# Endocrinology

**Endocrinology**

Endo = Internal and crinos = Secretion.

Endocrinology is a branch of medical science which deals with the study of different endocrine glands of the body.

**Endocrine gland** : Means ductless gland which directly poured their secretion into the blood.

*Endocrine glands are* :

1. Hypothalamus (neuroendocrine gland)
2. Pituitary ( master gland) gland
   a. Anterior pituitary gland
   b. Posterior pituitary gland
3. Thyroid gland.
4. Parathyroid glands
5. Adrenal glands
   a. Adrenal cortex
   b. Adrenal medulla
6. Pancrease (Endocrine portion Islets of Langerhans)
7. Testis (in case of male)
8. Ovaries (in case of female)
9. Placenta (during pregnancy).

*(Ref. Guyton & Hall-11th ed; Page 906)*

**Coordination of the body functions by chemical messengers**

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of communication systems, including :

1. *Neural*, in which chemicals (neurotransmitters) are released at synaptic junctions and act locally to control cell function
2. *Endocrine*, in which glands or specialized cells release into the circulating blood chemicals (hormones) that infuence the function of cells at another location in the body
3. *Neuroendocrine*, in which neurons secrete substances : (neurohormones) that reach the circulating blood and influence the function of cells at another location in the body
4. *Paracrine*, in which cells secrete substances that diffuse in to the extracellular fluid and affect neighboring cells
5. *Autocine*, in which a cell secretes substances that affect the function of the same cell by binding to the cell surface receptors.

***For example***, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including *antidiuretic hormone (ADH)*, *oxytocin*, and *hypophysiotropic hormones*, that control the secretion of anterior pituitary hormones.

The endocrine hormones are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many reactions. Some endocrine hormones affect most cells of the body; for example, *growth hormone* (from the anterior pituitary gland) causes growth in most parts of the body, and *thyroxine* (from the thyroid gland) increases the rate of many chemical reactions in almost all the body's cells.

Other hormones affect only specific tissues called *target tissues*, because only these tissues have receptors for the hormone. For example, *adrenocorticotropic hormone (ACTH)* from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the *ovarian hormones* have specific effects on the female sex organs as well as on the secondary sexual characteristics of the female body.

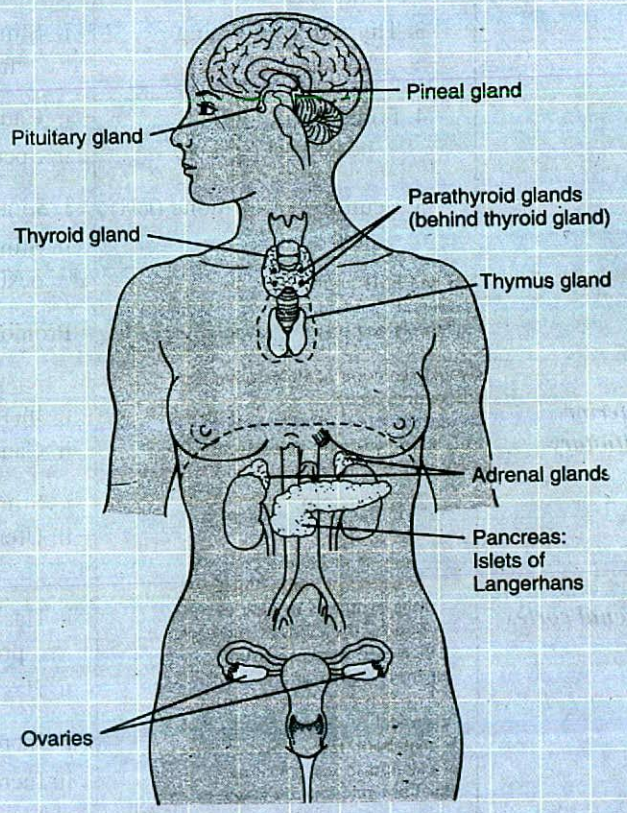



Fig. 8-1. *Anatomical loci of the major endocrine glands of the body except the placenta and testes.*

*Figure shows the anatomical loci of the major endocrine glands of the body except the placenta and testes, which are additional sources of the sex hormones, and the kidneys, provides an overview of the different hormone systems and their most important actions.*

*(Ref. Guyton & Hall-11th ed; Page 905)*

**Endocrine glands, Hormones and their important functions and structure :**

| *Gland* | *Name of the Hormone* | *Major functions* | *Structure* |
|---|---|---|---|
| *Hypothalamus* | Thyrotropin-releasing hormone (TRH) | i. Stimulates secretion of TSH and prolactin | Peptide |
| | Corticotropin-releasing hormone (CRH) | i. Causes release of ACTH | Peptide |
| | Growth hormone-releasing hormone (GHRH) | i. Causes release of growth hormone | Peptide |
| | Growth hormone-inhibitory hormone (GHRH) (somatostatin) | i. Inhibits release of growth hormone | Peptide |
| | Gonadotropin-releasing hormone (GnRH) | i. Causes release of LH and FSH | |
| | Dopamine or prolactin inhibiting factor (PIF) | i. Inhibit release of prolactin | Amine |
| *Anterior Pituitary* | 1. Growth hormone | i. Stimulates protein synthesis and<br>ii. Overall growth of most cells and tissues. | Peptide |
| | 2. Adrenocorticotropic hormone (ACTH) | i. Stimulate the adrenal cortex to secrete adrenocortical hormone. | Peptide |
| | 3. Thyroid stimulating hormone (TSH) | i. Stimulate synthesis and secretion of thyroxine and tri-iodothyronine. | Peptide |
| | 4. Follicle stimulating hormone (FSH). | i. Causes growth of follicle in the ovaries and<br>ii. Sperm maturation in Sertoli cells of testes. | Peptide |
| | 5. Leutinizing hormone (LH) | i. Stimulates testosterone synthesis in Leyding cells of testes;<br>ii. Stimulates ovulation, formation of corpus luteum, and oestrogen and progesteron synthesis in ovaries. | Peptide |
| | 6. Prolactin | Promotes development of the breasts and secretion of milk. | Peptide |
| *Posterior Pituitary* | 1. Antidiuretic hormone (ADH, Also called vasopressin) | i. Increases water reabsorption by the kidneys and<br>ii. Causes vasoconstriction and increased blood pressure. | Peptide |
| | 2. Oxytocin. | i. Stimulates milk ejection from breasts and<br>ii. Uterine contraction. | Peptide |
| *Adrenal cortex* | 1. Cortisol | i. Has multiple metabolic functions for controling metabolism of proteins, carbohydrates and fats.<br>ii. Has anti-inflammatory effects. | Steriod |
| | 2. Aldosterone | i. Increases renal sodium reabsorption<br>ii. Increases renal potassium secretion<br>iii. Increases renal hydrogen ion secretion | Steriod |
| *Thyroid* | 1. Thyroxine ($T_4$) & triidothyronine ($T_3$) | i. Increase the rates of chemical reactions in most cells.<br>ii. Thus increasing body metabolc rate. | Amine |
| | 2. Calcitonin. | i. Promotes the deposition of $Ca^{++}$ in the bones.<br>ii. Decreases the extracellular $Ca^{++}$ concentration. | Peptide |

*(Ref. Guyton & Hall-11th edition; Page 907)*

**Endocrine glands, Hormones and Their Important Functions and Structure :**

| *Gland* | *Name of the Hormone* | *Major functions* | *Structure* |
|---|---|---|---|
| ***Parathyroid*** | 1. Parathyroid hormone (PTH) | i. Controls serum $Ca^{++}$ concentration by increasing calcium absorption by the gut (GIT) and kidneys and release calcium from the bones. | Peptide |
| ***Pancrease*** Islets of Langerhans | 1. Insulin (β cells) | i. Promotes glucose entry in many cells and in this way controls carbohydrates metabolism. | Peptide |
| | 2. Glucagon (α cells) | i. Increases the synthesis and release of glucose from the liver into the circulating body fluids. | Peptide |
| Ovaries | 1. Estrogens | i. Promote growth and development of the female reproductive system, female breasts and female secondary sexual characteristics. | Steroid |
| | 2. Progesterone | i. Stimulate the secretion of *uterine milk* by the uterine endometrial glands<br>ii. Promote development of the secretory apparatus of the breast. | Steroid |
| Testes | 1. Testosterone | i. Promotes development of male reproductive system and<br>ii. Promotes development of male secondary sexual characteristics. | Steroid |
| Placenta | 1. Human chorionic gonadotropin (HCG) | i. Promotes growth of corpus luteum and secretion of estrogens and progesterone by the corpus luteum. | Peptide |
| | 2. Human somatomammotropin | i. Probably helps promote development of some fetal tissue as well as the mother's breasts. | Peptide |
| | 3. Estrogens | See actions of estrogen from ovaries | Steroid |
| | 4. Progesterone | See actions of progesterone from ovaries | Steroid |
| Kidney | 1. Renin | i. Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme) | Peptide |
| | 2. 1,25 Dihydroxychole-calciferol | i. Increases intestinal absorption of calcium and bone mineralization | Steroid |
| | 3. Erythropoietin | i. Increases erythrocyte production. | Peptide |
| Heart | 1. Atrial natriuretic peptide (ANP) | i. Increases sodium excretion by the kidneys<br>ii. Reduces blood pressure. | Peptide |
| Stomach | 1. Gastrin | i. Stimulates HCl secretion by parietal cells. | Peptide |
| Small Intestine | 1. Secretin | i. Stimulates pancreatic acinar cells to release bicarbonate and water. | Peptide |
| | 2. Cholecystokinin (CCK) | i. Stimulates gallbladder contraction and<br>ii. Release of pancreatic enzymes. | Peptide |

*(Ref. Guyton & Hall-11th edition; Page 907)*

**Functions of endocrine glands**

The multiple hormone systems of the body play a key role in regulating almost all its functions, including :

i. Metabolism
ii. Growth and development
iii. Water and electrolyte balance
iv. Reproduction
v. Behavior.

* For instance, without growth hormone, a person becomes a dwarf.
* Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body become sluggish, and the person becomes sluggish as well.
* Without insulin from the pancreas, the body's cells can use little of the food carbohydrates for energy.
* Without the sex hormones, sexual development and sexual functions are absent.

*(Ref. Guyton & hall-11th edition; Page 905)*

**Factor**

A substance that has the action of a hormones but that has not been purified and indentified as a distinct chemical compound is called factor.

*(Ref. Guyton & Hall-11th edition; Page 905)*

## Hormone

Hormone is a chemical substance that is secreted into the internal body fluid by one cell or group of cells and exerts a physiological control effect on other cells of the body.

*(Ref. Guyton & Hall-11th edition)*

**Classification of Hormone**

a. ***Based on chemical nature*** :

i. *Proteins or polypeptides hormone :* Hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone) and many others.

ii. *Steroid hormones :* Hormones secreted by the adrenal cortex (*cortisol* and *aldosterone*), the ovaries (*estrogen* and *progesterone*), the testes (*testosterone*), the placenta (*estrogen and progesterone*).

iii. *Derivatives of the amino acid tyrosine :* Hormones secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epineph- rine and norepinephrine).

There are no known polysaccha- rides or nucleic acid hormones.

*(Ref. Guyton & Hall-11th edition; Page 906)*

b. ***Based on the site of action*** :

i. *General hormone :* Has a generalized action through out the body e.g growth hormone, thyroid hormone, insulin.

ii. *Local hormone :* Has a localized function upon the local cells e.g Local hormones of GI tract. *(Described in digestive system).*

iii. *Trophic hormone :* Hormones which are secreted from an endocrine gland and acts upon another gland and produce their secretion, called trophic hormone. e.g TSH, ACTH, LH etc.

**Synthesis and storage of hormones**

1. ***Polypeptide and protein hormones*** *are stored in secretory vesicles until needed* : Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as three amino acids (*thyrotropin-releasing hormone*) to proteins almost 200 amino acids long (*growth hormone* and *prolactin*). In general, polypeptides with 100 or more amino acids are called *proteins*, and those with fewer that 100 amino acids are referred to as *peptides*.

Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells in the same fashion as most other proteins (Figure 8-2). They are usually synthesized first as larger proteins that are

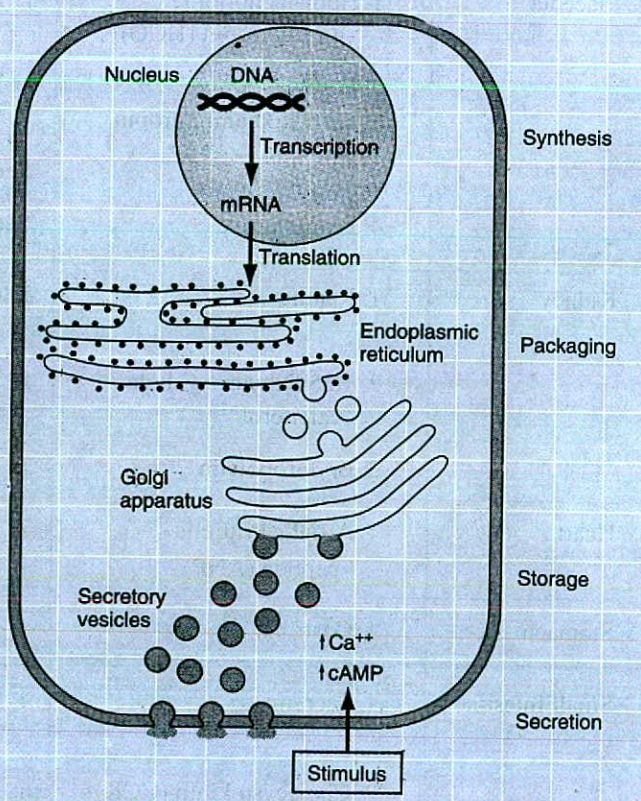



Fig. 8-2. *Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves increased intracellular calcium or decreased cAMP in the cell.*

not biologically active (*prepro- hormones*) and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the *prohomones* to produce smaller, biologically active *hormones* and *inactive fragments*. The vesicles are stored within the cytoplasm, and many are bound the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the bloood stream by *exocytosis*.

In many cases, the stimulus for exocytosis is an incrase in cytosolic calcium concentration caused by depolarization of the plasma membrane. In other instances, stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (*cAMP*) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily and be carried to their target tissues.

*(Ref. Guyton & Hall-11th edition; Page 906)*

2. ***Steroid hormones** are usually synthesized from cholesterol and are not stored* : The chemical structure of steroid hormones is similar to cholesterol, and in most instances they are synthesized from cholesterol itself. They are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure. Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

*(Ref. Guyton & Hall-11th edition; Page 906)*

3. ***Amine hormones** are derived from tyrosine* : The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin*, which is stored in large follicles within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormone combines with plasma proteins, especially *thyroxine-binding globulin*, which slowly releases the hormones to the target tissues.

*Epinephrine* and *norepinephrine* are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by *exocytosis*. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

*(Ref. Guyton & Hall-11th edition; Page 908)*

**Hormone Secretion**

*Onset of hormone secretion after a stimulus, and durations of action of different hormones* :

i. Some hormones, such as *norepinephrine* and *epinephrine*, are secreted within seconds after the gland is stimulated. and they may develop full action within another few seconds to minutes.

ii. The actions of other hormones, such as thyroxine or growth hormone, may require months for full effect. Thus, each of the different hormones has its own characteristic onset and duration of action- each tailored to perform its specific control function.

*(Ref. Guyton &Hall-11th edition; Page 908)*

**Feedback control of hormone secretion**

1. *Negative feedback prevents overactivity of hormone systems:* Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through negative feedback mechanisms that ensure a proper level of activity of the hormone at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue.

   The controlled variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in synthesis of the hormone and steps involved in processing the hormone or releasing the stored hormone.

2. *Surges of hormones can occur with positive feedback* : In a few instances, positive feedback occurs when the biological

action of the hormone causes additional secretion of the hormone. One example of this is the *surge of luteinizing hormone (LH)* that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration, and typical negative feedback control of honnone secretion is then exerted.

3. *Cyclical variations occur in hormone release* : Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle, or sleep. For example, the secretion of *growth hormone* is markedly increased during the early period of sleep but is reduced during the later stages of sleep. In many cases, these cyclical variations in hormone secretion are due to changes in activity of neural pathways involved in controlling hormone release.

*(Ref. Guyton & Hall-11th edition; Page 909)*

**Transport of hormones in the blood**

1. *Water-soluble hormones* (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells.

2. *Steroid and thyroid hormones*, in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 per cent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 per cent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their target cells and are therefore biologically inactive until they dissociate from plasma proteins.

   The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Also, binding of hormones to plasma proteins greatly slows their clearance from the plasma.

*(Ref. Guyton & Hall-11th edition; Page 909)*

**Clearance of hormones from the blood**

Two factors can increase or decrease the concentration of a hormone in the blood.

1. Rate of hormone secretion into the blood.
2. Rate of removal of the hormone from the blood, which is called the metabolic clearance rate. This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures- *i.* the rate of disappearance of the hormone from the plasma per minute and *ii.* the concentration of the hormone in each milliliter of plasma. Then, the metabolic clearance rate is calculated by the *following formula* :

   Metabolic clearance rate = Rate of disappearance of hormone from the plasma / Concentration of hormone in each milliliter of plasma.

*Hormones are 'cleared' from the plasma in several ways*, including :

i. Metabolic destruction by the tissues
ii. Binding with the tissues
iii. Excretion by the liver into the bile
iv. Excretion by the kidneys into the urine.

Hormones are sometimes degraded at their target cells by enzymatic processes that cause endocytosis of the cell membrane hormone-receptor complex; the hormone is then metabolized in the cell, and the receptors are usually recycled back to the cell membrane.

i. Most of the *peptide hormones* and *catecholamines* are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute.
ii. Hormones that are *bound to plasma proteins* are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.

*(Ref. Guyton & Hall-11th edition; Page 909)*

## Mechenisms of action of hormones

**Receptors for hormones, neurotransmitters & other ligands**

The first step of a hormone's action is to bind to *specific receptors* at the target cell. Cells that lack receptors for the hormones do not respond. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect.

***Hormonal receptors*** are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors.

*Location of receptors* : The locations for the different types of hormone receptors are generally the following :

1. *In or on the surface of the cell membrane* : The membrane receptors are specific mostly for the *protein, peptide*, and *catecholamine* hormones.
2. *In the cell cytoplasm* : The receptors for the different *steroid hormones* are found almost entirely in th cytoplasm.
3. *In the cell nucleus* : The receptors for the *thyroxine* hormones are found in the nucleus and are believed be located in direct association with one or more of the chromosomes.

***Regulation of the number of hormone receptors*** : The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute.

i. ***Down-regulation*** : When a hormone or neurotransmitter is present in excess, the number of active receptors generally decreases called down-regulation.

*Causes* :

a. In the case of receptors in the membrane, receptor-mediated endocytosis is responsible for down-regulation in some instances; ligands bind to their receptors, and the ligand-receptor complexes move laterally in the membrane to coated pits, where they are taken into the cell by endocytosis *(internalization)*. Internalization of $\beta_2$-adrenergic receptors triggers an increase in receptor mRNA degradation so that the number of receptors is decreased.

b. Some receptors are recycled after internalization, where as others are replaced by *de novo synthesis* in the cell.

c. Another type of down-regulation is *desensitization*, in which receptors are chemically modified in ways that make them less responsive.

ii. ***Up-regulation*** : Where as in the presence of a deficiency of the chemical messenger, there is an increase in the number of active receptors called up-regulation.

*Exception* : Angiotensin II in its actions on the adrenal cortex is an exception; it increases rather than decreases the number of its receptors in the adrenal.

*(Ref. Ganong 22th edition; page-37)*

**Desensitisation**

Prolonged exposure to their ligands causes most receptors to become unresponsive, ie. to undergo desensitisation.

*Types* :

i. *Homologous desensitisation* : Loss of responsiveness only to the particular ligand and maintained responsiveness of the cell to other ligands.

ii. *Heterologous desensitisation* : In which the cell becomes unresponsive to other ligands as well.

*(Ref. Ganong 22th edition; page 97)*

***Structure of receptor*** :

1. Ligand binding site :

*Function* :

a. Recognise the ligand

b. Affinity to specific ligand.

2. Active site :

*Function* : For post binding events. Also determines whether the ligand is agonist or antagonist and acts accordingly.

*Affinity* : Specific receptor has affinity to specific ligand.

**Target tissue** : The selective cell or tissue on which a particular hormone act is called target tissue.

**Ligand** : A ligand is a substance which can combine with the receptor. A ligand, thus may be a hormone or a drug molecule.

**Intracellular signaling after hormone receptor activation**

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects. To explain this, let us give a few examples.

1. *Some hormones change membrane permeability* : Virtually all the neurotransmitter substances, such. as *acetylcholine* and *norepinephrine*, combine with receptor in the postsynaptic membrane. Almost always this causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some receptors open (or close) *channels for sodium ions*, others for *potassium ions*, others for *calcium ions*, and so forth. It is the altered movement of these ions through the channels that causes the subsequent effects on the postsynaptic cells. A few of the circulating hormones, such as *epinephrine* and *norepinephrine* secreted by the adrenal medulla, have similar effects to open or close membrane ion channels.
2. *Some hormones activate intracellular enzymes when they combine with their receptors* : Another common effect of hormone binding to membrane receptors is activation (or occasionally inactivation) of an enzyme immediately inside the cell membrane. A good example of this is the effect of *insulin*. Insulin binds with that portion of its membrane receptor that protrudes to the exterior of the cell. This produces a structural change in the receptor molecule itself, causing the portion of the molecule that protrudes to the inside to become an *activated kinase*. This kinase then promotes phosphorylation several different substances inside the cell. Most of the actions of insulin on the cell result secondarily from these phosphorylation processes.

A second example, one widely used in hormonal control of cell function, is for the hormone to bind with a special transmembrane receptor that then becomes the activated enzyme *adenylyl cyclase* at the end that protrudes to the interior of the cell. This cyclase in turn catalyzes the formation of cAMP, and cAMP has a multitude of effects

inside the cell to control cell activity, as discussed in greater detail later, cAMP is called a *second messenger* because it is not the hormone itself that directly institutes the intracellular changes; instead, it is the cAMP that serves as a second messenger to cause these effects.

For a few peptide hormones, such as *atrial natriuretic peptide* (ANP), *cyclic guanosine monophosphate* (cGMP), which is only slightly different from cAMP, serves in a similar manner as a second messenger.

3. *Some hormones activate genes by binding with intracellular receptors* : Several hormones, especially the *steroid hormones* and *thyroid hormones*, bind with protein receptors inside the cell, not in the cell membrane. The activated hormone-receptor complex then binds with or activates specific portions of the DNA strands of the cell nucleus, which in turn initiates transcription of specific genes to form messenger RNA (mRNA). Therefore, minutes, hours, or even days after the hormone has entered the cell, newly formed proteins appear in the cell and become the controllers of new or increased cellular functions.

*(Ref. Guyton & Hall-11th edition; Page 910, 911)*

**Second messenger mechanisms for mediating intracellular hormonal functions**

We noted earlier that one of the means by which hormones exert intracellular actions is to stimulate formation of the second messenger cAMP inside the cell membrane. The cAMP in turn causes subsequent intracellular effects of the hormone. Thus, the only direct effect that the hormone has on the cell is to activate a single type of membrane receptor. The second messenger does the rest.

cAMP is not the only second messenger used by the different hormones. Two other especially important- i. calcium ions and associated calmodulin and ii. products of membrane phospholipid breakdown.

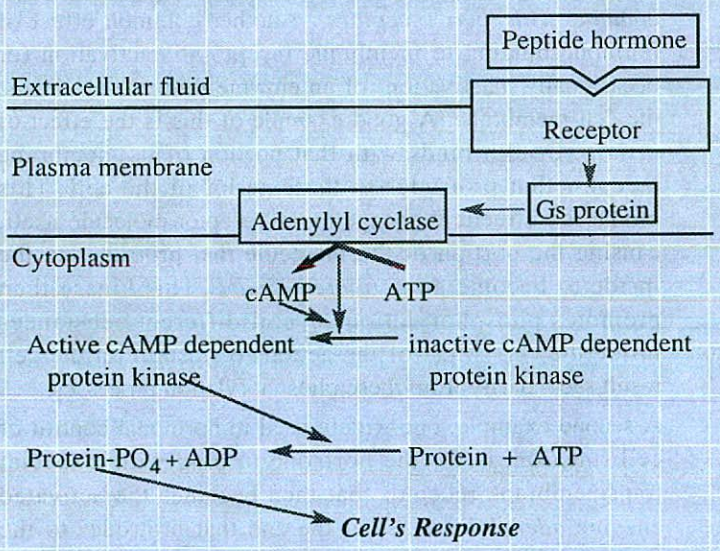



Fig 8-3. *Cyclic adenosine monophosphate (cAMP) mechenism by which many hormones exert their control of cell function.*

1. ***The adenylyl cyclase-cAMP second messenger system*** Binding of the hormones with the receptor allows coupling of the receptor to a *G-protein*. If the G-protein stimulates the adenylyl cyclase-cAMP system, it is called a $G_S$-protein, denoting a stimulatory G-protein. Stimulation of adenylyl cyclase, a membrane-bound enzyme, by the $G_S$-protein then catalyzes the conversion of a small amount of cytoplasmic *adenosine triphosphate* (ATP) into cAMP inside the cell. This then activates *cAMP dependent protein kinase*, which phosphorylates specific proteins in the cell, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

   Once cAMP is formed inside the cell, it usually activates a cascade of enzymes. That is, a first enzyme is activated, which then activates another enzyme, which activates a third, and so forth. The importance of this mechanism is that only a few molecules of activated adenylyl cyclase immediately inside the cell membrane can cause many more molecules of the next enzyme to be activated, which can cause still more molecules of the third enzyme to be activated, and so forth. In this way, even the slightest amount of hormone acting on the cell surface can initiate a powerful cascading activating force for the entire cell.

   If binding of the hormone to its receptors is coupled to an inhibitory G-protein (denoted $G_i$-protein), adenylyl cyclase will be inhibited, reducing the formation of cAMP and ultimately leading to an inhibitory action in the cell. Thus, depending on the coupling of the hormone receptor to an inhibitory or a stimulatory G-protein, a hormone can either increase or decrease the concentration of cAMP and phosphorylation of key proteins inside the cell.

   The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery- some cells having one set of enzymes, and other cells having other enzymes. Therefore, different functions are elicited in different target cells- such functions as initiating synthesis of specific intracellular chemicals, causing muscle contraction or relaxation, initiating secretion by the cells, and altering cell permeability.

   Thus, a thyroid cell stimulated by cAMP forms the metabolic hormones thyroxine and triiodothyronine, whereas the same cAMP in an adrenocortical cell causes secretion of the adrenocortical steroid hormones. However, cAMP affects epithelial cells of the renal tubules by increasing their permeability to water.

   *Hormones that use the adenylyl cyclase-cAMP second messenger system* :

   1. Adrenocorticotropic hormone (ACTH)
   2. Angiotensin II (epithelial cell)

3. Calcitonin
4. Catecholamines (β receptors)
5. Follicle-stimulating hormone (FSH)
6. Glucagon
7. Human chorionic gonadotropin (HCG)
8. Luteinizing hormone (LH)
9. Parathyroid hormone (PTH)
10. Secretin
11. Thyroid-stimulating hormone (TSH)
12. Vasopressin ($V_2$ receptor, epithelial cell).

*(Ref. Guyton & Hall-11th edition; Page 913)*

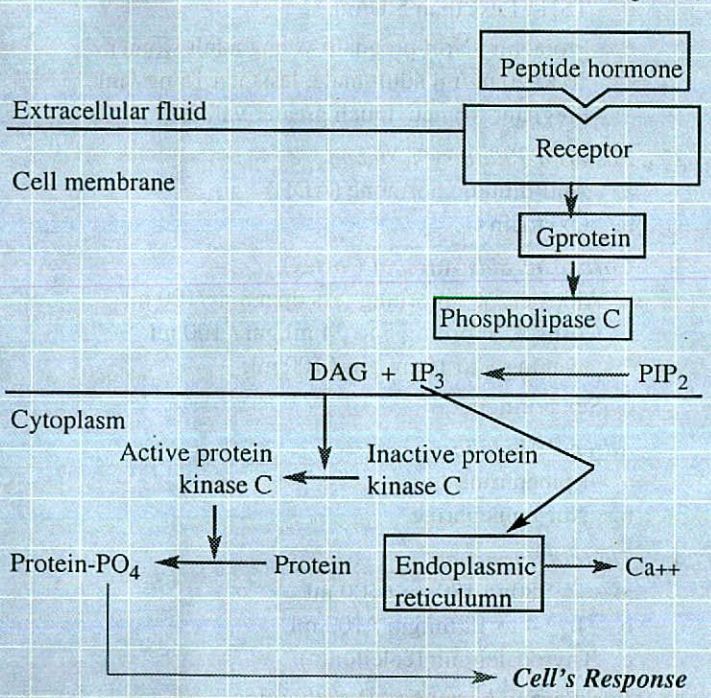



Fig 8-4. *Cell membrane phospholipids second messenger system by which some hormone exert their control of cell function. DAG, diacylglycerol; $IP_3$, inositol triphosphate; $PIP_2$, phosphatidylinositol biphosphate.*

2. ***The cell membrane phospholipids second messenger system*** : Some hormones activate transmembrane receptors that activate the enzyme *phospholipase C* attached to the inside projections of the receptors. This enzyme catalyzes the breakdown of some phospholipids in the cell membrane, especially *phosphatidylinositol biphosphate ($PIP_2$)*, into two different second messenger products, *inositol triphosphate ($IP_3$)* and *diacylglycerol (DAG)*. The $IP_3$ mobilizes calcium ions from mitochondna and the endoplasmic reticulum, and the calcium ions then have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

   DAG, the other lipid second messenger, activates the enzyme *protein kinase C (PKC)*, which then phosphorylates a large number of proteins, leading to the cell's response. In addition to these effects, the lipid portion of DAG is *arachidonic acid*, which is the precursor for the prostaglandins and other local hormones that cause multiple effects in tissues throughout the body.

   *Hormones use the phospholipase C second messenger system* :

   1. Angiotensin II (vascular smooth muscle)
   2. Catecholamines (α receptor)
   3. Gonadotropin-releasing hormone (GnRH)
   4. Growth hormone-releasing hormone (GHRH)
   5. Oxytocin
   7. Thyroid-releasing hormone
   8. Vassopressin ($V_1$ receptor, vascular smooth muscle).

   *(Ref. Guyton & Hall-11th edition; Page 914)*

3. ***The calcium-calmodulin second messenger system*** : This operates in response to the entry of calcium into the cells. The calcium entry may be initiated- i. by changes in membrane potential that open membrane calcium channels or ii. by a hormone interacting with membrane receptors that open calcium channels.

   On entering a cell, calcium ions bind with the protein *calmodulin*. This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin dependent protein kinases causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone. For example, one specific function of calmodulin is to activate myosin kinase, which acts directly on the myosin of smooth muscle to cause smooth muscle contraction.

   The normal calcium ion concentration in most cells of the body is $10^{-8}$ to $10^{-7}$ mol/L, which is not enough to activate the calmodulin system. But when the calcium ion concentration rises to $10^{-6}$ to $10^{-5}$ mol/L, enough binding occurs to cause all the intracellular actions of calmodulin. This is almost exactly the same amount of calcium ion change that is required in skeletal muscle to activate *troponin C*, which in turn causes skeletal muscle contraction. It is interesting that troponin C is similar to calmodulin both in function and in protein structure.

   *(Ref. Guyton & Hall-11th edition; Page 914)*

**Hormones that act mainly on the genetic machinery of the cell**

1. ***Steroid hormones increase protein synthesis*** : Another means by which hormones act - specifically the steroid hormones secreted by the *adrenal cortex, ovaries*, and *testes* - is to cause synthesis of proteins in the target cells; these proteins then function as enzymes, transport proteins, or

structural proteins that in turn provide other functions of the cells.

*The sequence of events in steroid function is essentially the following* :

1. The steroid hormone enters the cytoplasm of the cell, where it binds with a specific *receptor protein.*
2. The combined *receptor protein-hormone* then diffuses into or is transported into the nucleus.
3. The combination binds at specific points on the DNA strands in the chromosomes, which activates the transcription process of specific genes to form messenger RNA.
4. The messenger RNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins.

*Example* : ***Aldosterone***, one of the hormones secreted by the adrenal cortex, enters the cytoplasm of renal tubular cells, which contain a specific aldosterone receptor protein. Therefore, in these cells, the sequence of events cited earlier ensues. After about 45 minutes, proteins begin to appear in the renal tubular cells and promote sodium reabsorption from the tubules and potassium secretion into the tubules. Thus, there is a characteristic delay in the initial action of the steroid hormone of at least 45 minutes and up to several hours or even days for full action. This is in marked contrast to the almost instantaneous action of some of the peptide and amino acid-derived hormones, such as *vasopressin* and *norepinephrine*.

2. ***Thyroid hormones increase gene transcription in the cell nucleus*** : The thyroid hormones thyroxine and triiodothyronine cause increased transcription by specific genes in the nucleus. To accomplish this, these hormones first bind directly with receptor proteins in the nucleus itself; these receptors are probably protein molecules located within the chromosomal complex, and they probably control the function of the genetic promoters or operators.

   Two important features of thyroid hormone function in the nucleus are the following :

   i. They activate the genetic mechanisms for the formation of many types of intracellular proteins- probably 100 or more. Many of these are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.

   ii. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

*(Ref. Guyton & Hall-11th edition; Page 915)*

**Approximate normal values (by RIA method) of concentrations of some important hormones in plasma/serum.**

1. Adenohypophysial hormones ( Anterior Pituitary):
   a. ACTH : 10 to 80 pg /ml.
   b. Gonadotrop(h)ins :
      i. Women, reproducing age -
      *FSH :* 8 to 12 IU / liter; during FSH surge value may reach near 20 IU / liter.
      *LH :* about 15 IU/liter; during LH surge value may reach about 80 IU/liter.
      ii. Women, post menopausal age - values are shigher.
   c. Growth Hormone : Less than 5 ng / ml, after 100 gm of oral glucose.
   d. TSH : Less than 5 U/ml.
   e. Prolactin : Non-pregnant young adult women. 10 to 20 ng/ml adult male, lessthen 15 ng / ml. Pregnant women, much greater values.
2. *Posterior Pituitary hormone*
   a. Anti-diuretic hormone (ADH)
   b. Oxytocin.
3. *Corticosteroids(Adrenal Cortex)*
   a. Aldosterone : morning less than 8 ng/100 ml.
   b. Cortisol : morning 5 to 24 mi.gm / 100 ml, evening 3 to 10 mi.gm / 100 ml.
   c. Sex hormone

   *Adrenal Medulla:*
   a. Epinephrine
   b. Nor-epinephrine
4. *Thyroid hormones*
   a. $T_3$ : 80 to 180 ng / 100 ml.
   b. $T_4$ : 4 to 12 mi.gm / 100 ml.
   c. Thyrocalcitonin(calcitonin)

   *Parathyriod hormone: Parathormone.*
4. *Sex Steroids (Ovary)*
   a. In women reproducing age, *Estradiol :* 20 to 60 pg /ml; higher values in ovulation peak.
   *Progesterone :* pre ovulatory, <2 ng / ml, post ovulatory > 4.5 ng / ml.
   b. *Adult males (Testes)*
   Testosterone : 250 to 1000 ng / 100 ml.
5. *Pancreatic hormones*
   a. Glucagon : 50 to 100 pg / ml.
   b. Insulin : Fasting 5 to 25 m U/ml; value rises sharply after meals.
6. *Hyphothalamic Hormones (Hypothalamus)*
   a. Thyrotropin releasing hormone (TRH) : Which causes release of thyroid-stimulating hormone.
   b. Corticotropin releasing hormone (CRH) : Which causes release of adrenocorticotropin.
   c. Growth hormone releasing hormone (GHRH) : Which casues relase of growth hormone and growth hormone

inhibitory hormone (GHIH)- which is the same as the hormone somatostatin and which inhibits the release of growth hormone.

d. Gonadotropin releasing hormone (GnRH) : Which causes release of the two gonadotropic hormones, luteinizing hormone and follicle stimulating hormone.

e. Prolactin inhibitory hormone (PIH) : Which causes inhibition of prolactin secretion.

**Radioimmunoassay**

Antibodies to the polypeptides and proteins are readily produced, and, by using special techniques, it is possible to make antibodies to the other chemical messengers as well. The antibodies can be used to measure the messengers in body fluids and in tissue extracts by *radioimmunoassay*.

This technique depends on the fact that the naturally occurring, unlabeled ligand and added radioactive ligand compete to bind to an antibody to the ligand. The greater the amount of unlabeled ligand in the specimen being analysed, the more it competes and the smaller the amount of radioactive ligand that binds to the antibody.

*Use* : Radioimmunoassays are extensively used in research and in clinical medicine.

*(Ref. Ganong 22th edition; page 37)*

**Difference between hormones & enzymes**

| *Hormones* | *Enzymes* |
|---|---|
| 1. Hormone are generally both protein & steroid in nature. | 1. Enzymes are always protein in nature. |
| 2. They are secreted by definite endocrine glands or cell or group of cells. | 2. Enzymes are always secretedby any tissue or cell. |
| 3. Hormones act upon target tissue. It may be locally or distally. | 3. Enzyme generally acts locally. |
| 4. Hormones generally act by producing 3-5 cyclic AMP or specific protein which may be a enzyme. | 4. Enzymes are organic catalysts and they act upon biochemical reactions. |
| 5. Hormones are named according to the nature, source of origin & function. | 5. Enzymes are named according to the chemical change they have done. |
| 6. For hormone action definite receptor is required. | 6. For enzymes action no such receptor is required |
| 7. They generally regulate morphogenesis, development of gonads, secondary sex character etc. | 7. They cannot regulate morphogenesis. |
| 8. Hormones generally stimulate or inhibit hormone secretion by feed-back mechanism. | 8. Enzyme cannot do so. |

**Functions of Hormones** *(An overview)*

i. *Homeostasis* :
   a. Metabolism : e.g Insulin, Glucagon, Thyroid, Cortisol.
   b. Antistress action : eg Cortisol , ACTH, ADH Vaopressin, Adrenalin, Thyroid.
   c. Via water and mineral regulation : e.g ADH, Aldosterone, PTH.

ii. *Growth* : e.g Growth hormone, Somatomedin, IGF, Thyroid hormones, Testosterone.

iii. *Reproduction* : *e.g* Testicular/ovarian steroids, Gn RH Gonadotropins, Prolactin.

iv. *Combating emergency* : e.g Adrenalin and Noradrenalin.

**Estimation of Hormones & hormonal status**

1. Radioimmunoassay (RIA)
2. ELISA (enzyme linked immunosorvent assay) technic.
3. Flurimetric analysis
4. Cytochemical assay
5. Dynamic test.

**First Massenger** : These are the chemicals which directly acts on the receptor. These are-

1. Hormones
2. Neuro-transmitter.
3. Drugs.

**Second massenger** : These are the chemicals which are formed after the action of first massenger on the receptors. These are -

1. cAMP
2. $Ca^{++}$ ion
3. $IP_3$.

## Hypothalamus

*The hypothalamic releasing hormones* : Hypothalamus liberates hormones (or factors) which enter the adenohypophysis via the portal system of blood supply and strongly influences the secretions of the adenohypophysis.

1. *Thyrotropin releasing hormone (TRH) :* This is a tripeptide hormone. It acts on thyrotroph cells to cause secretion of TSH. TRH also acts on lactotroph and has some PRLRF like activities.

   Besides hypothalamus , TRH is also found in many other areas of the brain, spinal cord and even in the gastrointestinal tract.

2. *Corticotropin releasing hormone (CRH) :* It is a 41 amino acid peptide chain, secreted by the hypothalamus. The

posterior pituitary hormone ADH acts synergistically with the CRH on the corticotrophs to produce more ACTH. (CRH is produced by other areas of brain as well, most notably by the limbic system and cerebral cortex).

3. *Gonadotropin releasing hormone (GnRH)* : It is a decapeptide hormone. GnRH causes stimulation of secretion of both FSH and LH.
4. *Growth hormone releasing hormone GHRH (Somatocrinin)* : GHRH is a 44 amino acid peptide chain and it stimulates growth hormone secretion. Another GHRH with 40 amino acids is also known. The two GHRHs are known as GHRH 44 and GHRH 40 respectively.
5. *Somatostatin* : This contains 14 amino acids in the chain. In addition to the hypothalamus,the somatostatin is also secreted by the pancreatic islet cells and even gastric mucosa. Hypothalamic somatostatin depresses growth hormones secretion. Apart from its action on the somatotrophs of adenohypophysis, the somatostatin has many other functions.
6. Prolactin inhibitory factor (PIF).
7. Prolactin releasing factor : Its details are not known.

*(Ref. Guyton & Hall-11th ed and Concise Medical Physiology)*

## Anterior Pituitary Gland

*Physiological anatomy of pituitary gland* : The pituitary gland, also called the hypophysis, is a small gland - about 1 cm in diameter and 0.5 to 1 gm in weight that lies in the sella turcica at the base of the brain and is connected with the hypothalamus by the pituitary (or hypophysial) stalk.

The pituitary gland is divided into two parts. Anterior pituitary or adenohypophysis and posterior pituitary or neurohypophysis, between them a relatively avascular zone, called pars intermedia which is almost absent in human being. Anterior pituitary develops from *Rathke's pouch* which is an embryonic invagination of pharyngeal epithelium and posterior pituitary develops from an outgrowth of the hypothalamus.

*(Ref. Guyton & Hall-10th edition; Page 918)*

***Hormone secreting cells of the human anterior pituitary gland***

| *Cell Type* | *Hormones Secreted* | *% of Total secretory cells* | *Stain Affinity* | *Diameter of secretoty Granules (nm)* |
|---|---|---|---|---|
| Somatotrope | Growth hormone | 50 | Acidophilic | 300-400 |
| Lactotrope | Prolactin | 10-30 | Acidophilic | 200 |
| Corticotrope | ACTH, β-LPH | 10 | Basophilic | 400-550 |
| Thyrotrope | TSH | 5 | Basophilic | 120-200 |
| Gonadotrope | FSH, LH | 20 | Basophilic | 250-400 |

*(Ref. Ganong 22th edition, Page 397)*

**Q.** ***Name the hormones of the anterior pituitary gland and their major functins.***

Ans. Please go throuh the page 8.2 for pituitary hormone. Then-

***Intermediate lobe*** :

1. α-, β-, and γ-melanocyte-stimulating hormones (α-, β-, and γ-MSH; referred to collectively as melanotropin or intermedin).
   *Function* : Stimulate melanin synthesis in humans.
2. γ-Lipotropin (γ-LPH), corticotropin-like intermediate lobe peptide (CLIP), other fragments of pro-opiomelanocortin.
   *Function* : ?

*N.B. In addition*, a variety of gastrointestinal and other polypeptides are found in one or more lobes of the pituitary gland. These include CCK, gastrin, renin, angiotensin II, and calcitonin gene-related peptide (CGRP).

*(Ref. Ganong 22th edition, Page 396)*

**Hypothalamo-hypophysial portal system**

Hypothalamo-hypophysial portal system is a vascular connection which connects the hypothalamus with anterior pituitary.

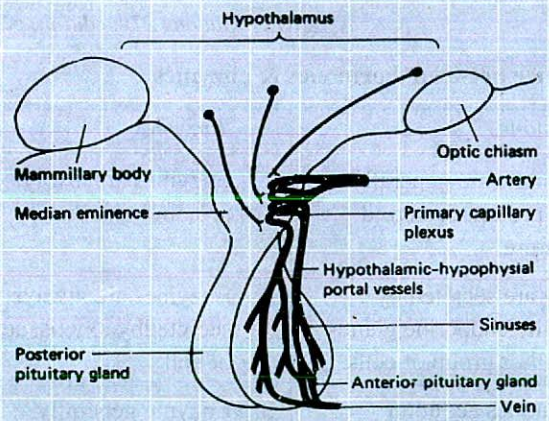



Fig. 8-5. *The hypothalamo hypophysial portal system.*

The anterior pitiutary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small *hypothalamic-hypophysial portal vessels* into the anterior pituitary sinuses. Figure 8-3. shows the lowermost portion of the hypothalamus called the *median eminence* that connects inferiorly with the pituitary stalk. Small arteries penetrate into the substance of the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal vessels. These in turn pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

*(Ref. Guyton & Hall-11th edition; Page 920)*

**Control of pituitary secretion by the hypothalamus**

Almost all the secretion of pituitary gland are controlled by either hormonal or nervous signals from the hypothalamus. Secretion from posterior pituitary is controlled by the nerve signals originate in the hypothalamus and terminate in the posterior pituitary.

In contrast, secretion by the anterior pituitary is controlled by the *hypothalamic releasing* or *hypothalamic inhibitory hormones (or factors)* secreted within the hypothalamus itself and then conducted to the anterior pituitary through minute blood vessels called *hypothalamic-hypophysial portal vessels.* In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion.

The hypothalamous in turn receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, a portion of the pain signal is transmitted into the hypothalamus. Likewise, when a person experiences some powerful depressing or exciting thought, a portion of the signal is transmitted into the hypothalamus. Olfactory stimuli denoting pleasant or unpleasant smells transmit strong signal components directly and through the amygdaloid nuclei into the hypothalamus. Even the concentration of the nutrients, electrolytes, water and various hormones in the blood excite or inhibit variuos portions of the hpothalamous. Thus the hypothalamous is a collecting center for information concerning the internal well being of the body, and in turn, much of this information is used to control secretions of the many globally important pituitary hormones.

*(Ref. Guyton & Hall-11th edition; Page 919)*

## Growth Hormone (GH)

*Chemistry of GH :* Growth hormone is a small protein molecule containing 191 amino acid in a single chain. Its molecular wt. is 22,005.

*( (Ref. Guyton & Hall-11th edition; Page 922)*

*Blood level of growth hormone :*

1. Adult : 1.6 to 3 ng/ml
2. Child : 6 ng/ml.

It may increase to as high as 50 ng/ml after depletion of the body stores proteins or carbohydrates during prolonged starvation.

*(Ref. Guyton & Hall-11th edition; Page 924)*

*Daily secretion and half life of growth hormone* : Growth hormone is metabolised rapidly, probably at least in part in the liver. The-half life of circulating growth hormone in humans is 6-20 minutes, and the daily growth hormone output has been calculated to be 0.2-1.0 mg/day in adults.

*(Ref. Ganong 22th edition, Page 400)*

**Funtion of Growth hormone**

1. ***Metabolic function :***
   a. *On protein metabolism : It increases protein deposition by :*
      i. Increasing amino acid transport through cell membrane.
      ii. Increasing protein synthesis by the ribosomes.
      iii. Increasing transcription of DNA to form RNA.
      iv. Decreasing catabolism of protein.
   b. *On fat metabolism : It increases fat utilization by -*
      i. Stimulating Beta oxidation of fatty acid
      ii. Increasing mobilization of fat from adipose tissue.
      iii. Increasing utilization of acetyl CoA.
      iv. It has ketogenic effect .
   c. *On carbohydrate metabolism :*
      i. Decreases peripheral utilization of glucose.
      ii. Increases gluconeogenesis.
      iii. Stimulate glycogenesis.
      iv. Decreases glycolysis.
2. ***Skeletal growth :*** Increase the growth of skeletal frame by-
   i. Increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth.
   ii. Increased rate of reproduction of these cells as well.
   iii. The specific effect of converting chondrocyte into osteogenic cells thus causing deposition of new bone.
3. ***General body growth :*** It stimulates the growth of all tissues of body which are capable of growing .
4. ***Miscellaneous function :*** Growth hormone increases the retention of some salt and electrolytes such as Na, K, Mg, Ca, $PH_4$, $SO_4$ etc.

*(Ref. Guyton & Hall-11th edition; Page 922, 923)*

**Regulation of Growth hormone secretion**

Secretion of growth hormones regulated by-

1. The precise mechenisms that control secretion of growth hormone are not fully understood, but several factors related to the person's state of nutrition or stress are known to stimulate secretion :
   i. Starvation, specially with severe *protein deficiency.*
   ii. Hypoglycemia or low concentration of fatty acids in the blood
   iii. Exercise
   iv. Excitement
   v. Trauma.

   And it characteristically increases during the first 2 hours of deep sleep.
2. *Hypothalamus :* Growth hormone secretion is controlled almost entirely in response to two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophysial portal vessels. These are growth hormone releasing hormone (GHRH).

and Growth hormone inhibitory hormone (GHIH), also called somatostatin.

3. Catecholamines, dopamine and serotonin, will also increase the rate of growth hormone secretion.

*(Ref. Guyton & Hall-11th edition; Page 924)*

**Stimuli that affect growth hormone secretion in humans**

A. ***Stimuli that increase growth hormone secretion*** :

1. Deficiency of energy substrate
   - Hypoglycemia
   - 2-Deoxyglucose
   - Exercise
   - Fasting
2. Increase in circulating levels of certain amino acids
   - Protein meal
   - Infusion of arginine and some other amino acids
3. Glucagon
4. Stressful stimuli
   - Pyrogen
   - Lysine vasopressin
   - Various psychologic stresses
5. Going to sleep
6. L-Dopa and α-adrenergic agonists that penetrate the brain
7. Apomorphine and other dopamine receptor agonists
   Estrogens and androgens.

B. ***Stimuli that decrease growth hormone secretion*** :

1. REM sleep
2. Glucose
3. Cortisol
4. FFA
5. Medroxyprogesterone
6. Growth hormone.

*(Ref. Ganong 22th edition, Page 405)*

**Ketogenic effect of growth hormone** : Under the influence of excessive amounts of growth hormone, fat mobilization from adipose tissue sometimes becomes so great that large quantities of acetoacetic acid are formed by the liver and released into the body fluids, thus causing *ketosis*. This excessive mobilization of fat from the aidipose tissue also frequently causes a fatty liver.

*(Ref. Guyton & Hall-11th edition; Page 923)*

**Growth hormone decreases carbohydrate utilization** *(Diabetogenic effects of growth hormone)* : Growth hormone causes multiple effects that influence carbohydrate metabolism, including- i. decreased glucose uptake in tissues such as skeletal muscle and fat, ii. increased glucose production by the liver, and iii. increased insulin secretion. Each of these changes results from growth hormone-induced *insulin resistance*, which attenuates insulin's actions to stimulate uptake and utilization of glucose in skeletal muscle and fat and to inhibit glucose output by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone's effects are called ***diabetogenic***, and excess secretion of growth hormone can produce metabolic disturbances very similar to those found in patients with type II diabetes (non-insulin-dependent diabetes), who are also very resistant to the metabolic effects of insulin.

*(Ref. Guyton & Hall-11th edition; Page 923)*

**Q. Why growth hormone is called protein and carbohydrate sparer?**

Ans. Growth hormone has a specific effect in causing release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, it enhances the conversion of fatty acids to acetyl coenzyme A (acetyl CoA) and subsequent utilization of this for energy. Therefore, under the influence of growth hormone, *fat is used for energy in preference to use of both carbohydrates and proteins.*

Growth hormone's effect to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, growth hormone mobilization of fat requires several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

*(Ref. Guyton & Hall-11th edition; Page 922, 923)*

**Growth factors**

Growth factors have become increasingly important in many different aspects of physiology. They are polypepides and proteins that are conveniently divided into three groups.

i. *One group* is made up of agents that foster the multiplication or development of various types of cells :
   a. Nerve growth factor
   b. Insulin-like growth factor I IGF-I)
   c. Activins
   d. Inhibins
   e. Epidermal growth factor (EGF) etc.
   *(More than 20 have been described)*

ii. *Second group* : The cytokines are a second group. These factors are produced by macrophages and lymphocytes and are important in regulation of the immune system.
   *Example* : IL-1, IL-3, IL-4, IL-5, IL-6, IL-11etc.
   (More than 20 have been described)

iii. *Third group* : is made up of the colony-stimulating factors that regulate proliferation and maturation of red and white blood cells.
   *Example* : Stem cell factor (SCF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor M-CSF), GM-CSF etc.

*(Ref. Ganong 22th edition; page- 44; 520)*

**Growth periods**

There are two periods of rapid growth, the first in *infancy* and the second in *late puberty* just before growth stops. The first period of accelerated growth is partly a continuation of the fetal growth period. The second growth spurt, at the time of puberty, is due to growth hormone, androgens, and estrogens, and the subsequent cessation of growth is due in large part to closure of the epiphyses by estrogens. Since girls mature earlier than boys, this growth spurt appears earlier in girls. Of course, in both sexes the rate of growth of individual tisstics varies.

It is interesting that at least during infancy, growth is not a continuous process but is episodic or saltatory. Increases in length of human infants of 0.5-2.5 cm in a few days are separated by periods of 2-63 days during which no measurable growth can be detected. The cause of the episodic growth is unknown.

*(Ref. Ganong 22th edition, Page-404)*

**Catch-up Growth**

Following illness or starvation in children, there is a period of *catch-up-growth* during which the growth rate is greater than normal. The acelerated growth usually continues until the previous growth curve is reached, then slows to normal. The mechenism that bring about and control catch-up growth are unknown.

*(Ref. Ganong 22th edition, Page 406)*

**Disorder of secretion of anterior pituitary**

1. *Hyperactivity or Hyperpituitarism* :
   a. *Gigantism or giantism* : In the young before union of the epiphysis of the long bones.
   b. *Acromegaly* : After union of the epiphysis of the long bones.
   c. *Cushing syndrome* : (Pituitary basophilism).
   d. Other Hormone-Secreting Tumors : Prolactin-secreting tumors are common.
2. *Hypoactivity or Hypopituitarism :*
   a. *Dwarfism* : Pituitary insufficiency in the young produces Dwarfism.
   b. In the adult it causes - Simmond's cachexiar or sheehan's syndrome.
   c. Acromicria (Rare).

*(Ref. (Ref. Ganong 21th edition; and Shahana 2nd-695)*

**Panhypopituitarisn**

This term means decreased secretion of all the anterior pituitary hormones.

*Cause :* It may be

i. Congenital (present from birth). Or,
ii. Suddenly occur. Or,
iii. May occur slowly at any period of life.

*Panhypopituitarism in adult* (Shelhan's syndrom) :

*Cause :* It occurs in two tumoric conditions

i. Cranipharyngiomas
ii. Chromophobe tumor.

It may also occurs in thrombosis of the pituitary blood vessel.

*Effect or features :*

i. Hypothyroidism.
ii. Decrease production of glucocorticoids by the adre nal gland.
iii. Suppressed secretion of the gonadotropic hormones to the point that sexual functions are lost.

*(Ref. Guyton & Hall-11th edition; Page 926)*

## Dwarfism

Most instances of dwarfism result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood. In general, all the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child of 4 to 5 years, and the same person on reaching the age of 20 years may have the bodily development of a child of 7 to 10 years.

*(Ref. Guyton & Hall-11th edition; Page 926)*

*Short stature* can be due to- i. GRH deficiency, ii. growth hormone deficiency, iii. deficient secretion of IGF-I, or iv. other causes. Isolated growth hormone deficiency is often due to GRH deficiency, and in these instances, the growth hormone response to GRH is normal. However some patient with isolated growth hormone deficiency have abnormalities of their growth hormone-secreting cells.

1. ***Laron dwarfism*** : In this group of dwarfed children, the plasma growth hormone concentration is normal or elevated but their growth hormone receptors are unresponsive as a result of loss-of-function mutations of the gene for the receptors. The resulting condition is known as *growth hormone insensitivity* or *Laron dwarfism*. Plasma IGF-I is markedly reduced, along with IGFBP-3, which is also growth hormone-dependent.
2. *Psychosocial dwarfism* or the ***Kaspar Hauser syndrome*** : Chronic abuse and neglect can also cause dwarfism in children. This condition is known as psychosocial dwarfism or the Kaspar Hauser syndrome, named for the patient with the first reported case.
3. ***Achondroplasia***, the most common form of dwarfism in humans, is characterized by short limbs with a normal trunk. It is an autosomal dominant condition caused by a mutation in the gene that codes for *fibrohlast growth factor receptor 3 (FGFR3)*. This member of the fibroblast growth receptor family is normally expressed in cartilage and the brain.

*(Ref. Ganong 22th edition, Page 407)*

## Gigantism

*Patho-physiology (cause)* : Occasionally, the acidophilic, growth hormone-producing cells of the anterior pituitary gland become excessively active, and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones. If the condition occurs before adolescence, before the epiphyses of the long bones have become fused with the shafts, height increases so that the person becomes a giant as tall as 8 feet.

*Effects* :

1. The giant ordinarily has *hyperglycemia*.
2. The *beta cells of the islets of Langerhans* in the pancreas are *prone to degenerate* because they become overactive owing to the hyperglycemia. Consequently, in about 10 per cent of giants, *full-blown diabetes mellitus* finally develops.
3. In most giants, *panhypopituitarism* eventually develops if they remain untreated, because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed.

   This eventual general deficiency of pituitary hormones usually causes death in early adulthood.

*Management* : However, once gigantism is diagnosed, further effects can often be blocked by microsurgical removal of the tumor from the pituitary gland or by irradiation of the gland.

*(Ref. Guyton & Hall-11th edition; Page 926)*

## Acromegaly

Tumors of the somatotropes of the anterior pituitary secrete large amounts of growth hormone, leading in adults to *acromegaly*. Hypersccretion of growth hormone is accompanied by hypersecretion of prolactin in 20-40% of patients with acromegaly. In addition, secretion of glycoprotein hormone α subunits is said to occur in up to 37% of patients. Acromegaly can be caused by extrapituitary as well as intrapituitary growth hormone-secreting tumors and by hypothalamic tumors that secrete GRH, but these are rare.

*Clinical features* :

1. The principal findings in acromegaly are those related to the local effects of the tumor
   a. Enlargement of the sella turcica
   b. Headache
   c. Visual disturbances.
2. Those due to growth hormone secretion.
   a. Enlargement of the hands and feet (***acral parts***; hence the term acromegaly) and a protrusion of the lower jaw (prognathism).
   b. Overgrowth of the malar, frontal, and facial bones combines with prognathism to produce the coarse facial features called *acromegalic facies*.
   c. Body hair is increased in amount.
   d. The skeletal changes predispose to osteoarthritis.

About 25% of patients have abnormal glucose tolerance tests, and 4% develop lactation in the absence of pregnancy.

*(Ref. Ganong 21th edition, Page-413)*

# Posterior Pituitary

The posterior ptuitary gland, also called *neurohypophysis*, is composed mainly of glial-like cells called *pituicytes*. However, the pituicytes do not secret hormones; they act simply as a supporting structure for large numbers of *terminal nerve fibres* and *terminal nerve endings* from nerve tracts that originate in the *supraoptic* and *paraventri cular nuclei* of the hypothalamus. These tract pass to the neurohypo physis through the pituitary stalk *(hypophy sial stalk)*.

*(Ref. Guyton & Hall-11th edition; Page 927)*

*Hormones of the posterior pituitary* :

i. Anti-diuretic homone (ADH), also called vasopressin.

ii. Oxytocin.

*(Ref. Guyton & Hall-11th edition; Page 927)*

*Site of ADH & oxytocin secretion* : ADH is fromed primarily in the the supraoptic nuclei, whereas oxytocin is fromed primarily in the the paraventricular nuclei of the hypothalamus. Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.

*(Ref. Guyton & Hall-11th edition; Page 928)*

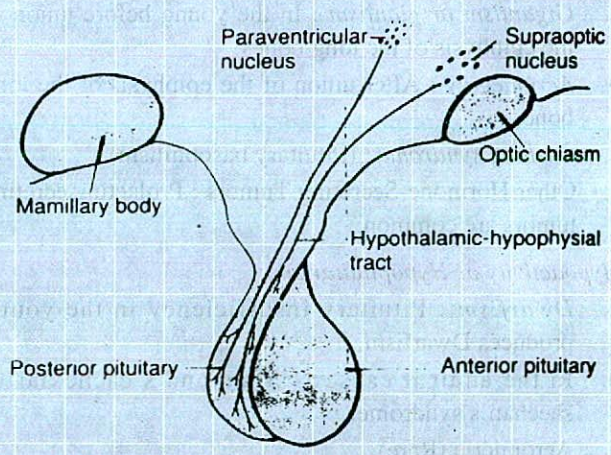



Fig. 8-6. *Hypothalamic control of the posterior pituitary.*

**Function of ADH**

A. *Antidiuretic effect :*

1. It causes reabsorption of water from kidney tubule (collecting ducts and tubules).
2. It maintains osmolarity and $Na^+$ concentration in extracellular fluid.
3. It reduces $Cl^-$ absorption and increases $Cl^-$ loss.

B. *Vasoconstrictor and pressure effects* : Higher concentration

of ADH have a potent effect of constricting the arterioles throughout the body and therefore of increasing the arterial pressure. For this reason, ADH has another name, *vasopressin*.

*(Ref. Guyton & Hall-11th edition; Page 928)*

**Function of Oxytocin**

1. *On pregnant uterus :* Toward the end of gestation it causes contraction of fundus and body and relaxation of cervix of uterus, hence helps in parturation.
2. *On non-pregnant uterus :* It increases the receptive contraction of non pregnant uterus during coitus and helps in transport of spermatoza.
3. *On milk ejection by the breast :* It causes constriction of myoepithelial cells of lactating mammary gland to expell the accumulated milk from the alveoli of the ducts after suckling stimuli on the nipple.

*(Ref. Guyton & Hall-11th edition; Page 929)*

***Mechanism of water reabsorption by ADH***

*or Physiologic functions of ADH* : Extremely minute quantities of ADH -as small as 2 nanograms when injected into a person can cause decreased excretion of water by the kidneys (antidiuresis).

*Briefly*, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

*Mechenism* : The mechanism by which ADH acts on the ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called aquaporins. When ADH acts on the cell, it first combines with membrane receptors that cause the formation of cAMP inside the tubular cell cytoplasm. This in turn causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability.

*Duration* : All this occurs within 5 to 10 minutes. Then in the absence of ADH, the entire process reverses in another 5 to 10 minutes.

*Effects* : Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid to the peritubular fluid. Water is then absorbed from the collecting tubules and ducts by osmosis.

*(Ref. Guyton & Hall-11th edition; Page 928)*

**Regulation of ADH production**

1. *Osmotic regulation* : When a concentrated electrolyte solution is injected into the artery that supplies the hyothalamus, the ADH neurons in the supraoptic and paraventricular nuclei immediately transmit impulses into the posterior pituitary to release large quantities of ADH into the circulating blood, sometimes increasing the ADH secretion to as high as 20 times normal. Conversely, injection of a dilute solution into this artery causes cessation of the impulses and therefore almost total cessation of ADH secretion. Thus, the concentraon of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

   The precise way that the osmotic concentration of the extracellular fluids controls ADH secretion is not clear. Yet somewhere in or near the hypothalamus are modified neuron receptors called *osrnoreceptors*.

   a. *When the extracellular fluid becomes too concentrated*, fluid is pulled by osmosis out of the osmoreceptor cell, dccreasg its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion.

   b. Conversely, *when the extracellular fluid becomes too dilute*, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion.

   Although some research workers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei themselves), others believe that they are located in the *organum vasculosum*, a highly vascular structure in the anteroventral wall of the third ventricle.

2. Regardless of the mechanism, concentrated body fluids do stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. Therefore, a feedback control system is available to control the total osmotic pressure of the body fluids.

*(Ref. Guyton & Hall-11th edition; Page 928, 929)*

**Inappropriate hypersecretion of antidiuretic hormone** (SIADH) : In this syndrome vasopressin (ADH) is responsible not only for dilutional hyponatremia but also for loss of salt in the urine when water retention is sufficient to expand the ECF volume, reducing aldesterone secretion. This occurs in patients with cerebral disease *(cerebral salt wasting)* and pulmonary disease *(pulmonary salt wasting)*.

Hypersecretion of vasopressin in patients with pulmonary diseases such as lung cancer may be due in part to the interruption of inhibitory impulses in vagal afferents from the stretch receptors in the atria and great veins. However, a significant number of lung tumors and some other cancers secrete vasopressin.

Patients with inappropriate hypersecretion of vassopressin have

been succesfully treated with demeclocycline, an antibiotic that reduces the renal response to vasopressin.

*(Ref. Ganong 22th edition; page-246)*

### Oxytocin

***Oxytocin causes contraction of the pregnant uterus*** : The hormone oxytocin, in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby. This is supported by the following facts :

i. In a hypophysectomized animal, the duration of labor is prolonged, thus indicating a possible effect of oxytocin during delivery.

ii. The amount of oxytocin in the plasma increases during labor, especially during the last stage.

iii. Stimulation of the cervix in a pregnant animal elicits nervous signals that pass to the hypothalamus and cause increased secretion of oxytocin.

*(Ref. Guyton & Hall-11th edition; Page 929)*

***Oxytocin aids in milk ejection by the breasts*** : Oxytocin also plays an especially important role in *lactation*. In lactation, it causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it from the ducts by suckling.

*Mechanism* : The suckling stimuli on the nipple of the breast cause signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin then is carried by the blood to the breasts, where it causes contraction of *myo-epithelial cells* that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called *milk letdown* or *milk ejection.*

*(Ref. Guyton & Hall-11th edition; Page 929)*

### Regulation of secretion of oxytocin

Stimulation of the paraventricular nucleus causes its neuronal cells to secrete the hormone oxytocin. This in turn causes increased contractility of the uterus as well as contraction of the myoepithelial cells that surround the alveoli of the breasts, which then causes the alveoli to empty the milk through the nipples. At the end of pregnancy, especially large quantities of oxytocin are secreted, and this secretion helps to promote labor contractions that expel the baby. Also, when a baby suckles the mother's breast, a reflex signal from the nipple to the posterior hypothalamus causes oxytocin release and the oxytocin then performs the necessary function of contracting the ductules of the breast, thereby expelling milk through the nipples so that the baby can nourish itself. *(Ref. Guyton & Hall-11th edition; Page 929)*

## Thyroid gland

*Physiologic anatomy of thyroid gland :* Thyroid gland consists of large numbers of follicles (100-300 meters in diameter) filled with a proteinous secretory substance called colloid. The follicle is lined by single layer of cuboidal epithelial cells which become flattened in inactive state and become tall columnar in active state.

Major constituent of colloid is thyroglobulin which contains the thyroid hormones within its molecules. It also contain mono-iodotyrosin, di-iodotyrosin, tri-iodotyrosin.

The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as rich as that of any other area of the body; with the possible exception of the adrenal cortex.

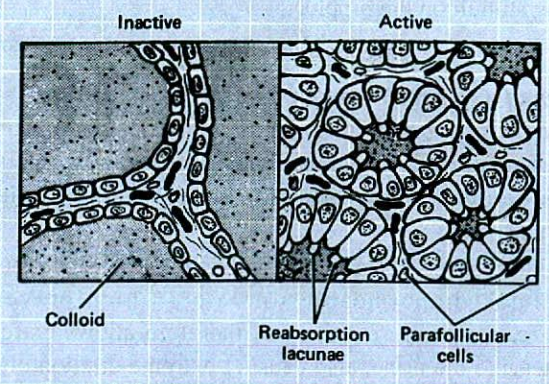



Fig. 8-7. *Thyriod histology.*

The thyroid gland begins to function from the midterm of fetal life. Food, iodine deficiency in the mother diet may lead to hypo function of the thyroid in the fetus and its consequent hazards.

i. *Weight :* 20 gm

ii. *Number of follicles :* 3 million.

iii. *Diameter of each follicle* : 100-300 μm

iv. *Types of cells :*

a. Follicular cells : These secrete *thyroxine ($T_4$) and Tri-iodothyronin ($T_3$).*

b. Para follicular cells : These secrete *thyrocalcitonin.*

About 93% of metabolically active hormones secreted by the thyroid gland is thyroxine and 7% is triiodothyronine. However, almost all the thyroxine is eventually converted to triidothyronine in the tissues.

*(Ref. Guyton & Hall-11th edition; Page 931)*

*Functions of thyroid cells :*

1. They collect and transport iodine.
2. They synthesize thyroglobulin and secret it into the colloid.
3. They remove the thyroid hormones from thyroglobulin and secret them into the circulation.

*(Ref. Ganong 22th edition, Page 319)*

**Difference between inactive and active condition of thyroid follicle :**

| *Active* | *Inactive* |
|---|---|
| 1. Cells become columner. | 1. Cells become flat and squamous. |
| 2. The lining epithelium increases and become folded. | 2. Do not increases. |
| 3. Mitochondria and golgi complex increases in the cell. | 3. Mitochondria less in number. |
| 4. Vesicles are irregular and basophilic in stain. | 4. Regular and acidic in stain. |

**Thyroglobulin**

This is a large glycoprotein molecules. This glycoprotein is made up of two subunits. $T_3$ and $T_4$ are synthesized in the colloid by iodination and condensation of tyrosine molecules bound in peptide linkage in thyroglobulin.

*Molecular weight* : 660,000.

*Content* :

i. Carbohydrate- 10% by weight.
ii. 123 tyrosine residues, but only 4-8 of these are normally incorporated into thyroid hormones.

*Site of synthesis :* Endoplasmic reticulumn and Golgi apparatus of thyroid cells synthesize and secrets into the colloids by exocytosis of granules that also contains thyroid peroxidase.

*Serum level :* 6 ng/ml *(Ref. Ganong 22th edition)*

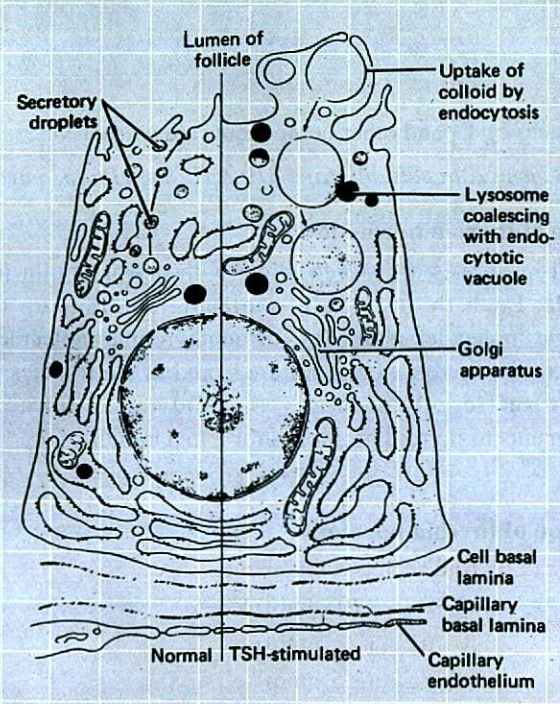



Fig. 8-8. *Thyroid cell.*

Thyroid hormones remain bound to thyroglobulin until secreted. When thyroid hormones are secreted , colloid is ingested by the thyroid cells, the peptide bonds are hydrolyzed, and free $T_4$ and $T_3$ are discharged into the capillaries.

*(Ref. Ganong 22th edition, Page 319 & Guyton 11th ed; P 932)*

**Requirement of iodine for formation of thyroxine**

To form normal quantities of thyroxin about 50 mg of iodine in the form of iodides are required each year and 1 mg/ week.

To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

*(Ref. Guyton & Hall-11th edition; Page 931)*

*Sources of iodine :*

1. Table salt : iodized salt
2. Sea fish, vegetables near sea land
3. Water etc.

*Fate of ingested iodine :* After absorption from the intestine into the blood most of them are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and for synthesis of the thyroid hormone.

*(Ref. Guyton & Hall-11th edition; Page 931)*

**Iodine metabolism**

Iodine is a raw material essential for thyroid hormone synthesis. Ingested iodine is converted to iodide and absorbed.

1. *Minimum daily iodine intake* : The minimum daily iodine intake that will maintain normal thyroid function is 150 µg in adults, but in the United States the average dietary intake is approximately 500 µg/d.
2. *Normal plasma $I^-$ level* is about : 0.3 µg/dL.
3. *$I^-$ distribution* :
   a. $I^-$ is distributed in a 'space' of approximately 25 L (35% of body weight). The principal organs that take up the $I^-$ are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in the urine.
   b. About 120 µg/d enter the thyroid at normal rates of thyroid hormone synthesis and secretion. The thyroid secretes 80 µg/d as iodine in $T_3$ and $T_4$.
   c. 40 micrograms of $I^-$ per day diffuses into the ECF.
   d. The secreted $T_3$ and $T_4$ are metabolized in the liver and other tissues, with the release of 60 mg of $I^-$ per day into the ECF.

   The total amount of $I^-$ entering the ECF is thus 500 + 40 + 60, or 600 µg/d; 20% of this $I^-$ enters the thyroid, whereas 80% is excreted in the urine.
5. *Excretion* : Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed (enterohepatic circulation), but there is a net loss of $I^-$ in the stool of approximately 20 µg/d.

*(Ref. Ganong 22th edition, Page-317)*

**Iodide trapping** or *iodide pump*

The thyroid concentrates iodide by actively transporting it from the circulation to the colloid. The transport mechanism is frequently called the *iodide-trapping mechanism* or *iodide pump*. The pump is an example of secondary active transport : $Na^+$ and $I^-$ are cotransported into the thyroid cell, and the $Na^+$ is pumped into the interstitium by $Na^+$-$K^+$ ATPase. The $Na^+$-$I^-$ cotransporter has been cloned and has 12 transmembrane domains with its amino and carboxyl terminals inside the cell.

The thyroid cell is about 50 mV negative relative to the interstitial area and the colloid; ie, it has a resting membrane potential of -50 mV. Iodide is pumped into the cell at its base against this electrical gradient, then diffuses down the electrical gradient into the colloid. In the gland, iodide is rapidly oxidized and bound to tyrosine.

N.B. The salivary glands, the gastric mucosa, the placenta, the ciliary body of the eye, the choroid plexus, and the mammary glands also transport iodide against a concentration gradient, but their uptake is not affected by TSH. The mammary glands also bind the iodine; diiodotyrosine is formed in mammary tissue, but $T_4$ and $T_3$ are not. The physiologic significance of all these extrathyroidal iodide-concentrating mechanisms is obscure.

*(Ref. Ganong 22th edition, Page-319)*

**Synthesis of thyroid hormone**

1. *Formation and secretion of thyroglobulin by the thyroid cells* : Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. The thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.
2. *Oxidation of iodide ion* : In the thyroid gland, iodide is oxidized to iodine and bound in a matter of seconds to the 3 position of tyrosine molecules attached to thyroglobulin. The enzyme responsible for the oxidation and binding of iodide is *thyroid peroxidase*, with hydrogen peroxide accepting the electrons.
3. *Iodination of tyrosin and formation of thyroid hormone-'organification' of thyroglobulin* : The binding of iodine with the thyroglobulin molecule is called *organification* of thyroglobulin. Tyrosine is first iodinised to monoiodotyrosine. Monoiodotyrosine (MIT) is next iodinated in the 5 position to form diiodotyrosine (DIT). Two DIT molecules then undergo an oxidative condensation to form $T_4$ with the elimination of the alanine side chain from the molecole that forms the outer ring.
4. *Coupling* : There are two theories of how this coupling reaction occurs :
   a. One holds that the coupling occurs with both DIT molecules attached to thyroglobulin (intramolecular coupling).
   b. The other holds that the DIT that forms the outer ring is first detached from thyroglobulin (intermolecular coupling).

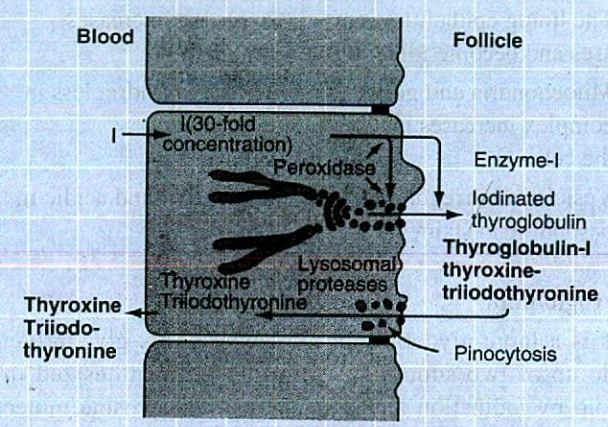



Fig. 8-9. *Thyroid cellular mechenisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood.*

In any case, thyroid peroxidase is probably involved in coupling as well as iodination. $T_3$ is probably formed by condensation of MIT with DIT. A small amount of $T_3$ is also formed, probably by condensation of DIT with MIT.

In the normal human thyroid, the average distribution of iodinated compounds is :

| | |
|---|---|
| MIT | : 23 % |
| DIT | : 33 % |
| $T_4$ | : 35 % |
| $T_3$ | : 07 % |

Only traces of $T_3$ and other components are present.

*(Ref. Ganong 22th edition, Page 319 & Guyton 11th ed; page 932)*

**Storage of thyroid hormone**

Thyroid hormones are stored along with thyroglobulin in the colloids. Each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.

*(Ref. Guyton & Hall-11th edition; Page 933)*

**Secretion of thyroid hormone**

The human thyroid secrets daily about-

1. $T_4$ : 80 µg (103 nmol)
2. $T_3$ : 04 µg (7 nmol)
3. $RT_3$ : 02 µg (3.5 nmol)

However, MIT and DIT are not secreted.

*Procedure* : The thyroid cells ingest colloid by endocytosis. This chewing away at the edge of the colloid produces the reabsorption lacunae seen in active glands. In the cells, the globules of colloid merge with lysosomes. The peptide bonds

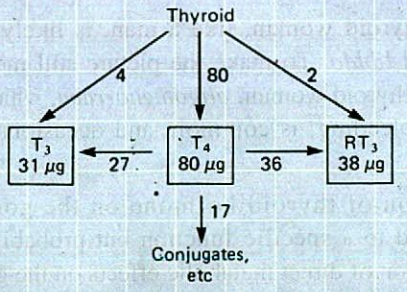



Fig. 8-10. *Secretion and interconversion of thyroid hormones in normal adult humans. Figures are in micrograms per day. Note that most of the $T_3$ and $RT_3$ are formed from $T_4$ deiodination in the tissues, and only small amounts are secreted by the thyroid.*

between the iodinated residues and the thyroglo bulin are broken by *proteases* in the lysosomes, and $T_4$, $T_3$, DIT, and MIT are liberated into the cytoplasm. The iodinated tyrosines are deiodinated by a microsomal *iodotyrosine deiodinase*. This enzyme does not attack iodinated thyronines, and $T_4$ and $T_3$ pass into the circulation. The iodine liberated by deiodination of MIT and DIT is reutilized in the gland and normally provides about twice as much iodide for hormone synthesis as the iodide pump does. In patients with congenital absence of the iodotyrosine deiodinase, MIT and DIT appear in the urine and there are symptoms of iodine deficiency.

*(Ref. Ganong 21th edition, Page-322)*

**Transport of thyroid hormone**

The normal total plasma level of thyroid hormone in adults is (approximately) :

1. $T_4$ : 8 μg/dL (103 nmol/L)
2. $T_3$ : 0.15 μg/dL (2.3 nmol/L).

*Protein binding* : Large amounts of both are bound to plasma proteins. Both are measured by radioimmunoassay.

The free thyroid hormones in plasma are in equilibrium with the protein-bound thyroid hormones in plasma and in tissues. Free thyroid hormones are added to the circulating pool by the thyroid. It is the free thyroid hormones in plasma that are physiologically active and that inhibit pituitary secretion of TSH.

Many other hormones are bound to plasma proteins, and there is an equilibrium between their free active forms and their bound inactive forms in the circulation. The function of protein-binding appears to be maintenance of a large pool of readily available free hormone. In addition, at least for $T_3$, hormone-binding prevents excess uptake by the first cells encountered and promotes uniform tissue distribution.

*(Ref. Ganong 22th edition)*

*Binding of thyroid hormones to plasma proteins in normal adult humans :*

| *Protein* | *Plasma Concentration (mg/dL)* | *Amount of Circulating Hormone Bound* | |
|---|---|---|---|
| | | $T_4$ | $T_3$ |
| Thyroxine binding globulin (TBG) | 2 | 67 | 46 |
| Thyroxine binding prealbumin (TBPA) | 15 | 20 | 1 |
| Albumin | 3500 | 13 | 53 |

*(Ref. Ganong 22 th edition; page-321)*

**Difference between $T_3$ & $T_4$**

| *$T_3$* | *$T_4$* |
|---|---|
| 1. Its rapidity and intensity of action is 4 times potent than $T_4$. | 1. It has less function than $T_3$ |
| 2. It has less affinity to bind with plasma protein. | 2. It has high affinity to bind with plasma protein. |
| 3. Its plasma concentration is less than $T_4$. | 3. Its plasma concentration is more than $T_3$. |
| 4. Duration of action is less. | 4. Duration of action is more. |
| 5. Contain one molecule of MIT & DIT. | 5. It contains two molecule of DIT. |

*(Ref. Guyton & Hall-11th edition)*

***Mechanism of action of thyroid hormone*** : Most of the thyroxine secreted by the thyroid is converted to triiodothyronine. Intracellular thyroid hormone receptors have a very high affinity for triiodothyronine. Consequently about 90 per cent of the thyroid hormone molecules that bind with the receptors is triiodothyronine, and only 10 per cent thyroxine.

*Thyroid hormones activate nuclear receptors* : The thyroid hormone receptors are either attached to the DNA genetic strands or located in proximity to them. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins. However not all the proteins are increased by similar percentages- some only slightly, and others at least as much as sixfold. It is believed that most, if not all, of the actions of thyroid hormone result from the subsequent enzymatic and other functions of these new proteins.

*(Ref. Guyton & Hall 11th edition)*

**Functions of thyroid hormone**

Some of the wide spread effects of thyroid hormones in the body are secondary to stimulation of $O_2$ consumption (*calorigenic action*), althogh the hormones also affect growth and development in mammals, help in regulation of lipid metabolism and increase the absorption of carbohydrates from the intestine. They also increase the dissociation of oxygen from hemoglobin by increasing red cell 2,3-diphosphoglycerate (DPG).

*Physiologic effects of thyroid hormones* :

| *Target tissue* | *Effect* | *Mechanism* |
|---|---|---|
| Heart | Chronotropic | Increase number & affinity of β-adrenergic receptors. |
| | Inotropic | Enhance responses to circulating catecholamines.<br>Increase proportion of alpha myosin heavy chain (with higher ATPase activity. |
| Adipose tissue | Catabolic | Stimulate lipolysis. |
| Muscle | Catabolic | Increase protein breakdown. |
| Bone | Developmental | Promote normal growth and skeletal development. |
| Nervous system | Developmental | Promote normal brain development. |
| Gut | Metabolic | Carbohydrate absorption |
| Lipo-protein | Metabolic | Stimulate formation of LDL receptors. |
| Other | Calorigenic | Stimulate oxygen consumption by metabobically active tissues (exceptions testes, uterus, lymph nodes, spleen, anterior pituitary)<br>Increase metabolic rate. |

*(Ref. Ganong 22th edition; page 324)*

***Effects of thyroid hormones on growth :*** Thyroid hormones are essential for normal growth and skeletal maturation. In hypothyroid children, bone growth is slowed and epiphysial closure delayed. In the absences of thyroid hormones, growth hormone secretion is also depressed, and thyroid hormones potentiate of effect of growth hormone on the tissue.

*(Ref. Ganong 22th edition, Page-326)*

***Effects of thyroid hormones on sextual function*** : For normal sexual function, thyroid secretion needs to be approximately normal. In men, lack of thyroid hormone is likely to cause *loss of libido*; great excesses of the hormone, however, sometimes cause *impotence*.

In women, lack of thyroid hormone often causes *menorrhagia* and *polymenorrhea*, that is, respectively, excessive and frequent menstrual bleeding. Yet, strongely enough, in other women thyroid lack may cause irregular periods and occasionally even *amenorrhea*.

A hypothyroid woman, like a man, is likely to have greatly *decreased libido*. To make the picture still more confusing, in the hyperthyroid woman, *oligomenorrhea*, which means greatly reduced bleeding, is common, and occasionally *amenorrhea* results.

The action of thyroid hormone on the gonads cannot be pinpointed to a specific function but probably results from a combination of direct metabolic effects on the gonads as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones that control the sexual functions.

*(Ref. Guyton & Hall-11th edition; Page 937)*

**Regulation of thyroid secretion**

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH. TSH secretion is increased by

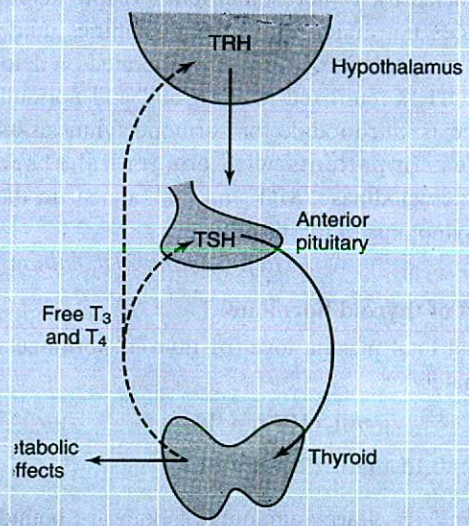



Fig. 8-11. *Feedback control of thyroid secretion. The dashed arrows indicate inhibitory effects, and the solid arrows indicate stimulatory effects*

the hypophysiotropic hormone *thyrotropin-releasing hormone (TRH)* and inhibited in a negative feedback fashion by circulating free $T_4$ and $T_3$. The effect of $T_4$ is enhanced by production of $T_3$ in the cytoplasm of the pituitary cells by the 5'-DII they contain. TSH secretion is also *inhibited by* stress, and in experimental animals it is *increased by* cold and *decreased by* warmth.

*(Ref. Ganong 22th edition, Page-326)*

**Thyroid functions tests :**

Thyroid functions tests are as follows-

1. *Determination of BMR* :
   In normal BMR : 40 cal/sq.m of surface

In hyperthyroidism : 50% above normal
In hypothyrodism : 30-40% below.

2. *Estimation of PBI (protein bind iodine) test* :
In normal : 4 to 8 µgm
In hyperthyroidism : More than 8 µgm
In hypothyroidism : Below than 4 µgm.

3. *Determination of Butanolextractable iodine test* :
In normal : 2-6 µgm/100 dl
In hyperthyroidism : Above 6 µgm %
In hypothyroidism : Below 2 µgm%.

4. *Determination of blood cholesterol level* :
In normal : 150 -300 mg%.
In hyperthyroidism : Become less than 150 mg %.
In hypothyroidism : Become more than 300 mg %.

5. *Determination of blood sugar level* :
Normally : 80-120 mg %
In hyperthyroidism : Above normal.
In hypothyroidism : Below normal.

6. *Determination of uptake of $I^{131}$ by thyroid gland* :
Normal value : 0.75 µgm/day.
In hyperthyroidism : 40% above normal.
In hypothyroidism : 20% below normal.

7. *Thyroid suppression test* : Normally $T_3$ administration suppress the uptake of $I^{131}$ by thyroid gland. In hyperthyroidism 20 times normal dose of $T_3$ cannot properly suppressed $I^{131}$ uptake by the thyroid gland.

** *Direct test* :

1. *RIA (Radio-immunoassay)* : Normal serumvalue-
$T_3$ : 0.15 µg/dl (2.3 nmol/L)
$T_4$ : 8 µg/dl (103 nmol/L).
TSH: In hyperthyroidism, TSH concentration will be near zero whereas it is very high in hypothyroidism.
2. Thyroid imaging
3. Radio-active iodine uptake by thyroid cells.
4. $FT_4$.

**Anti thyroid substances**

Drugs that suppress the thyroid secretion are called antithyroid substances. The three best known of these are thiocyanate, propylthiouracil and high concentration of inorganic iodides.

The mechanism by which each of these blocks thyroid secretion are as follows -

i. *Thiocyanate* : By decreasing iodide tapping.
ii. *Propylthiouracil* : By depressing thyroid hormone formation.
iii. High concentration of *inorganic iodides*: By decreasing thyroid activity and thyroid gland size.

*(Ref. Guyton & Hall-11th edition; Page 939).*

**Disorders of thyroid gland**

The thyroid gland may undergo two types of disorders-

1. *Hperthyroidism* : When there is over secretion of thyroid hormones, the clinical syndroms is named as thyrotoxicosis. The most common cause is *Graves' disease (exophthalmic goitre)*.

*Causes of hyperthyroidism* :

i. *Thyroid overactivity*
   a. Graves' disease
   b. Solitary toxic adenoma
   c. Toxic multinodular goiter
   d. TSH-secreting pituitary tumor
   e. Thyroiditis
   f. Mutations causing constitutive activation of TSH receptors.

ii. *Extrathyroidal* :
   a. Administration of T3 or T4 (factitious or iatrogenic hyperthyroidism)
   b. Ectopic thyroid tissue.

2. *Hypothyroidism* : When there is under-secretion of thyroid hormones. This may affect children as well as adults.
   a. When it occurs in infants and children is called *cretinism.*
   b. When it affects adults is called *myxedema.*

*Causes of congenital hypothyroidism* :

a. Maternal iodine deficiency
b. Fetal thyroid dysgenesis
c. Inborn errors of thyroid hormone synthesis
d. Maternal antithyroid antibodies that cross the placenta
e. Fetal hypopituitary hypothyroidism.

*(Ref. Ganong 22th edition, Page 328-329)*

**Hyperthyroidis (*thyrotoxicosis*)**

*Causes of thyrotoxicosis* : The most common cause is *Graves' disease (exophthalmic goiter)*, although it may be caused by a variety of other disorders, including, in rare instances TSH-secreting tumors of the anterior pituitary or constitutive activation of the TSH receptor.

Four kinds of antibodies against the thyroid are found in thyroid disease. The mechenism responsible for the production of autoimmune antibodies against the thyroid is still unknown.

*Hyperthyroidis (thyrotoxicosis) is characterized by / clinical F* :

1. Nervousness
2. Weight loss
3. Hyperphagia
4. Heat intolerance
5. Increased pulse pressure
6. A fine tremor of the outstretched fingers
7. A warm soft skin

8. Sweating
9. BMR from +10 to as high as +100.

Thyrotoxicosis places a considerable load on the cardiovascular system, and particularly in elderly patients, most or even all the symptoms are cardiovascular. There is an increased incidence of atrial fibrillation, and the decrease in peripheral resistance as a result of cutaneous vasodilation predisposes patients to high output failure.

*(Ref. Ganong 22th edition, Page 329)*

**Graves' disease** (***exophthalmic goiter***)

Graves' disease is an autoimmune disease in which circulating antibodies formed against the TSH receptor activate the receptor, making the gland hyperactive. ***TSH receptor-stimulating antibodies*** *(TSH-R [stim] Ab)* are the antibodies responsible for Graves' disease.

In Graves' disease, there is marked stimulation of the secretion of thyroid hormones, and the high circulating $T_4$ and $T_3$ levels inhibit TSH secretion, so the circulating TSH level is depressed. Increasing levels of thyroid hormones tend to cause increased formation of the antibodies, whereas decreased levels produced by treatment of the disease tend to lower but not completely prevent formation of the antibodies.

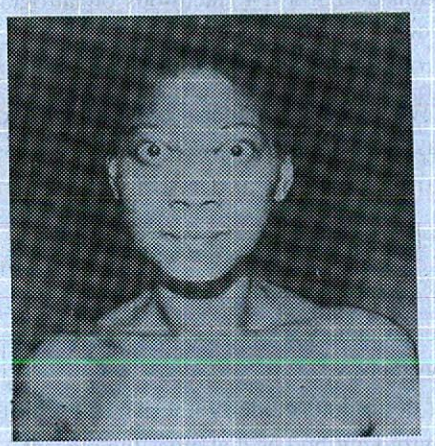


Fig. 8-12. *Graves' disease. Note the goiter and the exopthalmos.*

*Clinica features* : Same as thyrotoxicosis.

In Graves' disease, the thyroid is diffusely enlarged and there is often a protrusion of the eyeballs called *exophthalmos*.

*(Ref. Ganong 22th edition, Page 329)*

**Hashimoto's thyroiditis** : There are antibodies against thyroid peroxidase *(TPO Ab)* and TPO antibodies are elevated late in the course of chronic autoimmune thyroiditis (***Hashimoto's thyroiditis***), a condition in which thyroid cells are damaged and hypothyroidism may develop. In some cases of Hashimoto's thyroiditis, thyroid function is also inhibited by TSH-R [block] Ab.

*(Ref. Ganong 22th edition)*

**Exophthalmos**

*Cause* : The cause of of the exopthalmos is almost certainly an autoimmune attack on the extraocular muscles and orbital connective tissue by *cytotoxic antibodies*. The antibodies are formed to antigens common to the eye muscles and the thyroid. The condition responds to glucocorticoids or other agents that produce immunosuppression.

The exophthalmos in Graves' disease is due to swelling of the extraocular muscles and, to a lesser extent, the connective tissue within the rigid bony walls of the orbits. This pushes the eyeballs forward. Thyroid hormones are not directly responsible for the exophthalmos, and although exophthalmos is usually associated with hyperthyroidism and improves after treatment of the disease, it may occur before, during, or after the thyrotoxic state. In some patients with thyrotoxicosis, it is worse by thyroidectomy. In addition, it is occasionally seen in euthyroid patients with Hashimoto's thyroiditis, in patients with myxedema and in patients with no known thyroid disease.

*(Ref. Ganong 22th edition, Page 329)*

**Iodine deficiency**

When the dietary iodine intake falls below 50 µg/d, thyroid hormone synthesis is inadequate and secretion declines. As a result of increased TSH secretion, the thyroid hypertrophies, producing an ***iodine deficiency goiter*** that may become very large.

Such *endemic goiters* have been known since ancient times. Before the practice of adding iodide to table salt became widespread, they were very common in Central Europe and the area around the Great Lakes in the United States, the inland *goiter belts* where iodine has been leached out of the soil by rain so that food grown in the soil is iodine-deficient.

*(Ref. Ganong 22th edition, Page 330)*

**Hypothyroidism**

Hypothyroidism may be the end result of a number of diseases of the thyroid gland, or it may be secondary to pituitary failure (pituitary hypothyroidism) or hypothalamic failure (hypothalamic hypothyroidism). In the latter two conditions, unlike the first, the thyroid responds to a test dose of TSH, and at least in theory, hypothalamic hypothyroidism can be distinguished from the pituitary hypothyroidism by the presence in the former of a risc in plasma TSH following a test dose of TRH. The TSH response to TRH is usually normal in hypothalamic hypothyroidism, while it is increased in hypothyroidism caused by thyroid disease and decreased in hyperthyroidism because of the feedback of thyroid hormones on the pituitary gland.

*(Ref. Ganong 22th edition, Page 328)*

**Myxedema**

The syndrome of adult hypothyroidism is generally called *myxedema*, although this term is also used to refer specifically to the skin changes in this syndrome.

*Clinical features* :

1. In completely athyreotic humans, the BMR falls to about -40.
2. The hair is coarse and sparse

3. The skin is dry and yellowish (carotenemia)
4. Cold is poorly tolerated
5. The voice is husky and slow, the basis of the aphorism that '*myxedema is the one disease that can be diagnosed over the telephone.*'

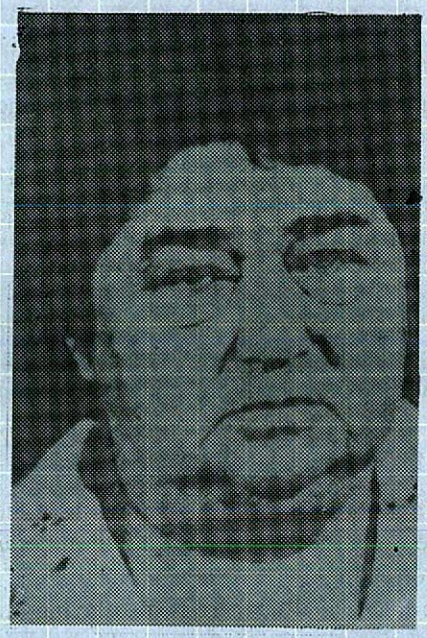


Fig. 8 -13. *A patient with myxedema.*

6. Mentation is slow
7. Memory is poor, and in some patients there are severe mental symptoms (*myxedema madness*).
8. Plasma cholesterol is elevated.

*(Ref. Ganong 22th edition, Page 328)*

## Cretinism

Children who are hypothyroid from birth or before are called *cretins.*

*Clinical features* :

1. They are dwarfed and mentally retarded.
2. They have potbellies and enlarged, protruding tongues.

Worldwide, congenital hypothyroidism is one of the most common causes of preventable mental retardation.

*Causes of cretinism or congenital hypothyroidism :*

a. Maternal iodine deficiency
b. Fetal thyroid dysgenesis
c. Inborn errors of thyroid hormone synthesis
d. Maternal antithyroid antibodies that cross the placenta
e. Fetal hypopituitary hypothyroidism.

They include not only maternal iodine deficiency and various congenital abnormalities of the fetal hypothalamo-pituitary thyroid axis but also maternal antithyroid antibodies that cross the placenta and damage the fetal thyroid.

$T_4$ crosses the placenta, and unless the mother is hypothyroid, growth and development are normal until birth. If treatment is started at birth, the prognosis for normal growth and development is good. and mental retardation can generally be avoided; for this reason, screening tests for congenital hypothyroidism are routine in all states of the USA and most other developed countries.

When the mother is hypothyroid as well, as in the case of iodine deliciency, the mental deficiency is more severe and less responsive to treatment after birth. In addition, there may be deaf-mutism and rigidity. Increased use of iodized salt has now reduced the incidence of maternal iodine deficiency. However, it is still common in many parts of the world, and it has been estimated that 20 million people in the world now have various degrees of brain damage caused by iodine deficiency in utero.

*(Ref. Ganong 22th edition, Page 328)*

## Goiter

Goiter means simply enlargement of thyroid gland. *Goiter is of two types* :

A. ***Endemic colloid goiter*** : This type of goiter occured specially in certain areas such as Swiss, Alps, in the Andes and in the great lakes region of US due to insufficient iodine present in the foodstuffs. So, this is called endemic colloid goiter.

*Mehanism :* Lack of iodine prevents the synthesis of thyroid hormone, as a result no hormone is available to inhibit the production of TSH by anterior pituitary, this allow the pituitary to secrete large quantities of TSH. This TSH causes the thyroid cells to secrete tremendous amount of *thyroglobulin colloid* in the follicle and the gland become larger and larger.

B. ***Idiopathic nontoxic colloid goiter :*** When enlargement of thyroid gland occurs in the person who do not have iodine deficiency. The exact cause of this goiter is unknown, but most patient show the signs of mild thyroioditis.

Therefore it is suggested that the thyroioditis causes slight hypothyroidism, which then increased TSH secretion and progressive enlargement of thyroid gland.

*(Ref. Guyton & Hall-11th edition; Page 941)*

*Prevention of endemic goiter :* Endemic goiter is prevented by :

1. Iodized salt : Common salt fortified with small quantities of sodium or potassium iodate. ( 1 in 100,000) .
2. Iodized oil : Intramuscular injection of iodized oil prevents endemic goitre.

*Dose* : 1-2 ml for adult.

*(Ref : Community medicine Park.)*

## Calcitonin

This hormone is synthesized by the C cells (the parafollicular cells) of the thyroid. It is a peptide hormone containing 32

amino acids with a molecular weight of approximately 3400. As a result of the action of calcitonin, the serum calcium is lowered (thus acting in the opposite direction to that of PTH). Calcitonin prevents bone resorption. Calcitonin secretion is stimulated when the serum calcium level becomes high.

It is now established that calcitonin secretion is stimulated when there is secretion of the gastro intestinal hormones, gastrin & cholecystokinin pancreozymin, which are secreted after meals ; and it is in this period, calcium absorption from the gut rises. Teleologically, this may mean a mechanism aimed to see that the serum calcium does not become dangerously high and the extra calcium (in the serum, coming from food) is deposited on the bone. In addition glucagon also stimulates it.

The exact importance of calcitonin in man, however, is still unsettled.

Calcitonin is of proven help in the pagets disease (a rare disease,characterized by bony resorption and replacement by fibrous tissues and blood vesels).

## Parathyroid Gland

*Physiologic anatomy of parathyroid gland :* Normally there are four parathyroid glands in the human being. These are located immediately behind the thyroid gland one behind each of the upper and each of the lower pole of the thyroid gland.

i. *Length :* 6 mm.
ii. *Wide :* 3 mm.
iii. *Thickness :* 2mm.
iv. *Parathyroid cells* :
   a. Chief cells : Secrets parathyroid (PTH).
   b. Oxyphil cells : Function is not certain but they are believed to be modified or depleted chief cells that no longer secrete hormone.

Removal of half of the parathyroid gland usually cause little physiological abnormality. Removal of 3of the 4 glands , cause *transient hypoparathyroidism*. But even a small quantity of parathyroid tissue is capable of hypertrophying satisfactorily to perform the function of all gland.

*(Ref. Guyton & Hall-11th edition; page 978)*

### Bone

The adult compact bone contains about 75% inorganic material and 25% organic material (dry weight). Most of the inorganic material is calcium phosphate occurring mostly in a typical crystal form, called hydroxyapatite. The shape of the hydroxyapatite is such that it causes an increase in the surface area. Rest of the calcium phosphate is in amorphous form. The amorphous form is precursor of the crystalline form.

The calcium of the bone is in dynamic equilibrium with the calcium of the ECF, i.e, the calcium leaves the bone to enter the ECF and at the same time the ECF calcium is deposited in the bone, but there is no net gain or loss of calcium in either the bone or in the ECF, this dynamic equilibrium is seen in healthy adults. In the growing children Ca deposits in the bone. In osteoporesis, Ca is lost from the bone.

Bone, basically speaking, consists of a matrix of organic matter and the minerals. The matrix (also called the ground substance) consists of mucopolysaccharide and contains large number of collagen fibers.The matrix is heavily impregnated with minerals,chiefly the calcium salts, but other minerals like Mg also occur. Strontium, another element deserves special mention.

Strontium, which is a foreign metal, once introduced in the body,replaces calcium in the hydroxyapatite and remains there for many many years. Therefore radioactive strontium, once introduced in the body is difficult to remove, and it continues to emit harmful rays from the bone.

Throughout life, portions of bone, as a result of the action of parathormone, undergo resorption. The term ***resorption*** here means, lysis or eating away of organic matrix and removal of the inorganic material. But there is also laying down of new matrix and its mineralization (new bone deposition). These two processes, viz, resorption and new bone deposition, taken together constitute the process known as *remodelling.*

***Bone cells*** : There are four tyes of bone cells
i. Osteoblasts
ii. Osteoclasts
iii. Osteocytes
iv. Osteoprogenitor or mesenchymal cells.

The osteoblasts have single nucleus and they deposit new bone. Osteoclasts are giant cells containing some 15 or 20 (sometimes as many as 100) nuclei. They cause resorption of bone. Functions of osteocyte, which are very small cells and are derived from osteoblasts, are not fully known.

***Bone development*** : *The adult bone may develop in either of the two ways :*
i. Cartilaginous ossification.
ii. Membranous ossification.

*In cartilaginous ossification*, firstly, a cartilage is formed, subsequently,the cartilage is calcified, then the calcified cartilage undergoes resorption and in its place, bone is deposited.

*In membranous ossfication*, the initial cartilaginous phase does not appear. In general, the long bones like the femur and humerus develop in the cartilaginous way whereas the flat bones of skull are examples of membranous ossification. It should be remembered that calcified cartilage is not bone.

## Parathormone

Is secreted by the chief cells of the parathyroid gland. It is protein in nature. It has a molecular weight 9,500 and is composed of 84 amino acids.

*Chemistry of parathyroid hormon (Synthesis)* : It is first synthesized on the *ribosomes* in the form of *prepro-parathormone*, a polypeptide chain of about 110 aminoacids. This is cleaved first to a prohormone 90 amino acids, then to the hormone itself with 84 amino acids by the *endoplasmic reticulumn* and *Golgi apparatus*, and finally is packaged in secretory granules in the cytoplasm of the cells.

Smaller compound with as few as *34 amino acids* adjacent to the N terminus of the molecule have also been isolated from the parathyroid glands that exhibit full PTH activity. In fact, because the kidneys rapidly removed the whole 84-amino acid hormone within minutes but fail to remove many of the *fragments* for hours, a large share of the hormonal activity is caused by the fragments.

*(Ref. Guyton & Hall-11th edition; page 986)*

*Functions :*

1. It increases the blood calcium level by -
   i. Resorption of $Ca^{++}$ and $PH_4^{+3}$ from bone.
   ii. Decreases excretion of calcium by the kidneys.
   iii. Absorption of $Ca^{++}$ and $PH_4^{+3}$ from intestine
2. It decreases the phosphate concentration by causing excessive renal phosphate excretion.

*(Ref. Guyton & Hall-11th edition; page 985, 986)*

### Role of Parathormone on blood $Ca^{++}$ level

Parathormone rises blood calcium level in three ways

A. *Resorption of $Ca^{++}$ from bone* : It occurs in two phases-
   i. Slow phase
   ii. Rapid phase.

   *In rapid phase,* this hormone activate the calcium pump thereby causing rapid removal of calcium salt from bones i.e $Ca^{++}$ mobilization from bone → this $Ca^{++}$ reaches plasma → hypercalcaemia.

   *In slow phase*, this hormone activate the osteoclast cells. The activated osteoclasts then decrease deposition of calcium salt on bone and increase the blood $Ca^{++}$ level.

B. *Decrease excretion of $Ca^{++}$ from kidney* : Parathhormone binds with the receptors of the tubular epithelium which causes formation of cAMP, this increases the permeability of $Ca^{++}$ through tubular epithelium and thus increases blood $Ca^{++}$ level.

C. *Increase absorption of $Ca^{++}$ from intestine* : Parathhormone increases the permeability of intestinal epithelium to calcium as that of kidney and thus increases the absorption of $Ca^{++}$ from intestine.

*(Ref. Guyton & Hall-11th edition; page 986)*

## Calcitonin

*Role of calcitonin on blood $Ca^{++}$ level* : It decreases blood calcium level in three ways :

1. *Immediate effect* : It decreases the absorptive activities of the osteoclasts and passibly the osteolytic effect of osteocytic membrane throughout the bones and thus increases the $Ca^{++}$ deposition in bony matrix.
2. *More prolonged effect* : It decreases the formation of new osteoclasts.
3. It reduce the osteoblastic activity.

*NB.* It prevents bone resorption.

*(Ref. Guyton & Hall-11th edition; page 988)*

## Calcium metabloism

***Distribution of $Ca^{++}$ in plasma*** :

i. Normal plasma concentration of calcium : 9.4 mg/dl (about)
   : 2.4 mmol/L

*(Ref. Guyton & Hall-11th edition; page 978)*

ii. Normal plasma concentration of calcium : 10 mg/dl (about)
   : 2.5 mmol/L
   : 5 meq/L

*(Ref. Ganong 22th edition, Page-382)*

***Distribution of calcium in normal human plasma*** :

1. *Nondiffusible (protein bound)* : Approximately 41% (1.0 mmol/L) of calcium combines with plasma protein which is nondiffusible through the capillary membrane.
2. *Diffusible combined with citrate and phosphate* : Approximately 9% (0.2 mmol/L) of the calcium is diffusible through the capillary membrane but is combined with ionic substances of plasma and inerstitial fluids (citrate and phosphate, for instance) in such a manner that it is not ionized.
3. *Diffusible and ionized* : The remaining 50% of the calcium in the plasma is both diffusible through the capillary membrane and ionized.

*(Ref. Guyton & Hall-11th edition; page 978)*

***or***

*Distribution (mmol/L) of calcium in normal human plasma* :

| | | |
|---|---|---|
| Total diffusible | | 1.34 |
| Ionized ($Ca^{++}$) | 1.18 | |
| Complexed to HCO3- , citrate etc. | 0.16 | |
| Total nondiffusible (protein-bound) | | 1.16 |
| Bound to albumin | 0.92 | |
| Bound to globulin | 0.24 | |
| Total plasma calcium | | 2.50 |

*It is the free, ionized calcium in the body fluids that is a vital*

*second messenger and is necessary for blood coagulation, muscle contraction, and nerve function.*

*(Ref. Ganong 22th edition, Page-383)*

*Total body calcium level* : 1100 gm
: 27.5 mol

*(Ref. Ganong 22th edition, Page-382)*

**Regulation of calcium metabolism**

Three hormones are primarily concerned with the regulation of calcium metabolism.

1. *1,25-Dihydroxy-cholecalciferol* : Is a steroid hormone formed from vitamin D by successive hydroxylations in the liver and kidneys.
   *Function* : Its primary action is to increase calcium absorption from the intestine.
2. *Parathyroid hormone (PTH)* : Is secreted by the parathyroid glands.
   *Function* : Its main action is to mobilize calcium from bone and increase urinary phosphate excretion.
3. *Calcitonin* : A calcium-lowering hormone that in mammals is secreted primanly by cells in the thyroid gland,.
   *Function* : Inhibits bone resorption.

Although the role of calcitonin seems to be relatively minor, all three hormones probably operate in concert to maintain the constancy of the $Ca^{2+}$ level in the body fluids.

A fourth hormone, *parathyroid hormone-related protein (PTHrP)*, acts on one of the PTH receptors and is important in skeletal development in utero. There may also be a phosphate-regulating hormone, and glucocorticoids, growth hormone, estrogens and various growth factors also affect calcium metabolism.

Other *electrolytes* and *pH* affect the $Ca^{2+}$ level. Thus for example, *symptoms of tetany* appear at much higher total calcium levels if the patient ***hyperventilates,*** increasing plasma pH. Plasma proteins are more ionized when the pH is high, providing more protein anion to bind with $Ca^{2+}$.

*(Ref. Ganong 22th edition, Page-382)*

**Calcium metabolism in an adult human**

*(ingesting 25 mmol; 1000 mg of calcium* :

***In bones*** : The calcium in bone is of two types : a *readily exchangeable reservoir* and a much larger pool of *stable calcium* that is only slowly exchangeable.

There are two *independent but interacting homeostatic systems* affecting the calcium in bone.

1. *One is the system* that regulates plasma $Ca^{2+}$ and in the operation of this system, about 500 mmol of $Ca^{2+}$ per day moves into and out of the readily exchangeable pool in the bone.
2. *The other system* is the one concerned with bone remodeling by the constant interplay of bone resorption and deposition, which, in the adult, accounts for 95% of bone formation. However, the $Ca^{2+}$ interchange between plasma and this stable pool of bone calcium is only about 7.5 mmol/L.

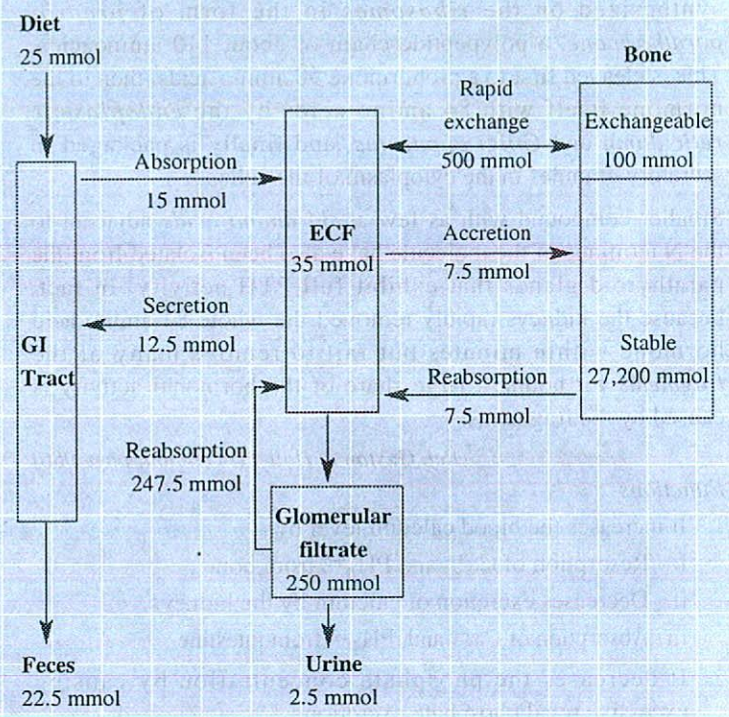



Figure 8-14. *Calcium metabolism in an adult human ingesting 25 mmol (1000 mg) of calcium per day.* (Ref. Ganong 22 th edition; page 386)

***In kidneys*** : A large amount of calcium is filtered in the kidneys. but 98-99% of the filtered calcium is reabsorbed. About 60% of the reabsorption occurs in the *proximal tubules* and the remainder in the *ascending limb of the loop of Henle* and the *distal tubule*. Distal tubuIar reabsorption is regulated by parathyroid hormone.

***In gastrointestinal tract*** : The absorption of $Ca^{2+}$ from the gastrointestinal tract is actively transported out of the intestine by a system in the brush-border of the epithelial cells that involves a calcium-dependent ATPase, and this process is regulated by 1,25-dihydroxy cholecalciferol. There is also some absorption by passive diffusion. When $Ca^{2+}$ intake is high, 1,25 dihydroxy cholecalciferol levels fall because of the increased plasma $Ca^{2+}$. Consequently, $Ca^{2+}$ absorption undergoes adaptation; ie, it is high when the calcium intake is low and decreased when the calcium intake is high. Calcium absorption is also decreased by substances that form insoluble salts with $Ca^{2+}$ (eg, phosphates and oxalates) or by alkalis, which favor formation of insoluble calcium soaps. A high-protein diet increases absorption in adults.

*(Ref. Ganong 22th edition, Page-382, 383)*

**Hypocalcemic tetany** : A decrease in extracellular $Ca^{2+}$ exerts a net excitatory effect on nerve and muscle cells in vivo. The result is *hypocalcemic tetany*

*Characteristics* :

1. *Extensive spasms of skeletal muscle*, involving especially the muscles of the extremities and the larynx.
2. *Laryngospasm* becomes so severe that the airway is obstructed and fatal asphyxia is produced.

$Ca^{2+}$plays an important role in clotting in vivo, however, the level of plasma $Ca^{2+}$ at which fatal tetany occurs is still above the level at which clotting defects would occur.

*(Ref. Ganong 22th edition, Page 382)*

## Phosphorus

Phosphate is found in ATP, cAMP, 2,3-diphospho-glycerate, many proteins, and other vital compounds in the body. Phosphorylation and dephosphorylation of protein are involved in the regulation of cell function. Therefore, it is not surprising that phosphate metabolism is closely regulated.

*Total body phosphorus* : 500-800 gm
: 16.1-25.8 mol
85-90% of which is in the skeleton.

*Total plasma phosphorus is about* : 12 mg/dL

1. *Organic compounds* : two-thirds of the total plasma phosphorus.
2. *Inorganic phosphorus* : Remaining one-third; inorganic phosphorus (Pi) mostly in $PO_4^{3-}$, $PO_4^{2-}$ and $H_2PO_4^-$.

*The amount of phosphorus normally entering bone* : is about 3 mg/kg/d (97 µmol/kg/d), with an equal amount leaving via reabsorption.

*Aabsorption in GIT* : Phosphorus is absorbed in the *duodenum* and *small intestine* by both *active transport* and *passive diffusion*. However, unlike the absorption of $Ca^{2+}$ the absorption of Pi is linearly proportionate to dietary intake. Many stimuli that increase $Ca^{2+}$ absorption, including 1,25-dihydroxycholecalciferol also increase Pi absorption.

*Reabsorption in kidneys* : The Pi in the plasma is filtered in the glomeruli, and 85-90% of the filtered Pi is reabsorbed. Active transport in the proximal tubule accounts for most of the reabsorption, and this active transport process is powerfully inhibited by parathyroid hormone.

*(Ref. Ganong 22th edition, Page 382, 383)*

### Control of secretion of Parathormone by calcium ion concentration

The calcium ion concentration in the ECF is the main factor, which controlls the secretion of parathormone.

Increase $Ca^{++}$ concentration decrease the rate of secretion of parathormone.

Decrease the $Ca^{++}$ concentration causes increase the parathormone secretion. Beside these some other factor also controls the parathormone secretion.

These includes-

i. Excessive quantities of calcium in the diet.
ii. Increase vit-D in diet.
iii. Bone absorbtion caused by the factors other than parathormone.

*(Ref. Guyton & Hall-11th ed; page-988)*

## Vitamin D

Vit-D plays an important role in $Ca^{++}$ absorption from the GIT and it also has important effect on bone deposition and bone reabsorption.

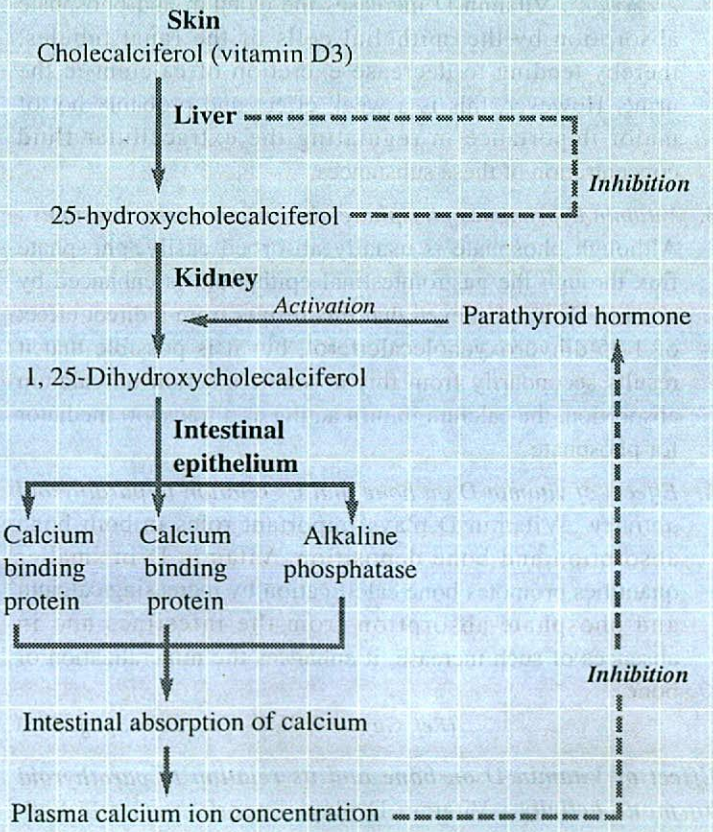
*Formation of 1,25-dihydroxycholecalciferol* : Vitamin $D_3$ (also called cholecalciferol) is formed in the skin as a result of irridation of *7-dehydrocholesterol*, a substance normally in the skin, by ultraviolet ray's from the sun.

The first step in the activation of cholecalciferol is to convert it to 25-hydroxycholecalciferol in the liver.

Then in the 2nd step 25-hydroxycholecalciferol converted into 1,25-dihydroxycholecalciferol with the help of PTH in the kidney.

*(Ref. Guyton & Hall-11th ed; page-983)*

***Activation of vitamin $D_3$ to form 1,25 dihydroxycholecalciferol and the role of vitamin D in the plasma calcium concentration*** *: (Ref. Guyton & Hall-11 edition; page 984)*



**Actions of vitamin D**

The active form of vitamin D, 1,25-dihydroxycholecalciferol, has several effects on the intestines, kidneys, and bones that increase absorption of calcium and phosphate into the extracellular fluid and contribute to feedback regulation of these substances.

1. *Hormonal effect of vitamin D to promote intestinal calcium absorption* : 1,25-dihydroxycholecalciferol itself functions as a type of *'hormone'* to promote intestinal absorption of calcium. It does this principally by increasing over a period of about 2 days, formation of a *calcium-binding protein* in the intestinal epithelial cells. This protein functions in the brush border of these cells to transport calcium into the cell cytoplasm, and the calcium then moves through the basolateral membrane of the cell by facilitated diffusion. The rate of calcium absorption is directly proportional to the quantity of this calcium-binding protein. Furthermore, this protein remains in the cells for several weeks after the 1,25-dihydroxychole calciferol has been removed from the body, thus causing a prolonged effect on calcium absorption.

   *Other effects of 1,25-dihydroxycholecalciferol that mght play a role in promoting calcium absorption are the formation of-* i. a calcium-stimulated ATPase in the brush border of the epithel ial cells and ii. an alkaline phosphatase in the epithelial cells. The precise details of all these effects are unclear.

2. *Vitamin D decreases the renal calcium and phosphate excretion* : Vitamin D increases the calcium and phosphate absorption by the epithelial cells of the ranal tubules, thereby tending to decrease excretion of calcium in the urine. However, this is a week effect and probably not of major importance in regulating the extracellular fluid concentration of these substances.

3. *Vitamin D promotes phosphate absorption by the intestines* : Although phosphate is usually absorbed easily, phosphate flux through the gastrointestinal epithelium is enhanced by vitamin D. It is believed that this results from a direct effect of 1.25-dihydroxycholecalciferol, but it is possible that it results secondarily from this hormone's action on calcium absorption, the calcium in turn acting as a transport mediator for phosphate.

4. *Effects of vitamin D on bone and its relation to parathyroid activiry* : Vitamin D plays important roles in both bone absorption and bone deposition. Vitamin D in smaller quantities promotes bone calcification by increasing calcium and phosphate absorption from the intestines and in absences of such increase, it enhances the mineralization of bone.

   *(Ref. Guyton & Hall-11th edition; page 985)*

***Effect of Vitamin D on bone and its relation to parathyroid hormone activity*** : Vitamin D plays important roles in both bone absorption and bone deposition. The administration of *extreme quantities* of vitamin D causes absorption of bone. In the absence of vitamin D, the effect of PTH in causing bone absorption is greatly reduced or even prevented. The mechanism of this action of vitamin D is not known, but it is believed to result from the effect of 1,25-dihydroxy-cholecalciferol to increase calcium transport through cellular membranes.

Vitamin D in smaller quantities promotes bone calcification. One of the ways in which it does this is to increase calcium and phosphate absorption from the intestines. However, even in the absence of such increase, it enhances the mineralisation of bone. Here again, the mechanism of the effect is unknown, but it probably also results from the ability of 1,25-dihydroxy-cholecalciferol to cause transport of calcium ions through cell membranes- but in this instance, perhaps in the opposite direction through the osteoblastic or osteocytic cell membranes.

*(Ref. Guyton & Hall-11th edition; page 985)*

**Disorder of parathyroid gland**

Disorders of parathyroid glands are :

1. *Hypoparathyroidism* : When secretion of parathyroid hormone is decreased. The clinical condition is - *Tetany.*
   *Cause :*
   i. Surgical removal of thyroid or parathyroid.
   ii. Disease of the parathyroids.

2. *Hyperparathyroidism* : Excessive secretion of parathyroid hormone. The clinical conditions- *Osteitis fibrosa cystica.*
   *Cause :*
   i. Hyperplasia of the gland or tumour.
   ii. Prolong administration of parathyroid extracts.

## Tetany

*Aetiology* : There is an increased excitability of peripheral nerves due either to a low serum calcium or to alkalosis in which the proportion of the serum calcium in the ionised form is decreased, although the total calcium concentration remains unaltered. Magnesium depletion should also be considered as a possible contributing factor, particularly in malabsorption. The most common cause of hypocalcaemia is a low serum concentration of albumin which does not result in tetany.

*Causes of tetany* :

1. Due to hypocalcaemia
   Malabsorption
   Osteomalacia
   Hypoparathyroidism
   Acute pancreatitis
   Chronic renal failure

2 Due to alkalosis
   Repeated vomiting of gastric juice
   Excessive intake of oral alkalis

Hyperventilation
Primary hyperaldosteronism.

* Coincident acidosis usually prevents tetany.

*Clinical feature :*

1. *In children :* a characteristic triad of carpopedal spasm, stridor and convulsions occurs, though one or more of these may be found independently of the others. The hands in carpal spasm adopt a characteristic position.The metacarpophalangeal joints are flexed, the interphalangeal joints of the fingers and thumb are extended and there is opposition of the thumb (main díaccoucheur). Pedal spasm is much less frequent. Stridor is caused by spasm of the glottis.
2. *Adult :* Complain of tingling in the hands, feet and around the mouth. Less often there is painful carpopedal spasm while stridor and fits are rare.

# Adrenal Gland

*Histological parts of adrenal gland* : The adernal glands each of which weights about 4 gms, lie at the superior poles of the two kidney.

*Histologically adrenal gland consist of two parts-*

A. Outer : cortex.
B. Inner : medulla.

A. ***Cortex*** : Cortex form the main mass of the gland and divided into three distinct zone :
   i. *Outer zona glomerulosa* : It constitutes about 15 per cent of the adrenal cortex. It secretes mineralocor ticoids such as *aldosterone*. The secretion of this cells is controlled mainly by the ECF concentrations of *angiotensin II* and *potassium,* both of which stimulates aldosterone secretion.
   ii. *Middle zona fasciculata* : It constitutes about 75 per cent of the adrenal cortex. It secretes the glucocor ticoids *cortisol* and *corticosterone*, as well as small amounts of *adrenal androgens* and *estrogens*. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via *adreno-corticotropic hormone (ACTH).*
   iii. *Inner zona reticularis* : It secretes the adrenal androgens *dehydroepiandrosterone (DHEA)* and *androstenedione,* as well as small amounts of *estrogens* and some *glucocorticoids*. ACTH also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone,* released from the pituitary, may also be involved.

B. ***Medulla*** : Medulla is the central 20 per cent of the glands, fuctionally related to the sympathetic nervous system. It secretes the hormones *epinephrine* and *nor epinephrine* and *dopamine* in response to sympathetic stimulation.

*(Ref. Guyton & Hall-11th edition, page 944)*

**Classification of adrenal hormone**

1. *On the basis of site of origin :*
   i. Adrenocortical hormone : These hormone again divides into three group ;
      a. Mineralocorticoids
      b. Glucocorticoids
      c. Sex hormones.
   ii. Medullary hormone : Epinephrine, norepine-phrine.
2. *On the basis of nature of hormone* :
   i. Steroid in nature : Cortical hormone e.g aldosterone, glucocorticoides or cortisol, sex hormones.
   ii. Derivatives of amino acid-Medullary hor-mone.

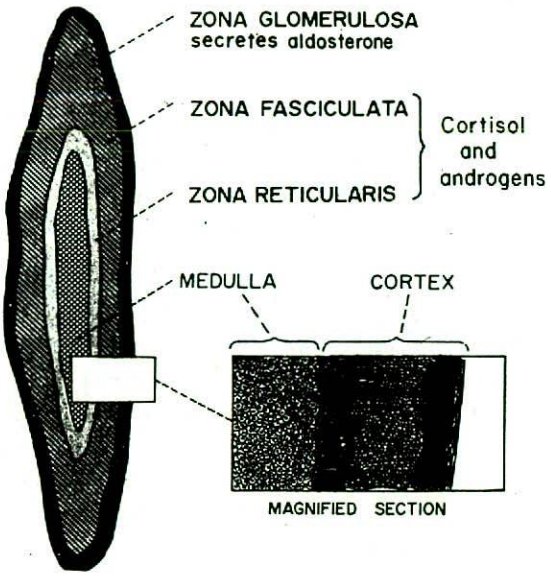



Fig. 8-15. *Secretion of adrenocortical hormones by different zones of the adrenal cortex.*

## Adrenal medullary hormone

***Structure and function of medullary hormone*** :

*Nonepinephrine* is formed by hydroxylation and decarboxy-lation of tyrosine, and epinephrine by methylation of norepinephrine. *PhenylethanolamineN-methyltransferase (PNMT)*, the enzyme that catalyzes the formation of epinephrine from norepinephrine, is found in appreciable quantities only in the *brain* and the *adrenal medulla*. Adrenal medullary PNMT is induced by glucocorticoids. Although relatively large amounts are required, the glucocorticoid concentration is high in the blood draining from the cortex to the medulla. After hypophysectomy, the glucocorticoid concentration of this blood falls and epinephrine synthesis is decreased.

***In plasma***, about 95% of the dopamine and 70% of the norepinephrine and epinephrine are conjugated to sulfate . Sulfate conjugates are inactive, and their function is unsettled.

***Normal plasma level of adrenal medullary hormone*** :

1. *Norepinephrine* : In recumbent humans, the normal plasma level of free norepinephrine is about 300 pg/mL (1.8 nmol/L). There is a 50-l00% increase upon standing. The plasma norepinephrine level is generally unchanged after adrenalectomy
2. Free *epinephrine* level, which is normally about 30 pg/mL (0.16 nmol/L), falls to essentially zero after adrenalectomy. The epinephrine found in tissues other than the adrenal medulla and the brain is for the most part absorbed from the bloodstream rather than synthesized in situ. Interestingly, low levels of epinephrine reappear in the blood some time after bilateral adrenalectomy, and these levels are regulated like those secreted by the adrenal medulla. They may come from cells such as the ICA cells, but their exact source is unknown.
3. The plasma *free dopamine* level is about : 35 pg/mL (0.23 nmol/L), and there are appreciable quantities of dopamine in the urine. Half the plasma dopamine comes from the adrenal medulla, whereas the remaining half presumably comes from the sympathetic ganglia or other components of the autonomic nervous system.

***Half-life of adrenal medullary hormone*** : The catecholamnines have a half-life of about 2 minutes in the circulation. For the most part, they are methoxylated and then oxidized to 3-methoxy-4-hydroxymandelic acid (vanillylman -delic acid, VMA;). About 50% of the secreted catecholamnines appear in the urine as free or conjugated metanephrine and normetanephrine, and 35% as VMA. Only small amounts of free norepinephrine and epinephrine are excreted.

***Excretion of adrenal medullary hormone*** : In normal humans, about 30 μg of norepinephrine, 6 μg of epinephrine, and 700 μg of VMA are excreted per day.

*(Ref. Ganong 22th edition, Page-358)*

**Epinephrine & norepinephrine**

*Receptors* : The effects of norepinephrine and epinephrine are brought about by actions on two classes of receptors, α-and β-adrenergic receptors. Alpha receptors are subdivided into two groups, $\alpha_1$ and $\alpha_2$ receptors and β receptors into $\beta_1$, $\beta_2$ and $\beta_3$ receptors. There are three subtypes of $\alpha_1$ receptors and three subtypes of $\alpha_2$ receptors.

*(Ref. Ganong 22th edition, Page-359)*

***Effects of epinephrine & norepinephrine*** : In addition to mimicking the effects of noradrenergic nervous discharge, *norepinephrine* and *epinephrine* exert-

1. Metabolic effects that include-
   a. Glycogenolysis in liver and skeletal muscle
   b. Mobilization of FFA
   c. Increased plasma lactate
   d. Stimulation of the metabolic rate.
2. *Effects on cardivascular system* :
   a. Norepinephrine and epinephrine both increase the force and rate of contraction of the isolated heart. These responses are mediated by $\beta_1$ receptors.
   b. The catecholarnines also increase myocardial excitability, causing extrasystoles and, occasionally, more serious cardiac arrhythmias.
   c. Norepinephrine produces vasoconstriction in most if not all organs via $\alpha_1$ receptors.
   d. Epinephrine dilates the blood vessels in skeletal muscle and the liver via $\beta_2$ receptors. This usually overbalances the vasoconstriction produced by epinephrine elsewhere, and the total peripheral resistance drops.
   e. When norepinephrine is infused slowly in normal animals or humans, the systolic and diastolic blood pressures rise. The hypertension stimulates the carotid and aortic baroreceptors, producing reflex bradycardia that overrides the direct cardioacceleratory effect of norepinephrine. Consequently, cardiac output per minute falls.
   f. Epinephrine causes a widening of the pulse pressure. but because baroreceptor stimulation is insufficient to obscure the direct effect of the hormone on the heart, cardiac rate and output increase.
3. Catecholaimnes increase alertness. Epinephrine and norepinephrine are equally potent in this regard, although in humans epinephrine usually evokes more anxiety and fear.
4. The catecholamines have several different actions that affect blood glucose. Epinephrine and norepinephrine both cause glycogenolysis. They produce this effect via β-adrenergic receptors that increase cAMP, with activation of phosphorylase, and via α-adrenergic receptors that increase intracellular $Ca^{2+}$.

   In addition. the catecholammes increase the secretion of insulin and glucagon via β-adrenergic mechanisms and inhibit the secretion of these hormones via α-adrenergic mechanisms.
5. When injected. epinephrine and norepinephrine cause an initial rise in plasma $K^+$ because of release of $K^+$ from the liver and then a prolonged fall in plasma $K^+$ because of an increased entry of $K^+$ into skeletal muscle that is mediated by $\beta_2$-adrenergic receptors. There is some evidence that activation of α receptors opposes this effect. Thus, the

catecholamines may play a significant role in regulating the ratio between extracellular and intracellular $K^+$.

*(Ref. Ganong 22th edition, Page-359, 360)*

***Effects of Dopamine*** : The physiologic function of the dopamine in the circulation is unknown.

1. Injected dopamine produces renal vasodilation, probably by acting on a specific dopaminergic receptor.
2. It also produces vasodilation in the mesentery. Elsewhere, it produces vasoconstrction, probably by releasing norepinephrine.
3. It has a positively inotropic effect on the heart by an action on $\beta_1$-adrenergic receptors.
4. The net effect of moderate doses of dopamine is an increase in systolic pressure and no change in diastolic pressure. Because of these actions, dopamine is useful in the treatment of traumatic and cardiogenic shock.

Dopatnine is made in the renal cortex, and there are appreciable amounts in the urine. It causes natriuresis and may exert this effect by inhibiting renal $Na^+$-$K^+$ ATPase.

*(Ref. Ganong 22th edition, Page-366)*

**Regulation of adrenal medullary secretion**

*Neural control* : Certain drugs act directjy on the adrenal medulla, but physiologic stimully affect medullary secretion through the nervous system. Catecholamine *secretion is low* in *basal states*, but the secretion of epincphnine and, to a lesser extent, that of norepinephrine is *reduced* even further *during* sleep.

*Increased adrenal medullary secretion* is part of the diffuse sympathetic discharge provoked in emergency situations, which Cannon called the "*emergency function of the sympathoadrenal system.*"

The metabolic effects of circulating catecholamines are probably important, especially in certain situations. The calorigenic action of catecholamines in animals exposed to cold is an example. Animals with denervated adrenal glands shiver sooner and more vigorously than normal controls when exposed to cold. The glycogenolysis produced by epinephrinc and norepinephrine in hypoglycemic animals is another example. *Hypoglycemia is a potent stimulus* to catecholamine secretion. Glucagon can substitute for catecholamines as a counterregulatory hormone, and vice versa, but if the secretion of both is blocked, insulin tolerance is markedly reduced.

*(Ref. Ganong 22th edition, Page-361)*

## Adrenal Cortical Hormone

***Chemistry of adrenocortical hormone*** : All these hormones are steroid in nature derived from cholesterol and each has a steroid nucleus in their structure.

Mineralocorticoid aldosterone has an *oxygen atom* bound at the number 18 carbon. The glucocorticoids cortisol has a *keto oxygen* on carbon number 3 and is hydroxylated at carbon numbers 11 and 21.

*(Ref. Guyton & Hall-11th edition; page 944)*

**Mineralocorticoid Hormones**

| | | |
|---|---|---|
| i. | *Aldosterone* | : very potent, account for about 90 per cent of all mineralocorticoid activity. |
| ii. | *Deoxycorticosterone* | : 1/30 as potent as aldosterone, but very small quantities secreted. |
| iii. | *Corticosterone* | : slight mineralocorticoid activity. |
| iv. | *9α -Fluorocortisol* | : synthetic, slightly more potent than aldosterone. |
| v. | *Cortisol* | : very slight mineralocorticoid activity, but large quantity secreted. |
| vi. | *Cortisone* | : synthetic, slight mineralocorticoid activity. |

*(Ref. Guyton & Hall-11th edition; page 945)*

*Origin of name of mineralocorticoides* : Mineralocorticoids are so called because they specially affect eletrolytes of the ECF-Sodium and Potassium in particular.

*(Ref. Guyton & Hall-11th edition; page 945)*

**Glucocorticoid Hormones**

| | | |
|---|---|---|
| i. | Cortisol | : very potent, account for about 95 per cent of all glucocorticoid activity. |
| ii. | Corticosterone | : provides about 4 per cent of total glucocorticoid activity, but less potent than cortisol. |
| iii. | Cortisone | : synthetic, almost as potent as cortisol. |
| iv. | Prednisone | : synthetic, *four times* as potent as cortisol. |
| v. | Methylprednisone | : synthetic, *five times* as potent as cortisol. |
| vi. | Dexamethasone | : synthetic, *30 times* as potent as cortisol. |

*(Ref. Guyton & Hall-11th edition; page 947)*

*Origin of name of glucocorticoids* : Glucocorticoids are so called because they exhibit an important effect in increasing the blood glucose concentration.

## Mineralocorticoids- Aldosterone

Aldosterone is bound to protein to only a slight extent.

Half-life is short about : 20 minutes

The amount secreted is small about : 0.15 mg/day
Total plasma aldosterone level about : 0.006 µg/dL
: 0.17 nmol/L.

*Metabolism of aldosterone* : Much of the aldosterone is converted in the liver to the tetrahydroglucuronide derivative, but some is changed in the liver and in the kidneys to an 18-glucuronide. This glucuronide, which is unlike the breakdown products of other steroids, is converted to free aldosterone by hydrolysis at pH 1.0, and it is therefore often referred to as the "*acid-labile conjugate.*" Less than 1% of the secreted aldosterone appears in the urine in the free form. Another 5% is in the form of the *acid-labile conjugate*, and up to 40% is in the form of the tetrahydroglucuronide.

*(Ref. Ganong 22th edition, Page 367)*

***Cellular mechenism of aldesterone action*** : The basic action of aldesterone on the tubular cells to increase transport of sodium is still not fully understood. However, the cellular sequence of events that leads to increased sodium reabsorption seems to be the following :

1. *First*, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.
2. *Second*, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific *cytoplasmic receptor protein*, a protein that has a stereomolecular configuration that allows only aldosterone or very similar compounds to combine with it.
3. *Third*, the *aldosterone-receptor complex* or a product of this complex diffuses into the nucleus, where it may undergo further alterations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.
4. *Fourth*, the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation. The proteins formed are a mixture of *i.* one or more enzymes and *ii.* membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane. One of the enzymes especially increased is ***sodium-potassium adenosine triphosphatase***, which serves as the principal part of the pump for sodium and potassium exchange at the *basolateral membranes* of the renal tubular cells. Another protein, perhaps equally important, is a *channel protein* inserted into the *luminal membrane* of the same tubular cells that allows rapid diffusion of sodium ions from the tubular lumen into the cell; then the sodium is pumped the rest of the way by the *sodium-potassium pump* located in the *basolateral membranes* of the cell.

Thus, aldosterone does not have an immediate effect on sodium transport; rather, this effect must await the sequence of events that leads to the formation of the specific intracellular substances required for sodium transport. About 30 minutes is required before new RNA appears in the cells, and about 45 minutes required before the rate of sodium transport begins to increase; the effect reaches maximum only after several hours.

*(Ref. Guyton & Hall-11th ed, page 949)*

***Functions of aldosterone :***

1. It increases the reabsorption of sodium from kidney tubule specially in the *principal cells of the collecting tubule* and, to a lesser extent, in the distal tubule and collecting duct.
2. It increases the excretion of potassium through DCT and CT.
3. It helps in the reabsorbtion of chloride along with sodium.
4. It increases the water reabsorption from kidney tubule along with sodium and increases ECF volume.
5. It causes reabsorption of sodium and chloride and excreation of potassium from ducts of sweat gland.
6. It increases the absorption of sodium from intestine.
7. Excess aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration.
8. Excess aldosterone causes hypokalemia and muscle weakness; too little aldosterone causes hyperkalemia, and cardiac toxicity.
9. Excess aldosterone increases tubular hydrogen ion secretion, with resultant mild alkalosis.

*(Ref. Guyton & Hall-11th ed, page 947, 948)*

***Regulation of aldosterone secretion*** :

The regulation of aldosterone secretion is so deeply intertwined with the- i. *regulation of extracellular fluid electrolyte concentrations*, ii. *extracellular fluid volume*, iii. *blood volume*, iv. *arterial pressure*, and v. *many special aspects of renal function* that it is difficult to discuss the regulation of aldosterone secretion independently of all these other factors. However, it is important to list here as well the more important points of aldosterone secretion control.

Four factors are known to play essential roles in the regulation of aldosterone. In the probable order of their importance, they are as follows :

1. Increased potassium ion concentration in the extracellular fluid *greatly increases* aldosterone secretion.
2. Increased activity of the renin-angiotensin system also *greatly increases* aldosterone secretion.
3. Increased sodium ion concentration in the extracellular fluid *very slightly decreases* aldosterone secretion.
4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion.

Of these factors, *potassium ion concentration* and the *renin-angiotensin system* are by far the most potent in regulating aldosterone secretion.

1. *Potassium ion concentration* : A small percentage increase in potassium concentration can cause a several-fold increase in aldosterone secretion.
2. *Renin-angiotensin system* : Likewise, activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss, can cause a several-fold increase in aldosterone secretion.

In turn, the aldosterone acts on the kidneys- i. to help them excrete the excess potassium ions and ii. to increase the blood volume and arterial pressure, thus returning the renin-angiotensin system toward its normal level of activity. These feedback control mechanisms are essential for maintaining life.

3. *Sodium ion concentration* : By contrast, the effects of sodium ion concentration in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 per cent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps double aldosterone secretion.
4. *ACTH* : By contrast, the effects of ACTH in controlling aldosterone secretion are usually minor. In the case of ACTH, if there is even a small amount of ACTH secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.

*(Ref. Guyton & Hall-11th ed, page 950)*

Q. ***Why mineralocorticoids or aldosterone is essential for life or why it is called life saving hormone?***

Ans. Total loss of adrenocortical secretion usually causes death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids. Without mineralocorticoids, *potassium ion concentration* of the extracellular fluid *rises markedly*, *sodium* and *chloride* are *rapidly lost* from the body, and the *total extracellular fluid volume* and *blood volume* become greatly reduced. The person soon develops diminished cardiac output, which progresses to a shocklike state, followed by death. This entire sequence can be prevented by the administration of aldosterone or some other mineralocorticoid. Therefore, the *mineralocorticoids* are said to be the acute "*lifesaving*" portion of the adrenocortical hormones. The glucocorticoids are equally necessary, however, allowing the person to resist the destructive effects of life's intermittent physical and mental "stresses".

*(Ref. Guyton & Hall-11th ed, page 950)*

***Aldosterone escape*** : Aldosterone is one of the body's most powerful sodium-retaining hormones, only transient sodium retention occurs when excess amounts are secreted. An aldosterone-mediated increase in extracellular fluid volume lasting more than 1 to 2 days also leads to an increase in arterial pressure. The rise in arterial pressure then increases kidney excretion of both salt and water, called *pressure natriuresis* and *pressure diuresis*, respectively.

Thus, after the extracellular fluid volume increases 5 to 15 per cent above normal, arterial pressure also increases 15 to 25 mm Hg, and this elevated blood pressure returns the renal output of salt and water to normal despite the excess aldosterone. This return to normal of salt and water excretion by the kidneys as a result of pressure natriuresis and diuresis is called *aldosterone escape*.

Thereafter, the rate of gain of salt and water by the body is zero, and balance is maintained between salt and water intake and output by the kidneys despite continued excess aldosterone. In the meantime, however, the person has developed hypertension, which lasts as long as the person exposed to high levels of aldesterone.

*(Ref. Guyton & Hall-11th ed, page 948, 949)*

## Glucocorticoids- Cortisol / Hydrocortisone

***Functions of glucocorticoids :***

1. *On carbohydrate metabolism :* increases blood glucose
   a. It stimulates the gluconeogenesis in liver,
   b. It decreases the peripheral utilization of glucose.
   c. It decreases the transport of glucose to the periphery.
   d. Ultimately it increases blood glucose.
2. *On protein metabolism :*
   a. It increases peripheral utilization of protein.
   b. It decreases the transport of amino acids to the cell.
   c. It converts the amino acids into glucose in liver.
   d. It decreases the synthesis of protein.
3. *On fat metabolism :*
   a. It increases the mobilization of fatty acid from adipose tissue.
   b. It promotes the conversion of fat to acetyl-CoA and subsequent utilization.
   c. It stimulates beta oxidation.
   d. It has a ketogenic effect.
4. Cortisol is important in resisting stress and inflammation.
5. ***Anti-inflammatory effects of high levels of cortisol*** : When large amount of cortisol are secreted or injected into a person, the cortisol has two basic anti-inflammatory effects :
   a. It can block the early stages of the inflammation process before inflammation even begins, or
   b. If inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.

*Cortisols prevents the development of inflammation by stabilizing lysosomes and by other effects* :

i. Cortisol stabilizes the lysosomal membranes
ii. Cortisol decreases the permeability of the capillaries
iii. Cortisol decreases both migration of white blood cells into the inflammed area and phagocytosis of the damaged cells.
iv. Cortisol supresses the immune system, causing lymphocyte reproduction to decreased markedly.
v. Cortisol lowers fever mainly because it reduces the release of interleukin-I from the white blood cells

Thus, cortisol has an global effect in reducing all aspects of the inflammatory process.

6. *Effect on allergy* : Cortisol block the inflammatory response to allergic reaction.
7. *Effect on immunity in infectious diseases* : Administration of large doses of cortisol causes significant atrophy of all the lymphoid tissue through out the body, which inturn decreases the output of both T cells and antbodies from the lymphoid tissues. As a result, immunity of the body is decreased.
8. *Effect on blood cells in infectious diseases* : Cortisol increases the production of red blood cells, the cause of wihch is unknown.

*(Ref. Guyton & Hall-11th edition, page 951, 952, 953)*

**Permissive action** *(of glucocorticoids)*

Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by themselves. This effect is called their *permissive action*. Permissive effects include the requirement for glucocorticoids to be present for glucagon and catecholamines to exert their calorigenic effects, for catecholamines to exert their lipolytic effects and for catecholamines to produce pressor responses and bronchodilation.

*(Ref. Ganong 22th edition; page-369)*

**Regulation of cortisol secretion**

The key to control of cortisol secretion is the excitation of the hypothalamus by different types of stress. Stress stimuli activate the entire system to cause rapid release of cortisol, and the cortisol in turn initiates a series of metabolic effects directed toward relieving the damaging nature of the stressful state. In addition, there is direct feedback of the cortisol to both the hypothalamus and the anterior pituitary gland to decrease the concentration of cortisol in the plasma at times when body is not experiencing stress. However, the stress stimuli are the prepotent ones; they can always break through this direct inhibitory feedback of cortisol, causing either periodic exacerbations of cortisol secretion at multiple times during the day or prolonged cortisol secretion in times of chronic stress.

***Carcadian rhythm of glucocorticoid secretion*** : The secretory rates of CRF, ACTH and cortisol are high in the early morning but low in the late evening; the plasma cortisol level ranges

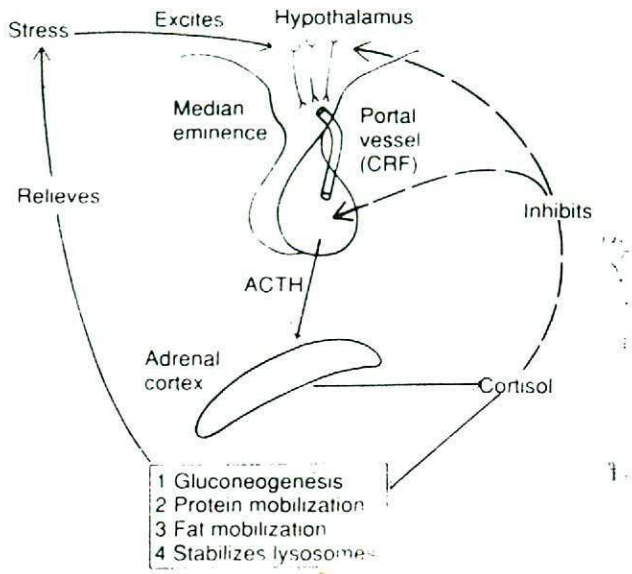



Fig. 8-16. *Mechenisms for regulation of glucocorticoid secretion.*

between a high of about 20 µg/dl an hour before arising in the morning and a low of about 5 µg/dl around midnight. This effect results from a 24 hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion. When a person changes daily sleeping habits, the cycle changes correspondingly.

Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

*(Ref. Guyton & Hall-11th edition, page 955)*

Q. ***Why cortisol is called emergency homone?***

Ans. Any type of stress such as trauma, infection, intense heat or cold, surgical operations increases ACTH secretion, which within minutes greatly increases cortisol secretion. This cortisol causes rapid mobili-zation of fat and amino acids from cellular stores, making them available both for energy and for synthesis of other compounds including glucose and new proteins. So cortisol is called emergency hormone.

*(Ref. Guyton & Hall-11th edition)*

*N.B If you are interested, please go through for-*

1. Cellular mechenism of cortisol action.

*(Ref. Guyton & Hall-11th edition, page 954)*

2. Adrenal androgen- secretion & effects

*(Ref. Guyton & Hall-11th edition, page 957)*

**Effects of adrenalectomy**

i. Loss of appetite and vomitting.

ii. Loss of body wt, and wasting of limb muscles.
iii. Reduced ECF volume, blood volume, blood pressure & low CO.
iv. Increased retention of $K^+$, Hyperkalaemia.
v. Excessive loss of salts and water through kidney and diuresis occurs.
vi. Ultimately death in 5-7 days.

**Disorders of adrenal cortex**

Disorders of adrenocortical function may be of two types -

1. Lack of secretion i,e. hyposecretion of the adrenal cortex :
   *It may be due to -*
   i. Destruction of adrenal cortex (adrenal-ectomy).
   ii. Tuberculosis.
   iii. Lack of secretion of corticotropin from adenohypophysis.
   iv. Congenital failure of cortisol secretion with over secretion of other hormones.

   *Two syndromes are encountered -*
   a. *Acute adrenal insufficiency or Adrenal crisis :* Due to failure of cortisol secretion.
   b. *Chronic adrenal insufficiency :* Addison's disease.
2. Excess of secretion, i,e. hypersecretion of adrenal cortex : It results from over activity of the adrenal gland.
   a. *Cushing syndrome :* Due to over secretion of cortisol due to hyperplasia of zona fasciculata and reticularis.
   b. *Hyperaldosteronism :* Due to over secre-tion of aldosterone due to hyperplasia of zona glomerulosa. It is of two types -
      i. Primary aldosteronism
      ii. Secondary aldosteronism.
   c. *Adrenogenital syndrome :* Due to hyperplasia of zona reticularis.

**Cushimg's Syndrome**

Hyperfunction of the adrenal cortex causes a complex cascade of hormone effects called Cushing's syndrome. By far the most common cause is *iatrogenic*, due to prolonged immunosuppre-ssion with synthetic glucocorticoids such as prednisolone (chronic therapy e.g. for asthma).

*Clinical features* :

1. Weight gain is the most common symptoms and centripetal obesity is the most frequent sign .
   Features which have the best predictive value in favour of Cushing's syndrome in an obese patient are-
   a. Brushing
   b. Myopathy
   c. Hypertension.
2. Psychiatric disturbances : Usually depression is also the most common in Cushing's syndrome
3. Moon face
4. Hair thinning- Hursutism
5. Wasting and weakness of proximal thigh muscles.
6. Loss of height and back pain from compression fractures. May have exuberant callus with fracture. Osteoporosis.

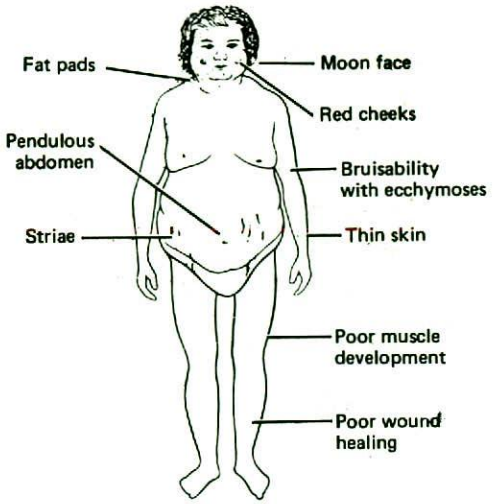



Fig. 8-17. *Typical findings in Cushing's syndrome.*

7. Menstrual disturbances.
8. Cataracts, mild exophthalmos.
9. Acne plethora
10. Tendency to infection with poor wound healing and inflammatory response.
11. Striae
12. Thin skin.

*(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)*

**Addision's Disease**

Adddison's disease results from failure of the adrenal cortices to produce adrenocortical hormones, and this in turn is the most frequently caused by *primary atrophy* of the adrenal cortices. It is the hypofunctional state of adrenal cortex. *(Guyton 11th ed)*

*Causes* :

1. *Common*
   a. Autoimmune
      Sporadic
      Polyglandular syndromes
   b. Tuberculosis
   c. Bilateral adrenalectomy
2. *Rare* :
   a. Metastatic carcinoma, lymphoma
   b. Intra-adrenal haemorrhage (waterhouse-Friedrichsen syndrome following meningococcal septicaemia)
   c. Amyloidosis
   d. Haemochromatosis
   e. Adrenal infection other than tuberculosis (esp. AIDS).

*(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)*

*Clinical features :*

1. *Glucocorticoid insufficiency*
   a. Weight loss
   b. Malaise
   c. Weakness
   d. Anorexia
   e. Nausea
   f. Vomitting
   g. Gastrointestinal- dirrhoea or constipation
   h. Postural hypotension
   i. Hypoglycaemia
2. Mineralocorticoid insuffiency
   a. Hypotension
3. Increased ACTH secretion
   a. Pigmentation
      i. Sun-exposed areas
      ii. Pressure areas, e.g. elbows, knees, palmar creases, knuckles, mucous membrane, conjunctivae, Recent scars
4. Loss of adrenal androgen
   Decrease in body hair, especially in female.

*(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)*

**Pheochromocytoma**

It is a benign chromaffin cell tumor of the sympatho-adrenal system that produces catecholamines, i.e., norepinephrine and epinephrine.

*Clinical features* : It produces hypertension that may be paroxysmal in about half the patients. The patient will complain of attacks of producing headaches, sweating, palpitation, apprehension, flushing of the face, nausea, vomiting and tingling of the extremities.

*Adrenal medullary tumours* which secrete norepinephrine, or epinephrine or both, and produce sustained hypertension. However, 15% of epinephrine secreting tumours secrete this catecholamine episodically producing intermittent bouts of palpitations, headache, glycosuria and extreme systolic hypertension.

*Treatment* : Surgical removal of the tumor.

*(Ref. Ganong 22th edition; page- 360)*

**Adrenogenital syndrome**

Condition caused by excess secretion of androgenic hormones by the adrenal gland or by excess medication with male hormones. In congenital forms, the female infant may be considered erroneously to be male and the male child will have accelerated growth and penile enlargement. In acquired forms, masculine secondary sex characteristics appear in the female; and there is precious puberty in the male.

# Pancrease

*Physiologic anatomy of pancreas* : Pancreas consist of two major types of tissues :

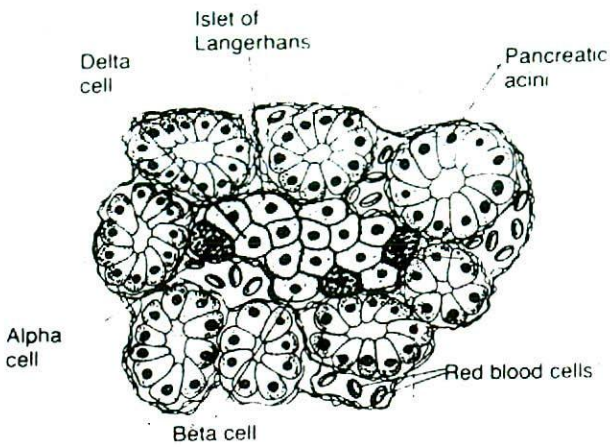



Fig. 8-18. *Physiological anatomy of Islets of langerhans in the pancreas.*

i. *The acini :* Which secretes digestive juice.

ii. *Islets of Langerhan's :* Which consist of different types of cells and secretes different hormone directly into the blood.

*Cells of Islets :*

1. Alpha (α) cell : Secretes glucagone.
2. Beta (β) cell : Secretes insulin.
3. Delta (δ) cell : Secretes somatostatin.
4. PP cell : Secrete pancreatic polypeptide.

These cells are distinguished from each other by their morphology and staining characteristic.

Alpha (α) cell constitute 25% of all cells,

Beta (β) cell constitute 60%,

Delta (δ) cell constitute 10%.

PP cell present in small number.

*(Ref. Guyton & Hall-11th edition; page 961)*

## Insulin

*Chemistry of insulin* : Insulin is protein in nature with a molecular wt. of about 5,808. It is composed of two amino acid chains connected to each other by disulfide linkages. A chain contains 21 amino acid and B chain contain 30 amino acids. When the two amino acid chains are split apart the functional activity of insulin is lost.

*(Ref. Guyton & Hall-11th edition; page 961)*

***Function of insulin***

1. *On carbohydrate metabolism* : Insulin increases uptake, uses, storage of glucose by the liver, muscle and all the cells of the body and decreases blood glucose level as follows :

a. Insulin increases the activity of enzyme *glucokinase* which enhanced the uptake of glucose from blood and initiate phosphorilation of glucose in liver.
b. Insulin inhibits the enzyme *phosphorilase* thus prevents break down of liver glycogen.
c. Insulin stimulate the enzyme *glycogen synthetase* thus promotes glycogenesis.
d. Insulin promotes conversion of excess liver glucose into fatty acid.
e. Insulin inhibits gluconeogenesis.

2. *On fat metabolism :*
   a. Insulin promotes fatty acid synthesis.
   b. Insulin increases fat storage in the adipose tissue.
   c. Insulin act as fat sparer by increasing utilization of carbohydrate in presence of fat.

3. *On protein metabolism :*
   a. It increases the transport of amino acid to cells.
   b. It increases translation of m RNA on ribosome thus forming new protein.
   c. Insulin promotes the rate of transcription of DNA to form RNA, which increases protein synthesis.
   d. Insulin inhibits gluconeogenesis.
   e. Insulin depressed protein catabolism.

*(Ref. Guyton & Hall-11th edition; page 963, 964, 965)*

Q. ***Write down the effect of insulin on glucose uptake in tissues in which it has been investigated?***

Ans.

1. *Tissues in which insulin facilitates glucose uptake :*
   i. Skeletal muscles
   ii. Cardiac muscles.
   iii. Smooth muscles
   iv. Adipose tissue.
   v. Leukocytes
   vi. Crystalline lens of the eye
   vii. Pituitary gland
   viii. Fibroblasts
   ix. Mammary gland
   x. Aorta
   xi. A cells of pancreatic islets.

2. *Tissues in which insulin does not facilitate glucose uptake :*
   i. Brain (Except part of hypothalamus)
   ii. Kidney tubules
   ii. Intestinal mucosa
   iv. Red blood cells.

***Effects of insulin on various tissues***

A. *On adipose tissue :*
   1. Increased glucose entry
   2. Increased fatty acid synthesis
   3. Increased glycerol phosphate synthesis
   4. Increased triglyceride deposition
   5. Activation of lipoprotein lipase
   6. Inhibition of hormone sensitive lipase
   7. Increased $K^+$ uptake.

B. *On muscle :*
   1. Increased glucose entry
   2. Increased glycogen synthesis
   3. Increased amino acid uptake
   4. Increased protein synthesis in ribosomes
   5. Decreased protein catabolism
   6. Decreased release of gluconeogenic amino acids
   7. Increased ketone uptake
   8. Increased $K^+$ uptake.

C. *On liver* :
   1. Decreased ketogenesis
   2. Increased protein synthesis
   3. Increased lipid synthesis
   4. Decreased glucose output due to decreased gluconeogenesis and increased glycogen synthesis.

D. *General* :
   1. Increased cell growth.

***Principal actions of insulin*** :

A. *Rapid (seconds)* :
   1. Increased transport of glucose, amino acids, and $K^+$ into insulin-sensitive cells.

B. *Intermediate (minutes)* :
   1. Stimulation of protein synthesis
   2. Inhibition of protein degradation
   3. Activation of glycogen synthase and glycolytic enzymes.
   4. Inhibition of phosphorylase and gluconeogenic enzymes.

C. *Delayed (hours)* :
   1. Increase in mRNAs for lipogenic and other enzymes.

**Control of insulin secretion**

Insulin secretion is regulated by following ways-

1. *Blood glucose level :* Increased blood glucose level increases insulin secretion. As the concentration of blood glucose rise above 100mg/dl of blood, the rate of insulin secretion rises rapidly, reaching a peak some 10 to 30 times the basal level at blood glucose concentration between 400 and 600 mg/dl.
2. *Amino acids :* Addition of excess amino acids stimulate insulin secretion.

3. *GI tract hormones :* Some GI Tract local hormones gastrin, secretin, GIP, CCK-PZ etc, moderately stimulate insulin secretion.
4. *Some other hormones of autonomic nervous system :* Glucagon, growth hormone, cortisol, and to a lesser extent, progesterone and estrogen either directly stimulate insulin secretion or potentiate the glucose stimulus for insulin secretion.

   Under some conditions, stimulation of the parasympathetic nerves to the pancrease can increase insulin secretion. However it is doubtful that this effect is of physiological significance for regulating insulin secretion.

*(Ref. Guyton & Hall-11th edition; page 968)*

**Factors affecting insulin secretion**

A. *Factors or conditions that increase insulin secretion* :
   1. Increased blood glucose
   2. Increased blood free fatty acids
   3. Increased blood amino acids
   4. Gastrointestinal hormones (Gastrin,cholecystokinin, secretin, gastric inhibitory peptide)
   5. Glucagon, growth hormone, cortisol
   6. Parasympathetic stimulation; acetylcholine
   7. Insulin resistance, obesity
   8. Sulfonylurea drugs (glyburide, tolbutamide).

*(Ref. Guyton & Hall-11th edition; page 968)*

B. *Factors or conditions that decrease insulin secretion* :
   1. Decreased blood glucose
   2. Fasting
   3. Somatostatin
   4. Catecholamines (α-agonist).

*(Ref. Guyton & Hall-11th edition; page 968)*

**Insulinoma- Hyperinsulinism**

Although much rarer than diabetes, excessive insulin production occasionally occurs from an adenoma of an islet of Langerhans.

About 10 to 15 per cent of these adenomas are malignant, and occasionally metastases from the islets of Langerhans spread throughout the body, causing tremendous production of insulin by both the primary and the metastatic cancers.

Indeed, more than 1000 grams of glucose has had to be administered every 24 hours to prevent hypoglycaemia in some of these patients.

*(Ref. Guyton & Hall-11th edition; page 976)*

**Insulin shock and hypoglycaemia**

The central nervous system normally derives essentially all its energy from glucose metabolism, and insulin is not necessary for this use of glucose. However, if high levels of insulin cause blood glucose to fall to low values, the metabolism of the central nervous system becomes depressed.

Consequently, in patients with insulin-secreting tumours or in patients with diabetes who administer too much insulin to themselves, the syndrome called *insulin shock may occur as follows* :

i. As the blood glucose level falls into the range of 50 to 70 mg/100 ml, the central nervous system usually becomes *quite excitable*, because this degree of hypoglycaemia sensitizes neuronal activity. Sometimes various forms of *hallucinations* result, but more often the patient simply experiences extreme nervousness, trembles all over, and breaks out in a sweat.
ii. As the blood glucose level falls to 20 to 50 mg/100 ml, clonic seizures and loss of consciousness are likely to occur. As the glucose level falls still lower, the seizures cease and only a state of *coma* remains.

Indeed, at times it is difficult by simple clinical observation to distinguish between diabetic coma as a result of insulin-lack acidosis and coma due to hypoglycaemia caused by excess insulin. The acetone breath and the rapid deep breathing of diabetic coma are not in hypoglycaemic coma.

*Treatment* :

i. Immediate intravenous administration of large quantities of *glucose*. This usually brings the patient out of shock within a minute or more.
ii. Administration of *glucagon* (or less effectively *epinephrine*) can cause glycogenolysis in the liver and thereby increase the blood glucose level extremely rapidly.

If treatment is not effected immediately, permanent damage to the neuronal cells of the central nervous system often occurs.

*(Ref. Guyton & Hall-11th edition; page 976)*

## Glucagon

***Function of glucagon***

A. *Effects on glucose metabolism* : The major effects of glucagon on glucose metabolism are-
   a. Breakdown of liver glycogen (*glycogenolysis*)
   b. Increased *gluconeogenesis* in the liver.

   Both of these effects greatly enhance the availability of glucose to the other organs of the body.

   *Break down of liver glycogen (glycogenolysis) :* Glucagon helps glycogenolysis and increase blood glucose level as follows :
   1. It activates *adenyl cyclase* in the hepatic cell membrane.
   2. Which causes the fomation of *cyclic AMP.*
   3. Which activates *protein kinase regulator protein.*
   4. Which activates *protein kinase.*
   5. Which activates *phosphorylase b kinase.*

6. Which converts *phosphorylase b* into *phosphorylase a.*
7. Which promotes the degradation of glycogen into glucose-1 phosphate.
8. Which then dephosphorylated; and the glucose is released from the liver cells.

*Glucagon increases gluconeogenesis :*

a. Increases the rate of amino acid uptake by the liver cells and then conversion of many of the amino acid to glucose by *gluconeogenesis.*

B. *Other effects of glucagon* : Most of the other effects of glucagon occur only when its concentration rises well above the maximum normally found in the blood.

1. Perhaps the most important effect is that glucagon *activates adipose cell lipase,* making increased quantities of fatty acids available to the energy systems of the body.
2. It also inhibits the the *storage of triglycerides* in the liver, which prevents the liver from removing fatty acids from the blood; this also helps make additional amounts of fatty acids available for the other tissues of the body.

*Glucagon in very large concentration also-*

a. Enhances the strength of the heart.
b. Increases blood flow in some tissues, especially by the kidneys.
c. Enhances bile secretion.
d. Inhibits gastric acid secretion.

*All these effects are probably of minimum importance in the normal function of the body.*

*(Ref. Guyton & Hall-11th edition; page 970)*

**Regulation of glucagon secretion**

1. *Increased blood glucose inhibit glucagon secretion :* Decreased blood glucose level increases glucagon secretion and increased blood glucose level conversly inhibit glucagon secretion.
2. *Increased blood amino acids stimulate glucagon secretion* : High concentration of amino acids, as occur in the blood after a protein meal (specially the amino acids *alanine* and *arginine*) stimulate secretion of glucagon.

   The importance of amino acid stimulation of glucagon secretion is that the glucagon then promotes rapid conversion of the amino acids to glucose, thus making even more glucose available to the tissue.
3. *Exercise stimulate glucagon secretion* : In exhaustive exercise, the blood concentration of glucagon often increases fourfold to fivefold.

*(Ref. Guyton & Hall-11th edition; page 971)*

***Factors affecting glucagon secretion***

A. *Stimulatos :*

1. Amino acids (particularly the glucogenic amino acids : alanine, serine, glycine, cysteine, threonine)
2. CCK, gastrin
3. Cortisol
4. Exercise
5. Infections
6. Other stresses
7. Beta adrenergic stimulators
8. Theophylline
9. Acetylcholine.

B. *Inhibitors :*

1. Glucose
2. Somatostatin
3. Secretin
4. FFA
5. Ketones
6. Insulin
7. Phenytoin
8. Alpha adrenergic stimulators
9. GABA.

*(Ref. Ganong 22th edition, Page 349)*

## Somastotin

***Somatostatin inhibits glucagon and insulin secretion*** : The delta cells of the islets of Langerhans secrete the hormone somatostatin, a polypeptide containing only 14 amino acids that has an extremely short half-life of only 3 minutes in the circulating blood.

*Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include-*

1. Icreased blood glucose
2. Increased amino acids
3. Increased fatty acids
4. Increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake.

*In turn, somatostatin has multiple inhibitory effects as follows :*

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.
2. Somatostatin decreases the motility of the stomach, duodenutm, and gallbladder.
3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time

over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to *depress insulin* and *glucagon secretion* decreases the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time.

It should also be recalled that somatostatin is the same chemical substance as *growth hormone inhibitory hormone*, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

*(Ref. Guyton & Hall-11th edition; page 971)*

**Normal blood sugar level**

i. In a normal person, the blood glucose concentration is narrowly controlled, usually between 80 and 90 mg per 100 ml of blood in the fasting person each morning before breakfast.

ii. This concentration increases to 120 to 140 mg per 100 ml during the first hour or so after a meal.

iii. But, the feedback systems for control of blood glucose return the glucose concentration rapidly back to the control level, usually within 2 hours after the last absorption of carbohydrates.

iv. Conversely, in starvation, the gluconeogenesis function of the liver provides the glucose that is required to maintain the fasting blood glucose level.

*(Ref. Guyton & Hall-11th edition)*

**Regulation of normal blood glucose level**

Factors maintaining blood glucose level are :

1. Humoral
2. Hormonal
3. Nervous.

1. ***Humoral factors*** : It includes :
   - i. *Role of liver* : The liver acts as an important *blood glucose buffer system.*
     - a. When blood glucose level rises to very high, after a meal, 2/3 of glucose absorbed from gut is almost immediately stored in liver as glycogen.
     - b. When blood glucose level falls, liver releases glucose back into blood due to presence of glucose-6-phosphatase.
     - c. When glycogen reservoir diminishes, liver enhances gluconeogenesis.
   - ii. *Role of muscle* :
     - a. During increase blood glucose level : Promotes glycogenesis and oxidation of glucose in muscle.
     - b. During decrease blood glucose level : Muscle glycogen supplies glucose to blood by cori cycle. It can not serve as a direct source of blood glucose during hypoglycaemia due to absence of glucose-6-phosphatase.
     - c. During exercise : It promotes entry of glucose into muscle cell thus decreasing blood glucose level.
   - iii. *Role of kidney* :
     - a. During increase blood glucose level : When blood glucose level exceeds the renal threshold level, excess glucose is excreted in urine, thus decreases blood glucose level.
     - b. During decrease blood glucose level : Kidney possesses gluconeogenesis, thus increases blood glucose level.

2. ***Hormonal factors*** :
   - I. *Main regulatory hormone (Antidiabetogenic hormone)* :
     - i. *Insulin* : Decrease blood glucose level.
       - a. Increase glucose uptake from blood to all cells of the body
       - b. Increase glycolysis
       - c. Increase glycogenesis
       - d. Decrease glycogenolysis
       - e. Decrease gluconeogenesis.
   - II. *Main counter regulatory hormone (Diabeto- genic hormone)* :
     - i. *Glucagon* : *Increase blood glucose level*
       - a. Increase glycogenolysis
       - b. Increase gluconeogenesis.
     - ii. *Glucocorticoids* : Increase blood glucose level :
       - a. It stimulates the gluconeogenesis in liver,
       - b. It decreases the peripheral utilization of glucose.
       - c. It decreases the transport of glucose to the periphery.
     - iv. *Growth hormone* : Increase blood glucose level :
       - a. Decrase uptake and utilization of glucose.
     - v. *Epinephrine* : Increase blood glucose level
       - a. Increase glycogenolysis.
     - vi. *Thyroid hormones* : Increase blood glucose level :
       - a. Increase glycogenolysis
       - b. Increase gluconeogenesis.
     - vii. *ACTH* : *Increase blood glucose level*
       - a. Increase gluconeogenesis.

3. ***Nervous factor*** :
   1. Hunger sensation : Raises blood glucose level by taking food during hypoglycemia.
   2. Satiety : Inhibits hunger centre, there by decreases blood glucose.

***Importance of blood glucose regulation*** :

1. Glucose is the only nutrient that normally can be used by the brain, retina, and germinal epithelium of the gonads in sufficient quantities to supply them optimally with their required energy. Therefore, it is important to maintain the blood glucose concentration at a sufficiently high level to provide this necessary nutrition.

2. Most of the glucose formed by gluconeogenesis during the interdigestive period is used for metabolism in the brain. Indeed, it is important that the pancreas not secrete any insulin during this time; otherwise, the scant supplies of glucose that are available would all go into the muscles and other peripheral tissues, leaving the brain without a nutritive source.
3. It is also important that the blood glucose concentration not rise too high for four reasons :
   i. *First*, glucose can exert a large amount of osmotic pressure in the extracellular fluid, and if the glucose concentration rises to excessive values, this can cause considerable cellular dehydration.
   ii. *Second*, an excessively high level of blood glucose concentration causes loss of glucose in the urine.
   iii. *Third*, this causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes.
   iv. *Fourth*, long-term increases in blood glucose may cause damage to many tissues, especially to blood vessels. Vascular injury, associated with uncontrolled diabetes mellitus, leads to increased risk for heart attack, stroke, end-stage renal disease, and blindness.

*(Ref. Guyton & Hall-11th edition; page 972)*

## Diabetes

***Diabetogenic hormone*** : Hormones increasing blood glucose level. These are :

i. Glucagon
ii. Cortisol
iii. GH
iv. Thyroid hormone
v. Epinephrine and norepinephrine.
vi. TSH
vii. ACTH.

*The diabetogenic hormone generally increasing blood sugar level in the follwing ways :*

i. By breaking down of liver glycogen.
ii. Increasing the gluconeogenesis.
iii. By increasing glycogenolysis.
iv. By decreasing peripheral utilization of glucose.
v. By decreasing the transport of glucose to the cell .
vi. By increasing the absorption of glucose from intestine.

***Antidiabetogenic hormone*** : Hormones decreasing blood glucose level. This is-

*Insulin* : It decreases blood glucose level by-

a. Insulin increases the activity of enzyme glucokinase which enhanced the uptake of glucose from blood and initiate phospho-rilation of glucose in liver.
b. Insulin inhibits the enzyme phosphorilase thus prevents break down of liver glycogen.
c. Insulin stimulate the enzyme glycogen synthetase thus promotes glycogenesis.
d. Insulin promotes conversion of excess liver glucose into fatty acid.
e. Insulin inhibits gluconeogenesis.

**Pituitary diabetes**

Specific increase in secretion of GH or generalized increase in secretion of all anteior pituitary hormones cuase elevated blood glucose level. This condition is called pituitary diabetes.

**Adrenal diabetes**

Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilisation by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that are not entirely clear, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilisation. One possible explanation is that high levels of fatty acids, caused by the effect of glucocorticoids to mobilise lipids from fat depots, may impair insulin's actions on the tissues. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism very similar to those found in patients with excess levels of growth hormone.

The increase in blood glucose concentration is occasionally great enough (50 per cent or more above normal) that the condition is called *adrenal diabetes*.

*Administration of insulin* lowers the blood glucose concentration only a moderate amount in adrenal diabetes- not nearly as much as it does in pancreatic diabetes- because the tissues are resistant to the effects of insulin.

*(Ref. Guyton & Hall-11th edition; page 972)*

**Diabetes insipidus**

Diabetes insipidus is the syndrome characterised by *polyuria* and *polydipsia* that results when there is a vasopressin (ADH) deficiency or when the kidney fail to respond to the hormone. More common in the young.

*Types* :

i. Central diabetes insipidus
ii. Nephrogenic diabetes insipidus.

***Central diabetes insipidus*** *(Failure to produce ADH)* : An inability to produce or release ADH from the posterior pituitary can be caused by head injuries or infections, or it can be congenital. Because the distal tubular segments cannot reabsorb water in the absence of ADH, this

condition, called *central diabetes insipidus.*

*Effects* : Formation of a large volume of dilute urine, with urine volumes that can exceed 15 L/day.

*Response* : The thirst mechanisms, are activated when excessive water is lost from the body; therefore, as long as the person drinks enough water, large decreases in body fluid water do not occur. The primary abnormality observed clinically in people with this condition is the large volume of dilute urine. However, if water intake is restricted, as can occur in a hospital setting when fluid intake is restricted or the patient is unconscious for example, because of a head injury, severe dehydration can rapidly occur.

***Nephrogenic diabetes insipidus*** *(Inability of the kidneys to respond to ADH)* : There are circumstances in which normal or elevated levels of ADH are present but the distal tubular segments cannot respond appropriately. This condition is referred to as *nephrogenic diabetes insipidus* because the abnormality resides in the kidneys.

*Cause* :

i. This abnormality can be due to either failure of the countercurrent mechanism to form a hyperosmotic renal medullary interstitium.

ii. Failure of the distal and collecting tubules and collecting ducts to respond to ADH.
Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla. May be due to-
   a. Diuretics
   b. Certain drugs, such as lithium, tetracyclines can impair the ability of the distal nephron segments to respond to ADH.

*Effects* :

i. Large volumes of *dilute urine* are formed, which tends to cause *dehydration* unless fluid intake is increased by the same amount as urine volume is increased.

*(Ref. Guyton & Hall-11th edition; Ganong 22th edition)*

**Diabetes Mellitus**

*Definition* : Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretim or decreased sensitivity of the tissues to insulin.

*Types of diabetes mellitus* : There are two general types of diabetes mellitus :

1. *Type I diabetes*, also called *insulin-dependent diabetes mellitus (IDDM)* : It is caused by lack of insulin secretion.
2. *Type II diabetes*, also called *non-insulin-dependent diabetes mellitus (NIDDM)* : It is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often referred to as *insulin resistance.*

*Effects of diabetes mellitus* : In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin -resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, *blood glucose concentration increases, cell utilization of glucose falls increasingly lower,* and *utilization of fats and proteins increases.*

*(Ref. Guyton & Hall-11th edition; page 971)*

***Metabolic changes in type I diabetes*** : Hyperglycemia and ketoacidasis are the hallmarks of untreated diabetes mellitus.

i. *Hyperglycemia* is caused by increased hepatic production of glucose combined with diminished peripheral utilization.

ii. *Ketosis* results from increased mobilization of fatty acids from adipose tissue combined with accelerated hepatic synthesis of 3-hydroxybutyrate and acetoacetate.

iii. However, not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. Fatty acids are also converted to *triacylglycerol*, which is packaged and secreted in *VLDL.*

iv. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal. Because lipoprotein degradation catalyzed by *lipoprotein lipase* in adipose tissue is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resuting in ***hypertiglyceridemia.***

v. These metabolic changes result from a deficiency of *insulin* and a relative excess of *glucagon*, the latter playing a critical role in stimulating *gluconeogenesis* and *ketogenesis.*

*(Ref. Lippincott's Illustrated Reviews of Biochemistry, 2nd Edition; page-297)*

***Chronic effects of diabetes*** : The long-standing elevation of blood glucose is widely believed (but not conclusively proved) to cause the *chronic complications of diabetes* :

i. Premature atherosclerosis
ii. Retinopathy
iii. Nephropathy
iv. Neuropathy.

Intensive treatment with insulin delays the onset and slows the progression of these long-term complications. The benefits of tight control of blood glucose outweigh the increased risk of severe hypoglycemia. How hyperglycemia causes the chonic complications of diabetes is unclear. In cells where entry of glucose is not dependent on insulin, elevated blood glucose leads to increased intracellular glucose and its metabolites. For example, increased intracellular sorbitol may contribute to the formation of cataracts. Further hyperglycemia may promote the

condensation of *glucose* (or *its metabolites*, particularly *Glyceraldehyde 3 phoshate*) with cellular *proteins*, in a reaction analogous to the formation of $HbA_{1c}$. These glycated proteins may mediate some of the early microvascular changes of diabetes.

*(Ref. Lippincott's Illustrated Reviews of Biochemistry, 2nd Edition; page-297)*

(Please see page 130 of Lippincott's Illustrated Reviews of Biochemistry for discussion of the sorbitol pathway).

**Clinical characteristics of patients with type I and type II diabetes mellitus** :

| *Features* | *Type I* | *Type II* |
|---|---|---|
| Age at onset | Usually <20 years | Usually >30 years |
| Body mass | Low (wasted) to normal | Obese |
| Plasma insulin | Low or absent | Normal to high initially |
| Plasma glucagon | High, can be supressed | High, resistant to supression |
| Plasma glucose | Increased | Increased |
| Insulin sensitivity | Normal | Reduced |
| Therapy | Insulin | Thiazolidinedione, metformin, sulfonyl-ureas, insulin. |

*(Ref. Guyton & Hall-11th edition; page 975)*

Q. 00. **What are the investigations used in clinical practice for diagonosis of diabetes mellitus?**

Ans. Investigations used in clinical practice for diagonosis of diabetes mellitus are :

i. *Fasting blood glucose (FBS) level* :
   a. Normal FBS : 4.5-5.6 mmol/L (70-110 mg/dl)
   b. Suspicious of diabetes : > 5.6 mmol/L
   c. Diabetic : > 6.7 mmol/L (120 mg/dl)

ii. *Random blood glucose RBS* : > 10 mmol/L (180 mg/dl).

iii. *Glucose tolerance test- OGTT* (2hrs after brekfast or 75 mg intake of glucose with 250-300 ml of water) : After taking glucose by mouth samples of blood are collected at half-hourly intervals for at least 2 hours and their glucose content is estimated.
   a. Normal : <7.8 mmol/L
   b. Diabetic : > 10 mmol/L.

iv. Urine R/M/E (sugar)

v. Serum urea and creatinin.

## Pineal gland

The pineal gland *(epiphysis)*, believed by Descartes to be the seat of the soul, has at one time or another been regarded as having a wide variety of functions.

i. *Anatomy* : The pineal arises from the roof of the third ventricle under the posterior end of the corpus callosum and is connected by a stalk to the posterior commissure and habenular commissure. There are nerve fibers in the stalk, but apparently do not reach the gland.

   The pineal stroma contains neuroglia and parenchymal cells with features suggesting that they have a secretory function. Like other endocrine glands, the pineal has highly permeable fenestrated capillaries. In young animals and infants, the pineal is large, and the cells tend to be arranged in alveoli.

   It begins to involute before puberty, and, in humans, small concretions of calcium phosphate and carbonate (***pineal sand***) appear in the tissue. Because the concretions are radiopaque, the normal pineal is often visible on x-ray films of the skull in adults. Displacement of a calcified pineal from its normal position indicates the presence of a space-occupying lesion such as a tumor in the brain.

ii. *Function* : It is now known to secrete *melatonin*, and it may function as a timing device to keep internal events synchronized with the light-dark cycle in the environment.

*(Ref. Ganong 21th Edition; page 462)*

**Difference between the different types of diabetes.**

| *Pituitary diabetes* | *Adrenal diabetes* | *Diabetes mellitus.* |
|---|---|---|
| 1. Due to increased secretion of anterior pituitary. | 1. Due to increased sceretion of glucocorticoid. | 1. Due to lack of insulin. |
| 2. Glucose utilization by the cell depressed. | 2. Glucose utiliztion by the cell depressed. | 2. No utilization of glucose by the cells. |
| 3. Weakly insulin sensitive. | 3. Moderately insulin sensitive. | 3. Strongly insulin sensitive. |

**Comparison of two types of diabetes mellitus**

| | *Insulin-dependent diabetes mellitus (IDDM)* | *Non-insulin-dependent diabetes meliitus (NIDDM)* |
|---|---|---|
| Synonym | Type I; juvenile-onset diabetes | Type II : adult-onset diabetes |
| Age of onset | Usually during childhood or puberty | Frequently after age 35 |
| Nutritional status at time of onset of disease | Frequentlv undernourished | Obesity usually present |
| Prevalence | 10%-20% of diagnosed diabetics | 80%-90% of diagnosed diabetics |
| Genetic predisposition | Moderate | Vety strong |
| Defect or deficiency | β-Cells destroyed, eliminating production of insulin | Inability of β-cells to produce appropriate quantities of insulin : *insulin resistance* |
| Ketosis | Common | Rare |
| Plasma insulin | Low to absent | Normal to high |
| Acute complications | Ketoacidosis | Hyperosmolar coma |
| Oral hypoglycemic drugs | Unresponsive | Responsive |
| Treatment with insulin | Always necessary | Usually not required. |

***Directions :*** Write T for true & F for false against each of the following statement.

## *Introduction*

Q. 01. **The essential glands are**
- T a. adrenal cortex
- T b. parathyroid gland
- F c. thyroid gland
- F d. adrenal medulla
- F e. ovary.

Q. 02. **The glands having both endocrine and non-endocrine functions are**
- T a. gonads
- T b. hypothalamus
- T c. pancreas
- F d. thyroid gland
- F e. anterior pituitary

Q. 03. **ECF volume is maintained by**
- T a. ADH,
- T b. aldoesterone.
- T c. osmolarity of plasma.
- T d. plasma $K^+$ level
- F e. oxytocin.

Q. 04. **Hormones are**
- T a. chemical substances
- T b. secreted into body fluids
- F c. devoid of physiological control effect
- F d. of five general classes
- F e. secreted only by one cell

Q. 05. **Mechenism of action of protein hormones**
- T a. activating c-AMP system
- T b. facilitating cellular protein synthesis
- T c. activating enzymes
- T d. modulating cell permeability.
- F e. reacting with the receptors present on the nuclear membrane

Q. 06. **Polypeptide or protein hormones are**
- T a. secreted by anterior and posterior pituitary glands
- T b. secreted by parathyroid glands
- T c. synthesized on the rough endoplasmreticulum
- T d. transported by exocytosis.
- F e. not secreted by pancreas

Q. 07. **The neuropeptide hormones are**
- T a. epinepbrine
- T b. antidiuretic hormone
- T c. oxytocin
- F d. thyroid releasing homone
- F e. somatomedin

Q. 08. **General hormone are**
- T a. thyroxin
- T b. growth hormone
- F c. secretin
- F d. epinephrin.
- F e. acetylecholine

Q. 09. **The local hormones are**
- T a. colecystokinin
- T b. gastrin
- T c. secretin
- F d. ACTH
- F e. TSH.

Q. 10. **Following are local hormones**
- T a. Insulin
- T b. gastrin
- F c. Heparin
- F d. Bradykinin
- F e. Acetyl choline

Q. 11. **Tropic hormone are**
- T a. LH.
- T b. TSH
- T c. FSH
- F d. Insulin
- F e. Epinephrin

Q. 12. **The hormone receptors are located in the**
- T a. nucleus.
- T b. surface of the cell membrane

F c. target organ
F d. cell cytoplasm
F e. organelles

Q. 13. **Hormones that act through gene activation are**
T a. estrogens
T b. testosterone.
T c. cortisol
T d. aldosterone
F e. glucose

Q. 14. **Cyclic AMP serves as a second messenger in the secretion**
T a. FSH
T b. Glucagon
T c. Epinephrine
F d. Estrogen
F e. All.

Q. 15. **Production of c-AMP from ATP requires**
T a. Adenylate cyclase
F b. ATP ase
F c. cAMP synthetase
F d. None
F e. All.

Q. 16. **Homiones that act through cAMP (second messen gers system) are**
T a. luteinizing hormone
T b. antidiuretic hormone.
T c. parathyroid hormone
F d. 1 ,25-dihydroxycholecalciferol
F e. progesterons

Q. 17. **Characteristics of cyclic AMP are**
T a. alters cell permeability
T b. causes protein synthesis
T c. activates enzymes
F d. activates neurotransmitter
F e. causes breakdown of membrane phospholipids.

Q. 18. **The second messenger systems include**
T a. calcium ion
T b. calmodulin.
T c. cAMP
T d. IP3
F e. phosphate ion

Q. 19. **Which hormone is not released following trauma**
T a. Thyroxine
F b. Glucagon
F c. ADH
F d. GH
F e. None.

Q. 20. **An adolescent desirous of increasing his muscle mass is advised to**
T a. Exercise the muscle
F b. Increase protein intake
F c. Take steroids
F d. Electrically stimulate the muscle
F e. None.

Q. 21. **All are seen in obesity except**
T a. Increased sensitivity to GH
F b. Diabetes
F c. Hyperuricemia
F d. Atherosclerosis
F e. All

Q. 22. **All are (may) seen in obesity**
T a. Diabetes
T b. Hyperuricemia
T c. Atherosclerosis
F d. Increased sensitivity to GH
F e. None.

Q. 23. **Energy for the brain in starvation is from**
T a. Glucose
T b. Ketones
F c. Fatty acids
F d. Amino acids
F e. None.

Q. 24. **Melatonin is secreted by**
T a. Pineal gland
F b. Hypothalamus
F c. Adrenal cortex
F d. Melanocytes
F e. None.

## Hypothalamus

Q. 25. **Hypothalamus**
T a. secret releasing hormone which stimulates their target tissues through c-AMP
T b. secrets both releasing and inhibitory hormones
T c. synthesizes ADH and oxytocin.
F d. controls the secretion of parathyroid gland.
F e. is connected with posterior pituitary by hypothalamic hypophysial portal system.

Q. 26. **The hypothalamic releasing hormones**
T a. are transpoted by the hypothalamic hypophysial portal vessels in to the anterior pituitaiy
T b. are released in the median eminence
T c. stimulate the secretion of specific hormone from the anterior pituitary
F d. control posterior pituitary secretion

F e. have positive feedback reationship with posterior pituitary.

Q. 27. **Hypothalamic releasing hormone are**
T a. gonadothyrotropin releasing hormone.
T b. gonadotropin releasing hormone.
T c. growth hormone releasing hormone.
F d. prolactin inhibiting hormone.
F e. growth hormone inhibiting hormone.

Q. 28. **Osmoreceptors**
T a. are located in or near the hypothalamus.
T b. control the secretion of anti diuretic hormone.
T c. increase the discharge of impulses when body fluid osmolality is increased.
F d. are receptors for the actionof aldosterone
F e. become shrunken when ECF osmolatity decrease.

Q. 29. **Adrenocorticotropic hormone (ACTH)**
T a. stimulates the secretion of adrenal androgen
T b. is secreted from anterior pituitary
T c. stimulates the secretion of cortisol
F d. is a hypothalamic hormone
F e. is chemically steroid in nature.

Q. 30. **ACTH secretion is increased due to**
T a. severe trauma
T b. decreased blood cortisol level.
T c. increased secretion of corticotropin releasing hormone.
F d. decreased blood aldosterone.
F e. increased blood cholesterol level.

Q. 31. **Regarding ACTH the following statements are true except**
T a. It is not protein in nature
F b. Secreted by the basophil cells
F c. Controls secretion of adrenal cortex
F d. It can withstand heating up to 100 degree C
F e. All.

Q. 32. **FSH is secreted by**
T a. Basophils
F b. Chromophobes
F c. Acidophils
F d. Theca interna cells
F e. All.

Q. 33. **Function of leutenizing hormone is**
T a. Follicle maturation and ovulation
F b. Milk secretion
F c. Causes progesterone secretion during ovulation
F d. Maintains placenta
F e. None

Q. 34. **TRH stimulates TSH and ...**
T a. Prolactin
F b. GH
F c. Oxytocin
F d. Gonadotrophin
F e. All.

Q. 35. **The satiety centre is located in the**
T a. Ventromedian nucleus of hypothalamus
F b. Dorsomedian nucleus of hypothalamus
F c. Perifornical region
F d. Lateral hypothalamic area
F e. All.

Q. 36. **Hypothalamus regulates all except**
T a. Anticipatory rise in heart rate
F b. Food intake
F c. Temperature
F d. Hypophysis
F e. All.

Q. 37. **Hypothalamus regulates**
T a. Hypophysis.
T b. Food intake
T c. Temperature
F d. Anticipatory rise in heart rate
F e. All.

Q. 38. **Decreased hypothalamic function casues depressed levels of all of following homones *except***
T a. Prolactin
F b. Growth hormone
F c. TSH
F d. ACTH
F e. None.

Q. 39. **Decreased hypothalamic function casues depressed levels of the following homones**
T a. Growth hormone
T b. TSH
T c. ACTH.
F d. Prolactin
F e. All.

Q. 40. **One of the following is a function of hypothalamus**
T a. Homeostasis of temperature
F b. Swallowing
F c. Vomiting
F d. Respiration
F e. All.

Q. 41. **Circadian rhythm is controlled by**
T a. Hypothalamus
F b. Supra chiasmatic nucleus
F c. Thalamus
F d. Pineal gland
F e. None.

Q. 42. **The effect of hypophysectomy is**
- T a. Glucocorticoid deficiency
- T b. Mineralo corticoid deficiency
- T c. Menstrual failure
- T d. All
- F e. None.

Q. 43. **Osmoreceptors are present in**
- T a. Anterior hypothalamus
- F b. Internal carotid artery
- F c. Left atrium
- F d. Ventricle
- F e. All.

## Pituitary

Q. 44. **The pituitary gland**
- T a. secretes prolactin.
- T b. is essential for life.
- T c. secretes anti-diuretic hormone.
- T d. secretion is under hypothalamic control.
- F es. regulates other endocrine glands.

Q. 45. **Beta endorphin is**
- T a. Hormone of the intermediate lobe of pituitary
- F b. A lipoprotein
- F c. Analogue of morphine
- F d. Morphine receptor in brain
- F e. All.

Q. 46. **Not a glycoprotein**
- T a. GH
- F b. FSH
- F c. LH
- F d. TSH
- F e. All.

Q. 47. **Effects of panhypopituitarism in the adult are**
- T a. loss of sexual function
- T b. hypothyroidism
- T c. decreased production of glucocorticoids
- F d. loss of weight
- F e. dwarfism.

Q. 48. **Panhypopituitarism causes all except**
- T a. Pigmentation
- F b. Infertility
- F c. Loss of secondary sexual characters
- F d. coid intolerance
- F e. None

Q. 49. **Panhypopituitarism causes all except**
- T a. Infertility
- T b. Loss of secondary sexual characters
- T c. coid intolerance
- F d. Pigmentation
- F e. All.

### Anterior pituitary gland

Q. 50. **Hormones secreted from the anterior pituitary gland**
- T a. Growth hormone
- T b. Prolactin
- T c. TSH
- T d. ACTH
- F e. Somatostatin

Q. 51. **Secretion of anterior pituitary gland**
- T a. shows a negative feed back mechanism.
- T b. depends on the release of hypothalamic releasing hormone.
- T c. is independent of CNS control from above the level of the hypothalamus.
- F d. depends on direct neural connection with hypothala -mus.
- F e. depends on the plasma glucose level.

Q. 52. **The anterior pritutary hormones are**
- T a. luteinizing hormone
- T b. thyroid stimulating hormone
- T c. corticotropin
- F d. antidiuretic hormone
- F e. aldosterone.

Q. 53. **Growth hormone**
- T a. increases utilization of fat for energy
- T b. is a diabetogenic hormone.
- T c. causes mobilization of fatty acid from adipose tissue
- T d. decreases carbohydrate utilization
- F e. causes breakdown of protein

Q. 54. **Growth hormone**
- T a. is a diabetogenic hormone.
- T b. promotes positive nitrogen balance.
- T c. secretion is under hypothalamic control.
- T d. stimulates the liver to secrete somatomedins.
- F e. acts directly to cause bone and cartilage growth.

Q. 55. **Human growth hormone**
- T a. acts as a *protein sparer*.
- T b. causes ketosis.
- T c. is a small protein molecule.
- F d. comes from lactotropes.
- F e. acts as a *fat sparer*.

Q. 56. **Growth hormone secretion increases during**
- T a. hypoglycemia.
- T b. exercise and excitement.

T c. young age.
T d. starvation.
F e. low concentration of fatty acid in the blood

Q. 57. **In a person who has fasted for 5 days all are seen except**
T a. GH levels decreased
F b. Glucose tolerance decreased
F c. Immunoreactive insulin decreased
F d. Free fatty acids (plasma) increased.
F e. None.

Q. 58. **In a person who has fasted for 5 days seen**
T a. Glucose tolerance decreased
T b. Immunoreactive insulin decreased
T c. Free fatty acids (plasma) increased.
F d. GH levels decreased
F e. All.

Q. 59. **True about growth hormone is that**
T a. It causes diabetes mellitus resistant to insulin
F b. Causes hyperglycemia
F c. Enhances lipogenesis
F d. Causes hypoglycemia
F e. None.

Q. 60. **Impaired growth hormone secretion in children**
T a. can be effectively treated by human growth hormone.
T b. leads to short stature.
F c. causes mental retardation.
F d. causes delayed puberty.
F e. increases size of the soft tissue.

Q. 61. **Pituitary dwarfism**
T a. occurs when growth hormone level declines.
T b. is associated with proportionate growth and development
F c. is not associated with short strature.
F d. includes mental retardation.
F e. occurs during adulthood.

Q. 62. **Dwarfism occurs due to deficiency of**
T a. somatomedins.
T b. growth hormone
T c. thyroid hormone
F d. insulin
F e. adrenocortical hormone

Q. 63. **Features of acromegaly are**
T a. kyphosis.
T b. enlargement of liver and kidney.
T c. enlargement of tongue.
T d. enlargement of hands and feet.
F e. deficiency of somatostatin.

Q. 64. **Transection of pituitary stalk leads to increase in**
T a. Prolactin
F b. TSH
F c. GH
F d. ACTH
F e. All.

Q. 65. **Prolactin**
T a. secretion is regulated by hypothalamus.
T b. is responsible for initiation and maintinance of milk production.
T c. is a hormone of anterior pituitary.
F d. is responsible for breast growth at puberty.
F e. causes ejection of milk during suckling of breast.

## Posterior pituitary gland

Q. 66. **Posterior pituitary gland**
T e. is called neurohypohysis.
T a. is composed of glial like cells i.e. pituicytes
T b. secretes hormone that binds with neurophysin.
F c. is a typical endocrine gland.
F d. secretes endorphin.

Q. 67. **Which is true regarding oxytocin**
T a. Secreted by para ventricular tissue
F b. Increased by stress
F c. Effective in males
F d. Important for maintaining pregnancy
F e. All.

Q. 68. **Oxytocin**
T a. causes contraction of myoepithelial cells and ejection of milk.
T b. causes contraction of uterus during labour.
T c. is a hormone of posterior pituitary.
F d. is formed mainly in the supraoptic nuclei.
F e. helps in development of breast.

Q. 69. **Oxytocin**
T a. reaches the posterior pituitary gland by hypothalamic hypophysial portal tract.
T b. is synthesized mainly by the paraventricular nucleus of the hypothalmus.
T c. causes contraction of the pregnant uterus at the time of parturition.
T d. concerned with ejection of milk
F e. is a steriod hormone.

Q. 70. **Oxytocin causes all except**
T a. Lactogenesis
F c. Contraction of uterine muscle
F b. Milk ejection
F d. Myoepithelial cell contraction.
F e. All.

Q. 71. **Oxytocin causes**
- T a. Contraction of uterine muscle
- T b. Milk ejection
- T c. Myoepithelial cell contraction.
- F d. Lactogenesis
- F e. All.

Q. 72. **Site of ADH action is**
- T a. Collecting tubule
- F b. Proximal tubule
- F c. Loop of Henle
- F d. Vasa recta
- F e. All.

Q. 73. **Antidiuretic hormone (ADH)**
- T a. decreases volume of urine.
- T b. deficiency causes diabetes insipidus.
- T c. at high concentration increases blood pressure.
- F d. is synthesized mainly by the paraventricular nucleus of the hypothalamus.
- F e. decreases reabsorption of water.

Q. 74. **Anti diuretic hormone (ADH)**
- T a. is mainly secreted from supraoptic nucleui.
- T b. secretion is regulated by osmoreceptor.
- T c. is a posterior pituitary hormone
- T d. increases reabsorption of water in the late distal tubules, colleting tubules and collecting duct
- F e. acts on proximal tubules.

Q. 75. **Anti-diuretic hormone is**
- T a. formed primarily in the supraoptic nuclei.
- T b. secreted when the osmolality of the body fluid is increased.
- F c. synthesized in the posterior pituitary.
- F d. stored in the hypothalamus.
- F e. increased during over hydration.

Q. 76. **Extracellular fluid volume is maintained by**
- T a. osmolarity of plasma.
- T b. plasma $K^+$ level.
- T c. ADH.
- T d. aldoesterone.
- F e. oxytocin.

Q. 77. **Oxytocin secretion promotes**
- T a. myometrial contraction.
- T b. myoepithetical cell contraction.
- T c. milk ejection.
- F d. lactogenesis.
- F e. galactopoiesis.

## Thyroid gland

Q. 78. **Thyroid gland**
- T a. has effect on growth and development of CNS.
- T b. stimulates the oxidative metabolism in general.
- T c. stores thyroid hormones extracellularly.
- F d. can concentrate iodine.
- F e. is stimulated by hot.

Q. 79. **Thyriod gland**
- T a. the requirement of iodine is 1 mg/week to form normal quantities of thyroxine.
- T b. it secrets thyroxine, tri-iodothyronine and thyrocalci -tonin.
- F c. thyroxine is more potent than tri-iodothyronine.
- F d. duration of action of thyroxine is less than that of tri-iodothyronine.
- F e. thyroxine remains in free form in the blood.

Q. 80. **Thyroid cells**
- T a. provide necessary enzymes for oxidation of iodide
- T b. are cuboidal epithelial cells.
- T c. are concerend with iodide pump.
- T d. form thyroglobulin.
- F e. contain amino acid arginine.

Q. 81. **Thyroid hormones are**
- T a. almost absent in patients with myxedema
- T b. important for growth and development of fetalbrain.
- F c. protein in nature.
- F d. formed by conversion of ferrous iron into ferric form.
- F e. regulated by positive feedback mechanism

Q. 82. **Thyroid hormone secretion occurs**
- T a. when $T_3$ and $T_4$ levels are decreased.
- T b. when excessive cold occurs.
- F c. when $T_3$ and $T_4$ levels are increased.
- F d. at the time of emotion, excitement, stress etc
- F e. when sympathetic activity is increased.

Q. 83. **Thyroid hormones**
- T a. increase secretion of digestive enzyme
- T b. increase motility of GI tract.
- T c. increase BMR
- F d. decrease appetite
- F e. decrease metabolic rate

Q. 84. **The substances required for the biosynthesis of thyroxin are**
- T a. thyroglobulin
- T b. peroxidase
- T c. iodine
- F d. iron
- F e. cholesterol.

Q. 85. **Thyroxine**
- T a. Helps in the development of brain in the fetal period
- T b. secretion is regulated by TSR.

T c. increases the basal metabolic rate
F d. decreases the number and size of the mitochondira
F e. decreases the enzyme $Na^+$-$K^+$ ATPase

Q. 86. **Thyroxine binding globulin is increased in**
T a. Pregnancy
F b. Nephrotic syndrome
F c. Glucocorticod treatment
F d. Cancer chemotherapy.

Q. 87. **The most biologically active iodothyronine secreted by thyroid follicle is**
T a. $T_3$
F b. $T_4$
F c. $RT_3$
F d. thyroglobulin
F e. tri-iodothyroacetic acid.

Q. 88. **Tri-iodothyonine**
T a. is about four time potent than thyroxine.
T b. is metabolically active hormone of thyroid gland.
T c. is present in the blood in small quantities.
F d. persists for a longer time.
F e. is about 50% of thyroid hormones.

Q. 89. **Tri-iodothyronine ($T_3$)**
T a. is more potent than $T_4$.Q.
T b. has less affinity for binding protein.
F c. is secreted from the parafollicular cells of thyroid.
F d. is converted to $T_4$ in the body
F e. is less active than $T_4$

Q. 90. **Iodide is**
T a. absorbed from GIT into the blood.
T b. actively transported into the cell.
T c. required for the formation of thyroid hormone.
F d. required 100 mg/week.
F e. not dependent on TSH.

Q. 91. **Iodide trapping is**
T a. stimulated by TSH.
T b. taking place at the basal membrane of the thyroid cell.
T c. called iodide pump.
T d. an active process.
F e. stimulated by $T_3$ and $T_4$

Q. 92. **Tyrosine derivative hormones are**
T a. epinephrine
T b. thyroxine
T c. norepinephirine
F d. estrogen
F e. antidiuretic hormone.

Q. 93. **The hormones causing glycolysis are**
T a. $T_3$ and $T_4$
T b. insulin
F c. glucagon
F d. cortisol
F e. pancreatic polypeptid

Q. 94. **In hyperthyroidism there are**
T a. exopthalmos.
T b. tachycardia
T c. increased secretion of $T_3$ and $T_4$
F d. high level TSH in plasma
F e. may be weight gain

Q. 95. **In hyporthyroidism**
T a. during fetal life, infancy and child hood is known as cretinsim
T b. the concentration of TSH is high.
T c. there is deficiency of iodine
F d. the size of the thyroid gland is reduced
F e. blood cholesterol level is decreased

Q. 96. **A Patient with hypothyroidism is likely to have**
T a. Subnormal mouth temperature
T b. Tendency to fall alseep frequently
F c. Increased body hair
F d. Moist hands and feet.
F e. All.

Q. 97. **Total thyroidectomy leads to**
T a. increase TSH level
T b. increase blood cholesterol level
F c. exopthalmos
F d. diarrhea
F e. tachycardia.

Q. 98. **Myxedema**
T a. can be diagnosed by telephone.
T b. is associated with huskye voice
F c. causes blackish pigmentation all over the body.
F d. decreases the body weight.
F e. occurs in children.

Q. 99. **Regarding Myxoedema the following are true**
T a. Dullness, loss of memory
T b. Swollen, Oedematous look of the face
T c. Impotency, amenorrhoea etc
F d. BMR increased by 30-45%

Q. 100. **The common feature of hyperparathyroidism are**
T a. weight loss.
T b. BMR increased.
T c. increased $T_3$ and $T_4$ level in the blood.
F d. increased TSH level.
F e. intolerance to cold.

Q. 101. **Simple enlargement of thyroid gland is**

T a. due to deficiency of iodine
T b. called goiter
F c. due to deficiency of protein
F d. due to deficiency of tyrosine
F e. occured due to excessive secretion of $T_3$ and $T_4$.

Q. 102. **Calcitonin hormone is**
T a. a peptide hormone.
T b. secreted by thyroid gland.
F c. secreted by parathyroid gland.
F d. a steroid hormone.
F e. secreted by adrenal cortex.

Q. 103. **Calcitonin hormone**
T a. deceases plasma calcium concentration.
F b. increases plasma calcium concentration.
F c. has no effect on calcium concentration in ECF.
F d. has same effects of parathormone.
F e. increases sodium ion concentration.

Q. 104. **Calcitonin secretion is stimulated by**
T a. increased plasma calcium concentration.
F b. decreased plasma potassium concentration
F c. decreased $Na^+$ concentration.
F d. phosphate concentration.
F e. decreased by plasma calcium concentration

Q. 105. **Calcitonin is produced by**
T a. Thyroid
F b. Parathyroid
F c. Thymus
F d. Kidney
F e. All.

## Parathyroid gland

Q. 106. **Parathyroid gland**
T a. regulates the $Ca^{++}$ and $PO_4^-$ metabolism in the body.
T b. is essential for life.
T c. secretes parathormone
F d. secretes calcitonin
F e. secretes calcitriol

Q. 107. **Parathormone**
T a. activates vitamin D
T b. enhances calcium absorption from the intestines
T c. acts by activating receptors on the cell membrane
F d. secretion is regulated by anterior pituitary gland
F e. enhances reabsorption of phosphate from renal tubules

Q. 108. **Parathormone**
T a. is a polypeptide
T b. controls calcium and phosphate concetration in ECF
F c. is not life saving hormone
F d. is a steroid hormone
F e. is tyrosine derivative.

Q. 109. **Parathormone**
T a. secretion is controlled by calcium ion concentration
T b. helps in calcium exchange between bone and ECF
T c. increases intestinal absorption of calcium
F d. decreases absorption of phosphate from intestine.
F e. helps in activation of vitamin-D.

Q. 110. **Parathormone**
T a. acts through second messenger
T b. increases blood calcium concentration
F c. is secreted by oxyphil cells of parathyroid gland
F d. decreases renal clearance of phosphate
F e. secretion rate is under control of hypothalamus

Q. 111. **Parathormone secretion regulator is**
T a. high level of phosphate in the plasma
T b. low ionized plasma $Ca^{++}$ level
F c. high level of 1,25-dihydroxycholecalciferol
F d. vitamin D.
F e. low level of parathormone

Q. 112. **The site of action of parathormone**
T a. distal convulated tubules of kidney
T b. small intestine
T c. bone
F d. duct of salivary gland
F e. liver.

Q. 113. **Parathormone secretion is usually increased during**
T c. rickets
T d. lactation
T e. pregnancy.
F a. excessive intake of vitamin-D
F b. hypercalcemia

Q. 114. **Calcium in the plasma is**
T a. about 2.4 mmol/L.
T b. present in three forms
T c. combined with plasma protein
F d. about 80 percent diffusible
F e. about 50 percent non-diffusible

Q. 115. **Hormones concerned with calcium metaolism are**
T a. calcitonin.
T b. 1 ,25-dihydroxycholecalciferol.
T c. parathormone
F d. androgen.
F e. aldosterone

Q. 116. **Metastatic calcification occurs when calcium is in**

T a. Alkaline pH
F b. Acidic pH
F c. Neutral pH
F d. Ionic equilibrium
F e. All.

Q. 117. **Hypercalcemia**
T a. decreases the reflex activities
T b. occurs when calcium level is increased above normal
T c. depresses nervous system
F d. increases muscle activity
F e. causes diarrhea and increase of appetite.

Q. 118. **Hypocalcemia causes**
T a. nervous system excitement
T b. tetany
F c. depression in nervous system
F d. constipation
F e. lack of appetite.

Q. 119. **Calcium ion concentration is**
T a. controlled by parathyroid secretion
T b. 2.4 mEq/L in ECF
T c. decreased in rickets
F d. increased in pregnancy
F e. not controlled by parathyroid gland.

Q. 120. **1,25-dihydorxycholecalciferol**
T a. increases binding protien
T b. increases alkaline phosphatase
T c. is a steroid hormone
T d. increases calcium-stimulated ATP ase
F e. is formed in the liver.

Q. 121. **Vitamin D**
T a. increases calcium absorption from intestinal tract
T b. has effects on bone deposition
T c. helps in $Ca^{++}$ absorption from bone.
F d. is converted to 1 ,25-dihydroxycholecalciferol in the liver
F e. is converted to 25-hydroxycholecalciferol in liver

Q. 122. **Vitamin-D**
T a. does not help in bone absorption and bone deposition
T b. causes transport of calcium ions.
T c. promotes intestinal calcium absorption
T d. promotes phosphate absorption by the intestines
F e. decreases renal calcium and phosphate excretion

Q. 123. **In hypoparathyroidism**
T a. tetanus develops
T b. bone usually remain strong.
T c. parathyroid glands do not secrete sufficient PTH.
F d. level of calcium in the body fluid increases
F e. calcium reabsorption from bone is increased

Q. 124. **Hypoparathyroidism is charaterized by**
T a. tetany
T b. hypocalcemia
T c. hyperphosphatemia.
F d. muscle weakness
F e. tetanic contraction of heart muscle.

Q. 125. **In hyperparathyroidism plasma $Ca^{++}$ level is**
T a. increased
T b. 12 to 15 mg/dl
F c. 5 to7 mg/dl
F d. 9.4 mg/dl
F e. decreased.

Q. 126. **In hyperparathyriodism**
T a. constipation and abdominal pain occurs
T b. lack of appetite develops.
T c. depression of CNS occurs
F d. stimulation of peripheral nervous system occurs
F e. muscle weakness does not develop

Q. 127. **Ricket occures mainly**
T a. due to calcium and phosphate deficiency
T b. in children
F c. in old people
F d. due to deficiency of vitamin E
F e. in adult.

Q. 128. **Osteoporosis occurs due to**
T a. malnutrition
T b. deficiency of vitamin C
F c. lack of calcium in the bones
F d. premenopasual period
F e. Addison's disease.

Q. 129. **Weightlessness results in**
T a. Decreased osteoporosis
F b. Decreased cardiac output
F c. Hypotension
F d. Gut motility
F e. All.

## Pancrease

*Introduction*

Q. 130. **Regarding islets of langerhans cells in the pancreas**
T a. there are 1-2 million cells in human pancreas.
T b. there are alpha, beta, delta and PP cells
F c. alpha cells are the most abundant cells
F d. they constitute exocrine part of the pancreas
F e. beta cells secretes glucagon

Q. 131. **An adult human pancreas has about**

T a. 250,000-750,000 islets
F b. 100-2000 islets
F c. 100,000-200,000 islets
F d. Above 1000,000 islets
F e. 1500-2000 islets

Q. 132. **Beta cells of pancreas produce**
T a. Insulin
F b. Glucagon
F c. Gastrin
F d. Pancreatin
F e. All.

Q. 133. **Increase in insulin receptors is seen in**
T a. Starvation
F b. Obesity
F c. Acromegaly
F d. Diabetes
F e. All.

Q. 134. **Amino acid sequence of human insulin differs from porcine insulin in**
T a. 1 amino acid
F b. 3 amino acids
F c. 5 amino acids
F d. None of the above
F e. All.

Q. 135. **The hormones causing glycolysis are**
T a. $T_3$ and $T_4$
T b. insulin
F c. glucagon
F d. cortisol
F e. pancreatic polypeptid

Q. 136. **The hormones regulating blood glucose concentration are**
T a. insulin
T b. cortisol
F c. ADH
F d. oxytocin
F e. calcitonin.

## *Insulin*

Q. 137. **How many parts are there in insulin receptor** :
T a. 4
F b. 1
F c. 2
F d. 3
F e. 5

Q. 138. **Insulin stress test assay estimates**
T a. Growth hormone
F b. Diabetes mellitus
F c. Glucagon assay
F d. Catecholamines.
F e. All.

Q. 139. **Insulin**
T a. increases permeability to amino acid
T b. binds with its membrane receptor
T c. increases uptake of glucose by muscle cells and adapter cells
F d. causes more excretion of potassium ions.
F e. has diabetogenic effect.

Q. 140. **Insulin is**
T a. an anabolic hormone.
T b. a small protein
F c. a small peptide
F d. secreted from the delta cell of islets of langerhans
F e. a catabolic hormone

Q. 141. **Biphasic release of insulin secretion occurs**
T a. in basal fasting state
T b. after intravenous injection of 20 gm glucose
T c. in the second phase from a stable pool
F d. in the first phase from a stable pool
F e. in non-fasting state.

Q. 142. **The site of action of insulin is the**
T a. adipose tissue
T b. muscle.
T c. liver
F d. kidney
F e. brain

Q. 143. **Mechanisms of insulin to regulates glucose metabolism are**
T a. phosphorylation of glucose.
T b. polymerization of the monosaccharide units to form glycogen.
T c. inactivation of liver phophorylase
F d. decreasing the activity of glucokinase
F e. depressing the activity of glycogensyn thetase.

Q. 144. **Insulin stimulates the**
T a. translation of messenger RNA
T b. rate of transcription
T c. protein synthesis.
T d. transport of amino acid into the cells
F e. catabolism of protein

Q. 145. **Insulin secretion is regulated by**
T a. glucagon
T b. high blood glucose level
F c. adrenalin
F d. somatostatin.
F e. low blood glucose level

Q. 146. **Insulin secretion is increased by**

T a. gastrin
T b. excess blood glucose
F c. decreased concentration of amino acid
F d. somatostatin
F e. cholecystokinin.

Q. 147. **Lack of insulin is characterized by**
T a. glycosuria
T b. hyperglycemia
T c. cellular dehydration
F d. alkalosis
F e. water diuresis.

Q. 148. **Insulin deficiency causes**
T a. ketoacidosis
T b. lipolysis of stored fat
F c. drecreased free fatty acid
F d. increased utilization of acetoacetic acid
F e. decreased plasma cholesterol

Q. 149. **Insulin causes lipogenesis by**
T a. decreasing the free fatty acid in the blood
T b. inhibiting the enzyme hormone-sensitive lipase
F c. stimulating the enzyme hormone sensitive lipase
F d. the breakdown of adipose tissue
F e. inhibiting the lipoprotein lipase

### *Glucagon*

Q. 150. **Glucagon**
T a. increases blood glucose level
T b. increases gluconeogenesis.
T c. is secreted by the alpha cells of the islets of Langerhans of pancrease
F d. is a steroid hormone
F e. decreases glycogenolysis

Q. 151. **Glueagon increases the blood glucose level by**
T a. glycogenolysis
T b. gluconeogenesis
T c. lipolysis.
F d. glycolysis
F e. glycogenesis

Q. 152. **Pancreatic glucagon**
T a. increases blood glucose concetration
T b. causes gluconeogensis and glycogenolysis
T c. acts through second messenger
F d. is a steroid hormone
F e. is produced by delta cells of islets of langerhans.

### *Somatostatin*

Q. 153. **Somatostatin**
T a. is secreted by the delta cells of the islets of Langerhans of pancreas
T b. is a polypeptide
T c. depresses the secretion of both insulin and glucagon
F d. increases the motility of the stomach
F e. increases both secretion and absorption in the gastrointestinal tract.

Q. 154. **Delta cells of pancreas secrete**
T a. Somatostatin.
F b. Insulin
F c. Glucagon
F d. VIP
F e. All.

Q. 155. **Regarding somatostatin**
T a. they are also called insulin like growth factors.
T b. they are small proteins
T c. mainly synthesize in liver
T d. at least four somatomedins are isolated
F e. metabolic function of growth hormones exerted through somatostatin

Q. 156. **Somatostatin is produced by ..... cells of the pancreas**
T a. Delta
F b. Alpha
F c. Beta
F d. Acinar
F e. All.

## *Diabetes*

Q. 157. **Diabetes mellitus is**
T a. of two types
T b. associated with increased blood glucose level.
T c. metabolic disorder
T d. caused by lack of insulin secretion
F e. not caused by decreased sensitibility of the tissues to insulin

Q. 158. **Blood glucose level is increased by**
T a. cortisol
T b. thyroid hormone.
T c. growth hormone
F d. insulin
F e. vit-D

Q. 159. **Increased blood glucose level causes**
T a. tissue injury
T b. increased utilization of fats
T c. loss of glucose in the urine
F d. over hydration
F e. increased storage of protein.

Q. 160. **Estimation of diabetes by**
T a. urinary glucose
T b. fasting blood glucose

T c. glucose tolerance test
T d. insulin level
F e. glucagon level

Q. 161. **Experimental diabetes is caused by**
T a. Alloxan
F b. $PgE_1$
F c. Radioactive yittrium
F d. Gold chloride
F e. All.

Q. 162. **Somyogi phenomenon is**
T a. Hypoglycemia followed by hyperglycemia
F b. Hyperglycemia followed by hypoglycemia
F c. Glycosuria with normal blood sugar
F d. Reactive hyperglycemia.
F e. All.

Q. 163. **Urinary osmolality in Diabetes Insipidus is**
T a. 300 mmol/Litre
F b. 100 mmol/Litre
F c. 150 mmol/Litre
F d. 900 mmol/Litre
F d. 500 mmol/Litre

Q. 164. **Hypertonic contraction of fluid volume is caused by**
T a. Diabetes Insipidus
F b. Addisons disease
F c. Cushings disease
F d. Salt losing nephropathy
F e. All.

## Adrenal gland

Q. 165. **Life saving hormones are**
T a. parathyroid hormone
T b. aldosterone
F c. thyroid hormones
F d. growth hormone
F e. adrenocorticotropic hormone.

Q. 166. **Extracellular fluid volume is maintained by**
T a. ADH.
T b. aldoesterone.
T c. osmolarity of plasma.
T d. plasma $K^+$ level.
F e. oxytocin.

Q. 167. **Urinary osmolality in Diabetes insipidus is**
T a. 300 mmol/Litre
F b. 100 mmol/Litre
F c. 150 mmol/Litre
F d. 900 mmol/Litre
F c. 400 mmol/Litre

Q. 168. **Osmoreceptor is located at which site?**
T a. Anterior hypothalamus
F b. Renal medulla
F c. Carotid body
F d. Atrial chamber.
F e. All.

Q. 169. **In the adrenal gland, androgens are produced by the cells in the**
T a. Zona reticularis
F b. Zona glomerulosa
F c. Zona fasciculata
F d. Medulla
F e. All.

Q. 170. **Regarding ACTH the following statements are true except**
T a. It is not protein in nature
F b. Secreted by the basophil cells
F d. Controls secretion of adrenal cortex
F e. It can withstand heating up to 100 degree C
F e. All.

Q. 171. **The adrenal cortex**
T a. secretes cortisol
T b. secretes some androgens
F c. is not essential for life
F d. secretes calcitonin
F e. is under control of thyroid gland.

Q. 172. **Stimulator of the adrenal medulla to secrete epinephrine is**
T a. sympathetic nerve
F b. thyroid stimulating hormone
F c. ACTH
F d. corticotropin releasing hormone
F e. acetylecholine.

Q. 173. **The hormones secreted from adrenal gland are**
T a. epinephrine
T b. cortisol
T c. androgens
F d. calcitonin
F e. adrenocorticotropin.

Q. 174. **Sources of steroid hormone are**
T a. corpus luteum
T b. ovary
T c. testis
T d. adrenal cortex
F e. thyroid glands

Q. 175. **Steroid hormones**
T a. act through gene activation
T b. have cyclopentano-perhydrophenanthren nucleus.
T c. are synthesized from cholesterol.

F d. are secreted from hypothalamus
F e. act directly on target cell membrane

Q. 176. **Steroid hormones are**
T a. vitamin D
T b. aldosterone
T c. estrogen
F d. insulin
F e. calcitonin.

Q. 177. **Cortisol**
T a. Secretion increases following injury
F b. Favours protein synthesis
F c. Enhances effects of antigen-antibody reactions
F d. Tends to lower blood pressure

Q. 178. **Cortisol**
T a. causes gluconeogenesis
T b. has anti-inflammatory effect
T c. is synthesized from cholesterol
F d. is secreted from zona glumerulosa of adrenal cortex
F e. decreases blood glucose level.

Q. 179. **The permissive role of cortisol on other hormones are**
T a. glucagon
T b. catecholamine
F c. insulin
F d. growth hormone
F e. aectycholine.

Q. 180. **Aldosterone**
T a. is chemically steroid in nature
T b. is a life saving hormone.
T c. is an adrenocortical hormone
F d. secretion is controlled by osmoreceptor mechanism
F e. acts on blood vessels to increases blood pressure

Q. 181. **Excess aldosterone is associated with all except**
T a. Hyperkalemia
F b. Water retention
F c. Hypokalemia
F d. Hypertension
F e. All.

Q. 182. **Aldosterone**
T a. acts on the distal segment of renal tubule.
T b. secretion is increased during hyperkalemia .
F c. secretion is increased during hypernatremia
F d. secretion is decreased by the activation of renin angiotensin mechanism.
F e. is chemically protein in nature

Q. 183. **What is not true for aldosterone?**
T a. Is a polypeptide
F b. Secreted in increased amounts when blood volume falls
F c. Secretion tends to increase renal arterial rressure
F d. Secretion results in a reduction in uninary volume
F e. All.

Q. 184. **Adreno-cortical hormones**
T a. are called corticosteroids
T b. bind with receptor located in the cytoplasm
T c. are steroid hormones
F d. are protein in nature
F e. act through second messenger mechanism

Q. 185. **Aldosterone secretion is regulated by**
T a. sodium ion concentration in extracellular fluid
T b. ACTH secretion from the anterior pituitary.
T c. potassium ion concentration in extracelular fluid
T d. renin-angiotensin mechanism
F e. osmoreceptor mechanism

Q. 186. **Aldosterone secretion is increased by an increase in**
T a. renin secretion
T b. ACTH secretion
F c. red cell volume
F d. plasma pH
F e. plasma volume

Q. 187. **Reabsorption of $Na^+$ and excretion of $K^+$ especially in the collecting tubule is the function of**
T a. aldosterone
F b. cortisol
F c. norepinephrine
F d. anti-diuretic hormone
F e. steroid hormone

Q. 188. **The hyposecretion of adrenocortical hormone**
T a. causes addisons disease
T b. is associated with melanin pigmentation
T c. causes death resulting from cardiac arrest.
F d. is called addisonian crisis
F e. copes up the person in any adverse condition

Q. 189. **Adrenaline insufficiency causes**
T a. A fall in extracellular fluid volume
T b. Low blood pressure
F c. Increased breakdown of protein
F d. A rise in plasma sodium/potassium ratio
F e. All.

Q. 190. **Removal of adrenal glands will cause**
T a. decreased blood volume
T b. death in less than 2 weeks
F c. increased excretion of potassium
F d. increased blood pressure
F e. increased retention of sodium.

Q. 191. **All are seen in cushings syndrome except**
- T a. Hypoglycemia
- F b. Truncal obesity
- F c. Hypertension
- F d. Poor wound healing
- F e. All.

Q. 192. **In Cushing syndrome the following features are found**
- T a. Impotence with atrophy of testis
- T b. Rapidly increasing adiposity
- T c. Polycythaemia
- F d. Hypotension
- F e. All.

Q. 193. **Cushing syndrome**
- T a. is associated with increased blood glucose concentration
- T b. is associated with hypertension.
- T c. is associated with moon face
- T d. occurs in hypersecretion of cortisol
- F e. occurs due to excessive secretion of growth hormone

Q. 194. **Addison's disease**
- T a. present with hyponatremia and hyperkalemia
- T b. is characterised by melanin pigmentation of the mucous membrane
- T c. results from lack of adrenocortical hormones
- F d. presents with hyperglycemia
- F e. does not affcet the muscular activity.

Q. 195. **Addisons disease causes**
- T a. hypoglycemia
- T b. increase melanin formation and pigmentation.
- T c. hypokalemia
- F d. hypernatremia
- F e. alkalosis

Q. 196. **In addisons disease the following is seen**
- T a. Hyperkalemia
- F b. Hypernatremla
- F c. Hyperglycemia
- F d. High blood pressure
- F e. All.

Q. 197. **BMR is decreased in**
- T a. Addisons disease
- F b. Hyperthyroidism
- F c. Increased body temperature
- F d. Cushings syndrome
- F e. All.

Q. 198. **Primary aldosteronism**
- T a. is known as Conn's syndrome
- T b. is characterized by hypertension
- T c. is accompanied by hypokalaemia
- F d. is due to deficiency of aldosterone
- F e. shows high plasma renin level.

Q. 199. **Adrenogenital syndrome**
- T a. is diagnosed by urinary excretion of excess 17-keto steroid
- T b. occurs due to excessive secretion of androgens
- T c. causes masculinizing effect in female
- F d. is not associated with precocious puberty in male
- F e. occurs due to excessive secretion of cortisol.