Endocrine system and nervous system are the two main control & integration system of the body. The two systems are linked through the hypothalamus.

- Hypothalamus controls secretion of many glands.
The nervous and the endocrine systems are inter-related in the hypothalamus through the:
- The hypothalamo-hypophyseal tract.
- The hypothalamo-hypophyseal–portal circulation.
Control of hormone secretion

- **1- Nervous control**: through the hypothalamus.

- **2- Feedback control**:
  - * -Ve feedback.
  - * +Ve feedback.
The Principle Endocrine Glands Are :-

• 1. Pituitary gland (anterior & posterior)
• 2. Thyroid gland.
• 3. Parathyroid gland.
• 4. Suprarenal or adrenal gland (cortex & medulla)
• 5. Islets of langerhans (in the pancreas)
• 6. Male gonads (testes) & Female gonads
• 7. Placenta.
Endocrine Glands

- Pineal gland
- Pituitary gland
- Thyroid gland
- Parathyroid glands (behind thyroid gland)
- Thymus gland
- Adrenal glands
- Pancreas: Islets of Langerhans
- Ovaries
Other Endocrine Organs :-

1. The kidney secrete:
   a) renin
   b) Erythropoietin,
   c) 1.25 dihydroxy cholecalciferol,
   d) Certain Prostaglandin.


3. Local hormones secreted at: - GIT,
   - Chemical transmitters,
   released by nerve endings.
Hormones

• Are chemical substances *synthesized & secreted* by specific cells, they are transported by the *circulation at very low concentration*. It elicits a specific response in distant *target* tissues.
Forms of Hormones in the Blood

1- Free.
   * It is not carried on a plasma protein.
   * It can bind directly to the receptors: active.
   * It is small in size, so can be filtered in urine.

2- Protein bound.
   * Carried on plasma protein.
   * It acts as a reservoir.
   * It increases the half life of the hormone.
   * It is more soluble in plasma (the lipid steroids, when bound to plasma proteins they are transformed into water soluble.
   * It is large in size, and so is not filtered in urine.
Hormone Transport & inactivation

- **Water insoluble hormones**: Steroid & thyroxin are bound to plasma proteins in blood stream. Only free hormones (not in bound form) can affect its target cells.

  **Inactivation in liver by**:
  - degradation
  - oxidation
  - reduction
  - methylation
  - Conjugation to glucoronic acid

  **Then excreted in**: urine.
Hormone Receptors & their activation:

- Hormone never act directly.
- They combine with Specific receptors.
- Receptors are large protein molecules, they are
- Present either:
  - On the surface of cells or inside the cells cytoplasm or in nucleus.
LOCATIONS

Receptors of protein, peptide hormones & catecholamines located in the membrane.

Receptors of steroid hormones located in cytoplasm.

Receptors of thyroxin located in nucleus.
Mechanism of action of hormones which are protein in nature

1- On cell membrane of target cell: hormone combines with its specific receptor.
2- This combination activates: adenyl cyclase protein enzyme which is also located in the membrane also, but a large portion of it protrudes in the cytoplasm.
3- The activated adenyl cyclase ATP converts into Cyclic AMP.
4- Cyclic AMP activates protein Kinases.
5- The activated protein catalyses phosphorelation of proteins and alter their functions. So few molecules of Activated adenyl cyclase in the cell membrane can cause man molecule of the next enzyme to be activated.
Effect of Hormones on the cells
- Membrane Permeability changes.
- Alteration of Enzyme Activity

- ATP → Cyclic AMP → Protein Kinase
- Protein Synthesis
- Gene activation
- Initiate secretion
- Causing muscle contraction or relaxation
Mechanism of action of Steroid Hormone

That secreted by: adrenal cortex, ovaries & testes.

1) The steroid hormone enters the cytoplasm of the cell where it binds with a specific receptor (protein in nature).

2) The combined hormone receptor diffuse into the nucleus.

3) Then it activates the transcription process of specific genes to form a messenger RNA.

4) The messenger RNA diffuse to the cytoplasm to promote synthesis of specific protein & enzymes within ribosomes.
Action of thyroid hormones in cell nuclei

The hormone bind directly with receptors { protein in nature } inside nucleus itself. This combination activates genetic mechanism for formation of many enzymes that promote intra–cellular metabolic activity.

Second messenger:

Calmodulin: Some hormones combine with Membrane receptors leading to opening of Ca channels. Ca enter cell combine with protein called calmodulin leading to changes inside cell as: activation Of myosin kinase that act on smooth muscle myosin † contraction.

Cyclic GMP: some h. combine with receptors activate guanyl cyclase enzyme leading to‡ formation of cyclic GMP‡ activate other enzymes inside cell.
The Pituitary Gland

Situated at the base of the skull in sella tursica. It is connected to ‘brain by’ pituitary stalk.

Physiologically it is divided :-
A) Anterior Pituitary : adeno hypophysis
B) Posterior Pituitary : neuro hypophysis.

Hormones of anterior pituitary :

Thyroid stimulating H. TSH : acts on thyroid gland.
Adreno-cortico trophic H. ACTH: acts on adrenal cortex.
Gonado trophic H. FSH &LT: act on ovaries & testes.
Prolactin H. PH : act on mammary gland.
Growth H. GH : generalized effects.
Figure 18-10  Anatomy of the Pituitary Gland (a) Relation of the pituitary gland to the hypothalamus and to the remainder of the brain. (b) Schematic enlargement of the pituitary gland and its connection to the hypothalamus.
**Figure 18-14** Vascular Link between the Hypothalamus and Anterior Pituitary

Hypothalamic capillaries, which pick up the hypophysiotropic hormones, rejoin to form the hypothalamic-hypophyseal portal system. This vascular link passes to the anterior pituitary where it branches into the anterior pituitary capillaries. The hypophysiotropic hormones leave the blood across the anterior pituitary capillaries and control the release of anterior pituitary hormones, which enter these capillaries for distribution throughout the body.

- Neurosecretory neuron
- Systemic arterial inflow
- Hypothalamic-hypophyseal portal system
- Anterior pituitary
- Systemic venous outflow

* • = Hypophysiotropic hormones
* • = Anterior pituitary hormone

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Hypothalamo-hypophyseal Tract

- Paraventricular nucleus
- Supraoptic nucleus
- Optic chiasm
- Hypothalamic-hypophysial tract
- Mamillary body
- Posterior pituitary
- Anterior pituitary
•Hormones of the Posterior Pituitary:

1) Anti diuretic hormone.

2) Oxytocin.

Hypothalamic – Hypophyseal connection

Two types of connections:

1) A vascular connection: hypothalamic – Hypophyseal portal circulation.

2) A nervous connection: hypothalamic– Hypophyseal tract.
Hypothalamic-hypophyseal connections

- There are two types of connection between the hypothalamus and pituitary:
  - 1-Vascular connection between the hypothalamus and anterior Pituitary gland in the form of hypothalamic-hypophyseal portal circulation.
  - 2-nervous connection between hypothalamus and posterior Pituitary gland in form of hypothalamic-hypophyseal tract.
- The hypothalamus receives signals from almost all sources in the nervous system, thus when a person is exposed to pain, a portion of the signals is transmitted to the hypothalamus that acts as a collecting center for internal body informations then Control secretion of pituitary glands.
Control of anterior pituitary secretion by hypothalamus

- There are neurohormones produced by the median eminence of the hypothalamus that regulate the functions of anterior pituitary.
- These neurohormones diffuse into a primary plexus of capillaries
- and are transported down in large portal vessels in the pituitary stalk to a secondary set of capillaries in the anterior pituitary gland: it is called the hypophyseal portal system.
- These neurohormones comprise both releasing & inhibitory hormones.

For each type of anterior pituitary hormone, there is a corresponding hypothalamic releasing hormone.
Note

• The anterior pituitary receives portal blood

• The posterior pituitary receives arterial blood.
Actions of Ant. Pituitary H.
Actions and Control of GH
Growth Hormone

- **Somatotrophic H. = Somatotropin**
- It is formed of multiple amino acids.
- It causes growth of all tissues.
- It promotes both size and number of cells.
- It promotes protein synthesis and deposition.
Metabolic effects of Growth Hormone

A) **Growth h. increases protein synthesis:**
- Increase transport of amino acid through cell wall.
- Increase protein synthesis by ribosome.
- Stimulates nucleus for formation of RNA.
- It decreases protein catabolism (i.e. protein sparer)

B) **Effect on fats is:** it has a lipolytic effect:
To give energy.

C) **Effect on CHO:** It has diabetogenic effect
   - Decrease glucose utilization
   - Increase glycogen deposition.
   - Decrease number of insulin receptors.
   - Decrease glucose uptake by the cells
Other Effects of Growth H.:

- Stimulates Erythropoiesis.
- Increase Ca\(^{+}\) absorption at GIT & produce phosphate balance.
- Decrease urinary excretion of Na\(^{+}\), K\(^{+}\): both needed for growth of tissues.
Regulation Of Growth H. Secretion

• **A) Hypothalamic control**: 1- G H R H & Somatostatin H. (G H I H )

• Mainly by **negative Feed - Back Control**

• **Somatostatin** produced by: hypothalamus and delta cell of islets of langerhans of pancreas

  Somatostatin inhibits secretion of: Growth Hormone, insulin glucagon.

2-IGFs: it is produced by the liver, it decrease G H secretion by direct inhibition of pituitary & ↑somatostatin.

3-**Ghrelin H**, secreted by stomach → ↑G H + ↑appetite.
B) Stimuli that increase GH secretion:

- Hypoglycemia
- Decrease level of cell protein.
- Increase conc. of fatty acids in blood.
- Deep sleep.
- Exercise, emotions, stress.
- Growth Hormone level has diurnal variation.
Effect of sleep & exercise on GH secretion
<table>
<thead>
<tr>
<th>OTHER GROWTH FACTORS AFFECTING GROWTH</th>
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<tbody>
<tr>
<td>Nerve growth factor (NGF)</td>
</tr>
<tr>
<td>Fibroblast growth factor (FGF)</td>
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<tr>
<td>Angiogenesis factor</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
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<tr>
<td>Epidermal growth factor (EGF)</td>
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<tr>
<td>Hepatocyte growth factor (HGF)</td>
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Growth hormone exerts its effects on bones through somatomedins

- Growth hormone causes the liver to form somatomedins that strongly increase all aspects of bone growth as: stimulation of osteoblasts, increased protein deposition by chondrocytic & osteogenic cells. Effects of somatomedins on growth are similar to that of insulin so it is called Insulin like growth factors (IGFs). It causes increase glucose & amino acids uptake by the cells. It also decrease lipolysis.
Prolactin

- Secreted by anterior Pituitary.
- **Function**: 
  - Stimulation. Of milk secretion by mammary gland.
  - Stimulation Of synthesis. Of fat & lactose mammary gland.
  - Inhibit the action Of gonadoropin ‡ inhibition of ovulation amenorrhea & lactation.
  - In males : unknown functions:--
  - If excess Prolactin ‡ impotence.
- **Regulation of Secretion**: Prolactin Releasing H. From hypothalamus and Prolactin inhibitory H.(dopamine)
1. Normally Prolactin inhibitory H. Predominates or overbalances the effect of PRH.
2. Prolactin Facilitated PIH from hypothalamus. = negative feed-back mechanism to inhibit its own secret.
3. Increase secret. Of Prolactin in:
   - exercise
   - stress
   - suckling
   - sleep.

- Tumour of cells: Excessive secretion:
   - Galactorrhea.
   - Amenorrhea.
   - Impotence in males.
POSTERIOR PITUITARY

• The posterior lobe of the pituitary secretes two peptide hormones, antidiuretic hormone (ADH) and oxytocin.
• The posterior pituitary hormones are initially synthesized in the cell bodies of the supraoptic & paraventricular nuclei of the hypothalamus, & then transported in combination with “carrier” proteins called neurophysins down to the nerve ending in the posterior pituitary. Stimulation of the hypothamic nuclei initiate action potentials in their neurones, transmitted downward along the fibers from the supraoptic or paraventricular nuclei on reaching the nerve ending, cause release of hormone by the usual secretory mechanism of exocytosis and is absorbed into adjacent capillaries from which they reach the general circulation. This process is known as neurosecretion (hormone secreted into the circulation by nerve cells.)
Functions Of Antidiuretic Hormone

(Vasopressin, ADH):

A) On the kidneys:

ADH increases the reabsorption of water by the kidney. These reduce the excretion of water from the body. The urine becomes concentrated and its volume is reduced (antidiuretic effect). It acts on the distal portions of nephrones (in the collecting duct and collecting tubules), increasing their permeability to water. ADH causes opening of many protein water channels.
B) On the blood vessels

• ADH is a potent vasoconstrictor. It acts on vascular smooth muscle. ADH in moderate concentration has a very potent effect of constricting the arterioles so, increasing the arterial pressure.
Control Of ADH

1. **Osmotic stimuli** :-

   The release of ADH is controlled by a feedback mechanism that act to maintain the plasma osmolality close to 290 mosm/L. When the osmolarity of the plasma is increased (as in dehydration or high salt level) **the rate of discharge of vasopressin** from the posterior pituitary increases leading to water retention by its action on the kidney.

   The change in osmolality is sensed by osmoreceptor cells present in the hypothalamus which transmit signals to cells secreting ADH.
2. Volume depletion

- Decrease in circulatory volume and mean arterial pressure will increase ADH. They are sensed by baroreceptors in left atrium, pulmonary veins, carotid sinus and aortic arch. Impulses are transmitted to the central nervous system through vagal and glossopharyngeal nerves.

- In hemorrhage, ADH is secreted in large amount. It promotes water conservation to reestablish circulatory volume and causes vasoconstriction to maintain blood pressure.
3. Angiotensin II:

Acting on the brain to increase vasopressin secretion.
4. Drugs

Some drugs such as nicotine, morphine, tranquilizer and some anesthetics lead to increase ADH secretion. Alcohol decreases secretion of ADH.
5. Stress:

Lead to increase ADH as severe pain, trauma, exercise and surgical operation.

Diabetes insipidus is a disease caused by ADH deficiency.
OXYTOCIN HORMONE

It is polypeptide hormone secreted by hypothalamus and stored in posterior pituitary. It is acting on the target cells by increasing the intracellular Ca++ content.
Function Of Oxytocin

1. **Milk Ejection**: It causes contraction of special smooth muscle like cells known as myoepithelial cells that line the alveoli and ducts of the mammary gland thus squeezing milk outwards through the nipple.

2. **Contraction of smooth muscle of uterus**: It causes contraction of the smooth muscle fibers of both pregnant or non-pregnant uterus. It is used clinically for the induction of labor.
Control Of Oxytocin Secretion

1. The sucking of the breast stimulates touch receptors in the nipple, sensory nerves transmit impulse upward to the hypothalamus to cause release of oxytocin.

2. The secretion of oxytocin is increased by genital stimulation.

Figure 18-15 Comparison of the Hypothalamic Relationship to the Anterior Pituitary and Posterior Pituitary

Hypothalamic releasing and inhibiting hormones pass through the hypothalamic-hypophyseal portal system to the anterior pituitary. Anterior pituitary hormones are secreted into the systemic circulation. Vasopressin and oxytocin are stored in the posterior pituitary and released as needed.
Figure 18-12 Functions of the Anterior Pituitary Hormones Five different endocrine cell types produce the six anterior pituitary hormones—TSH, ACTH, growth hormone, LH and FSH (produced by the same cell type), and prolactin—which exert a wide range of effects throughout the body.
Figure 18-16  Negative Feedback in Hypothalamic–Anterior Pituitary Control Systems

Hypothalamus

Hormone 1

Anterior pituitary

Hormone 2

Target endocrine gland

Hormone 3

Target tissue

Short-loop negative feedback

Long-loop negative feedback

Principles of Endocrinology: The Central Endocrine Glands
Fig. 9: Panhypopituitarism.
Thyroid Gland
• Thyroid Gland Secretes:

• 1. Thyroxine (T4)
• 2. Tri-io-do thyronine (T3)
• 3. Calcitonin: Plasma Calcium Lowering Hormone.
Steps Of Formation Of Thyroid Hormone

1. Iodide trapping (pump): From bld. To gland needs AT pase = active process.
2. Oxidation of iodide to iodine: by peroxidase enzyme.
3. Thyroglobulin synthesis: by thyroid cells, it is glyco protein from tyrosine amino acid.
4. Exocytosis: Glyco protein pass to cavity.
5. Iodination: Oxidised iodine bound to glyco protein Mono & Di iodo throsine = Inactive.
6. Coupling: 2 di Tetra iodo tyrosin thyroxine T4 or 1 mono +1 di – tri-iodo tyrosine T3.
7. Storagre: Stored several months: bound with thyroglobulin.
Thyroid cells exert 3 functions:

1- They actively collect, transport & concentrate iodide.

2- They synthesize the colloid and secrete in it both thyroglobulin and iodine.

3- They ingest the colloid and thyroglobulin, separate the hormones and then secrete them into the blood stream.
Secretion Of Thyroid Hormone

1. Uptake of colloid gobules, by follicular Cells by endocytosis, globules fuse with lysosome.
2. Hydrolysed by protease enzyme.
3. Liberation of Mono, di, tetra & Triiodothyronine.

The liberated T3, T4 diffuse out of the follicle, to surrounding capillaries. The mono & di-iodo tyrosine are splitted to iodine & tyrosine, recycled again.
Transport of Thyroid Hormones

bound to plasma protein, then released at tissue cells as free hormone.

The protein bound fraction act as a store, the free form on entering the cell, will bind again with intra-cellular protein & used slowly over days or weeks. (in plasma there is balance between bound & free forms)
Functions of the Thyroid Hormones

- They have a wide spread effect because it stimulates oxygen consumption (calorigenic action)

A) Metabolic functions:

1. On metabolic rate:

   They increase the metabolic rate and oxygen consumption of most of tissues of the body. The basal metabolic rate can increase to as much as 60 to 100% above normal when large quantities of the hormones are secreted.
2. They increase:

   Synthesis of many intracellular enzymes and increase its activity as Na\(^+\) K\(^+\) –ATPase which increase rate of transport of both sodium and potassium through the cell membrane. This processes utilized energy and increase heat production i.e. increase metabolic rate.

3. On Mitochondria:

   They increase the size, number & activity of mitochondria & this in turn increase the rate of formation of ATP to energise cellular function.
4. On Protein synthesis

- Small doses of thyroid hormone increase the rate of formation of proteins by the ribosomes.
- It increase RNA synthesis by the genes, which leads to a generalized increase in synthesis of many types of protein within the cells.
- Large doses of thyroid hormone lead to excess catabolism of muscle protein.
5. On carbohydrate metabolism

A. It **increase the rate of absorption of carbohydrate** from the gastrointestinal tract, thus the **blood glucose level increase** after carbohydrate meals. However, it normally falls again rapidly because the **rate of glucose utilization is also increased**. The effects of thyroid H. on carbohydrate result from **increase in the activity of enzymes**.

B. They **enhance gluconeogenesis & glycolysis**, 

C. They **increase cell metabolic enzymes acting on CHO**.
6. On fat metabolism

- All aspects of fat metabolism are increased under the effect of thyroid hormone including synthesis, mobilization and utilisation.
- Thyroid hormone accelerates the oxidation of fatty acids by the cells. Thus lipolytic effect more than lipogenic effect.
- They lower the level of, cholesterol, phospholipid & tryglycerides in the blood.
7. Thyroid Hormone are necessary for the hepatic conversion of carotene to Vit. A, so if thyroid hormones are decreased carotenaemia result causing yellow colouration of the skin.
B) On growth and development

1. On skeletal growth and development

Thyroxine is essential for normal growth of soft tissue and skeleton due to: Its stimulation to protein synthesis by ribosomes.

Thyroid hormones are required for production & action of growth hormones and insulin like growth factors.
2. On nervous system

- Thyroid hormone promoted **growth** and **development** of the brain during fetal life & for the first few years of life. The thyroid hormones are essential for normal **myelination** & development of the nervous system in infant. If there is a deficiency in thyroid hormone growth & maturation of the brain is retarded, myelination is defective, the reflex time is prolonged.
In adult, thyroid hormone causes an increased response of the brain to catecholamines & increases activation of reticular activating system. An excess of thyroid hormone leads to restlessness & hyper excitability.
On Sleep

- Because of the exhausting effect of thyroid hormones on the musculature and on the CNS, the hyperthyroid subject often has a feeling of constant Tiredness, but because of the excitable effect of thyroid hormone on the reticular activating system the patient cannot sleep.
C.) The cardiovascular system

1. Thyroid hormone increase the number & affinity of beta-1, adrenergic receptors in the heart, also it increase its sensitivity to catecholamine. (catecholamine increase all properties of the heart).
2. Increased metabolism in the tissues causes more rapid utilization of oxygen & causes greater metabolic end products to be released from the tissues. These effects cause vasodilatation, thus increasing the rate of blood flow in the skin for heat elimination.
3. Increase blood flow leads to increase venous return leading to increase in cardiac output so the systolic blood pressure rises, but vasodilatation causes decrease diastolic blood pressure thus, pulse pressure is increased.
D.) On Respiration

- Thyroid hormone increase respiration due to increase rate of metabolism which increase the utilization of oxygen & the formation of carbon dioxide. Also it helps dissociation of O2 from haemoglobin by increasing the amount of 2,3 diphosphoglyceride (DPG) in the RBCs.
E.) On The G.I.T.

- They increase the rate of secretion of the digestive juice and motility. This leads to increase appetite and food intake.
F.) On Sexual functions

- For normal sexual function to act, thyroid hormone secretion needs to be approximately normal. Thyroid Hs. are essential for normal menstrual cycles and fertility. They increase milk secretion in lactating women.
Regulation of Thyroid Hormones secretion

1) Hypothalamic regulation:

Stimulation of the hypothalamus leads to release of thyrotropin releasing hormone (TRH) which is transported to the anterior pituitary, & directly affects it to increase its output of thyroid stimulating hormone.

Hypothalamus can also inhibits the secretion of TSH and growth hormone by secreting somatostation.
2) Pituitary regulation

- Anterior pituitary secretes Thyroid Stimulating Hormone (TSH) which has important role on thyroid gland. It increase the secretion of thyroxin. **TSH** is a glycoprotein. Its secretion **increases by cold, TRH and decreases by heat, stress, somatostatin and excess thyroid hormones.**

- TSH activates cAMP (second messenger) which activates phosphorylation inside thyroid cells that increases its secretion.
Effects of TSH on the thyroid gland

1. Increase **size** and **secretory** activity of the thyroid cells.

2. Increase **number** of thyroid cells plus change from cuboidal to **columnar** cells by prolonged stimulation.

3. Increase **blood supply** to the thyroid gland.

4. Increase activity of the iodide pump which **increase** the rate of iodide trapping in the glandular cell.
5. Increase **iodination of tyrosine** and increased coupling to from the thyroid hormones.

6. Increase **proteolysis of the thyroglobulin** that has already been stored in the follicle, with resultant release of the thyroid hormones into the circulating blood.
3) Feed back regulation of thyroid secretion

- Increased thyroid hormones decrease the secretion of TSH by the anterior pituitary mainly by a direct negative feedback effect on the anterior pituitary and secondarily by weaker effects on the hypothalamus. This mechanism maintains a constant hormonal blood level.
4) Blood iodine level

• As adequate dietary iodine intake is essential for normal thyroid function, when the intake of iodine falls, the synthesis and secretion of thyroid hormone are decreased and as a result the secretion of TSH increases leading to thyroid enlargement (goiter).
5) Prolonged emotional reactions can affect the output of TRH & TSH, therefore, indirectly affect the secretion of thyroid hormone.

Excitement and anxiety (conditions that greatly stimulate the sympathetic nervous system) cause acute decrease in secretion of TSH, perhaps because these states increase the metabolic rate and the body heat.
Effect of stress on TSH

- Stress leads to release of catecolamines that increases metabolic activities and heat production by body cells, these effects leads to suppression of hypothalamus & inturn suppress the TSH of anterior pituitary, so the thyroid gland is suppressed.
6) Effect of cold on TSH & TRH secretion

- Exposure of the animal for several weeks to very severe cold increase the output of thyroid hormone which increase the (B.M.R.)
Antithyroid Substances

- Drugs that suppresses thyroid secretion are thiocyanate, prophyl thiouracil, and high concentration of inorganic iodides.

1. **Thiocyanate ions**: cause competitive of iodide transport into the cell, it decrease iodide trapping & ↓ hormone formation.

2. **Propylthiouracil**: It blocks peroxidase enzyme thus inhibits formation of thyroid hormone from iodides and tyrosine. It blocks iodination of tyrosine.
These two substances cause deficiency in thyroid hormone which leads to increase secretion of TSH by the anterior pituitary gland. Excess TSH causes:

A) Overgrowth of the thyroid gland.
B) Formation of thyroglobulin.

But since there is no iodine present to combine with thyroglobulin, the gland fills with colloid and increases in size (= goiter)
3. Excess iodides

- High iodides concentration inhibit the thyroid stimulating effect of TSH, which lead to decrease all phase of thyroid activity and decrease the size and the blood supply of the thyroid gland. Iodides are frequency administered to patients for two or three weeks before surgical removal of the thyroid gland to decrease its blood supply.
Fig. 16: Graves disease.
Fig. 17: Myxedema.
Manifestations of hyperthyroidism

Toxic goiter or thyrotoxicosis = Graves disease is manifested by:

1. Diffusely enlarged gland with increased number of active cells & increased rate of secretion.
2. Increased metabolic rate 60-100% above normal.
3. Intolerance to heat, ↑heat production.
4. Increased sweating, skin is warm.
5. Tachycardia, palpitation & ↑cardiac output.
6. Irritability, anxiety & nervousness.
8. Weight loss, ↑appetite.
10. Exophthalmos due to retrobulbar tissue swelling.
Manifestations of hypothyroidism

• 1-decrease BMR & decrease tolerance to cold.
• 2-dry, cold, yellowish skin, brittle nails, coarse sparse hair,
• Edematous swelling allover the body, face & bagging under the eyes (myxedema). 3- husky slow voice.
• 4-muscle weakness, cramps & stiffness.
• 5-decreased cardiac properties, blood flow.
• 6-constipation, loss of appetite & increased body wt.
• 7-depressed mental functions, thiking, memory & increased sleeping hours. 8-anemia, arteriosclerosis, ↑bld.
• lipids
Adrenal gland

DR AMAL
The adrenal cortex

• It is the outer part of the adrenal gland and forms about 80% of the gland.
• It secretes steroid hormones. It is divided into three distinct zones:
  • Zona Glomerulosa, the outermost layer, secretes mineralocorticoids, aldosterone, desoxycorticosterone and corticosterone. They maintain Na\(^+\) and K\(^+\) balance and ECF volume.
  • Zona Fasciculata: is the middle widest zone and secretes glucocorticoids: cortisol and corticosterone that have widespread effects on carbohydrate and protein metabolism.
  • Zona Reticularis: is the innermost layer and secretes mainly sex hormones, dehydroepiandrosterone (DHEA), androstenedione (androgens) and small amounts of estrogen.
Actions of cortisole

On carbohydrate metabolism:

• 1- Stimulation of gluconeogenesis by the liver from amino acids. It decreases glucose utilization (anti insulin action).
• 2- Increased gluconeogenesis leads to the build up of sufficient glycogen. (all lead to hyperglycemia & make diabetes worse).

On protein metabolism:

• 1- Cortisol reduces protein synthesis & increases protein catabolism in all body cells except liver cells which ↑ synthesis.
• 2- It increases plasma amino acid level & plasma proteins.
• 3- It inhibits amino acid transport to extrahepatic cells and stimulates amino acid transport into liver cells.

On fat metabolism:

• 1- Cortisol has a lipolytic action. It enhances lipolytic effect of catecholamines. It increases FA mobilization from adipose tissue.
• 2- It increases FFA in plasma.
Actions of cortisole

**Effect on vascular system:**

- Cortisole is required for the maintenance of normal arterial blood pressure in response to the vasoconstrictor effect of catecholamines (permissive action). It decreases endothelial permeability of blood vessels.

- **Effects of cortisol on bone & calcium metabolism:**
  
  Long use of cortisol lowers plasma calcium by decreasing its absorption from the intestine, it increases its renal excretion. It decreases bone formation & increases resorption causing osteoporosis.
Actions of cortisole

Effect on Kidney:
• Cortisole is essential for rapid excretion of excess water load, as it inhibits ADH secretion and action.

Functions of cortisole in stress:
• Cortisole is required for catecholamines to exert their pressor and lipolytic actions.
• It increases FFA that are important as emergency energy source, and raises blood glucose level together with catecholamines to protect against hypoglycemia.
Effect of cortisol on skeletal muscles

• It is essential for maintenance of muscle activity, great excess of cortisol the muscles become very weak due to protein catabolism

Effect of cortisol on nervous system:
Changes in cortisol levels affect certain sensations and higher functions as concentration, memory & intellectual performance (these effects may be through modulation of neurotransmitters in the reticular activating system & ↑sensitivity of β-receptors.)
Actions of cortisole

Effect of cortisole on blood cells and immunity:
• Cortisole decreases the number of circulating eosinphils and the number of lymphocytes (T lymphocytes) mainly. It increase production of RBCs.
• It increases number of neutrophils (but inhibits their function).
• It inhibits production of interleukin 2 (IL-2) by lymphocytes.
• It antagonizes the synthesis, secretion and actions of interleukin 1.
• High concentrations of glucocorticoids interfere with antibody production from B-lymphocytes. Long use causes atrophy of lymphoid tissue.

N.B.
• * Large doses of glucocorticoids can lead to fulminating infection.
• * On the other hand, this ability of glucocorticoids to suppress immunity makes them useful in prevention of immunological rejection of transplanted organs.

Anti – Inflammatory Effects of Cortisole:
• Cortisol stabilizes the membranes of lysosomes so prevents the release of their proteolytic enzymes.
• It diminishes vasodilation. It decreases release of histamine & prostaglandins.
• It decreases migration of white blood cells into the inflamed area.
• It decreases capillary permeability & inhibits fibrosis so prevents adhesions.
Regulation of cortisol secretion

1- Hypothalamic regulation: it produces corticotropin releasing factor (CRF).

2- Pituitary regulation: it produces ACTH in response to CRF. ACTH causes formation of adrenocortical hormones.

3- Negative feedback: cortisol has direct –ve feedback effect on hypothalamus to decrease CRF & on pituitary to decrease secretion of ACTH.

4- Effect of physiological stress on ACTH secretion: Physical & mental stress can lead to increase cortisol secretion within minutes via increase ACTH.
Circadian rhythm of glucocorticoid secretion

Cortisol is high in the early morning but low in the late evening, this due to a 24 hour cyclic alteration in signals from the hypothalamus. When ACTH is secreted from ant. pituitary, other hormones are also secreted: melanocyte-stimulating h., lipotropin & endorphin. (Their normal levels are not significant, but if secretion is high, MSH causes melanocytes to form melanin pigments, ..ACTH has also melanocyte stimulating effect.
Relative potency of cortisole and some synthetic steroids

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<thead>
<tr>
<th>COMPOUND</th>
<th>GLUCOCORTICOID EFFECT</th>
<th>MINERALOCORTICOID EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3–4</td>
<td>0.5</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>12</td>
<td>125</td>
</tr>
</tbody>
</table>
Pattern of cortisole level during the day

![Graph showing the pattern of cortisol level during the day. The graph indicates a rise in cortisol concentration from mid-morning to early afternoon, followed by a decline into the evening.](image-url)
Pattern of cortisole and ACTH level during the day
Effect of stress on cortisole secretion

1. Gluconeogenesis
2. Protein mobilization
3. Fat mobilization
4. Stabilizes lysosomes
Control of cortisole secretion
Chronotropic variations in the level of some hormones
# Manifestations of hypercortisism

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Metabolic results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>Centripetal fat distribution, increased appetite</td>
</tr>
<tr>
<td>Protein wasting</td>
<td>Thin skin, abdominal striae</td>
</tr>
<tr>
<td></td>
<td>Capillary fragility (ecchymoses)</td>
</tr>
<tr>
<td></td>
<td>Muscle wasting, muscle weakness</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Poor wound healing</td>
</tr>
<tr>
<td></td>
<td>Growth retardation</td>
</tr>
<tr>
<td>Carbohydrate intolerance</td>
<td>Impaired glucose use, hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Mineralocorticoid effects of cortisol</td>
<td>Hypertension, hypokalemia</td>
</tr>
<tr>
<td>Immunologic suppression</td>
<td>Increased susceptibility to infections</td>
</tr>
<tr>
<td>Other manifestations</td>
<td>Hirsutism, oligomenorrhea, polycythemia, personality changes</td>
</tr>
</tbody>
</table>
Cushing’s disease

A patient with Cushing’s disease before and after subtotal adrenalectomy
Actions of aldosterone

– Aldosterone increases the reabsorption of Na$^+$ from urine, sweat, saliva, gastric juice and colon.
– It stimulates secretion of K$^+$ by the kidney.
– Because H$_2$O is passively reabsorbed with Na$^+$, there is no increase in plasma Na$^+$ concentration. so ECFV expands in an isotonic manner.

Aldosterone also causes H$^+$ to be secreted into renal tubules.
Control of aldosterone level

- Renin-angiotensin system
- Atrial natriuretic peptide
- Plasma k+ level
- Role of ACTH
- Plasma Na+ level
Effect of renin-angiotensin system on aldosterone secretion

Angiotensin II is responsible for increased synthesis & release of aldosterone from cells of zona glomerulosa. The level of renin release from juxta glomerular apparatus affects the level of aldosterone.

- Effect of potassium ion conc. on aldosterone secretion: increase in K+ conc. causes direct stim. of zona glomerulosa to increase aldosterone secretion with excessive excretion of potassium in urine, so its conc. returns to normal level.
Effect of decreased Na+ on aldosterone secretion

1- Lack of Na+ enhances aldosterone secretion from zona glomerulosa.

2-Lack of Na+ causes retention of K+ which stimulates aldosterone secretion.

3-Lack of Na+ leads to decreased ECF volume which causes ↓ CO& ↓ renal blood flow → formation of angiotensinII which stimulates aldosterone secretion.

4-Lack of Na+ stimulates the anterior pituitary to produce what is called the unidentified pituitary factor that stimulate the suprarenal to produce aldosterone.

ACTH: has a permissive role on aldosterone secretion and all the above regulatory factors.
Actions and control of aldosterone

- Blood volume
- Renal factors
  - Renin
  - Angiotensin II
- Hyperkalemia
- Cardiac factors
  - Atrial natriuretic peptide

Stimulation
- Adrenal gland
  - Medulla
  - Cortex
  - Circulating blood
- Altersonone

Inhibition

Glomerulus

- Kidney tubule

- Aldosterone retains sodium and water
- Enhances excretion of potassium and hydrogen ion
- Aldosterone tends to increase blood volume
- Aldosterone plays supportive role in raising blood pressure

Sweat gland

Salivary gland

Intestine

Extracellular fluid and sodium increased

$\text{Na}^+$, $\text{K}^+$, $\text{H}_2\text{O}$
Addison’s disease

**Manifestations of Primary Adrenocortical Insufficiency**

<table>
<thead>
<tr>
<th>Cortisol Deficiency</th>
<th>Aldosterone Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Inability to conserve sodium</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Decreased extracellular fluid volume</td>
</tr>
<tr>
<td>Nausea</td>
<td>Decreased blood volume</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Decreased cardiac output</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Increased renin production</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Mental</td>
<td>Shock</td>
</tr>
<tr>
<td>Confusion</td>
<td>Impaired renal secretion of potassium and</td>
</tr>
<tr>
<td>Psychosis</td>
<td>hydrogen</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Impaired gluconeogenesis</td>
<td></td>
</tr>
<tr>
<td>Increased insulin sensitivity</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular/renal</td>
<td></td>
</tr>
<tr>
<td>Impaired free water clearance</td>
<td></td>
</tr>
<tr>
<td>Impaired pressor response to catecholamines</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td></td>
</tr>
<tr>
<td>Increased adrenocorticotropic hormone</td>
<td></td>
</tr>
<tr>
<td>secretion</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td></td>
</tr>
</tbody>
</table>
Action Of Catecholamines:

Catecholamines are secreted mainly in emergency conditions to support the actions of sympathetic nervous system. They enable the body to perform extra work. These actions are produced through exerting the following effects:

1. Catecholamines increase the metabolic rate and O2 consumption leading to increased heat production.
2. They stimulate glycogenolysis in the liver, so increase the blood glucose level.
3. Catecholamines mobilize free fatty acids from adipose tissue, so their plasma level increased.
4. Catecholamines directly increase both heart rate and its force of contraction. Norepinephrine produces vasoconstriction in most organs which increases both systolic and diastolic blood pressures.
5. They cause splenic contraction which adds concentrated blood to the general circulation.

6. They cause vasoconstriction to the renal blood vessels which may decrease urine volume.

7. They increase the rate and depth of respiration by direct excitation of the respiratory centre and by increased metabolic rate.

8. Catecholamines potentiate skeletal muscle contraction and delay the onset of its fatigue. They also cause vasodilatation of skeletal muscle blood vessels.

9. Catecholamines excite the nervous system and increase the mental activity and alertness.

10. They increase the visual fields.
Control Of Secretion:

Catecholamines secretion is low in basal states but is markedly increased during emergencies as a part of the diffuse sympathetic discharge. There is a special centre in the medulla oblongata, connected to the greater splanchnic nerve which supplies the gland. When such centre is stimulated, the neural discharge to the adrenal medulla is increased leading to an increase in catecholamine secretion and vice versa.

They are essential for preparing the body to (with-stand) emergencies as in muscular exercise, hemorrhage, hypoglycemia and exposure to cold.
Best of luck
• Calcium Homeostasis
Three hormones are concerned with regulation of calcium metabolism:

1- **1,25-dihydrocholecalcifiro** (a steroid hormone formed from Vitamin D: it is important in calcium absorption at the intestine.

2- **Parathyroid hormone** (secreted from parathyroid gland): it is Calcium ions elevating hormone in extracellular fluid & phosphate lowering effect by its effect on bones, kidney & GIT.

3- **Calcitonin** (secreted from perifollicular cells of thyroid gland): It reduces blood calcium ion.

All the three hormones operate to maintain the constancy of calcium level in the body fluids.

Glucocorticoids, growth hormone, estrogen and various other hormones also affect calcium metabolism.
Action of parathyroid hormone
(Ca elevating H)

Effect on bone:
1- a very rapid phase: it activates (within minutes) the existing bone osteoclasts to promote calcium & phosphate absorption.
2- a slower phase (within days or weeks) by developing proliferation of osteoclasts with increased osteoclastic resorption of bone.

On the kidney: diminished absorption with loss of phosphate in urine, while increasing Ca absorption.

On intestine, it increases absorption of Ca & phosphate.
Functions of calcitonin (Ca lowering H)
Calcitonin has marked effects in children more than adults, because bone remodeling occurs rapidly in children with ↑ absorption & deposition of Ca.

It has a weaker effect than parathormone, but it acts rapidly in short term regulation of Ca level.

1-it increases calcium excretion in urine & decreases blood calcium ion concentration.

2-it inhibits osteoclasts function, so it reduce bone resorption, thus decreasing serum Ca & phosphate.

3-it decreases formation of new osteoclasts.
• Absorption of calcium and phosphate:
  Calcium is actively absorbed in the upper small intestine. It is facilitated by 1,25 dihydroxycholecalciferol. Calcium absorption is adjusted to body needs, absorption is increased in cases of calcium deficiency & decreased in presence of calcium excess. Calcium absorption is facilitated by lactose and proteins, it is inhibited by phosphate and oxalate because these form insoluble salts with calcium in the intestine.
  Phosphate is absorbed in intestine, when excess calcium is in the diet, an insoluble calcium phosphate is formed that fail to be absorbed.
Functions of calcium in the body

• 1- it enters in the structure of bones, teeth, connective tissue elements and cellular cement substances.

  2- ionized calcium is necessary for blood coagulation, muscle contraction & nerve function.

The function of phosphate: it enters in formation of ATP & cyclic AMP.
Concentration of calcium in plasma

The concentration of calcium in plasma is 9.4mg/dL (range: 9-10mg/dL)

Calcium in plasma is present in three different forms:

1- 40% of calcium is combined with plasma proteins. It is none diffusible through capillary membrane.

2- 10% of calcium is combined with other substances as anions, it is diffusible and not ionized.

3- 50% is diffusible & ionized: it is important for the functions of heart, nervous system & bone formation.
Role of vitamin D in calcium and phosphate absorption

The active form of vitamin D: 1,25-dihydroxycholecalciferol has a potent effect on increasing calcium absorption from the intestine and also on bone deposition.

Vitamin D itself is not the active substance, it is converted in the liver and kidney to the final active product 1,25-dihydroxy cholecalciferol.
1. Vitamin D3 (cholecalciferol) is formed in the skin as a result of irradiation of 7-dehydrocholesterol by ultraviolet rays. Exposure to the sun prevents Vit. D deficiency.

2. Cholecalciferol is converted to 25–hydroxy–cholecalciferol in the liver which has a feedback inhibitory effect on the conversion reactions. Feedback mechanism regulates the concentration of 25-hydroxycholecalciferol in the plasma and conserves the vitamin D for future use because once converted, it persists in the body for short time but vitamin D can be stored in the liver for several months.
3. In the kidney 25-hydroxycholecalciferol is converted to 1,25-dehydoxycholecalciferol which is the active form of vitamin D, this conversion requires parathyroid hormone. Parathyroid hormone exerts a potent effect in determining the functional effects of vitamin D in the body.

4. Dihydroxy cholecalciferol (calcitriol) causes formation of calcium binding protein in the intestinal epithelial cells. The rate of calcium absorption is proportional to the quantity of calcium binding protein.
5. When the plasma calcium concentration is increased, it inhibits parathyroid hormone secretion which lead to decrease formation of 1,25-dihydroxycholecalciferol. Lack of this in turn decreases the absorption of calcium from the intestine, from the renal tubules,

Thus causing ion concentration to fall back toward its normal level. 1,25-dihydroxy – cholecalciferol itself functions as a “hormone” to promote intestinal absorption of calcium.

The concentration of calcium in the plasma is 9.4 mg/dl, varying between 9.0 & 10.0 mg/dl
Activation of vitamin D₃ to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.
Bone calcium and its relationships to Extracellular calcium& phosphate

The tough organic matrix of bone is strengthened by deposits of calcium salts (calcium& phosphate crystals). About 0.5-1% is in form of readily mobilizable amorphous Calcium phosphate, it is exchangeable calcium, it is always in equilibrium with calcium ions in extracellular fluids, it provides a rapid buffering mechanisms that keeps Ca++ ion concentration of extracellular fluids (prevent excessive rising or falling). The mitochondria of liver& intestine contain a reasonable amount of exchangeable calcium that provide an additional buffersystem that maintains constancy of extracellular Ca++ concentration.