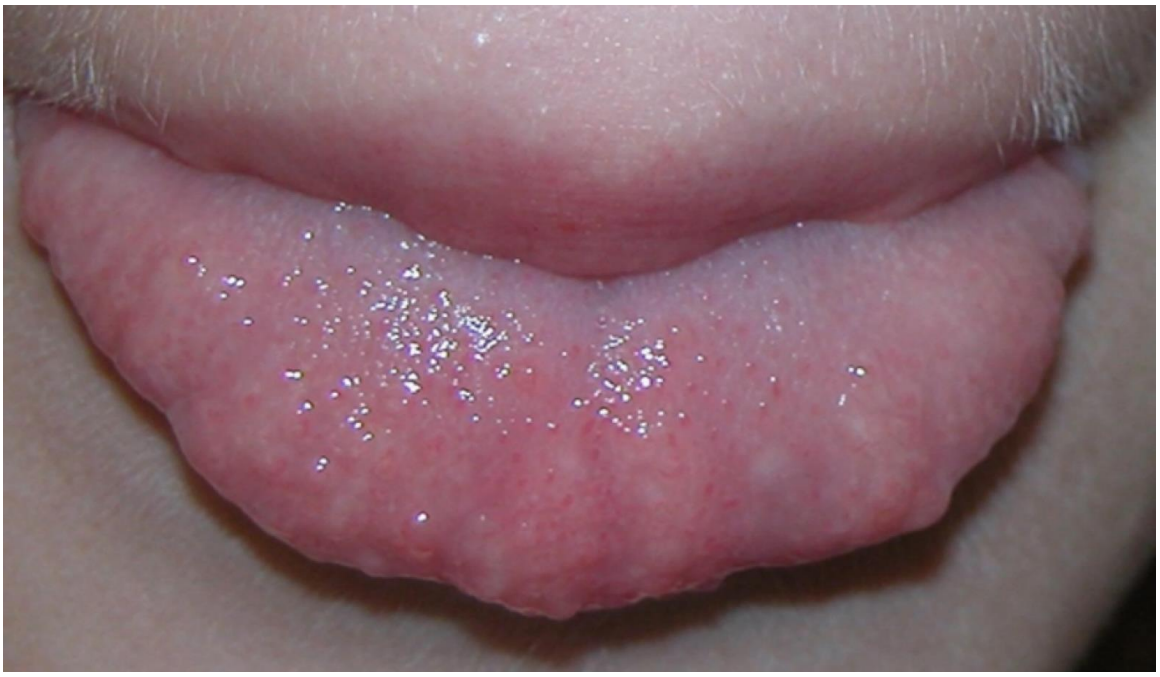
- Parathyroid tumors (parathyroid adenoma or hyperplasia).
- Pituitary tumors (prolactin or GH).
- Pancreatic endocrine tumors: Zollinger- Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare).
- Associated with mutation of MEN1 gene (menin, a tumor suppressor).
- MEN 1 = 3 P's: Pituitary, Parathyroid, and Pancreas.

MEN 2A

- Pheochromocytoma (episodic headache).
- Parathyroid hyperplasia.
- Medullary thyroid carcinoma (secretes calcitonin).
- Mutation in RET gene (codes for receptor tyrosine kinase).
- MEN 2A = 2 P's: Parathyroids and Pheochromocytoma.

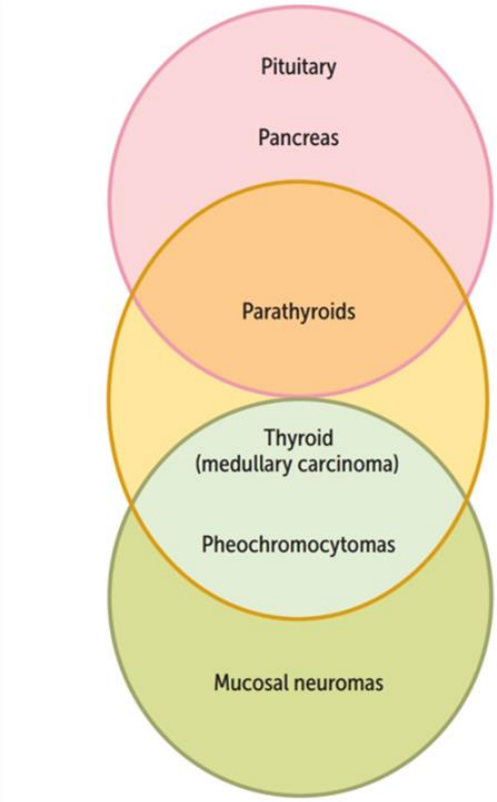
MEN 2B

- Pheochromocytoma (episodic headache).
- Medullary thyroid carcinoma (secretes calcitonin).
- Mucosal neuromas which are flesh-colored nodules on his lips and tongue (unencapsulated, thickened proliferations of neural tissue).
- Associated with marfanoid habitus (tall and slender with disproportionately long arms, legs, and fingers); mutation in RET gene.
- MEN 2B = 1 P: Pheochromocytoma.



❖ N.B:

- The genetic defect associated with MEN 2A and 2B is a germ-line mutation of the RET proto-oncogene.



MEN 1 = 3 P's: Pituitary, Parathyroid, and Pancreas
MEN 2A = 2 P's: Parathyroid and Pheochromocytoma
MEN 2B = 1 P: Pheochromocytoma

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

Appetite regulation

Ghrelin

- Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor).
- Produced by stomach.
- Acts on lateral area of hypothalamus (hunger center) to ↑ appetite.
- Sleep deprivation, fasting, or Prader-Willi syndrome → ↑ ghrelin production.
- Ghrelin makes you hunghre and ghrow.

Leptin

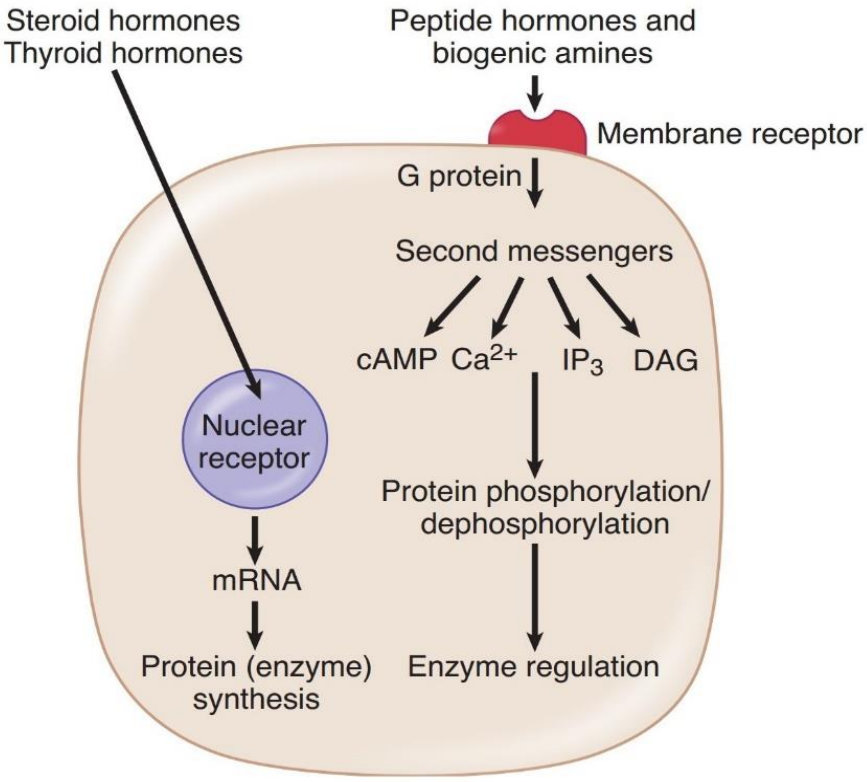
- Satiety hormone.
- Produced by adipose tissue.
- Acts on ventromedial area of hypothalamus (satiety center) to ↓ appetite.
- Obese people have ↑ leptin due to ↑ adipose tissue but also appear resistant to leptin's anorexigenic effect.
- Mutation of leptin gene → central obesity.
- Sleep deprivation or starvation → ↓ leptin production.
- Leptin keeps you thin.

Endocannabinoid

- Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake → ↑ appetite.
- Exogenous cannabinoids cause "the munchies".

Signaling pathways of endocrine hormones

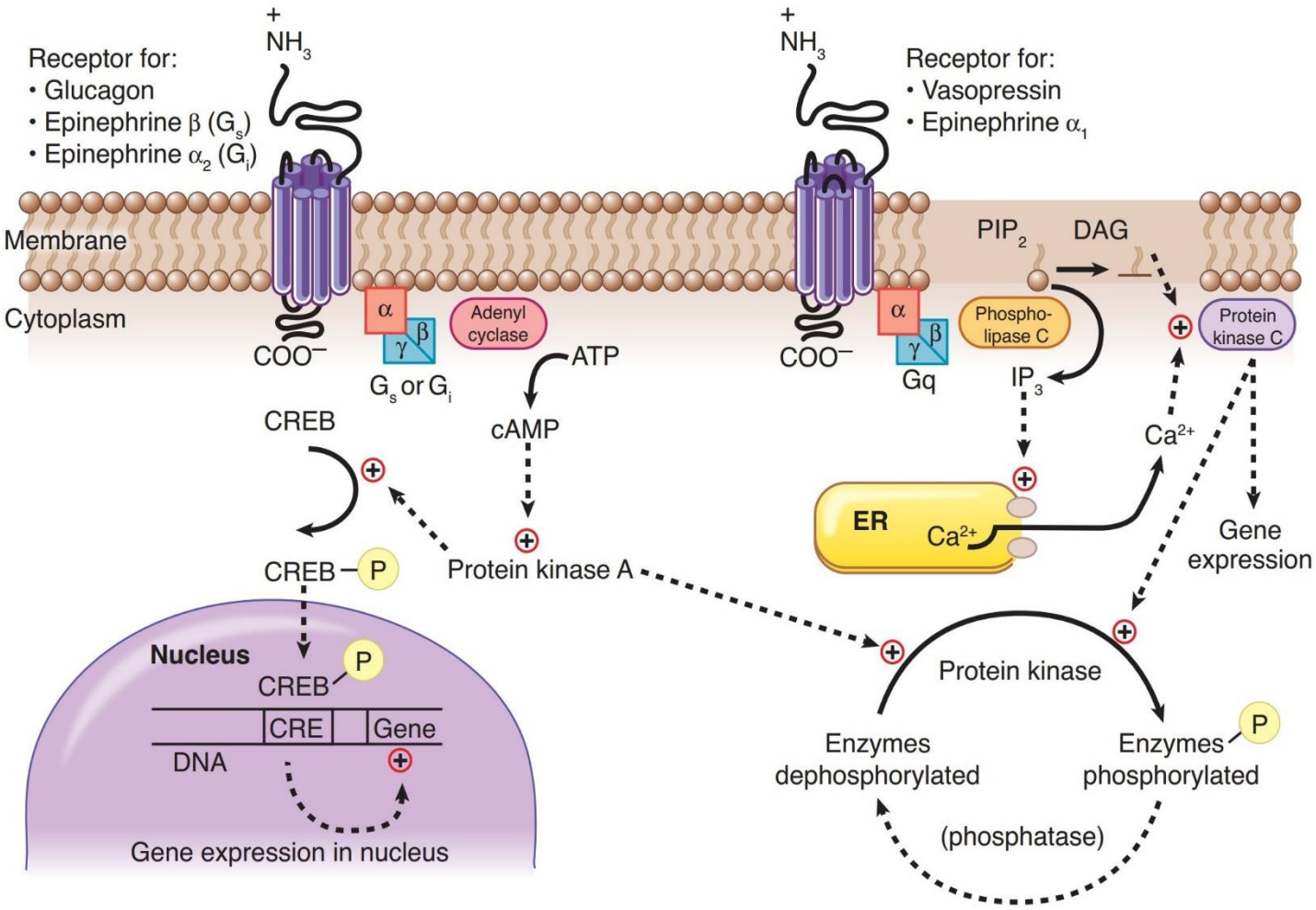
- Several major differences between the lipid-soluble hormones and the water-soluble hormones.



	Lipid-Soluble Hormones **(Steroids, thyroid hormones, vitamin D)**	**Water-Soluble Hormones** **(Peptides, proteins)**
Receptors	Inside the cell, usually in the nucleus	Outer surface of the cell membrane
Intracellular Action	Stimulates the synthesis of specific new proteins	Production of second messengers (cAMP) Insulin does not utilize cAMP, instead activates membrane-bound tyrosine kinase Second messengers modify action of intracellular proteins (enzymes)
Storage	Synthesized as needed Exception: thyroid Hormones	• In some cases, prohormone stored in vesicle along with an enzyme that splits off the active hormone
Plasma transport	Attached to proteins that serve as carriers	Dissolved in plasma (free, unbound)
Half-life	Long (hours, days)	Short (minutes)

- Signaling pathways of endocrine hormones:

cAMP	**FSH, LH, ACTH, TSH, CRH, hCG, ADH (V2 receptors), MSH, PTH, calcitonin, Histamine (H2-receptor), Glucagon, GHRH**	**FLAT ChAMPs CHuGG**
cGMP	BNP, ANP, EDRF (NO)	BAD GraMPa Think vasodilation and diuresis
IP3	GnRH, Oxytocin, ADH (V1-receptor), TRH, Histamine (H1 receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Progesterone, Estrogen, Testosterone, Cortisol, Aldosterone, T3/T4, Vitamin D	PET CAT on TV
Intrinsic tyrosine kinase	IGF-1, FGF, PDGF, EGF, TGF-β, Insulin	MAP kinase pathway Get Found In the MAP
Receptor-associated tyrosine kinase	Prolactin, Immunomodulators (cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin	JAK/STAT pathway Think acidophils and cytokines PIGGLET

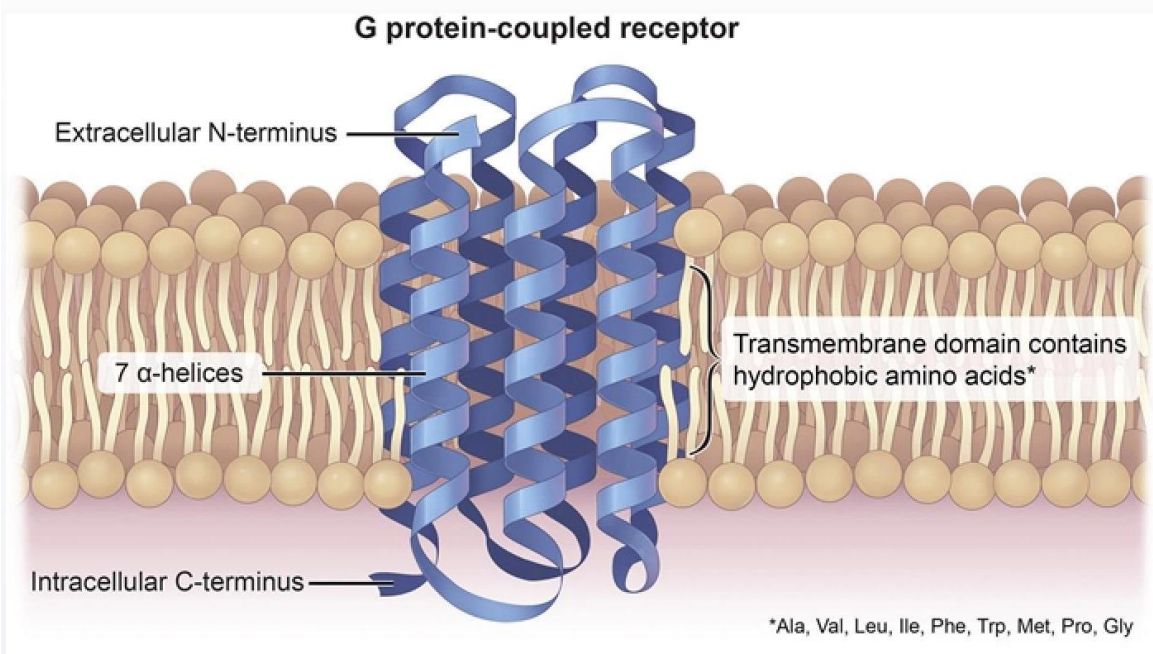


❖ N.B:

1. G protein-coupled receptors that bind glycoprotein hormones contain 3 major domains:

- Extracellular domain responsible for ligand binding.
- Seven transmembrane domain.
- Intracellular domain coupled with heterotrimeric G proteins.

▪ The transmembrane domain is made up of nonpolar, hydrophobic amino acids (alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups outwardly, anchoring the transmembrane region of the protein to the hydrophobic core of the phospholipid bilayer.



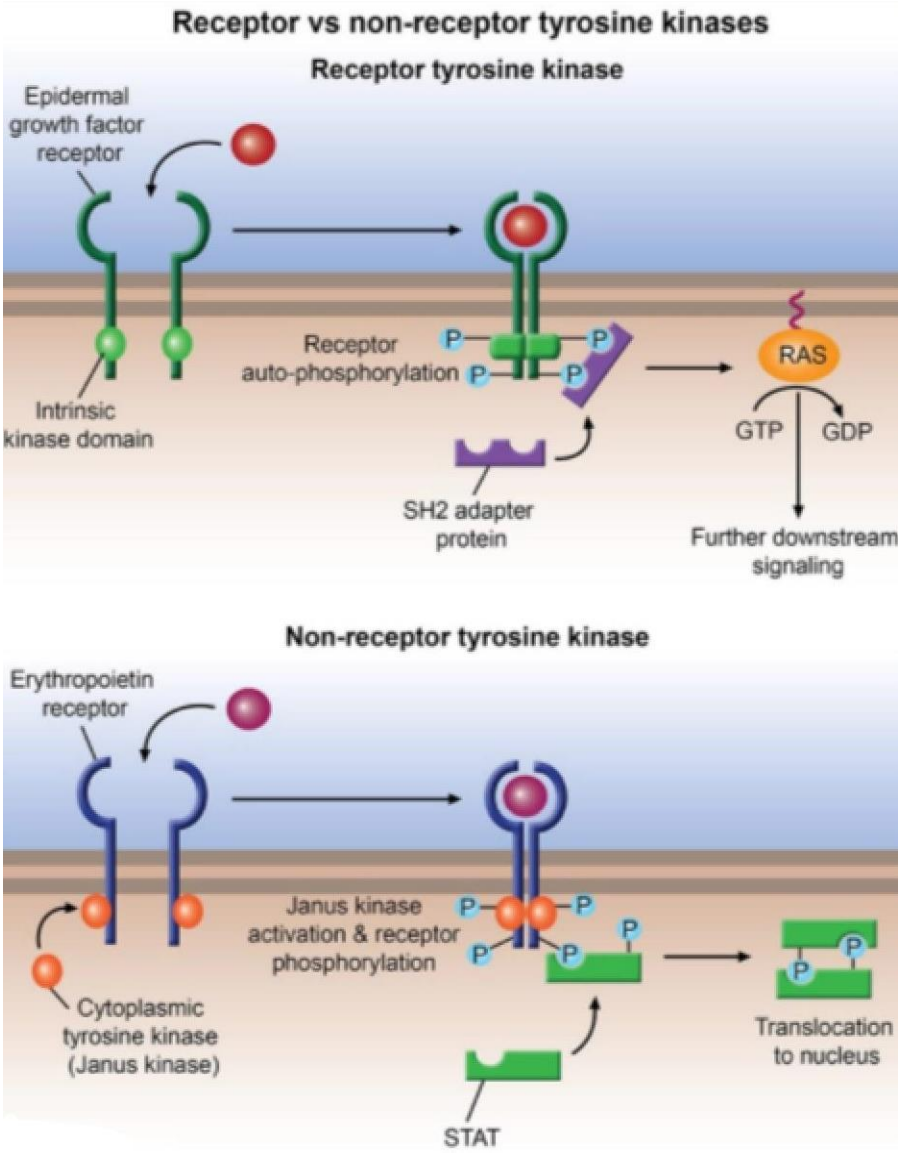
2. The G-protein-coupled-receptors have a very characteristic structure with seven transmembrane regions, an extracellular domain and an intracellular domain coupled with the trimeric G-protein.

▪ In their inactivated state, G-proteins exist as heterotrimers consisting of alpha, beta and gamma subunits with guanosine diphosphate (GDP) tightly bound to the alpha subunit.

▪ G proteins are activated after binding of hormone to the extracellular domain. The first step in activation of a G-protein occurs when GDP is exchanged for GTP on the alpha subunit.

▪ Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and exposes its catalytic domain for either adenylate cyclase or phospholipase C depending on the ligand.

Receptor	With intrinsic enzyme activity (receptor tyrosine kinase)	Without intrinsic enzyme activity (tyrosine-kinase associated receptor)
Structure	Extracellular domain (binds the growth factor) Transmembrane domain Cytosolic domain (enzyme)	Extracellular domain Transmembrane domain Cytosolic domain (lacks enzymatic activity)
Signaling pathway	MAP-kinase Receptor autophosphorylates and triggers phosphorylation of Ras protein	JAK/STAT Receptor activates Janus kinases (JAKs), which phosphorylate STATs (signal transducers and activators of transcription)
Examples	Growth factor receptors: EGF, PDGF, FGF, etc.	Receptors for cytokines, growth hormone, prolactin, IL-2

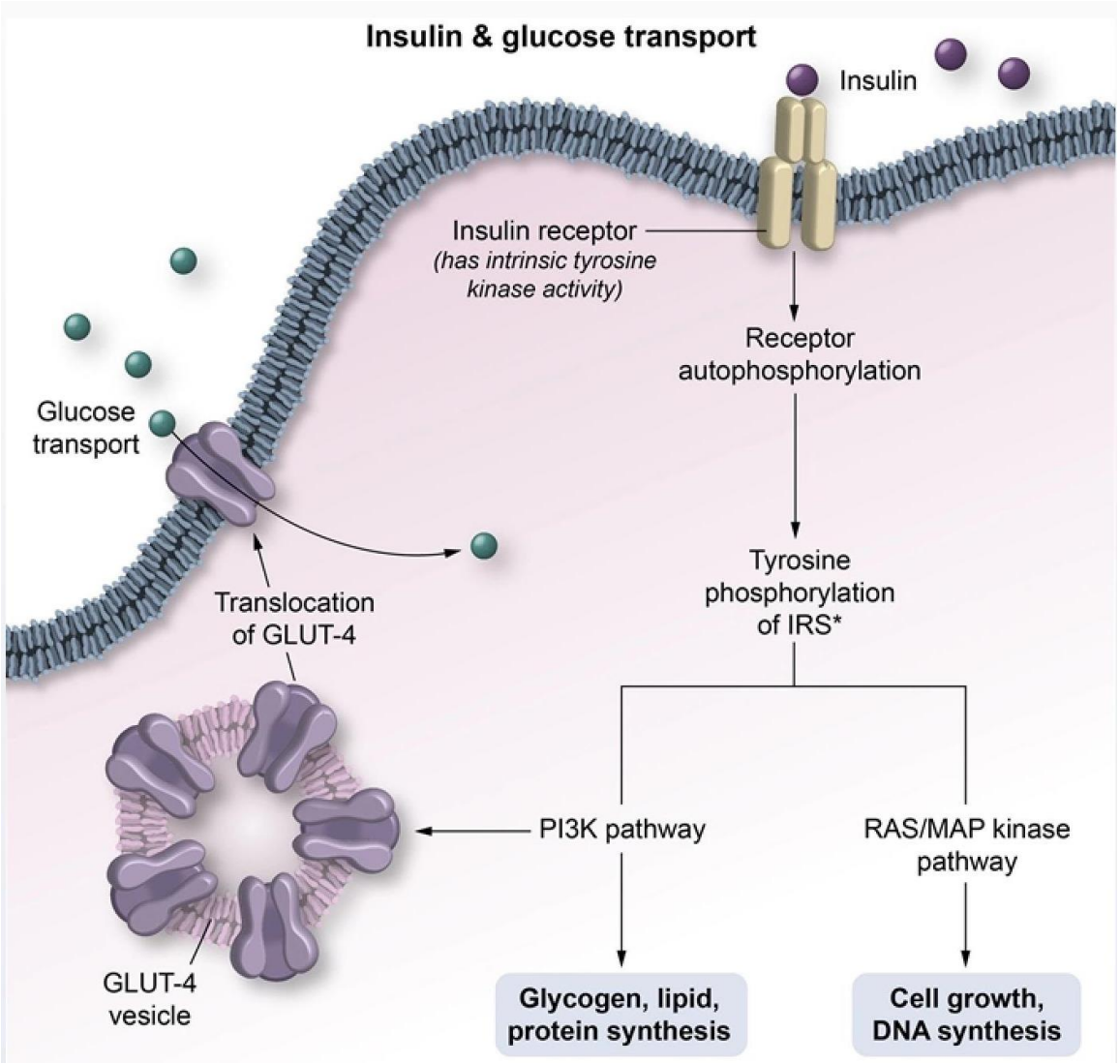


Insulin

- One of the important actions of insulin is the facilitation of glucose uptake by adipocytes and muscle cells.
- This is achieved by the movement of cytoplasmic GLUT-4 to plasma membranes in muscle and fat cells.
- This and the many other actions of insulin are mediated through cell-surface receptors.
- The insulin receptor (IR) is a tetrameric structure consisting of two alpha and two beta subunits:

- The alpha subunits are extracellular, and they provide the binding site for insulin.
- The beta subunits are intracellular and contain tyrosine kinase domains that are activated when insulin attaches to the alpha subunits.

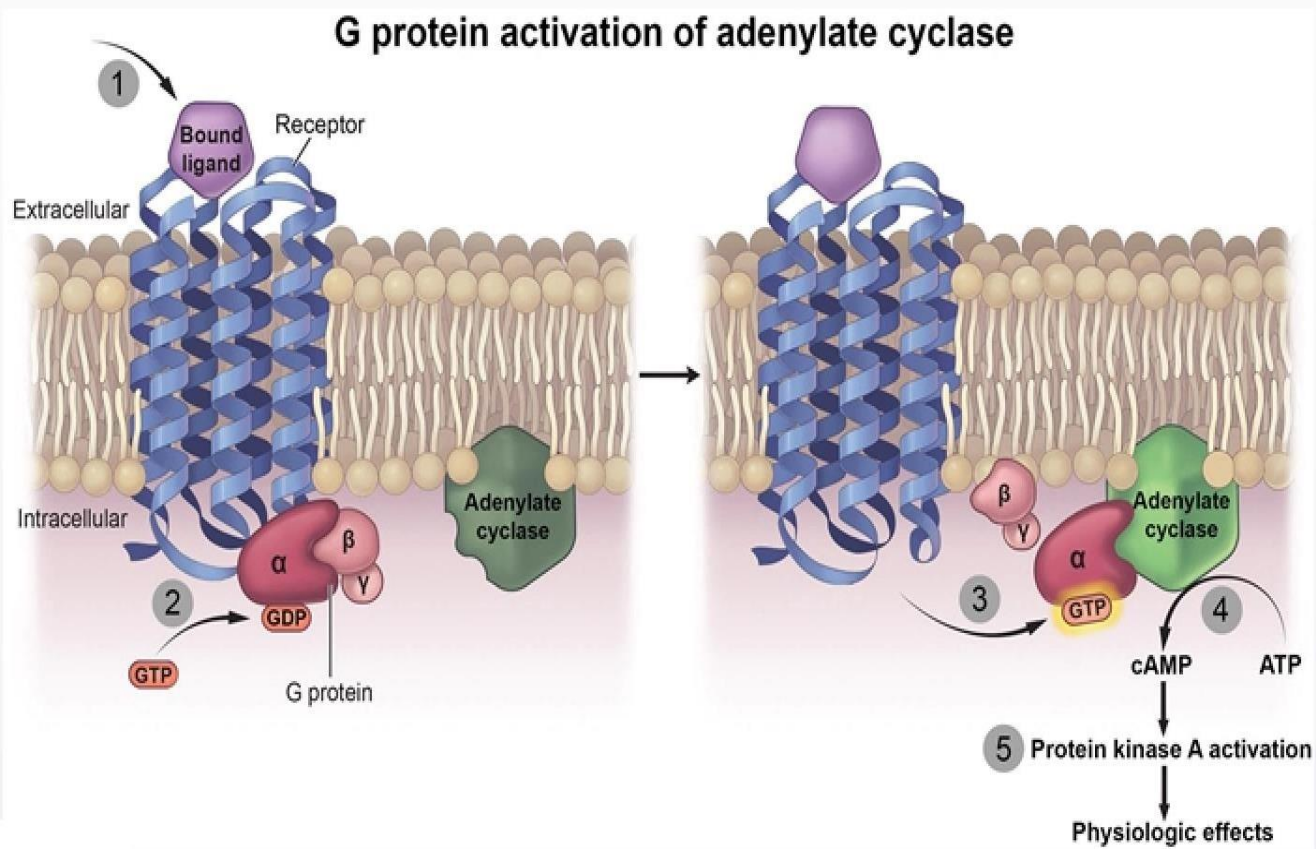
- The surface receptor for insulin is a transmembrane protein with intrinsic tyrosine kinase activity in its cytoplasmic domain.
- Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1).
- IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin.
- Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth.
- In contrast, activation of phosphatidylinositol-3-kinase (PI3K) stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, glycogen synthesis, and fat synthesis.
- PI3K promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates glycogen synthase, leading to its activation.



Glucagon

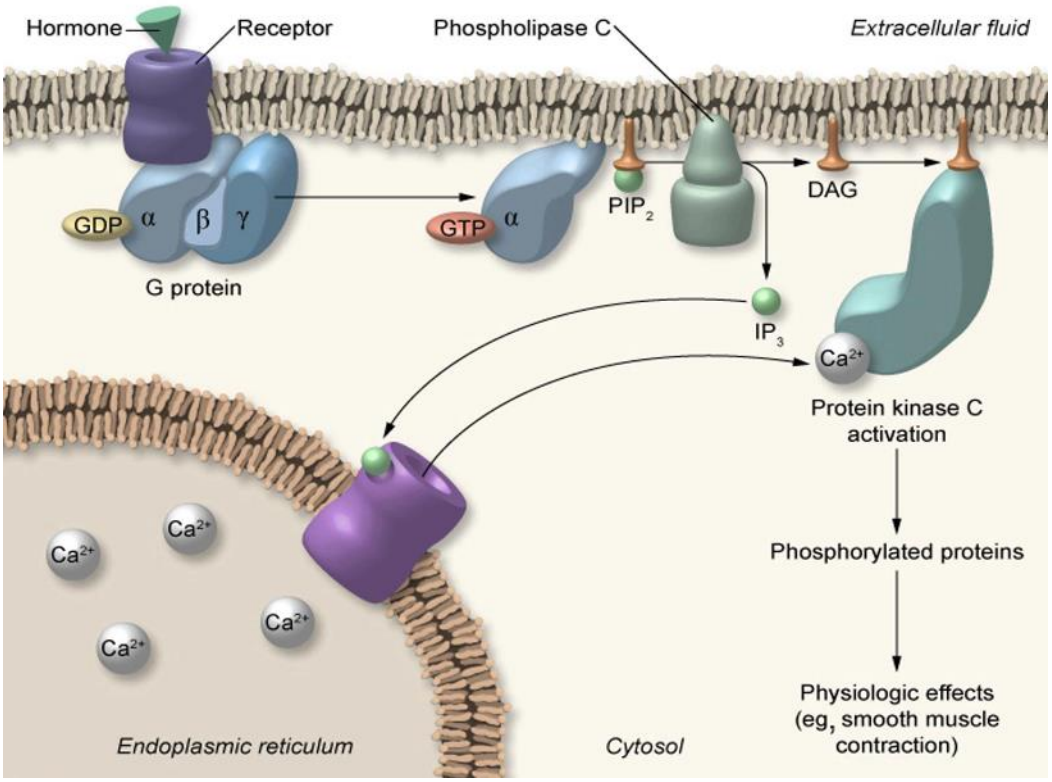
- A specific alpha subunit known as Gs present in the glucagon activates adenylate cyclase when released from the G-protein complex.
- Once formed from ATP, cyclic AMP activates a family of enzymes known as the cAMP-dependent protein kinases, or protein kinase A → Protein kinase A phosphorylates specific serine or threonine residues in some enzymes, thereby leading to their activation or deactivation.
- Protein kinase A also phosphorylates several proteins that bind to regulatory regions of genes on the DNA molecule itself.
- Protein kinase A is primarily responsible for the intracellular effects of the G-protein/adenylate cyclase second messenger system.

- Some hormone receptors that use this mechanism include the TSH, glucagon, PTH, and beta-adrenergic receptors.



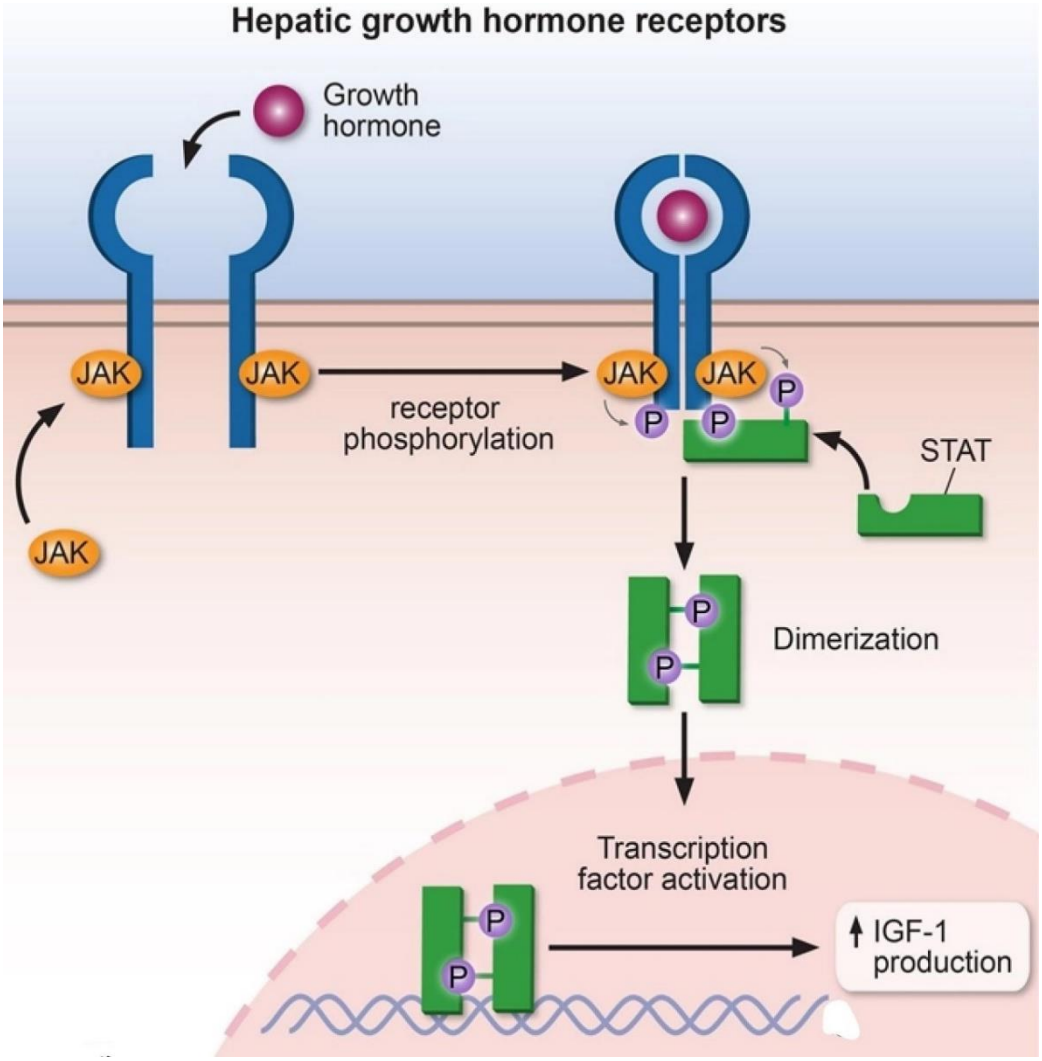
Epinephrine (α_1)

- If the G-protein alpha subunit activates phospholipase C, then the degradation of phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) occurs.
- Diacylglycerol stimulates protein kinase C, which is responsible for some intracellular effects.
- Inositol 1,4,5-triphosphate (IP3) produces most of the intracellular effects of this pathway by increasing intracellular calcium, and elevated intracellular calcium activates protein kinase C.
- SO, Protein kinase C is activated by DAG as well as calcium released from sarcoplasmic reticulum under the influence of IP3.



Growth hormone

- One GH molecule binds to 2 receptors on the cell surface, leading to activation of Janus kinase (JAK), a nonreceptor tyrosine kinase.
- JAK subsequently phosphorylates several tyrosine residues in the intracellular domain of the GH receptor.
- These phosphorylated tyrosine residues function as docking sites for STAT (signal transducer and activator of transcription).
- Once STAT is recruited to the receptor, it is also phosphorylated by JAK.
- STAT then dimerizes and translocates to the nucleus (act as a transcription factor), where it induces IGF-1 gene transcription by binding to the promoter region.
- Other molecules that use the JAK-STAT pathway include cytokines (interferon) and hematopoietic growth factors (erythropoietin, G-CSF).



Growth factors

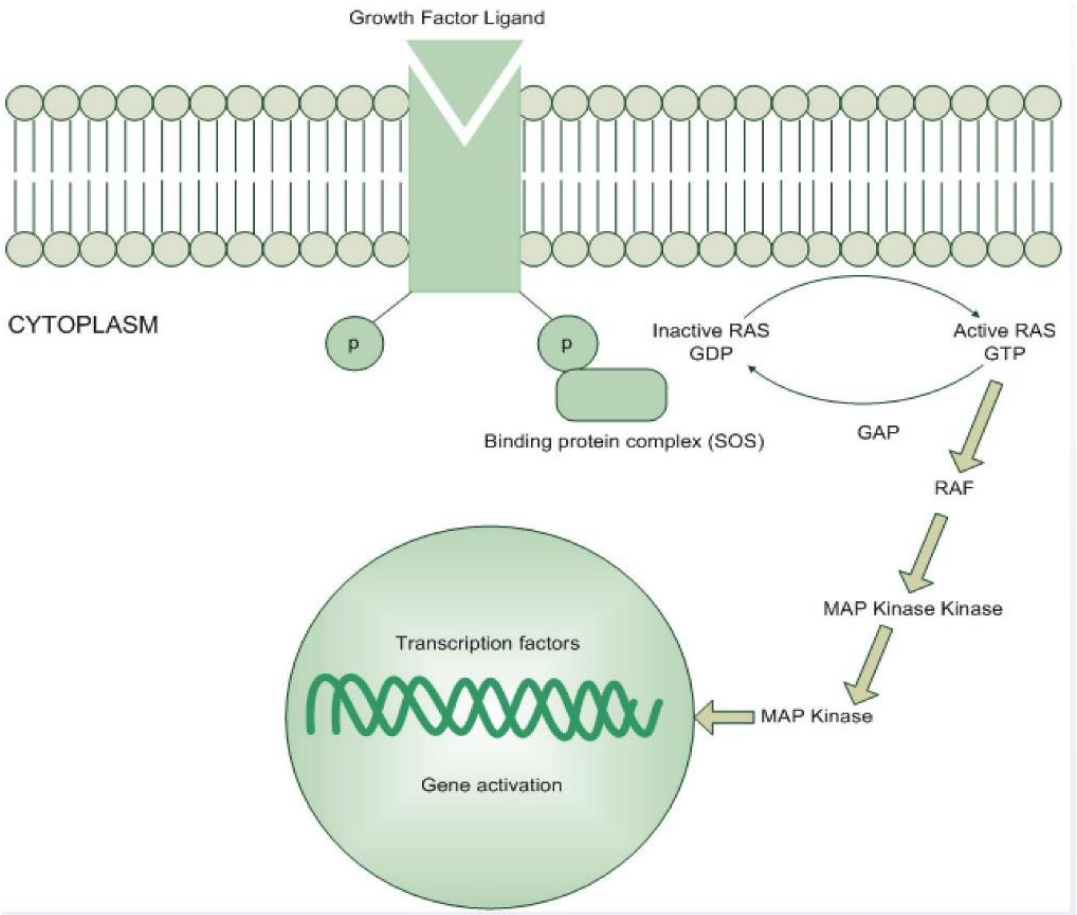
- Growth factors can stimulate cell proliferation by altering the expression of certain genes in the nucleus.

- <u>After a growth factor binds to its cell membrane receptor, signal transduction systems transfer the signal to the nucleus. Examples of signal transduction systems include:</u>

- MAP-kinase pathway.
- PI3K/Akt/mTOR pathway.
- Inositol phospholipid pathway.
- cAMP pathway.
- JAK/STAT pathway.

A. RAS/MAP-kinase pathway:

- Ras proteins exist in 2 different states: an inactive GDP-bound state and an active GTP-bound state.
- Ras becomes activated when a growth factor ligand binds to a receptor tyrosine kinase located on the cell membrane, causing autophosphorylation of the receptor.
- This triggers binding of adaptor proteins that interact with Ras, promoting GDP removal and GTP binding.
- Activated Ras then begins a phosphorylation cascade that results in the activation of mitogen-activated protein kinase (MAPK), which enters the nucleus to influence gene transcription.
- Ras proteins have intrinsic GTPase activity that allows them to hydrolyze GTP; this mechanism prevents accumulation of active Ras (GTP-bound) in the absence of hormonal signaling.
- RAS gene mutations can lead to decreased intrinsic GTPase activity: this results in a constitutively activated Ras protein that causes constant and unregulated cell proliferation.
- RAS mutations are commonly identified in cancerous tumors, specifically colorectal and pancreatic malignancies.



B. PI3K/Akt/mTOR pathway:

- The PI3K/Akt/mTOR pathway is an intracellular signaling pathway that is important for cellular proliferation. This pathway is typically activated when a growth factor binds to its receptor tyrosine kinase, causing auto-phosphorylation of specific tyrosine residues within the receptor.

- These phosphotyrosine residues activate phosphoinositide 3-kinase (PI3K), which then phosphorylates PIP2 found in the plasma membrane to PIP3.

- This leads to activation of a protein called Akt (or protein kinase B), a serine/threonine-specific protein kinase.

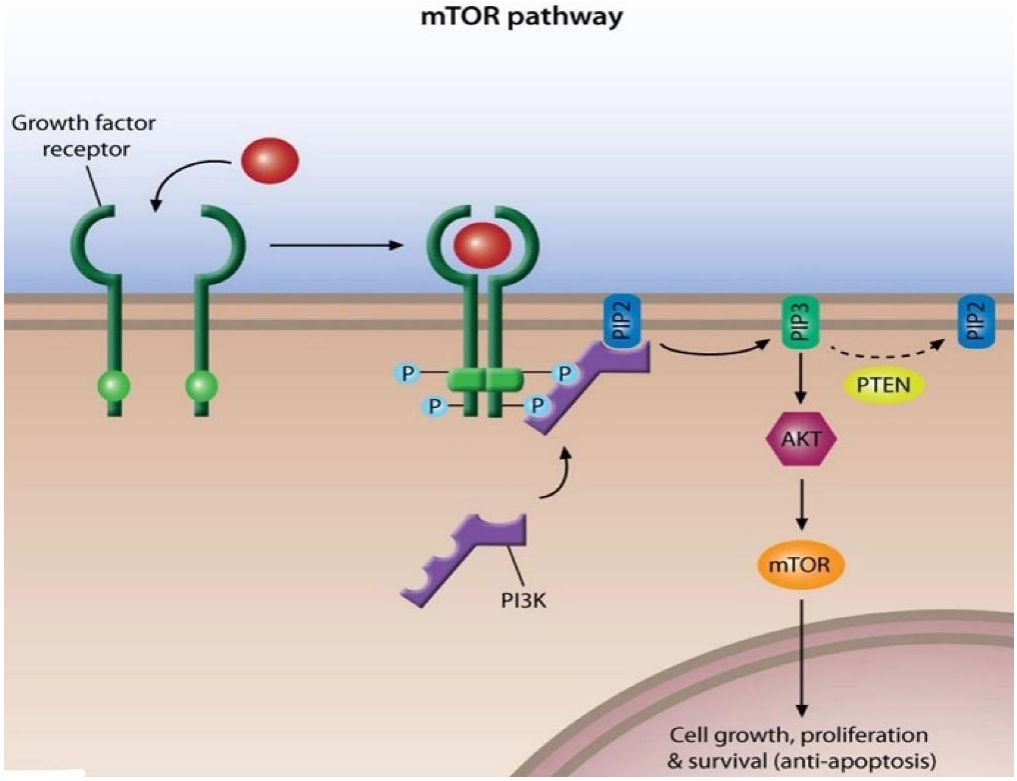
- Subsequently, Akt activates mTOR (mammalian target of rapamycin), which translocates to the nucleus to induce genes involved in cell survival, anti-apoptosis, and angiogenesis.

- mTOR activation is inhibited by PTEN (phosphatase and tensin homolog), a tumor suppressor protein that removes the phosphate group from PIP3.

- The PI3K/Akt/mTOR pathway is highly active in many cancer cells as a result of mutations causing increased activity of PI3K or Akt or loss of function of PTEN.

- Mutations involving certain growth factor receptors (epidermal growth factor) can also enhance activity.

- Several drugs targeting this pathway (mTOR inhibitors including rapamycin [sirolimus]) have shown benefit in treating certain cancers.



CHAPTER 3

Pharmacology

Diabetes mellitus drugs

- All patients with diabetes mellitus should receive education on diet, exercise, blood glucose monitoring, and complication management.

- Treatment differs based on the type of diabetes and glycemic control:

- Type 1 DM: insulin replacement.

- Type 2 DM: oral agents (metformin is first line), non-insulin injectables, insulin replacement; weight loss particularly helpful in lowering blood glucose.

- Gestational DM: insulin replacement if nutrition therapy and exercise alone fail.

Insulin preparations

- Diabetic patients often need 2 types of insulin, a basal long-acting insulin and a postprandial short-acting insulin.

A. Short acting insulin (Regular):

- It starts working 30 minutes after subcutaneous injection, with peak effects occurring between 2-4 hours.

- Unfortunately, the peak effect of regular insulin occurs after the postprandial peak in blood glucose concentration.

- This mismatch between the insulin and glucose peaks generally leads to inadequate control of glucose following meals.

- Preferred for DKA (because it can be used intravenously), hyperkalemia (with glucose to prevent hypoglycemia), stress hyperglycemia.

B. Rapid acting insulin (Lispro, Aspart, Glulisine):

- Rapid-acting insulins (lispro, aspart, and glulisine) have significantly improved postprandial insulin therapy.

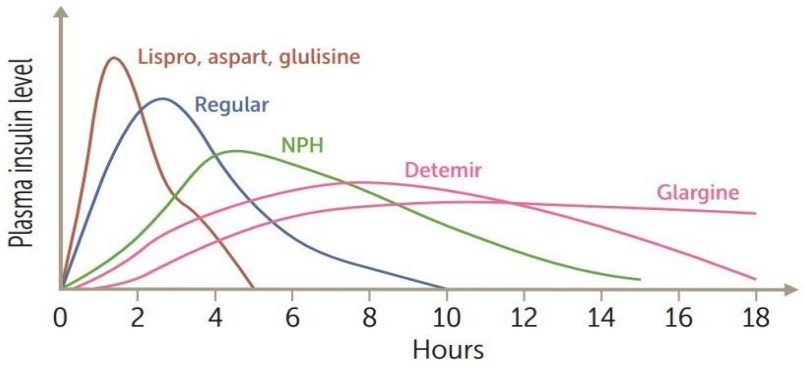
- Their onset of action is under 15 minutes and peaks between 45-75 minutes, a pattern that closely mimics the endogenous postprandial insulin response of normal individuals.

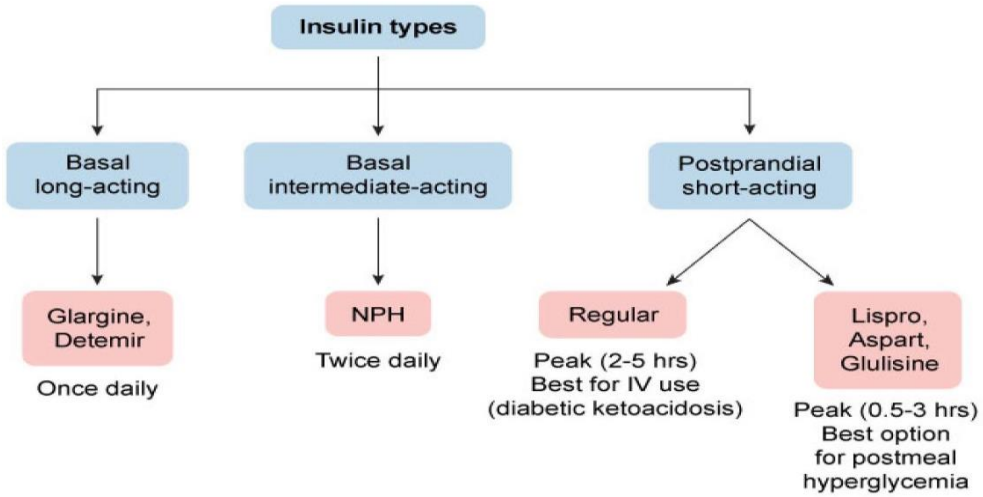
C. Intermediate acting insulin (NPH): NPH is good for about 16 hours (shots given twice a day).

D. Long-acting insulin (Detemir, Galargine):

- The best basal long-acting insulins are glargine and detemir insulin (administered as once-a-day shots).

- Insulin analog with no peak "peakless", used to supply a constant background level.





- Mechanism of action:

- Binds insulin receptor (tyrosine kinase activity):

  - Liver: ↑ glucose stored as glycogen.
  - Muscle: ↑ glycogen, protein synthesis; ↑ K uptake.
  - Fat: ↑TG storage.
  - Cell membrane: ↑ K uptake.

- Side effects:

- The most common side effects of insulin are hypoglycemia and weight gain. Hypersensitivity reactions (rare).

- Insulin has both renal and hepatic clearance. In patients with advanced chronic kidney disease and diabetes mellitus, decreased renal clearance of insulin can lead to symptomatic hypoglycemia if exogenous insulin doses are not adjusted based on the change in renal function.

Oral hypoglycemic drugs

- The 2 most important contributing factors in the pathophysiology of type 2 diabetes mellitus are insulin resistance and relative insulin deficiency.

- Several classes of oral antidiabetic medications are used for treating type 2 diabetes mellitus.

A. Biguanides (Metformin):

- Mechanism of action:

- The anti-diabetic mechanism of metformin is not clearly understood.

- It is known that metformin decreases blood sugar by inhibition of hepatic gluconeogenesis and the action of glucagon, ↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).

- Clinical use:

- First-line therapy in type 2 DM, causes modest weight loss (often desired).

- Metformin is the most commonly prescribed medication for the treatment of type 2 diabetes mellitus.

- There is no risk of hypoglycemia with metformin use "Euglycemic".

- Side effects:

- The major side effects of metformin are gastrointestinal upset and lactic acidosis.

- Metformin increases the intestinal production of lactate by anaerobic glycolysis.

- In normal individuals, the lactate produced in the intestine is converted to glucose via gluconeogenesis in the liver. Yet, metformin inhibits this very same process of gluconeogenesis, which results in elevated circulating lactate levels, and puts some patients at risk for lactic acidosis.

- In young individuals with normal renal and hepatic functions, lactic acidosis is a very rare complication of metformin therapy.

- Contraindications to metformin use include renal failure (as denoted by a serum creatinine 1.5 mg/dl in males or 1.4 mg/dl in females), significant hepatic dysfunction, and hypersensitivity to metformin.

- Serum creatinine is monitored periodically in patients taking metformin.

B. Sulfonylureas:

- Drugs:

- First generation: Chlorpropamide, Tolbutamide.

- Second generation: Glimepiride, Glipizide, Glyburide.

- Mechanism of action: Close K channel in β-cell membrane → cell depolarizes →insulin release via ↑ Ca influx.

- Clinical use:

- Stimulate release of endogenous insulin in type 2 DM.

- Require some islet function, so useless in type 1 DM.

- Side effects:

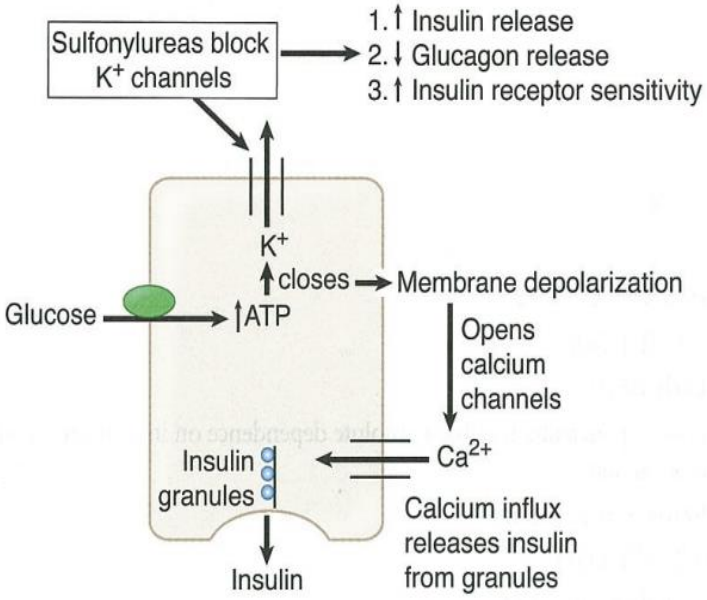
- First generation: disulfiram-like effects in alcholics.

- Second generation: hypoglycemia.

- Risk of hypoglycemia ↑ in renal failure.

❖ N.B:

- Meglitinides (repaglinide, nateglinide) are short-acting glucose-lowering medications. They are functionally similar to sulfonylureas and act by binding to and closing the ATP-dependent K channel (membrane ion channels) in the pancreatic beta cell membrane but have a weaker binding affinity and faster dissociation from the binding site.
- Their short half-life requires frequent dosing, typically with each meal, but may reduce the risk of hypoglycemia.



C. Glitazones/thiazolidinediones:

- Drugs: Pioglitazone,Rosiglitazone.

- Mechanism of action:

- Thiazolidinediones (TZDs) exert their glucose-lowering effect by decreasing insulin resistance through transcription modulation.

- TZDs bind to peroxisome proliferator activated receptor gamma (PPAR-gamma, nuclear receptors), which is a transcriptional regulator of the genes involved in glucose and lipid metabolism. One of the most crucial genes regulated by PPAR-gamma is adiponectin, which is a cytokine secreted by fat tissue (adipocytokine).

- Adiponectin levels are low in type 2 diabetes. Treatment with TZDs increases adiponectin levels. Increased levels of adiponectin are one of the main mechanisms by which TZDs decrease insulin resistance.

- As the glucose lowering effect of TZDs requires alteration in gene transcription and protein synthesis, it takes days to weeks after initiation of therapy to observe a significant reduction in glucose levels.

- Clinical use:

- Used as monotherapy in type 2 DM or combined with above agents.

- In addition to treating type 2 diabetes, TZDs have beneficial effects in other disorders associated with insulin resistance (metabolic syndrome, nonalcoholic fatty liver disease, polycystic ovarian disease).

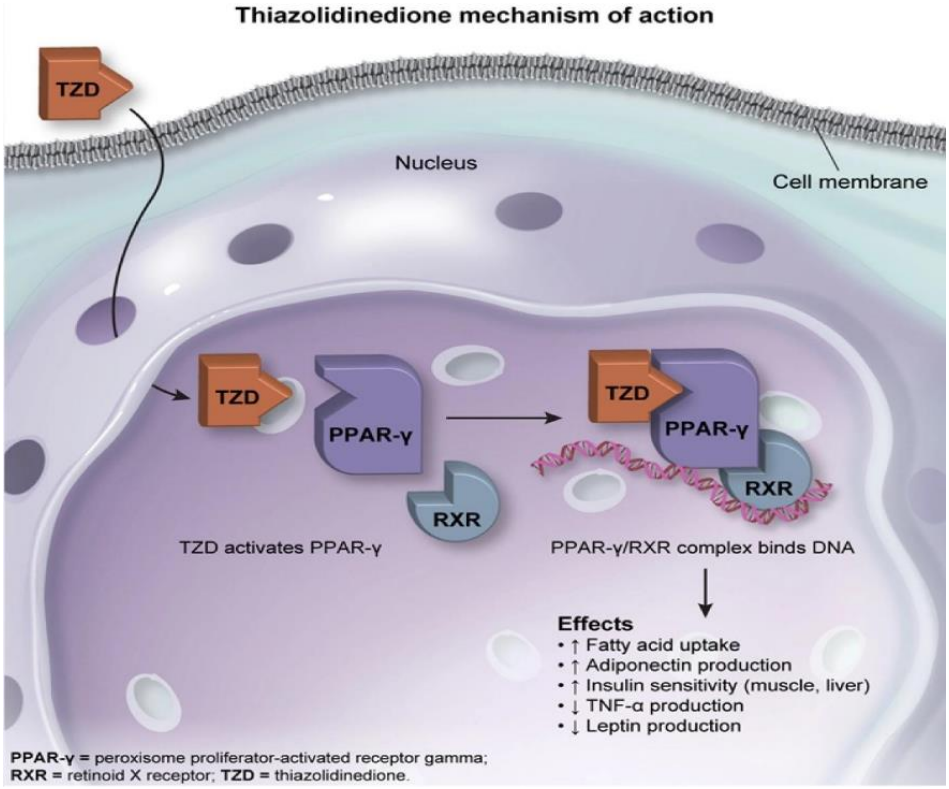
- Side effects:

- TZDs do not cause hypoglycemia.

- The main side effects of TZDs are fluid retention, weight gain, and the precipitation of congestive heart failure from fluid retention. This excess fluid can exacerbate underlying congestive heart failure

- It also increases the risk of bone fracture.

- Troglitazone was the first TZD released for clinical use but was withdrawn from the market due to a high incidence of severe hepatotoxicity. Newer TZDs such as pioglitazone and rosiglitazone have a lower risk of hepatotoxicity. However, it is recommended that liver function tests be performed before starting TZDs, followed by periodic monitoring. Initiation of TZD therapy should be avoided if serum aminotransferases are significantly elevated.



D. GLP-1 analogs:

- Drugs: Exenatide, Liraglutide.

- Mechanism of action:

- Glucagon like Peptide-1 (GLP-1) and gastric inhibitory peptide (also known as glucose dependent insulinotropic polypeptide or GIP), both of them are called incretins.

- Incretin mimetics are a direct replacement of incretins except that their actions last much longer.

- Incretins, especially GLP-1 and GIP are secreted by K and L cells in the gut and stimulate a decrease in blood glucose level by causing an increase in the amount of insulin released from pancreatic beta cells after eating, before blood glucose level become elevated.

- They also inhibit the release of glucagon from alpha cells.

- They have an outstanding effect on slowing gastric motility and promoting weight loss (often desired).

- Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

- Exenatide ↑ insulin release and ↓ glucagon release by acting as a GLP-1 analog.

- Clinical use: type 2 DM.

- Side effects: Nausea, vomiting; pancreatitis.

E. DPP-4 inhibitors:

- Drugs: Linagliptin, Saxagliptin, Sitagliptin.

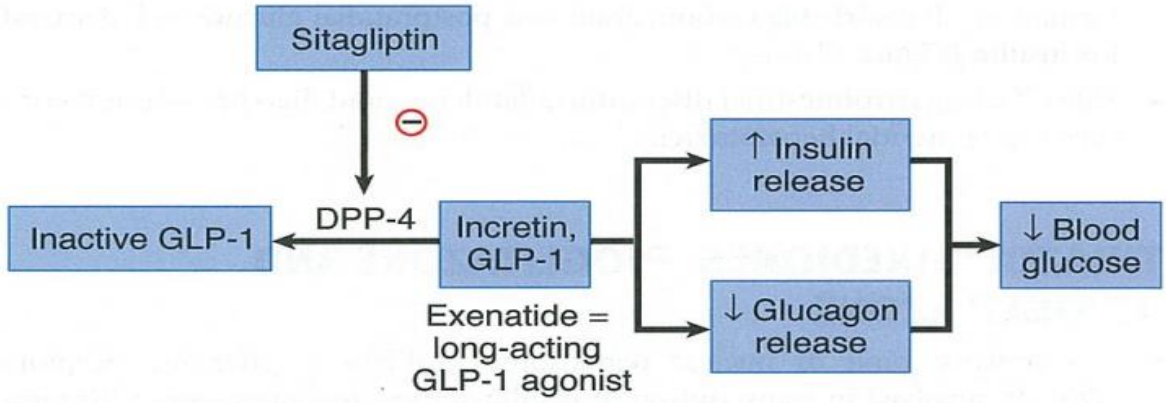
- Mechanism of action:

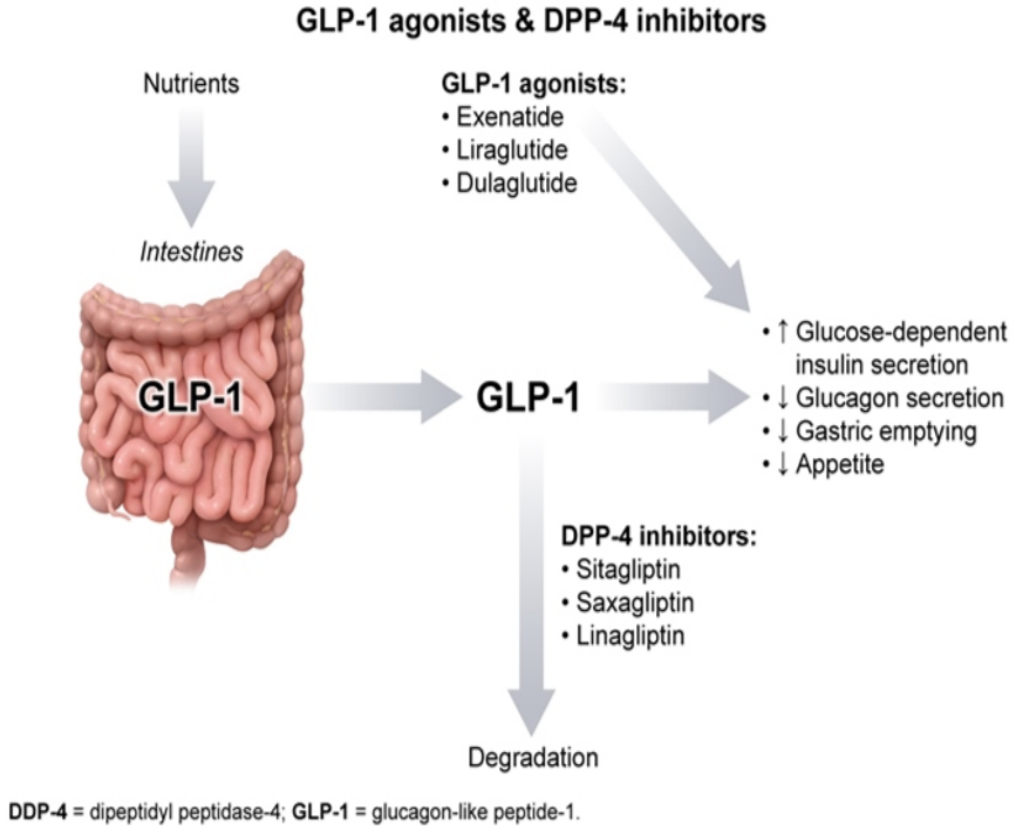
- Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).

- Saxagliptin and sitaglibtin inhibit DPP-4 leaving GLP-1 and GIP without inactivation to ↑ insulin release and ↓ glucagon secretion from alpha cells.

- Mechanism of action: type 2 DM.

- Side effects: Mild urinary or respiratory infections.





DDP-4 = dipeptidyl peptidase-4; **GLP-1** = glucagon-like peptide-1.

F. Alpha-glucosidase inhibitors:

- Drugs: Acarbose, Miglitol.

- Mechanism of action:

- Alpha-glucosidase inhibitors decrease the activity of disaccharides on the intestinal brush border (disaccharides are membrane-bound enzymes).

- Since carbohydrates are absorbed as monosaccharides, the inhibition of disaccharide breakdown by alpha-glucosidase inhibitors delays carbohydrate absorption.

- Both acarbose and miglitol are taken with meals for maximal effect.

- Clinical use: Used as monotherapy in type 2 DM or in combination with above agents.

- Side effects:

- The major side effects of alpha-glucosidase inhibitors are flatulence, gastrointestinal bloating, abdominal pain, and rash.

- These drugs should therefore not be used in patients with inflammatory bowel disease, malabsorption, intestinal obstruction, or colonic ulceration.

G. SGLT-2 inhibitors:

- Drugs: Canagliflozin, dapagliflozin, empagliflozin.

- Mechanism of action: Block reabsorption of glucose in PCT. The effectiveness of SGLT2 inhibitors is dependent on glomerular filtration of glucose, which is decreased in patients with chronic kidney disease. Serum creatinine should be measured prior to therapy.

- Clinical use: Type 2 DM.

- Side effects: Glycosuria, UTIs, vaginal yeast infections.

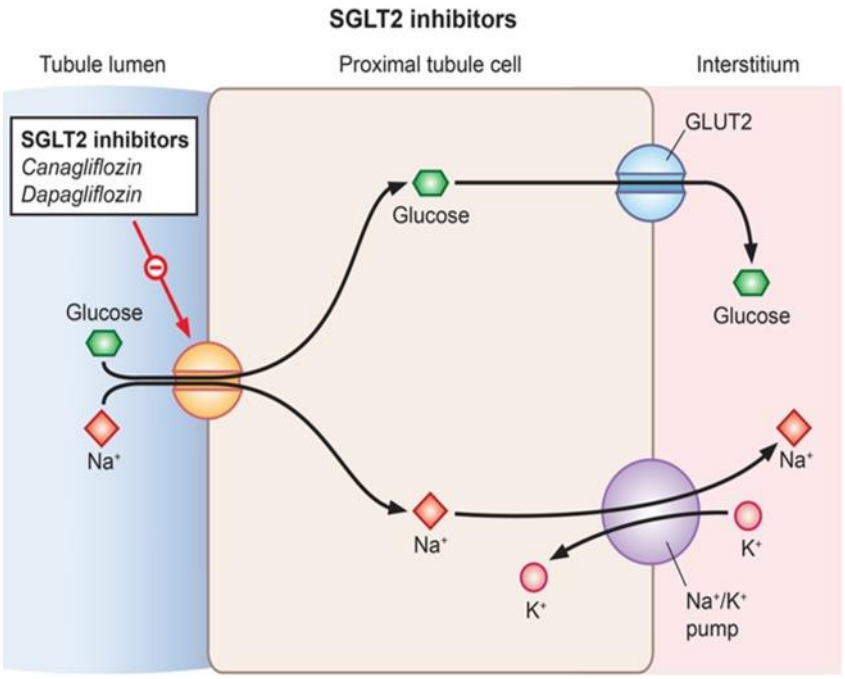
H. Amylin analogs:

- Drugs: Pramlintide.

- Mechanism of action: ↓ gastric emptying, ↓ glucagon release.

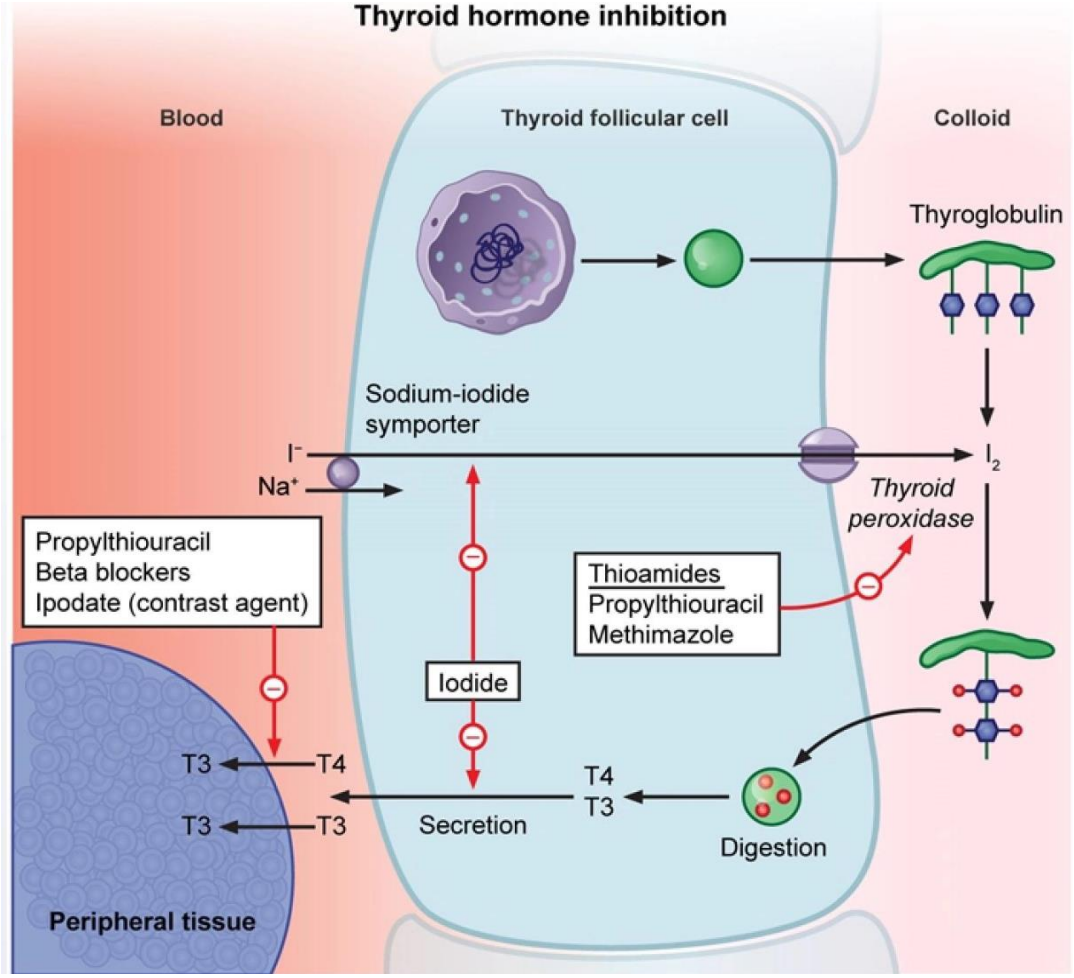
- Clinical use: Type 1 DM, type 2 DM.

- Side effects: Hypoglycemia, nausea, diarrhea.



Thionamides

- Drugs: Propylthiouracil, methimazole.



- Mechanism of action:

- The two antithyroid drugs available in the United States are propylthiouracil (PTU) and methimazole; both belong to the thionamide class.

- Thionamides (methimazole and propylthiouracil) act as antithyroid medications by decreasing the formation of thyroid hormones via inhibition of the enzyme thyroid peroxidase. Propylthiouracil also decreases the peripheral conversion of T 4 to T3.

- Thyroid peroxidase is responsible for the oxidation of inorganic iodide, formation of monoiodotyrosine and diiodotyrosine, and coupling of these iodotyrosines.

- Clinical use:

- Hyperthyroidism. They differ in that PTU also decreases the peripheral conversion of T4 to T3, has a shorter half-life, and is the drug of choice in pregnancy, as methimazole is teratogenic.

- PTU blocks Peripheral conversion, used in Pregnancy and cause hePatotoxicity.

- Side effects:

- Skin rash, aplastic anemia, hePatotoxicity (Propylthiouracil).

- Agranulocytosis is a rare but very serious complication of antithyroid drugs that results from drug-induced granulocyte destruction and consequent neutropenia. A WBC count with a differential is necessary in any patient receiving either methimazole or PTU who presents with a fever.

- Agranulocytosis describes an absolute neutrophil count of less than 500 /ml.

- Although agranulocytosis only occurs in approximately 0.5% of cases treated with antithyroid medications, it is a serious complication because neutrophils are vital in mounting an immune response to many pathogens. Patients typically present with fever and a sore throat. If thionamide-associated agranulocytosis is suspected, the drug is immediately discontinued and a white blood cell count with differential is drawn.

- Methimazole is a possible teratogen (can cause aplasia cutis).

Radioactive iodine

- There are three major treatment modalities for hyperthyroidism: antithyroid drugs, radioactive iodine, and surgical thyroidectomy.

- Most patients with hyperthyroidism in the United States are treated with ablating doses of radioactive iodine.

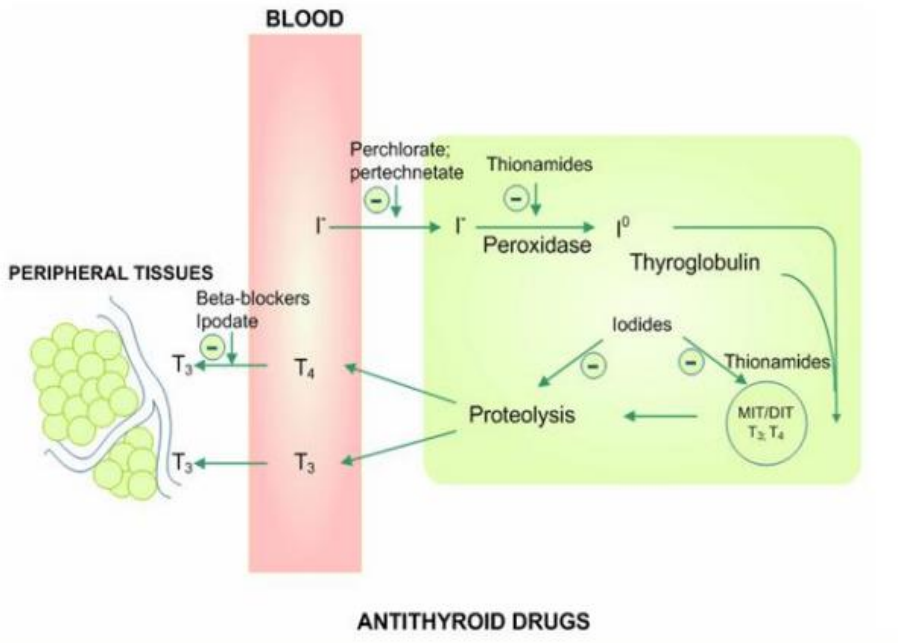
- Radioactive iodine affects only thyroid gland. Thyroid cells are the main cells in the body that can absorb iodine, so there is very little radiation exposure to the rest of the body.

- When thyroid gland absorbs radioactive iodine, it emits beta rays that destroys major part of the gland without affecting the adjacent structures.

❖ N.B:

1. The concentration of iodine levels within the thyroid gland is much higher compared to anywhere else in the body because thyroid follicles transport inorganic iodine against a concentration gradient. This iodine is needed to make the thyroid hormones, which are iodinated amino acids. This is achieved via a sodium iodide symporter (NIS) located at the basolateral membrane of the thyroid follicular cell.

- Ions such as perchlorate and pertechnetate and radioactive iodine are also all taken up by the thyroid gland using the same NIS mechanism. All forms of iodine compete for receptors on the NIS.
- If perchlorate is present, the uptake of radioactive iodine will decrease due to competitive inhibition.
- Administration of potassium iodide may also prevent thyroid absorption of radioactive iodine isotopes by competitive inhibition and is often administered following nuclear accidents to protect the thyroid and prevent development of radiation- induced thyroid carcinoma.



2. High-dose glucocorticoids such as prednisone are used to control severe Graves' ophthalmopathy. They are helpful in decreasing the severity of inflammation and decreasing extraocular volume.

- Conventional antithyroid drugs do not improve ophthalmopathy.

Levothyroxine (T4), liothyronine (T3)

- Mechanism of action: Thyroid hormone replacement.

- Clinical use: Hypothyroidism, myxedema. Used off-label as weight loss supplements.

- Side effects: Tachycardia, heat intolerance, tremors, arrhythmias.

Hypothalamic/pituitary drugs

1. ADH antagonists (conivaptan, tolvaptan): used in treatment of SIADH by blocking the action of ADH at V2-receptor.

2. Desmopressin acetate: Central (not nephrogenic) DI, sleep enuresis, von Willebrand disease and hemophilia A.

3. GH: GH deficiency, Turner syndrome.

4. Oxytocin: Stimulates labor, uterine contractions, milk let-down; controls uterine hemorrhage.

5. Somatostatin (octreotide): Acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, esophageal varices.

Demeclocycline

- Mechanism of action: ADH antagonist (member of tetracycline family).

- Clinical use: SIADH.

- Side effects: Nephrogenic DI, photosensitivity, abnormalities of bone and teeth.

Glucocorticoids

- Drugs: Beclomethasone, dexamethasone, fludrocortisone (mineralocorticoid and glucocorticoid activity), hydrocortisone, methylprednisolone, prednisone, triamcinolone.

- Mechanism of action: we talked about it in details before.

- Clinical use: Addison disease, inflammation, immunosuppression, asthma.

- Side effects:

- Iatrogenic Cushing syndrome (hypertension, weight gain, moon facies, truncal obesity, buffalo hump, thinning of skin, striae, osteoporosis, hyperglycemia, amenorrhea, immunosuppression),

- Adrenocortical atrophy, peptic ulcers (because it inhibits phospholipase A2 → decreases prostaglandins which has a protective effect on gastric mucosa), steroid diabetes, steroid psychosis.

- Adrenal insufficiency when drug stopped abruptly after chronic use.

❖ N.B:

- The acute effects of corticosteroids on the CBC include increased neutrophil count, and decreased lymphocyte, monocyte, basophil, and eosinophil counts. The increase in neutrophil count results from "demargination" of neutrophils previously attached to the vessel wall.

Fludrocortisone

- Mechanism of action: Synthetic analog of aldosterone with little glucocorticoid effects.
- Clinical use: Mineralocorticoid replacement in 1° adrenal insufficiency.
- Adverse effects: Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

Cinacalcet

- Mechanism of action: Sensitizes Ca-sensing receptor (CaSR) in parathyroid gland to circulating Ca2+ → ↓ PTH.
- Clinical use: Hypercalcemia due to 1° or 2° hyperparathyroidism.
- Side effects: Hypocalcemia.

Sevelamer

- Mechanism of action: Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.
- Clinical use: Hyperphosphatemia in CKD.
- Adverse effects: Hypophosphatemia, GI upset.