**Endocrinology**

The endocrine system is made up of secretory tissues (glands) whose secretions (hormones) are discharged directly into the blood.

**Hormones:** Are chemical substances secreted by the endocrine glands in low concentrations and are highly effective without being used as a source of energy and they show their physiological effect on distant tissues and cells.

**Chemistry of Hormones:**
1. **Steroid Hormones:** Include hormones having chemical structure similar or derived from cholesterol e.g. adrenal cortex hormones, ovarian and testicular hormones.
2. **Tyrosine derived hormones:** Such as thyroid hormones and adrenal medulla hormones.
3. **Protein or peptide type:** Include all the remaining hormones.

**Synthesis and Storage of Hormones:** Synthesis of peptide and protein hormones is similar to that of all proteins made by other cells. Transcription of genetic message involves synthesis of messenger ribonucleic acid (m-RNA) from the DNA template. Translation of message occur in the polysomes of the rough endoplasmic reticulum where amino acids are polymerized into a polypeptide chain called preprohormone. Then this large protein is further cleaved, usually while still in the endoplasmic reticulum, to form a smaller protein called the prohormone. This in turn is transported in the endoplasmic reticulum transport vesicles to the Golgi apparatus where still another section of the protein is cleaved, in this way the final active protein hormone is formed. Following this step the hormone is packaged into secretory granules and vesicles. This storage is ended when appropriate signal is received by the endocrine cell resulting in hormonal release to the extracellular space by a process of exocytosis.

**Control of Secretion:** The serum concentration of a hormone is a function of both its production rate and it’s metabolic clearance rate. The hormone secretion is controlled primarily by feedback regulation. Elevated serum level of one hormone that stimulates release of another is termed positive feedback regulation. Conversely, increased circulation levels of one hormone suppressing secretion of another is referred to as negative feedback regulation (the most common way of control of secretion).

**Hormone Receptors:** The biological effects of hormones are dependent upon hormonal binding to tissue receptors. These receptors are characterized by being:
1. Made up of high molecular weight proteins or glycoprotein.
2. Located in different sites of the cell.
   - [a] On cell membrane as catecholamine and insulin receptors.
   - [b] In the cytoplasm as in glucocorticoids.
   - [c] In the nucleus as for thyroid.
3. Specific for hormone type.
4. Different in number and affinity depending on the hormonal effective level such as decrease in number and affinity if the hormone level is high (Down regulation) or increase in number and affinity if the hormonal level is low (Up regulation).

**Mechanism of Action of Hormones:** Hormones act through the following mechanisms:
A. Change in membrane permeability, by opening or closing of ionic channels as in catecholamines.
B. Activation of gene formation by the hormone-receptor (M-R) complex, which may act on the DNA (as by thyroid or steroid hormones) or on the RNA (as for insulin and growth hormones) to form m-RNA which in turn produce a new protein that gives the physiological effect.
C. Activation of intracellular enzymes that initiate a series of events through the formation of second messenger (cAMP, cGMP, Ca ions, IP3, DAG, G protein) to produce the biological effect of the hormone.

The Thyroid gland

The thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal functions. Thyroid hormones stimulate the O₂ consumption of most of the cells of the body and in regulation of lipid and carbohydrate metabolism and necessary for normal growth and maturation. It is not essential for life but in it’s absence, there is poor resistance to cold, mental and physical slowing with mental retardation and dwarfism in children. In adults the gland contain two lateral lobes connected by medial band of thyroid tissue (Isthmus) which lies at the level of 2nd – 3rd tracheal rings. It had the highest rate of blood flow per gram of tissue of any organ in the body. The gland is made up of multiple acini (follicles) each on is surrounded by a single layer of columnar cells and containing proteineous material called the colloid.

Formation and Secretion of Thyroid Hormones: The principle hormones secreted by the thyroid are thyroxine (tetraiodothyronine or T₄) and triiodothyronine (T₃). T₃ is 3 - 5 times as potent as T₄. So T₄ is regarded as inert hormone metabolically until it is converted to T₃. Most of T₄ is converted to T₃ and RT₃ (Reversed T₃, inactive) in tissue. T₄ is considered as the major precursor of T₃. T₃ has the major role in feedback mechanism of thyroid hormones to inhibit the anterior pituitary TSH secretion.

Thyroglobulin: Is a glycoprotein made up of two subunits, with 140 tyrosine residue. It is synthesized in the thyroid cells and secreted into the colloid by exocytosis of granules that also contain thyroid peroxidase. Thyroid hormones remain bound to thyroglobulin until secreted.

Thyroid cells have three functions:
- Collect and transport iodine.
- Synthesize and secrete thyroglobulin into the colloid.
- They remove thyroid hormones from thyroglobulin and secrete them into circulation.

Synthesis of thyroid hormones: Iodine (I) is a raw material essential for thyroid hormone synthesis. Ingested iodine is converted to iodide (I⁻) and absorbed from GIT. The thyroid concentrates iodide by actively transporting it from the circulation to the colloid (named iodide trapping mechanism or iodide pump). I⁻ transport is an active transport aided by Na⁺ - K⁺ ATPase and thyroid stimulating hormone (TSH). Iodide pump can be inhibited by thiocyanate and perchlorate anions and by high level of iodide. Thyroid hormones synthesis can be summerized as follow:
1. Begins in thyroid gland when iodide is oxidized by peroxidase in
the presence of $H_2O_2$ and then bound to amino acid tyrosine molecules attached to thyroglobulin within the colloid in the follicular lumen (by iodinase enzyme) forming monoiodotyrosine (MIT) which is further iodinated to form diiodotyrosine (DIT). The peroxidase enzyme can be inhibited by propylthiouracil, which is used therapeutically to reduce thyroid hormone synthesis for the treatment of hyperthyroidism.
2. Two DIT undergo oxidative condensation to form thyroxine (T4) with alanine release.
3. DIT with MIT will form T3.
4. Within the follicular lumen, both T4 and T3 are still linked to thyroglobulin by peptide bonds. By endocytosis (pinocytosis), thyroid cells take up the thyroglobulin stored in the colloid and the resulting vesicle is joined by lysosomes which hydrolyze the peptide bonds of thyroglobulin and thereby release T4 and T3 into the intracellular space which are then released into the bloodstream. In normal human thyroid, the average distribution of iodinated compounds is 23% MIT, 33% DIT, 35% T4 and 7% T3. RT3 is trace.

**Transport and Metabolism of Thyroid Hormones:** The total normal plasma T4 level is 8 $\mu g/dl$ and for T3 is 0.15 $\mu g/dl$. However, the free circulating levels of T3 and T4 are much less than the total level, this is because most (99%) of T4 and T3 are bound to plasma proteins (albumin, thyroxine binding prealbumin [TBPA] and thyroxine binding globulin [TBG]). Albumin has the largest capacity to bind T4 (can bind most of T4 before it is saturated), while under physiological conditions most of circulating T4 is bound to TBG. Free thyroid hormones in plasma are in equilibrium with protein bound thyroid hormones in the plasma and tissues. Therefore, the thyroid hormones binding proteins are important to provide an equilibrium of free thyroid hormone levels within the physiological needs. In hepatic failure, TBG levels decrease and lead to an increase in free thyroid hormone levels. In pregnancy, TBG levels increase and lead to a decrease in free thyroid hormone levels. T4 and T3 are deiodinated in liver and kidney by 5-deiodinase to 2,3 and 3,1-DIT.

When thyroxine binding proteins level is increased in the plasma:
1. Free T3 and T4 levels are decreased. Consequently, the rate of T3 and T4 entry to tissues is decreased.
2. The low free hormones stimulate TSH. Consequently, TSH release from pituitary gland is increased, leading to increase secretion of T3 and T4 from thyroid gland.
3. Increase free T3 and T4 back to normal level (euthyroid).

**Regulation of thyroid hormones secretion:** thyroid function is regulated primarily by variation in the circulating levels of pituitary thyroid stimulating hormone (TSH or thyrotropin). TSH secretion is stimulated by the hypothalamic hormone called thyrotrophic-releasing hormone (TRH). TSH stimulates the thyroid gland to secrete T3 and T4. The increased T3 and T4 inhibit mainly anterior pituitary secretion of TSH and to much less extent the hypothalamus by a direct negative feedback fashion. The feedback inhibitory effect of T4 is enganced by the production of T3 in the cytoplasm of pituitary cells by the 5-deiodinase they contain. Stress inhibit TSH secretion, and in experimental animals it is increased by cold and decreased by warmth.

When the pituitary is removed, thyroid function is depressed and gland atrophied. When TSH is administered, thyroid function is stimulated causing increase iodied binding, increased synthesis of T3, T4, and iodotyrosine, increase secretion of thyroglobulin to colloid, increase iodin trapping, increase blood flow, and increase size and weight of thyroid cell.
Effects of thyroid hormones:

1. **Calorigenic Action:** Is due to the increase O₂ consumption (as a result of increase synthesis and activity of Na-K pump) of almost all tissues with increase of basal metabolic rate (BMR), except adult brain, retina, uterus, gonads, lymph nodes, spleen, and lungs. The resulting increase in heat production underlies the role of thyroid hormone in temperature regulation.

2. **Effect on the nervous system:** The cerebral blood flow, O₂ consumption and glucose are not affected by thyroid hormones, but some of the thyroid effects on the brain is due to increased responsiveness to catecholamines with consequent increase in activation of the reticular activating system. Hypothyroidism in adult associated with slow mentation and increase CSF protein levels while hyperthyroidism is associated with normal or rapid mentation, irritability and restlessness. In Infants, Hypothyroidism is associated with abnormal development of synapses, defective myelination. Mental retardation is irreversible if replacement therapy is not begun soon after birth. Ankle jerk (Achilles reflex) showed prolonged reaction time in hypothyroidism.

3. **Effect on CVS:** Increase number and affinity of beta-adrenergic receptors and consequently increase their sensitivity to the inotropic and chronotropic effects of catecholamines on the heart. Thus, increasing heart rate, myocardial contractility, cardiac output, blood flow and decrease circulation time. Higher level of thyroid hormones increase systolic pressure, and decreases diastolic pressure due to vasodilatation as a result of overproduction of metabolic end-products.

4. **Effect on metabolism:** Increase protein anabolism and catabolism with a net result of catabolism with consequent increase of N₂ excretion. Increase fat catabolism. They decrease circulating levels of cholesterol, phospholipids, and triglycerides and increase the levels of low density lipoprotein (LDL). In addition, T3 and T4 increase absorption of glucose by the GIT, stimulate glucose uptake by the cells, increase glycolysis and gluconeogenesis. Therefore, excess of thyroid hormones gives diabetogenic curve of oral glucose tolerance test (OGTT).

5. **Other effects:**

[A] **On the growth:** It is essential for normal growth and skeletal maturation because they potentiate the effect of growth hormone (GH) and somatomedins on the bone formation. In absence T4, the GH secretion is delayed.

[B] **On Respiration:** Increase rate and depth of respiration and increase O₂ dissociation from Hb by increase 2,3 DPG (shift to the right).

[C] **On Other Endocrine Glands:** Increase insulin secretion indirectly due to increase glucose absorption.

[D] **On Sexual Function:** It increases milk secretion. Thyroid hormones do not stimulate metabolism of the uterus but are essential for normal menstrual cycles and fertility. Hyperthyroidism causes impotence in male and oligominorrhoea in female while, hypothyroidism causes loss of libido in male with menorrhagia in female.

**Hypothyroidism:** The syndrome of adult hypothyroidism is called **Myxedema.** Hypothyroidism may arise [1] **primarily** from thyroid failure or [2] **secondary** to pituitary or hypothalamic failure (Pituitary hypothyroidism or hypothalamic hypothyroidism). In the latter two conditions, unlike the first, the thyroid responds to a test dose of TSH or TRH.

Myxedema is characterized by a fall in BMR, weight gain, the hair is coarse and sparse, skin is dry and yellowish (carotenemia) with poor tolerance to cold, low cardiac output, hypoventilation. The voice is husky and slow. Mentation is slow, memory is poor and in some patients there are severe mental symptoms (myxedema madness), plasma cholesterol is elevated.

**Cretinism:** Children who are hypothyroid from birth or before are called **cretins.** They are dwarfed and mentally retarded, having potbellies with enlarged protruded tongues. Various congenital abnormalities of the hypothalamo-pituitary thyroid axis that cause enlarge thyroid size (goiter) can cause congenital hypothyroidism with cretinism. T4 crosses the placenta and unless the mother is hypothyroid, growth and development are normal until birth. When there is maternal iodine deficiency, the mental deficiency of the cretin is more severe and less responsive to treatment (deaf-mutism).
**Hyperthyroidism (Thyrotoxicosis):** is characterized by nervousness, weight loss, hyperphagia, heat intolerance, increase cardiac output, increased pulse pressure, a fine tremor of the outstretched fingers, sweating and variable increment in BMR.

**Graves Disease:** Also called exophthalmic goiter, characterized by diffuse hyperplastic enlargement of thyroid gland with protrusions of the eyeballs. Graves disease is an autoimmune disease in which circulating antibodies formed against TSH receptors will activate these receptors making the gland hyperactive (called TSH receptor stimulating antibodies).

**Endemic Goiter:** When the dietary intake is less than 10 μg/day, the thyroid hormone synthesis is inadequate and T3 and T4 levels decline. As a result TSH is stimulated leading the thyroid to be hypertrophied producing an iodine deficiency endemic goiter which may be very large. It occurs in certain areas around the great lakes and in inlands where the iodine is leached out of the soil by the rain so food will be grown in the soil is iodine deficient.

**Physiological Goiter:** Occurs during puberty due to increase stress and increase demand for T3 and T4 necessary for growth.

---

**Endocrine Functions of the Pancreas**

At least 4 peptides with hormonal activity are secreted by the islets of Langerhans in the pancreas. **Insulin** (from beta cells) and **glucagon** (from alpha cells) have important functions in the regulation of intermediary metabolism of carbohydrates, proteins and fats. **Somatostatin** (from delta cells which also secrete gastrin) plays a role in the regulation of islet cell secretion while the last hormone, **Pancreatic polypeptide** (from other cells) is concerned primarily with gastrointestinal function. Gap junctions link these cells together for rapid communication.

**Insulin**

- Insulin is a polypeptide containing two chains of amino acids A and B of 21 and 30 amino acid respectively linked by desulfied bridges.
- Insulin is synthesized in the endoplasmic reticulum of β-cells as single chain of amino acids called pre-proinsulin but it is then cleaved in the endoplasmic reticulum to form a proinsulin. Most of this is further cleaved and then folded with the formation of disulfied bonds in the Golgi apparatus and result in formation of insulin and C-peptide which are packed and stored in secretory granules or vesicles. So for each molecule of insulin formed and secreted, an equivalent amount of C-peptide is formed and secreted as well, thus C-peptide measurement can provide an excellent index for endogenous insulin in insulin treated diabetics.
- Insulin is secreted to blood stream from the secretory vesicles by exocytosis. There are minor differences in amino acid composition of insulin molecule from species to species. The differences are generally not sufficient to affect the biological activity of particular insulin in heterologous species but are sufficient to make the insulin antigenic. 80% of secreted insulin is normally degraded in the liver and kidney.

**Effects of Insulin:** Insulin is an anabolic hormone and it’s net effect is storage of carbohydrates, proteins and fat. Therefore, it is called **Hormone of Abundance.**

- **A. Rapid action of insulin (within seconds):** Increases the glucose uptake into target cells by directing the insertion of glucose transporters into cell membrane.
- **B. Intermediate action (within minutes):** Involves the action on liver and muscles.
- **C. Delayed effects include effects on adipose tissue (within hours):**

  The target tissues of insulin are liver, adipose tissue, and muscles.

A. **Insulin decreases blood glucose concentration** by the following mechanisms

1. It increases glucose uptake into target cells by directing the insertion of glucose transporters into cell membrane.
2. It promotes formation of glycogen from glucose in muscles and liver, and simultaneously inhibits glycogenolysis.
3. **It decreases gluconeogenesis.** Insulin increases the production of fructose 2,6 biphosphate, increasing phosphofructokinase activity. In effect, substrate is directed away from glucose formation.

**B. Insulin decreases blood fatty acid and keto acid concentrations.**

1. In adipose tissue, insulin stimulates fat deposition and inhibits lipolysis.
2. Insulin inhibits keto acid formation in the liver because decreased fatty acid degradation provides less acetyl-Co A substrate for keto acid formation.

**C. Insulin decreases blood amino acid concentration.** Insulin stimulates amino acid uptake into cells, increases protein synthesis, and inhibits protein degradation. Thus, insulin is anabolic.

**D. Insulin decreases blood K ion concentration** by increasing K uptake into the cells.

**The liver as a glucose buffer system:** After the meal is over and the blood glucose level begins to fall to a low level causing the pancreas to decrease its insulin secretion. The lack of insulin secretion then reverses all the effects listed above for glycogen storage and prevents further uptake of glucose by the liver from the blood. Furthermore, the lack of insulin (along with increase of glucagon) activates phosphorylase enzyme which causes the splitting of glycogen into glucose phosphate from which phosphate radical will split away from glucose by glucose phosphatase. Then the free glucose diffuse back into the blood. Therefore, the liver acts as glucose buffer system.

**Note:** During most of the day, the resting muscle membrane is almost impermeable to glucose and muscle tissues depend on fatty acids for its energy. During severe exercise, the muscle membrane become highly permeable to glucose (independent of insulin) and start to use glucose for its energy. However, during the few hours after a meal, when the blood glucose concentration is high and the pancreas is secreting large amounts of insulin, this extra insulin causes rapid transport of glucose into the muscle cells which is then used as the source for energy instead of fatty acids and increases glycogen synthesis. The glycogen can later be used for energy by the muscle. The muscle glycogen cannot be reconverted into free glucose and released back into the blood because there is no glucose phosphatase in muscle cells, in contrast to the liver cells.

**Glucose can enter the cells by:**

1. **Facilitated diffusion:** In most of tissues by the aid of special glucose transporters (skeletal and cardiac muscle, adipocytes, and RBCs). The glucose transport in skeletal and cardiac muscle, and in adipose tissue is facilitated by insulin (insulin-dependent) as insulin increases the number of glucose transporters in the cell membranes, whereas in RBCs, the glucose transport is occurred by insulin-independent mechanism.
2. **Secondary active transport with Na**⁺ by the aid of sodium dependent glucose transporter in the intestine and in the kidney.
3. **Simple diffusion** as in CNS cells and hepatocytes. However, insulin increases the entry of glucose into liver cells by trapping glucose through the effect of hexokinase which phosphorylate glucose and keeping intracellular free glucose concentration low which will facilitate glucose entry to the cell by facilitated diffusion.

**Factors affecting insulin Secretion:** The amount of insulin secreted in the basal state is about 1 U/hour, with 5 - 10 folds increase following ingestion of food. The average amount secreted per day in a normal human is about 40 U. The factors that affect insulin secretion are:

- Plasma Glucose Level
- Protein and fat Derivatives
- Cyclic AMP
- Autonomic Nerves
• GIT Hormones
• Other hormones

[1] Effect of Plasma Glucose Level: The major control of insulin secretion is exerted by a feedback effect of plasma glucose directly on β cells of pancreas. High plasma glucose level will increase the free Ca^{++} level in cytoplasm which in turn activate Ca^{++} dependent kinases. This will initiate events leading to stimulation of insulin release by exocytosis. If extracellular glucose remains high, the cycle repeats itself and more insulin is secreted.

[21] Protein and Fat Derivatives: Arginine, leucine and β-ketoacids as acetoacetic acid stimulates insulin secretion.

[31] Cyclic AMP: Stimuli that increase cAMP in β cells increases insulin secretion by increasing intracellular Ca^{++}. They include 3-adrenergic agonists, glucagon and theophylline. Catecholamines have a dual effect on insulin secretion (stimulation and inhibition) but the net effect of epinephrine and norepinephrine is inhibition.

[41] Autonomic Nerves:

[a] Stimulation of parasympathetic Rt. vagus stimulates insulin secretion via muscarinic receptors.

[b] Sympathetic nerve stimulation to pancreas inhibits insulin secretion due to the release of norepinephrine.

[SI] GIT Hormones: Orally administered glucose and amino acids exerts greater insulin stimulating effect than i.v administration, this is due to the presence of CIT hormones (glucagon, secretin, CCK, gastrin)

[61] Other hormones: Other hormones that either directly increase insulin secretion or potentiate the glucose stimulus for insulin secretion include glucagon, growth hormone, cortisol, and to lesser extent progesterone and estrogen. The prolong and high level of secretion of these hormones can occasionally lead to exhaustion of the beta cells of the islets of Langerhans and thereby cause diabetes.

Note: B-cell Exhaustion: In long term high glucose level in plasma leads to hypertrophy of β-cells at first but later on an exhaustion of β-cell secretion occur. Even with long duration of diabetes exhaustion does not occur completely (residual β-cells secretion still present in duration of 40 years of diabetes mellitus). Complete exhaustion of β-cells occurs in partial pancreatectomy, continuous high glucose diet or due to hormonal effects as high growth hormone level and in thyrotoxicosis.

Diabetes Mellitus: Is defined as a clinical syndrome characterized by sustained hyperglycemia which may result due to lack of insulin secretion or to an excess of factors that oppose it’s action. It may result from many environmental and genetic factors often acting jointly. These abnormalities lead to abnormalities in carbohydrate, protein and fat metabolism. It’s major effects include characteristic symptoms, ketoacidosis, progressive microvascular diseases of retina and kidney, damage to peripheral nerves and excessive arteriosclerosis.

Consequences of Insulin Deficiency: The fundamental defects to which most of the abnormalities are secondary to it are: Reduced entry of glucose to various peripheral tissues and increased liberation of glucose into the circulation from the liver (hepatic gluconeogenesis) due in part to glucagon excess.

So there is extracellular glucose
excess and intracellular glucose deficiency “starvation in the mid of plenty” with a consequent increase in lipolysis and reduction in amino acid entry into muscle.

[A] Hyperglycemia leads to glycosuria as blood sugar level exceeds the renal threshold for glucose reabsorption. This leads to osmotic diuresis and loss of large amounts of water and electrolytes (Na and K) with consequent dehydration and polydipsia leading to hypovolemia, and hypotension.

[B] Deficient glucose utilization in the cells of hypothalamic ventromedial nucleus is the cause of hyperphagia in diabetes probably as the activity of satiety center is reduced, so the lateral appetite area operates unopposed.

[D] The increased gluconeogenesis in diabetes has many causes:
1. Glucagon excess causes increase gluconeogenesis.
2. Adrenal glucocorticoids are increased in severe diabetes mellitus and consequently increase gluconeogenesis leading to elevated blood sugar level.
3. In insulin deficiency the protein synthesis is stopped and amino acids are shifted for gluconeogenesis resulting in protein breakdown, negative nitrogen balance, wasting, poor resistance to infection.

[E] In diabetes there is increased lipid catabolism leads to high levels of free fatty acids (FFA). FFA are catabolized in liver to form acetyl CoA which enters the citric acid cycle to produce CO₂, and H₂O. Therefore, in diabetes, large amounts of acetyl CoA are produced that the body cannot handle their catabolism to malonyl CoA leading to the formation of keton bodies. Ketone bodies (acetoacelate, β-hydroxybutyrate and aceton) are an important source of energy in small amounts and in fasting state. In severe insulin deficiency, the production of keton bodies is uncontrolled leading to ketosis, and finally ketonuria leading to metabolic acidosis. In addition, Acetyl CoA increases pyruvate carboxylase activity which catalyses the conversion of pyruvate to oxaloacetate.

Coma is the final result of diabetic complications because of toxic effects of acidosis, dehydration and hyperosmolarity on the nervous system. In metabolic acidosis there is low plasma pH with the stimulation of respiratory center resulting in deep respiration called “Kussmaul breathing” “air hunger” with aceton smell.

**Insulin Excess:** Insulin excess caused by hyperfunctioning pancreatic tumor or increased dose of insulin in insulin dependent diabetes leads to hypoglycemia and manifested by symptoms of hypoglycemia on nervous system. Carbohydrate stores in neural tissues are very limited and normal function depends upon a continuous glucose supply. As plasma glucose level falls, the first symptoms are palpitations, sweating and nervousness due to autonomic discharge. At lower plasma glucose level (neuroglycopenic symptoms) appear including hunger, confusion, lethargy, convulsions, coma and eventually death.

**Glycosylated Haemoglobin:** When plasma glucose is episodically elevated over time, small amounts of hemoglobin A is glycosylated by non-enzymatic pathway to form HbAlc. Level of HbAlc is an index of control of diabetes for 6 - 10 weeks before measurement.
Glucagon

It is produced by the alpha-cells of pancreas and upper gastrointestinal tract. This hormone causes an increase in the plasma glucose level. This is achieved through the following effects:

1. [glycogenolytic effects](#), it causes glycogenolysis in liver (not in the muscle).
2. [gluconeogenic effects](#) in liver.

Other effects, it increases the quantities of fatty acids available to the energy systems of the body through its [lipolytic effects](#) and through the inhibition of the storage of triglycerides in the liver. Consequently, it increases ketone bodies formation (ketogenic effect).

**Control of Secretion:** The low blood glucose concentration is by far the most potent factor for stimulation of glucagon secretion. A decrease in the blood glucose concentration from its normal fasting level of about 90 mg/dl of blood down to hypoglycemic levels can increase glucagon secretion as well as its plasma concentration several folds and vice versa.

### Somatostatin

This hormone is secreted from delta cells (δ-cells) of pancreas. Somatostatin secretion is affected by same factors stimulating insulin secretion (increased blood glucose, increased amino acids, increased fatty acids, and increased concentration of several GIT hormones released in response to food intake).

Somatostatin acts:
1. As paracrine hormone by inhibiting the secretion of insulin, glucagon and pancreatic polypeptide.
2. Slows motility, and decreases both secretion and absorption in the GIT including gallbladder (may cause gallbladder stones in excessive secretion).

Somatostatin is the same chemical substance as growth hormone inhibitory hormone that is secreted in the hypothalamus.
**Pancreatic Polypeptide**

Human pancreatic polypeptide is secreted by PP-cells of pancreas. It is closely related to other peptides found in intestine and may be a gastrointestinal hormone and the neuropeptide found in the brain and autonomic nervous system.

PP secretion is increased by protein meal, fasting, exercise, and acute hypoglycemia. Its exact physiological function is uncertain but it slows the absorption of food and may smooth out the peak and valleys of absorption curves.

**The Adrenal Medulla and adrenal Cortex**

There are two endocrine organs in the adrenal gland. The inner adrenal medulla secretes catecholamines (epinephrine, norepinephrine, and dopamine) while the outer adrenal cortex secretes cortisol and aldosterone.

**Adrenal medulla**

It consists 28% of adrenal gland mass. It contains two types of cells, epinephrine secreting cells (90%) and norepinephrine secreting cells (10%) while the type of cells that secretes dopamine is unknown.

Adrenal medulla is regarded as sympathetic ganglion in which the axons of their post ganglionic neurons losted and become secretary cells. Adrenal hormones are not essential for life but they help to prepare the individual to deal with emergencies.

**Adrenal medulla secretes:**

1. **Catecholamines:** The pathway for biosynthesis of epinephrine, norepinephrine and dopamine are shown.

   Half life of catecholamines is about 2 minutes in circulation. Then they are destroyed by catechol-O-methyl transferase in all tissues especially in the liver to vanillylmandelic acid (VMA). 50% of secreted catecholamines appear in urine as free or conjugated metanephrine and normetanephrine and 35% as VMA and small amounts as epinephrine and norepinephrine. Destruction of epinephrine and norepinephrine can occur in the nerve endings by enzymes one of them is monoamine oxidase.

2. **Opioid peptide:** Secreted by norepinephrine cells, they do not cross the blood-brain barrier, and their function is yet unknown.
Effects of Epinephrine and Norepinephrine:
1. CVS:
   - **Net effect of epinephrine**
     1. Constriction of the arterioles in the skin and splanchnic circulation but it dilates the arterioles in skeletal muscles (through $\alpha_1$ receptors)
     2. Reduce peripheral resistance
     3. Increase systolic BP, but the diastolic blood pressure is lowered or increased depending on the quantities
     4. Increase heart rate
     5. Increase cardiac output
   - **Net effect of norepinephrine**
     1. generalized vasoconstriction (through $\alpha_1$ receptors)
     2. Increase total peripheral resistance
     3. Increase systolic and diastolic BP.
     4. A reflex decrease of heart rate
     5. Much less rise in cardiac output because of reflex bradycardia

2. Others:
   - 6. Causes relaxation of bronchioles
   - 7. It causes hepatic glycogen breakdown
   - 8. Weak in causing the release of free fatty acids from adipose tissue
   - 6. Does not cause relaxation of bronchioles
   - 7. Very weak in causing hepatic glycogen breakdown
   - 8. Potent in causing the release of free fatty acids from adipose tissue

3. On CNS: Increase alertness (epinephrine evokes anxiety and fear).
4. Effect on BMR: The initial rise in BMR is due to cutaneous vasoconstriction that prevent heat loss or increase muscular activity followed by a smaller delayed rise in BMR due to oxidation of lactic acid in liver.
5. Effect on $K^+$: Initial rise in $K^+$ due to release of $K^+$ from liver followed by a prolonged fall in $K^+$ due to increased entry of $K^+$ into skeletal muscles (as a result of stimulation of $\beta$-adrenergic receptors).

Effects of Dopamine:
1. Vasodilatation: In kidney and mesentry by acting on dopaminergic receptors.
2. Vasoconstriction in other sites due to release of norepinephrine.
3. Positive inotropic effect on the heart (through $\beta$ receptors).
4. Increase in systolic B.P with no change in diastolic B.P.
5. Natriuresis by inhibiting the Na$^+$ - K$^+$ ATPase of the kidney.

Regulation of adrenal medullary secretion: Catecholamine secretion is under the effect of sympathetic nervous system and it is low at basal state. Secretions are decreased in recumbent subject and more reduction during sleep while increased in standing up. The metabolic effects of circulating catecholamines are important in exposure to cold or hunger. Increased adrenal medullary secretion is part of diffuse sympathetic discharge provoked by emergency situation (Fight or Flight).

The output of norepinephrine is increased selectively as in emotional stress with which the individual is familiar where as epinephrine is selectively increased in hemorrhage (as it reduce peripheral resistance) and in situations in which the individual do not know what to expect.

Adrenal Cortex

The cortex of adrenal glands is the source of all the known steroid hormones (adrenocorticosteroids) elaborated in the body except for those derived from the gonads and placenta. The adrenocorticosteroids are either having predominant effects on carbohydrate metabolism (glucocorticoids) or sodium and potassium metabolism (mineralocorticoids), or responsible for secondary sexual characters in males and females (androgens). However, considerable overlap is likely to exist.
Adrenal cortex is divided into 3 layers:

1. Outer *Zona glomerularis* which secretes **mineralocorticoids** (aldosterone) and has the ability to produce new cortical cells.
2. Middle *Zona fasciculata* which secretes mostly **glucocorticoids** (cortisol and corticosterone).
3. Inner *Zona reticularis* which secretes mostly **androgens** (dehydroepiandrosterone, androstenedione, and testosterone).

The steriod hormones of the adrenal cortex play an important role in the regulation of the body's metabolic processes and without them life is hazardous. In particular, they play a major part in the regulation of salt and water metabolism, renal function, carbohydrate and protein metabolism and in response of the body to such noxious stimuli as severe injury, surgical operations and infections (i.e. resistance to stress). The adrenal cortex also produces weak androgens which are physiologically important as the principal source of androgens in women throughout their life and, by conversion in peripheral tissues, as the principal source of oestrogens after the menopause.

**Adrenal glucocorticoids:** Glucocorticoides secreted by human adrenal cortex consist mainly of cortisol and corticosterone (cortisone). Cortisol is more potent and predominantly secreted in ratio of (7:1). Glucocorticoides secreted by human adrenal cortex consist mainly of cortisol and corticosterone (cortisone). Cortisol is more potent and predominantly secreted.

**[I].** Effect on carbohydrates: Cortisol is a carbohydrate-sparing hormone and therefore, exerts an anti-insulin effect, which leads to hyperglycaemia and insulin resistance. It increases blood glucose level due to:

1. Stimulation of gluconeogenesis. Therefore, deficiency of glucocorticoids causes a lowered fasting blood sugar which is largely the result of depressed gluconeogenesis
2. Decreases glucose utilization peripherally by blocking glucose transport in muscle and adipose tissue (it has an anti-insulin activity) and indirectly by inhibition of glycolysis in peripheral tissues.
3. Increases glycogen deposition in the liver by promoting the conversion of amino acids to carbohydrates and the storage of carbohydrate as hepatic glycogen.

**[II].** Effect on protein metabolism: Increase protein catabolism in periphery tissues such as muscles (except in the liver where cortisol has an anabolic effect on proteins) resulting in negative nitrogen balance and increase of amino acid concentration in plasma with an increase of hepatic uptake (trapping) of amino acids (especially the amino acid alanine) with consequent increase of gluconeogenesis. This gluconeogenesis is associated with increased urea production via the conversion of amino nitrogen to urea with consequent increase of urinary nitrogen excretion.

**[III].** Effects on Fat metabolism: Glucocorticoids are lipolytic hormones (with consequent increase in plasma free fatty acids) and favor the mobilization of fatty acids from adipose tissue to the liver to be oxidized (with consequent increase keton formation in diabetes). Glucocorticoids inhibit fatty acid synthesis in the liver (an effect not observed in adipose tissue).

**[IV].** Permissive action: Small amounts of glucocorticoids must be present for a number of metabolic reaction to occur although glucocorticoids do not produce the reactions by themselves. This effect is called the permissive action. It includes:
1. For glucagon and catecholamines to produce their calorigenic effect.

2. For catecholamine to induce lipolytic effect, bronchodilatation and vascular pressor responses. In adrenal insufficiency, the vascular smooth muscles become unresponsive to catecholamines resulting in dilatation of the vessels, hypotension, and exudation. So glucocorticoids are necessary for restoration of vascular responses.

[V]. Effects on nervous system: Changes in the nervous system in adrenal insufficiency causes slow α waves rhythm on ECG, personality changes include irritability, apprehension and inability to concentrate.

[VI]. Effect on water metabolism: Glucocorticoids probably help to maintain a normal rate of glomerular filtration and they promote free water excretion. In adrenal insufficiency, water intoxication occurs due to high levels of vasopressin and low GFR, and is corrected by glucocorticoids. Water intoxication due to adrenal insufficiency can be seen in condition known as glucose fever in which glucose infusion may cause high fever (glucose fever) followed by collapse and death. Presumably the glucose is metabolized, the water will dilute the plasma resulting in high osmotic gradient between plasma and the cell causes the cells of thermoregulatory centers in the hypothalamus to be swollen and disrupted function.

[VII]. Effects on blood cells and lymphatic organs:
1. Decrease number of eosinophils, basophils and lymphocytes.
2. Increase number of neutrophils, platelets and RBCs.
3. Inhibit lymphocyte mitotic activity so reduce the size of lymph node and thymus.
4. Inhibit production of IL-2 by T-lymphocyte so effectively stop lymphocyte proliferation.
5. Inhibition of IL-1 by monocyte and macrophage.

[VIII]. Resistance to stress: Stress is defined as any noxious stimuli that increases ACTH and so glucocorticoids are increased for vascular reactivity to occur in response to stress and also for their permissive action to catecholamines for full FFA mobilization (important emergency energy supply), so glucocorticoids are necessary to resist stress. Stress causes increase in plasma glucocorticoids to high pharmacologic levels that in short run are life saving but in long run are definitely harmful and disruptive.

[IX]. Other Effects:
Glucocorticoids in high doses leads to:
1. Decrease growth hormone secretion.
2. Decrease TSH secretion.
3. Accelerate the maturation of surfactant in the lungs of foetus.

Anti-Inflammatory and antiallergic effects of glucocorticoids: In large pharmacological doses, glucocorticoids inhibit the inflammatory response to tissue injury and also suppress the manifestation of allergic diseases that are due to histamine release from tissues.

[I] The antiallergic effects due to inhibition of release of histamine from mast cells in response to Ag-Ab reaction. Glucocorticoids do not affect the Ag-Ab combination and have no effects of histamine once it is released.

[2] Anti-inflammatory effect is due to:
[a] Inhibition of phospholipase A2 resulting in decrease release of arachidonic acids from tissue phospholipids and decrease formation of leukotrienes, thromboxane, prostaglandins and prostacyclin and consequently decreased local inflammatory reaction. A decrease of prostaglandins and leukotriens formation decreases vasodilatation and reduce capillary permeability leading to decrease plasma loss and local swelling.
[b] Stabilization of lysosomal membrane and inhibit release of mediators of inflammation as leukotrienes in inflammed tissue.
[c] Slowing of degrading effect of collagenase in joint tissues in rheumatoid arthritis and this is the basis of their effectiveness in local intra-articular administration.
[d] It lowers fever by inhibit the release of IL-1 from W.B.Cs. IL-1 is one of the principal excitants of hypothalamic temperature control system.
[e] Cortisol suppresses:
- WBC migration to the inflammed area.
- Phagocytosis of damaged cells.
- The immune system by lowering the production of T-lymphocyte and reduce antibody formation.
[f] Inhibit fibroplastic activity.
[g] Cortisol increase the rate of resolution of inflammation (healing) due to increased amino acids, glucose and FFA necessary for resolution or by inactivating the inflammatory products.

**Regulation of Glucocorticoids Secretion:** Glucocorticoids secretion is regulated by ACTH and by the free cortisol level.

1. **Role of adrenocorticotropic hormone (ACTH):** The hypothalamus via release of corticotrophic releasing hormone (CRH), that will be transferred by hypothalamo-hypophyseal portal system to anterior pituitary gland, stimulates the release of ACTH. ACTH affects the inner two zones of adrenal cortex. Basal and stimulated secretion (stress) of glucocorticoids are dependent upon ACTH from anterior pituitary. It is a single polypeptide chain of 39 amino acids, the active core is the first 23 amino acids similar in all species. It’s half life in human is about 10 minutes and mainly metabolized in kidneys.

   ACTH bind to ACTH receptors and activate adenyl cyclase and increase cAMP which in turn increases the activity of enzymes responsible for increase free cholesterol formation resulting in increase pregnenolone.

   So ACTH leads to increase glucocorticoids formation and at the same time increases responsiveness of adrenal cortex to subsequent doses of ACTH.

   Severe stress (body injury, emotional stress, anxiety and fear) increases ACTH secretion which is mediated through hypothalamus via release of corticotrophic releasing hormone (CRH).

   **Dexamethasone suppression test:** This test is based on the ability of dexamethasone (which is a potent synthetic glucocorticoid) to inhibit ACTH secretion. If the hypothalamic-pituitary-adrenocortical axis is normal, then the administration of dexamethasone inhibits the secretion of ACTH and cortisol.

2. **Role of Cortisol:** Free cortisol inhibits ACTH secretion and the degree of pituitary inhibition is proportional to the circulating glucocorticoid level. The inhibitory effect is exerted at both levels, pituitary and hypothalamic. This is called Glucocorticoid negative feedback.

   When prolonged treatment with anti-inflammatory doses of glucocorticoids is stopped suddenly, not only the adrenal become atrophic and unresponsive after such treatment, but even if it’s responsiveness is restored, the pituitary may be unable to secrete normal amounts of ACTH for as long as a month, this is because of diminished ACTH synthesis.

**Circadian rhythm:** ACTH is secreted in irregular burst throughout the day and plasma cortisol tends to rise and fall in response to these bursts. In humans, the bursts are most frequent in early morning and about 75% of the daily production of cortisol is secreted between 4 – 10 AM. The bursts are least frequent in the evening. This diurnal (circadian) rhythm in ACTH secretion is not due to stress or trauma or getting up in the morning as it occurs even before waking up. The biological clock responsible for the diurnal ACTH rhythm is located in the suprachiasmatic nuclei of the hypothalamus.

**Adrenal Androgens:** Adrenal androgens are responsible for secondary sexual characters in males and females (museulizing effect, pubic and axillary hair and voice changes). They are under the control of ACTH secretion and they exert about 20% of testicular hormones activity because some of the adrenal androgens are converted to testosterone, the major male sex hormone in the extra-adrenal tissues. They also promote protein anabolism and growth. Adrenal gland is the source of estrogen in males and post menopausal women.
Adrenal mineralocorticoids: They include aldosterone, deoxycorticosterone and corticosterone. Aldosterone is most potent while corticosterone is the weakest one. They primarily influence the rate of sodium and potassium transport across cell membranes especially of renal tubular walls and to a lesser extent, transport of hydrogen ions, promoting entry of Na into cells, and extrusion of K from them. Other adrenal steroids secreted in small amounts that have mineralocorticoid effects are corticosterone and deoxycorticosterone, which have almost the same effects as aldosterone but with a potency 1/15 that of aldosterone.

Physiological Effects:
[1] Increases renal reabsorption of Na⁺ (action on the principal cells of the late distal tubule and collecting duct). Thus, causing water retention. It also increases reabsorption of Na ions from the sweat, saliva, gastric juice and intestinal secretions
[2] Increase renal K⁺ secretion (action on the principal cells of the late distal tubule and collecting duct).
[3] Increase renal H⁺ ions secretion (action on the α-intercalated cells of the late distal tubules and collecting ducts). Thus, causing urine acidity and decrease hydrogen ion concentration in the ECF.

Regulation of Aldosterone Secretion: Four different factors are presently known to play essential roles in the regulation of aldosterone. In the probable order of their importance these are:
[1] K ion concentration of the ECF: Even I meq/l increase in ECF K⁺ concentration can directly stimulate the zona glomerulosa cells to secrete aldosterone.
[3] Quantify of body Na: Diminished Na leads to: Decrease ECF volume ➔ decrease cardiac output ➔ decrease renal blood flow ➔ increase renin secretion ➔ enhanced formation of angiotensin ➔ stimulation of aldosteron secretion.
[4] ACTH: It causes stimulation of aldosterone output as well as that of glucocorticoids and sex hormones. The effect is transient and aldosterone secretion declines in 1 - 2 days. ACTH also has a permissive effect on aldosterone secretion of all the above factors to stimulate zona glomerulosa.

Diurnal Changes: Plasma aldosterone concentration increases during upright position due to postural elevation of renin secretion. Individuals who are confined to bed, show a circadian rhythm in aldosterone secretion and renin with highest values in the early morning before awakening.

Adrenocortical Hyperfunction: For example is Cushing’s syndrome. It is most commonly caused by the administration of pharmacologic doses of glucocorticoids and less commonly caused by bilateral hyperplasia of the adrenal glands. If the adrenocortical hyperfunction is due to overproduction of ACTH, the condition is called Cushing’s disease. All of which manifested by:
[A] Increase cortisol and androgen levels.
[B] Increase ACTH in Cushing’s disease or decrease in ACTH in Cushing’s syndrome.
[C] Hyperglycaemia (caused by elevated cortisol level).
[D] Increase protein catabolism (muscle wasting, thin skin and subcutaneous tissues).
[E] Central (or trunk) obesity (moon face, buffalo-hump).
[F] Poor wound healing.
[G] Virilization of women (caused by elevated levels of adrenal androgens).
[H] Hypertension (caused by elevated levels of cortisol and aldosterone).
[I] Osteoporosis (elevated cortisol levels cause increased bone resorption).
[J] Plethoric appearance, purple abdominal striae and mental abnormality.

Hyperaldosteronism – Conn’s syndrome: It is caused by an aldosterone-secreting tumor and characterized by the following:
[A] Hypertension (because aldosterone increases renal Na⁺ reabsorption, which leads to increase in ECF volume and blood volume).
[B] Hypokalaemia (because aldosterone increases renal K⁺ secretion).
[C] Metabolic alkalosis (because aldosterone increases renal H⁺ secretion).
[D] Decrease renin secretion (because increased ECF volume and blood pressure inhibit renin secretion
Effects of Adrenalectomy: In adrenal insufficiency: Excess Na\(^+\) loss, excess water loss, excess K\(^+\) retention, Hypovolemia, hypotension, circulatory failure, weakness of cardiac muscles and consequently death.

**Calcium metabolism and bone physiology**

**Calcium:** In adult human body, 1.5% of body weight is Ca. 99% of Ca is in the bones (two forms, rapid and a much larger slow exchangeable reservoirs).

98% - 99% of the filtered Ca\(^++\) in kidney is reabsorbed, 60% of reabsorption occurs in the proximal tubule and less in ascending loop of Henle and distal tubules.

The plasma Ca\(^++\) is about 10 mg/dl, and it is in 3 forms:
- Ca\(^++\) bound to plasma proteins, about 40%, it is non diffusable through capillary membranes.
- Ca\(^++\) free which is diffusible and ionized, 60%. It is the most important form of Ca\(^++\) in the body fluids that is vital in:
  a. Second messenger.
  b. Blood coagulation.
  c. Muscle contraction.
  d. Heme function.

To maintain Ca\(^++\) balance, net intestinal absorption must be balanced by urinary excretion. **Positive Ca\(^++\) balance** is seen in growing children in which intestinal Ca\(^++\) absorption exceeds urinary excretion, and the excess is deposited in the growing bones. **Negative Ca\(^++\) balance** is seen in women during pregnancy or lactation in which intestinal Ca\(^++\) absorption is less than Ca\(^++\) excretion, and the deficit comes from the maternal bones.

**Hypocalcemia:** A decrease of plasma calcium (free and bound forms).
1. It can cause muscle tetany (occurs at a blood Ca level of about 6 mg/dl) and subsequently increases motor nerves excitability leading to carpopedal and laryngeal spasm.
2. It can cause prolongation of ST-segment and prolonged QT-interval in ECG.

**Hypercalcemia:** An increase of plasma calcium (free and bound forms). It is associated with depressed nervous system activity, sluggish reflex activity, shortened QT-interval in ECG, enhanced myocardial contractility, constipation and reduced appetite, and predispose to renal stone formation.

**Phosphorus:** About 90% of which is found in skeleton. Plasma phosphorus is about 12 mg/dl, two third of it is present in organic compounds and the rest is inorganic phosphorus (Pi) mostly in PO\(_4\)^{3-}, HPO\(_4\)^{2-} and H\(_2\)PO\(_4\)^{1-}.

Pi is absorbed in duodenum and small intestine by active transport and passive diffusion. Absorption is linearly correlated with dietary intake. 1,25 dihydrocholecalciferol increases Pi absorption.

Pi is filtered in glomeruli, 85% - 90% is reabsorbed by proximal tubules and the active transport is powerfully inhibited by PTH.

**Bone structure and physiology:** Bone is a special form of connective tissue made up of microscopic crystals of phosphates and calcium within a matrix of collagen. The cells that are concerned primarily with bone formation and resorption are osteoblasts and osteoclasts, both derived from bone marrow.

**Bone growth:** Specialized areas at the end of each long bone (epiphysis) are separated from the shaft by a plate of actively proliferating cartilage, epiphyseal plate. The bone increases in length as this plate lays down new bone at the end of the shaft. The width of the plate is proportional to the rate of growth.

The width of the plate is mostly affected by pituitary growth hormone. The growth of the bone stops when the epiphyses unite with the shaft (epiphyseal closure), the last epiphyses closure occur after puberty.
Bone formation and resorption: Through the life, bone is a dynamic rather than static organ, being constantly resorbed and new bone being formed. The calcium in bone turns over at a rate of 100% per year in infants and 18% per year in adults. Bone remodeling is mainly a local process carried out in small areas by populations of cells called bone-remodelling units. First osteoclasts resorb bone forming a tunnel of few millimeters in length, then osteoblasts lay down new bone in the same area in successive layers of concentric circles (Larnellae). If blood vessels run through the tunnel it is called Haversian Canal.

The benefit of remodeling is to adjust the shape and strength of bone in response to stress (bone thickened when subjected to heavy load and resorbed in long bed rest). The calcium precipitates in bone when it exceeds the saturation point. Osteoblasts secrete an alkaline phosphatase that hydrolyzes phosphate esters, thus providing the necessary phosphate for new bone formation (precipitation of Ca-P04).

Regulation of Ca metabolism: Three hormones are primarily concerned with the regulation of calcium metabolism:

1. **1-25 Dihydroxycholecalciferol (calcitriol):** Is a steroid hormone formed from vit. D by successive hydroxylation in kidney and liver. It’s primary function is to increase Ca absorption from GIT.
2. **Parathyroid hormone (PTH):** It’s main action is to mobilize calcium from the bone (bone resorption) and to increase urinary phosphate excretion.
3. **Calcitonin:** It is a calcium lowering enzyme in plasma and it’s main action is to inhibit bone resorption.

The receptors of calcitriol is found mainly in intestine, kidney and bone.

**Action:**
1. Increased Ca++ and phosphate absorption from intestine.
2. Increased Ca++ and phosphate reabsorption in the kidney.
3. The most important net effect of vit. D is to ensure that newly formed bone is calcified by stimulation osteoclasts to provide Ca++ and phosphate ions from “old bone” to mineralize “new bone”. Without vit. D, the bone matrix remains uncalcified leading to the development of rickets in children and osteomalacia in adults.

The net results of the previous effects are increased Ca++ and phosphate plasma levels

Regulation of Synthesis: Illustrated in the diagram below.

[2] **Parathyroid hormone:** This hormone which is secreted by the chief cells of parathyroid hormone, it is metabolized by the liver and excreted by the kidney.

**Actions:**
1. Bone resorption: This is achieved by stimulation of osteoclasts and consequently increase Ca and phosphate mobilization to the blood.
2. Increases reabsorption of Ca++ in distal tubule and collecting ducts and increases excretion of PO4^3- by lowering proximal tubular reabsorption of PO4^3- (phosphaturic action).
3. Increases the renal formation of 1,25 (OH)2 D3 and consequently increases Ca++ reabsorption in the intestine.

The net results of the previous effects are increased Ca++ plasma level and a decreased phosphate plasma level

Regulation of Secretion: Circulating ionized Ca acts directly on parathyroid glands in a negative
feedback fashion to regulate the secretion of PTH. PTH is stimulated by low Ca, Mg, and high phosphate. While it is inhibited by high Ca, Mg, and active Vit D3.

Hyperparathyroidism:
1. Primary Hyperparathyroidism: Usually increased PTH level in functioning parathyroid tumor is characterized by hypercalcemia, hypophosphatemia, demineralization of bone (increase bone resorption), hypercalcuria, increase urinary phosphate excretion, and calcium containing renal stones.
2. Secondary Hyperparathyroidism: In disease of kidney and in rickets, chronic low Ca\(^{++}\) level exert a feedback stimulation on PTH.

Hypoparathyroidism: PTH is essential for life. After parathyroidectomy, steady decline in plasma Ca\(^{++}\) level causes hyperexcitability followed by hypocalcemic tetany. Can occur following thyroid surgery. Signs of tetany in human include:
1. Chvostek's sign: Quick contraction of ipsilateral facial muscles elicited by tapping on facial nerve at jaw.
2. Trousseau's sign: Spasm of the muscles of upper extremities, flexion of the wrist and thumb and extension of the fingers, can be produced by occluding the circulation for few minutes with
sphygmomanometer cuff.

**Chronic renal failure:** It is characterized by decreased glomerular filtration rate which leads to:
- Decreased filtration of phosphate, phosphate retention, and increased serum phosphate concentration.
- Increased serum phosphate complexes Ca\(^{++}\) and leads to decreased ionized Ca\(^{++}\) concentration.
- Decreased production of active vitamine D3 by the diseased renal tissues also contributes to the decreased ionized Ca\(^{++}\) concentration.
- Decreased Ca\(^{++}\) concentration causes secondary hyperparathyroidism.
- The combination of increased PTH levels and decreased active vit D3 produces renal osteodystrophy, in which there is increased bone resorption and osteomalacia.

[3] **Calcitonin** (Ca lowering hormone): It is secreted from parafollicular cells (C cells) of the thyroid gland.

**Action:** Calcitonin receptors are mainly found in bones and kidneys. Calcitonin lowers circulating Ca\(^{++}\) and PO\(_4^{3-}\) levels by:
1. Direct (immediate) effect by inhibiting the activity of osteoclasts (inhibit bone resorption).
2. Indirect (prolonged) effect by reducing the formation of new osteoclasts.
3. Increases Ca\(^{++}\) and phosphate excretion in urine.

The net results of the previous effects are decreased Ca\(^{++}\) and phosphate plasma levels.

**Control of Secretion:** When Ca\(^{++}\) level is 9.5 mg/dl and more, calcitonin secretion is increased (calcitonin level is proportional to calcium level) and vice versa.

**Bone Disease:**
1. **Rickets** and **Osteomalacia:** Due to deficiency of calcium concentration per unit bone matrix occurs due to:
   - Inadequate vit. D intake.
   - Abnormalities in vit. D receptors.
   - Inadequate exposure to sunlight.
   - Abnormal 1-α hydroxylase. It causes bone weakness broadening of ends of ulna and radius, growth retardation in children, abnormal skull sutures and in adults causes easy fractures especially in hip joint.
2. **Osteoporosis:** Matrix and minerals are both lost with loss of bone mass and strength with increased incidence of fractures. Involutional osteoporosis occurs in advancing age and menopause as estrogen has direct stimulating effect on osteoblasts (estrogen receptors are present on osteoblasts). Other causes of osteoporosis are:
   - Lack of physical activity.
   - Malnutrition and Vit. C deficiency (necessary for osteoblast activity).
   - Old age.
   - Excess glucocorticoids.

**The pituitary gland**

The anterior, intermediate and posterior lobes of the pituitary gland are actually three more or less separate endocrine organs that in some species contain 14 or more hormonally active substances. The intermediate lobe is rudimentary in humans.

- The anterior pituitary (adenohypophysis) secretes, **TSH** (thyroid stimulating hormone), **ACTH** (adrenocorticotropic hormone), **FSH** (follicular stimulating hormone), **LH** (luteinizing hormone) **Prolactin** and **GH** (growth hormone).
- The posterior pituitary lobe (neurohypophysis) secretes **oxytocin** and **vasopressin** (antidiuretic hormone, ADH).
Hypothalamic-Pituitary Connection: There are neural connections between the hypothalamus and the post. pituitary lobe of the pituitary gland, and vascular connections between the hypothalamus and the anterior lobe.

Embryologically, the post. pituitary lobe arises as an evagination of the floor of the third ventricle. It is made up in large part of the endings of axons that arises from cell bodies, in supra-optic and paraventricular nuclei and pass to the post. pituitary via the hypothalamo-hypophysial tract.

The portal hypophysial vessels form a direct vascular link between the hypothalamus and the anterior pituitary. Arterial twigs from the carotid arteries and circle of Willis form a network of fenestrated capillaries called the (primary plexus) on the ventral surface of hypothalamus. Then capillary loops and penetrate the median eminence and drain into the sinusoidal portal hypophysial vessels that carry blood down the pituitary stalk to the capillaries of the anterior pituitary. This system begins and ends in capillaries without going through the heart and is therefore a true portal system.

The median eminence is generally defined as the portion of the ventral hypothalamus from which the portal vessels arises. This region is outside the blood brain barrier.

Posterior pituitary lobe

Vasopressin and oxytocin are formed primarily by supraoptic and paraventricular nuclei of the hypothalamus and carried to the posterior lobe of pituitary by the nerve track along the pituitary stalk and secreted at the nerve endings (true neural hormones).

Vasopressin

It is called antidiuretic hormone (ADH) as its principal action is the retention of water by the kidney. It is composed of a mino acids, in location 8 is arginine so human ADH is called arginine vasopressin.

Vasopressin Effects:

1. Antidiuretic effect: It causes the synthesis of many protein water channels in the luminal membrane of late distal tubule and collecting duct cells increasing their permeability to water and urea. This causes concentrated urine and decreases urine volume, osmotic pressure of the body fluids is decreased.

2. Vasoconstriction: In moderate to high concentration of ADH, vasoconstriction occurs and increasing the arterial blood pressure. However, no change in blood pressure was observed in low concentration of ADH.

Control of Secretion:

1. Osmotic Stimuli: Normal plasma osmolality is about 285 mosm/L. Changes in osmolality of 1% affect vasopressin secretion through the osmoreceptors found in anterior hypothalamus which are outside blood-brain barrier. When the effective osmotic pressure of plasma is increased above the normal 285 mosm/L, the rate of discharge of neurons will be increased and vasopressin secretion is increased, thus correcting the plasma osmolality.

2. Volume effec: ECF volume affect vasopressin secretion. ADH secretion is increased when ECF volume is low, and decreased when ECF volume is high. The rate of discharge of stretch receptors found in low and high-pressure portions of vascular system plays an important role in ADH secretion. The low-pressure receptor are found in great veins, right and left atrium and in pulmonary vessels. While the high pressure receptors are found in carotid sinuses and aortic arch. In hypovolemnia and hypotension as in hemorrhage, the low pressure receptors will be sensitized and increase discharge to hypothalamus, so ADH secretion is increased.

3. Other Stimuli include: pain, nausea, surgical stress, and emotions increase ADH secretion while alcohol decrease ADH secretion.

Clinical Implications:

1. Syndrome of Inappropriate ADH Secretion (SIADHS): Increased ADH secretion occur in patients with cerebral disease and pulmonary disease (salt wasting), some secreting lung cancers. This may be due to interruption of inhibitory impulses in vagal afferents from stretch receptors in the atria and great veins.
In this syndrome, oedema and dilutional hyponatremia occur. Treatment is by Demeclocycline, an antibiotic that reduces the renal response to ADH.

2. **Diabetes insipidus**: Is the syndrome that results from ADH deficiency or the target organ (the kidney) fails to respond to the hormone. The disease is characterized by polyuria and polydipsia provided that thirst mechanism is intact, and it is the polydipsia that keeps these patients healthy.

### Oxytocin

**Effects of oxytocin:**

1. **On breast (milk ejection reflex):** Milk ejection is initiated by a neuroendocrine reflex. Touch receptors in areola initiate impulses generated by suckling of newborn to the somatic touch pathways to supraoptic and paraventricular nuclei of hypothalamus. Discharge of oxytocin containing neurons result in oxytocin release from posterior pituitary, oxytocin causes contraction of myoepithelial cells on the mammary glands ducts causing milk ejection, so milk is expressed into the sinuses out of the nipple (milk ejection). In lactating women, stimulation of the nipple by suckling infant, genital stimulation and emotion can all stimulate oxytocin release.

2. **On uterus:**
   A. **Gravid uterus:** The normal oxytocin level will initiate uterine contraction and through positive feedback, then the amount of oxytocin is increased producing more uterine contraction. Oxytocin acts on uterine muscles directly or indirectly through prostaglandin formation.
      The number of oxytocin receptors in uterus is increased during cervical dilatation (reaching it’s peak in early labour).
   B. **Non gravid uterus:** Genital stimulation during coitus causes oxytocin release leading to uterine contraction which help in pushing sperms upward.

3. **In males:** oxytocin increases at time of ejaculation which causes smooth muscle contraction of vas deference, so propelling the sperms toward the urethra.

### Anterior Pituitary lobe

Human anterior pituitary cells are divided into:

1. Agranular chromophobes secrete ACTH.
2. Granular Chromaphils are of two types, (a) acidophils secrete GH and prolactin, (b) Basophils secrete TSH, LH and FSH. ACTH, Prolactin and GH are simple polypeptides or proteins while FSH, LH and TSH are glycoproteins.

### Growth Hormone (GH)

Also called somatotropic hormone (SH) or somatotropin. The basal plasma GH level measured by radioimmunoassay in adult humans is normally less than 3 ng/ml, in children and adolescence it is up to 10 ng/ml. The half life of circulating hGH is 6 - 20 minutes and daily output of GH is 0.2 - 1.0 mg/day in adults. GH is metabolized rapidly, in part in the liver.

**Effects of Growth Hormone:**

1. **Effects on Growth:** GH increases the size and mitotic activity of the cells of most of tissues. The most affected tissues are the bones, before epiphyseal closure, GH increases the length of long bones by:
   a. Increases deposition of protein by ehondroeytes and osteogenic cells and increases the rate of reproduction of these cells.
   b. Increases osteoblasts activity and inhibits osteoclastic activity.

2. **Effects on Carbohydrates:**
   a. Enhance glycogen deposition in the cells.
   b. Diminished glucose uptake by cells by decreasing glucose phosphorylation causing and at the same time increases hepatic glucose output. In addition, it decreases the number and affinity of insulin receptors.
causing the condition called (Pituitary Diabetes).

[3] Effect on Fat: GH increase FFA and keton body formation with subsequent utilization of them for energy. Therefore, metabolic rate is increased. In addition, GH decreases cholesterol (decrease body fat).

[4] Effect on Protein: GH has anabolic effect on protein: GH enhances almost all facets of amino acid uptake and protein synthesis by cells, while at the same time reducing the breakdown of proteins. Therefore, it has a positive nitrogen.

[5] Effects on Electrolytes:
   a. Increase GIT absorption of calcium and phosphate. Therefore, plasma Ca and phosphate are increased.
   b. Reduced excretion of Na⁺ and K⁺ due to shift of electrolyte from kidney to growth tissues.

Somatomedins: The effects of growth hormone on growth, cartilage and protein metabolism depend on interaction between growth hormone and somatomedins, which are polypeptide growth factors secreted by the liver and other tissues in response to stimulation by growth hormone and tightly bound to plasma protein (so have longer half life). In human 4 types of somatomedins growth factors are isolated, two are insulin like growth factors I and II (IGF I and II) and two are relaxin hormones.

IGF - I has insulin and growth hormones activity, as it’s receptors are similar to that of insulin. JGF- II is much less affected by growth hormone and plays a role in the growth of fetus during intrauterine life, while in adults it is found in choroid plexus and menings.

The secretion of somatomedins is affected by various factors. Glucocorticoids and protein deficiency reduces somatomedins activity, large doses of estrogen and hyperglycaemia inhibit somatomedins production. The reduced secretion of somatomedin in hyperglycemia restored to normal by insulin treatment.

Control of GH Secretion:
[1] Via Hypothalamus which secretes GH releasing hormone (GHRH) and GH inhibiting hormone (Somatostatin).
[2] GH secretion is under feedback control, GH increases IGF-I which exerts inhibitory action on growth hormone secretion from the pituitary and hypothalamus.

Stimuli affecting GH secretion:
1. Stimuli that increases secretion:
   a. Deficiency of energy substrate such as hypoglycemia, starvation, exercise, fasting.
   b. Stressful stimuli such as pyrogen, trauma, psychological stress.
   c. Hormones like glucagon, sex hormones (oestrogen and androgen).
   d. Increased certain amino acids such as Arginine.
   e. Going to sleep.
2. Stimuli that decreases GH secretion:
   a. Glucose and FFA
   b. Cortisol and Growth hormone (IGF-1).
   c. REM sleep.

**Physiology of Growth**

Growth is a complex phenomenon that affected by many factors:

[Al Genetic factors:]

[Bl Nutrition: Most important extrinsic factors. Food must be balanced containing adequate carbohydrates, protein, minerals and vitamins (balanced caloric intake). The age at which dietary insufficiency occurs is important factor. Injuries and chronic illnesses stunt growth because they increase protein catabolism (slowing of growth rate) after which a period of “catch up growth” as growth rate may be a 400% above normal. Then growth slows to normal.

[C] Hormonal effect: There are two periods of growth:
1. **Growth hormone:** The GH plasma level is elevated in newborn than average resting level and falls down and another increase GH secretion (spikes) occurs during puberty. IGF-I is also increased during childhood reaching a peak at 13–17 years age, while IGF-II level is constant through out postnatal growth.

2. **Sex hormones:** The growth spurt that occurs at puberty is due to in part to protein anabolic effect of androgens. It is also due to interaction between sex steroids, growth hormone and IGF-I. Sex hormones increase growth hormone and IGF-I secretion. Sex hormones also increases GH response to stimuli such as insulin and arginine.

   Androgens and estrogens stimulate growth initially then they terminate growth by causing closure of epiphyseal plate of long bones so linear growth stopped.

3. **Thyroid hormones:** The action of thyroid hormone is permissive to that of growth hormone via the potentiation of somatomedins. T3 and T4 are important for normal GH secretion. Thyroid hormones are necessary for osification of cartilage, teeth growth for normal contour of face and for normal proportions of body parts.

4. **Insulin:** Important for normal growth as growth is appreciable only when large amounts of carbohydrates and proteins are supplied with insulin.

5. **Adrenocortical hormones:** Normal levels of adrenocortical hormones are needed for normal growth and they are having permissive action on growth on sense that adrenalectomized animals fail to grow. However, high pharmacological doses of these hormones slows or stops growth as long as treatment is continued.

**Dwarfism:** Short stature can be due to GHRH deficiency, OH deficiency, IGF-I deficiency or other causes.

**Gigantism and Acromegaly:** Tumors of somatotropes of anterior pituitary secrete large amount of growth hormone leading in children to gigantism and in adults to acromegally.

**MSH**

When ACTH is secreted by the anterior pituitary gland, several other hormones that have similar chemical structure are secreted simultaneously. These are melanocyte-stimulating hormone (MSH), β-lipotropin, and 3-endorphin. Under normal condition, non of these hormones have a significant effect (secreted in small quantities) except MSH which is secreted in higher concentration in condition of high secretion of ACTH (hypofunction of adrenal cortex as in Addison’s disease). Melanin is synthesized from tyrosin via dopa and dopaquinon. MSH stimulates melanocytes for the synthesis of black pigment, melanin, which is responsible for the dark colour of the skin. Because of the similarity of the chemical structure, ACTH has considerable MSH activity.

MSH is also produced from the intermediate lobe (rudimentary in human). Treatment with MSH accelerates melanin synthesis and causes detectable darkening of the skin of humans in 24 hours.

**Pigment Abnormalities in Humans:** Abnormal pallor is a hallmark for hypopituitarism. Hyperpigmentation occurs due to adrenal insufficiency due to primary adrenal disease and not secondary to pituitary disease as the pituitary must be intact for pigmentation to occur.

**Albinism:** is congenital inability to synthesize melanin.

**Vitiligo:** Patchy loss of melanin which is progressive and develops after birth, occur due to genetic dececi in the migration of pigment cells precursor from neural crest to the skin.
The reproductive system

Genetic sex is defined by the sex chromosomes XY in males and XX in females. Gonadal sex is defined by the presence of testes in males and ovaries in females. Phenotypic sex is defined by the characteristics of the internal genital tract and the external genitalia.

[A] Male phenotype: The testes of gonadal male secrete antimullerian hormone and testosterone. Testosterone stimulates the growth and differentiation of the wolffian ducts, which develop into the male internal genital tract. Antimullerian hormone causes atrophy of the mullerian ducts (which would have become the female internal genital tract).

[B] Female phenotype: The ovaries of gonadal females secrete estrogen, but not antimullerian hormone or testosterone. Without testosterone, the wolffian ducts do not differentiate. Without antimullerian hormone, the mullerian ducts are not suppressed and therefore develop into the female internal genital tract.

The Male reproductive system

The testes are made up of loops of convoluted seminiferous tubules. In the walls of which the spermatozoa are formed from the primitive germ cells (spermatogenesis). Both ends of each loop drain into a network of ducts in the head of epididymis, from there spermatozoa pass through the tail of epididymis into the vas deference. They enter the ejaculatory ducts into the urethra in the body of prostate at time of ejaculation. Between the tubules of testes there are nests of cells containing lipid granules called interstitial cells of Leydig which secrete testosterone.

Gametogenesis and ejaculation:

The walls of seminiferous tubules are lined by primitive cells and by Sertoli cells which are large complex glycogen-containing cells that stretch from the basal lamina of the tubule to the lumen. Tight junctions between adjacent sertoli cells near the basal lamina form a blood-testis barrier which has the following functions:

[1]. Prevent large molecules from passing to lumen of tubule, allowing germ cells to pass only.

[2]. Maintains the composition of fluid in the lumen of seminiferous tubule. This fluid contains very little protein and sugar but it is rich in androgens, estrogen, K⁺, inositol, glutamic acid and aspartic acid.

[31]. Protects the germ cells from blood-borne noxious agents.

[41]. Prevents antigenic products of germ cell division and maturation from entering the circulation and generating an autoimmune response.
Helps to establish an osmotic gradient that facilitate movement of fluid into tubular lumen.

The Sertoli cells secrete:

1. **Mullerian inhibiting substance (MIS, or antimullerian hormone)** causes regression of Mullerian ducts in male during fetal life (as Mullerian duct form the fallopian tubes in female leaving the Wolffian duct that forms the Vas deference in male).
2. **Inhibin** that inhibit FSH secretion.
3. **Androgen binding protein (ABP)** which function to maintain highly stable supply of androgen in tubular fluid.
4. **Estrogen** is produced as Sertoli cells contain (aromatase) the enzyme responsible for conversion of androgen to estrogen.

**Spermatogenesis**: Spermatogenesis follows the following steps: Spermatogonin (primitive germ cell at basal lamina) \(\rightarrow\) primary spermatocytes \(\rightarrow\) secondary spermatocytes \(\rightarrow\) spermatids \(\rightarrow\) spermatozoa (sperm). A process of division and maturation begins during adolescence. Each spermatogonium gives 512 sperms, in humans it takes an average of 74 days to form a mature sperm. Both testes forms 120 x 10^6 sperms per day.

**Several hormones play essential roles in spermatogenesis:**
1. **Testosterone**: necessary for maturation of spermatids to spermatozoa.
3. **LH**: stimulates the production of androgen from interstitial cells of Leydig.
4. **Estrogen**.
5. **Growth hormones**: necessary for controlling background metabolic function of testes and promote early maturation of spermatogonia.

The sperm had 4 parts: Head, middle piece, main piece and tail and the end piece of tail. The head is made up of chromosomal material with head-like cap called **acrosome** which is a lysosome-like organelle rich in enzymes involved in sperm penetration of ovum and other events involved in fertilization. The middle piece is composed of centriole and mitochondrial sheath. The membrane of late spermatozoa contain a small form of germinal angiotensin-converting enzyme which may had a role in fertility capacity. Spermatozoa leaving the testes are not fully mobile, motility and ability to adhere to ovum are increased by:

1. **Relaxin**: which is produced by the prostate.
2. **In female genital tract**: There are changes occurred which are:
   A. Removal of inhibitory factor that suppress sperm activity.
   B. Removal of cholesterol cover of acrosome that prevent proteolytic activity in male genitalia.
   C. Head of sperm become more permeable to calcium, so increase the flagellated movement of sperm and activate the acrosome enzymes.

**Effect of temperature**: Spermatogenesis requires a temperature considerably lower than that of the interior of the body. Testes are normally maintained at a temperature of about 32°C by air circulating round the scrotum and by heat exchange in a countercurrent fashion between spermatic arteries and veins. On cold days scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body, whereas on warm days the musculature of the scrotum becomes almost totally relaxed so that the testes hang far from the body. When testes are held close to the body (tight close binders, improper descended testes) a degeneration of tubular walls lead to sterility. Hot baths (43 - 45°C) for so minutes daily and insulated athletic supporters reduce the sperm count by 50%-90%.

**Semen**: It is the fluid that is ejaculated at the time of orgasm. The average volume is 2.5 - 3.5 ml after 4
- 5 days of abstinence. It is composed of the fluids from the vas deferens, from the seminal vesicles, from the prostate gland, and from the mucous gland, especially bulbo-urethral glands. Its composition includes:

- colour ➔ white opalescent.
- Specific gravity ➔ 1.028
- pH ➔ 7.35 - 7.50.
- Sperm ➔ about 100 million/ml (not more than 20% of them are of abnormal forms).
- Seminal vesicle fluid forms 60% of total volume and contains fructose (1.5-6.5 mg/ml), fibrinogen, sorbic acid, prostaglandins, phosphorylcholine, ergothionine. It is the last to be ejaculated and serves to wash the sperm out of the ejaculatory duct and urethra. The seminal vesicle fluid and the mucous glands give the semen a mucoid consistancy.
- Prostatic fluid forms 30% of total volume. It gives the semen a milky appearance. It contains spermine, citric acid, cholesterol, phospholipids, fibrinolysin, fibrinogenase, zinc and acid phosphatase. The clotting enzyme of the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak coagulum, which then dissolves during the next 15-20 minutes because of lysis by fibrinolysin formed from the prostatic protinogen. The sperm in the epididymis become motile and mature (capable of fertilization due to the effect of estrogen and testosterone secreted by the epithelium of epididymis although it secretes several inhibitory proteins that prevent actual motility, but sperms take several days to pass the 6 meter long of epididymis.

Men become non-fertile if:
1. Sperm count below 20 million/ml ➔ oligosperma.
2. Large number of non motile sperms.
3. Large number of abnormal shaped sperms.

Human sperms move at a speed of 3 mm/mm. through the female genital tract reaching the uterine tubes 30 - 60 minutes after copulation and can live 1-2 days in female genitalia. The clotting enzyme of prostate forms a weak coagulum that held the sperm in the deeper region of the vagina where the uterine cervix is present. The coagulum then dissolves during next 15 - 30 minutes by the lysis action of fibrinolysin.
The sperm in the epididymis become motile and mature (capable of fertilization due to the effect of estrogen and testosterone secreted by the epithelium of epididymis although it secretes several inhibitory proteins that prevent actual motility, but sperms take several days to pass the 6 meter long of epididymis.

In vas deference sperms can be stored up to one month. The seminal glangs secrete fructose, (which is essential for sperm nutrition) citric acid, fibrinogen and PG which help the cervical mucus becoming more receptive to sperm movement and reverse the peristaltic contraction in uterus and fallopian tubes to move the sperms towards the ovaries.

The prostatic gland secretion is alkaline which is necessary to neutralize the fluid of vas deferenc (citric acid) and to neutralize the vaginal secretion which is a acidic pH (3.5 - 4.0) as the sperm needs alkaline media to be completely mobile.

---

**Male sex act**

Consist of **Erection (parasympathetic reflex)** and **Ejaculation (sympathetic reflex)**.

**Erection:** Erection is initiated by dilatation of arterioles of the penis, as the erectile tissue of the penis become filled with blood, veins are compressed blocking outflow and adding to the turgor of organ.

**The erection reflex:**
1. Afferent impulses from genitalia (glans penis) and from high center (erotic psychic stimuli).
2. The erection center is located in the lumbar segment of spinal cord.
3. Efferent parasympathetic fibers are in the pelvic splanchnic nerve (nervi erigentis) and their neurotransmitters are Ach. Which dilate the arteries of the penis, thus allowing arterial blood to build up under high pressure in the erectile tissue of the penis since the venous outflow is partially occluded. Ach. Also act on muscarinic receptor to decrease the release of vasoconstrictor agent (norepinephrine). in addition, noradrenergic noncholinergic fibers in nervi erigentes contains large amounts of NO synthase, the enzyme that catalyzes the formation of NO which is a powerful vasodilator (mechanism of action of viagra). Parasympathetic stimulation, in addition to promoting erection, cause the urethral glands and the bulbourethral glands to secrete mucus which aid in the lubrication of coitus. Reflex of erection is terminated by sympathetic vasoconstrictor impulses to the arterioles.
Ejaculation: It is a two part spinal reflex that involves emission, the movement of semen into the urethra and ejaculation proper which is the propulsion of semen out of the urethra at the time of orgasm. Emission is a sympathetic response integrated in upper lumbar segments of spinal cord and affected by contraction of smooth muscles of vas deference and seminal vesicles in response to stimuli in the hypogastric nerve.

Ejaculation occur due to contraction of bulbocavernosus muscles. It is sympathetic reflex, the center in upper sacral and lower lumbar segment while efferent motor pathway is SI — S3 roots and internal pudendal nerves.

Endocrine Function of Testes: Testosterone, the principal hormone of the testes. It is synthesized from cholesterol in the Leydig cells and also formed from androsterone secreted by adrenal cortex. Secretion of testosterone is under the control of LH as LH stimulates Leydig cells by increase formation of cAMP. cAMP increases the formation of cholesterol from cholesterol esters and conversion of cholesterol to pregnolone. Cholesterol $\rightarrow$ Pregnenolone $\rightarrow$ 17-Hydroxypregnenolone $\rightarrow$ Dehydroepiandrosterone $\rightarrow$ Androstenedione $\rightarrow$ Testosterone. In the accessory sex organs (e.g., prostate) 5α-reductase enzyme converts testosterone to its active form, dihydrotestosterone. While in kidney, pregnenolone and 17-Hydroxypregnenolone are converted to 17-ketosteroids (dehydroepiandrosterone and androstenedione). The later are weak androgens (had 20% of androgenic activity). Dihydrotestosterone and androstendione are another two androgens secreted with testosterone.

Secretion: Secretion rate of testosterone is high in normal adult male, but small amounts in female are secreted by adrenals. 98% of testosterone is bound to plasma proteins (65% to β-globulin and 33% to albumin) and only 2% is freely present. The plasma level is (18.2 nmol/L) in male and (1.0 nmol/L) in female.

Actions of Testosterone: During development it is responsible for development of male internal and external sex organs and also help in testes descending.

1. Development of secondary sexual characters of males at puberty.
   • Mental: More aggressive, active attitude, interest in opposite sex develops.
   • External genitalia: Penis increase in size and width, scrotum becomes pigmented and rugged.
   • Internal genitalia: Seminal vesicles enlarges and secretes and begins to form fructose.
   • Prostate: With bulbourethral glands enlarge and secretes.
   • Voice: Larynx enlarge, vocal cords increase in length and thickness, voice becomes deeper.
   • Hair growth: Beard appears, male pattern hair of scalp and pubic and axilla, general body hair increase and may result in androgenic alopecia.
   • Body conformation: Shoulder broaden, muscle enlargement.
   Skin: Acne formation.

2. Anabolic Effects: In general increase synthesis and decrease breakdown of protein, secondary effects of increased protein anabolism are: increase musculature and bone growth after puberty, increase of BMR by 5 - 10%, increase number of RBCs by 15 - 20%. It has a feedback mechanism to inhibit pituitary LH secretion and GnRH secretion from hypothalamus.

Regulation of male reproductive hormones: Is shown in the diagram:
Female reproductive system

The reproductive system of the female, unlike that of the male, shows regular (Cyclic) rhythmical changes in the rate of secretion of female hormones and corresponding changes in ovaries and sexual organs, which may be regarded as periodic preparation for fertilization and pregnancy.

Control of ovarian functions:

[1] Hypothalamus control: Hypothalamus secretes gonadotrophin-releasing hormone (GnRH) into portal hypophysial vessel to the pituitary gland. GnRH stimulates FSH and LH secretion. GnRH is secreted in pulses every 1-3 hours, each pulse lasting several minutes. This pulsatile release of GnRH causes pulsatile output of LH and FSH (lasting many hours).

Continuous GnRH infusion experimentally causes inhibition of LH and FSH secretion and down regulation of it’s receptors. Frequency of GnRH secretion is increased by estrogen and decreased by progesterone and testosterone. Arcuate nucleus in hypothalamns is responsible for release of GnRH, so it is regarded as nuclei of female sexual activity. There are multiple neurons connect arcuate nuclei to limbic system that is why psychic factors modify sexual function.

[2] Pituitary control: FSH from pituitary is responsible for maturation of ovarian follicles. The ovarian follicles, under the effect of FSH, secrete estrogen. Then at the end of follicular phase, a burst of LH secretion occurs (LH surge) which is responsible for ovulation and initial formation of corpus luteum. LH stimulates the secretion of estrogen and progesterone from the corpus luteum.

[3] Cyclic control: Small amounts of estrogen had –ve Feedback on FSH, LH and GnRH, while large amounts of estrogen had +ve Feedback on the FSH, LH and GnRH. Progesterone and inhibin had –ve feedback effect on FSH, LH, and GnRH.

Estrogen had two peaks during menstrual cycle; first one is two days before ovulation and the second peak during luteal phase while progesterone had only one peak in luteal phase. FSH and LH had one peak 36-48 hours before ovulation and this peak could be explained by feedback effects of:

Ovarian (menstrual) cycle: During development of fetus there are 7 millions primordial follicles in the ovaries, at time of birth there are only 2 million ova, at time of puberty there are less than 300,000 ova, only one ova per cycle become mature i.e only 500 ova in the whole reproductive life, the rest of the ova degenerates. Ovarian cycle has 3 phases:
[A] The first phase: The Follicular phase: The first day of bleeding is regarded as first day of the cycle. The follicular phase extends from the 5th day of the cycle to the 14th day during which FSH will induce maturation of the primordial follicles → vesicular follicles → mature follicles (called Graffian follicles). Many follicles start to mature but only one follicle reaches maturation per cycle. The Graffian follicle contains 3 layers, theca externa, theca interna and granulosa layer with the follicular fluid inside the antrum which contains the estrogen secreted by theca interna and granulosa under the influence of FSH. The main source of circulating estrogen is the theca interna while the granulosa cells mainly form the estrogen in the antral fluid.

In early part of this phase, inhibin is low and FSH is modestly elevated fostering the follicular growth. LH secretion is held in check by the negative feedback of the rising plasma estrogen level.

[B] The second phase: Ovulation: Occurs 14 days before menses, regardless of the cycle length. Thus, in a 28-day cycle, ovulation occurs on day 15; in 35-day cycle, ovulation occurs on day 22. In ovulation, rupture of Graffian follicle occurs, this process consists of two events, occur under the effect of LH.

1- Theca externa release proteolytic enzymes leading to dissolution of the wall.
2- Rapid growth of new blood vessels into the follicle wall and at the same time prostaglandins are secreted (local hormones that cause vasodilatation) into the follicular fluid leading to plasma transudation into the follicle and follicular swelling, then rupture, and discharges the ovum to the abdominal cavity.

36 – 48 h. before ovulation, the estrogen feedback becomes positive leading to burst in LH secretion (LH surge) that produce ovulation. FSH also peaks despite little rise of inhibin level probably because of strong stimulation of FSH and LH by GnRH.

[C] The third phase: Luteal phase: Begins from the 14th – 28th day of the cycle, under the control of LH. The high levels of estrogen, progesterone and inhibin lead to – ve feedback so result in low FSH and LH.

The ruptured follicle is filled with blood forming corpus haemorrhagicum. Minor bleeding from the rupture follicle in to the abdominal cavity causes lower abdominal pain due to peritoneal irritation which may be severe and misdiagnosed as acute appendicitis. The theca cells and granulosa cells start to proliferate and blood inside the corpus haemorrhagicum is replaced by luteal cells forming mature corpus luteum. Luteal cells secrete estrogen and progesterone. If pregnancy occur, corpus luteum will persist and no menstruation occur till pregnancy is over. If pregnancy does not occur, corpus luteum will degenerate in the 24th day of the cycle forming regressed corpus luteum and then replaced by scar forming corpus albicans.
Uterine cycle:

**[A] Proliferative phase (estrogen phase):** Under the influence of estrogen from the developing follicle, the endometrium increases rapidly in thickness and uterine glands increases in length from the 5th to the 14th days of menstrual cycle.

**[B] Secretory or luteal phase (progestational phase):** After ovulation the endometrium becomes more vascular and slightly edematous and the glands start to secrete clear fluid this occurs under the influence of estrogen and progesterone from corpus luteum during the 14th to 28th days of menstrual cycle. So this phase is regarded as preparation of uterus for implantation of fertilized ovum.
**Desquamation of endometrium (menstruation):** Approximately, two days before the end of the monthly cycle, regression of corpus luteum occurs and leads to a sharp hormonal withdrawal of estrogen and progesterone leading to shedding of endometrial tissue resulting in spotty hemorrhages that become confluent and produce the menstrual flow. The amount of blood ranges from few drops to 80 ml (average 30 ml), 75% of it is arterial blood and 25% is venous, it contains tissue debris, prostaglandins (PGs), fibrinolysin from endometrial tissue that prevent clotting of menstrual blood. The onset of menstrual bleeding is thought to be induced by (1) the release of PGs from the cellular phospholipids and causes spasm of spiral arteries and (2) by the release of lysosomal enzymes from the necrotic endometrial cells. During menstruation, large number of leukocytes are released along with the necrotic material and blood (Leukorrhea), these leukocytes may help to make the uterus highly resistant to infection during menstruation.

**Cyclic changes in uterine cervix:** Although the cervix is continuous with the body of the uterus, the mucosa of it does not undergo cyclic desquamation but there are regular changes in the cervical mucus. Estrogen during the proliferative phase makes the mucus thinner and more alkaline, which promotes survival and transport of sperms while progesterone during secretory phase makes mucus more thick, tenacious and cellular. At time of ovulation the mucus elasticity is increased so that single drop can be stretched to more than 8 – 12 cms length, under slide when it dries gives fernlike pattern. In pregnancy the mucus becomes thick and fail to form fern pattern.

**Vaginal Cycle:** Under the influence of estrogen, the vaginal epithelium becomes cornified (seen clearly in vaginal smear). The progesterone influence lead to the secretion of thick mucus and the epithelium proliferate and become infiltrated with leukocytes.

**Cyclic changes in the Breasts:** Estrogen causes proliferation of mammary ducts while progesterone causes growth of lobules and alveoli and leads to breast swelling, tenderness and pain felt by many women about 10 days before menstruation. These changes regress along with the symptoms during menstruation.

**Indications of ovulation:**
1- **Endometrial biopsy:** If biopsy shows secretory pattern indicates functioning corpus luteum.
2- **Cervical mucus:** Thick, cellular and no Fernlike pattern indicate functioning corpus luteum.
3- **Basal body temp:** Since progesterone is thermogenic, therefore, at the time of ovulation, basal body temp is increased by 0.5°C.
4- **Progesterone level:** Is increased in blood and urine during ovulation because LH is increased.

Ovum can survive for 72 hours and sperm can survive 72 hours in the female genital tract so the fertile period is about 120 hours (taking in consideration 24 hours of overlapping time). Therefore, before the 9th days and after the 20th days of the cycle there is a little chance of conception.

**Ovarian Hormones:**

**[1] Estrogens:** The naturally occurring estrogens are estradiol, estrone and estriol. Estradiol is the most potent and estriol is the least. They are secreted by theca interna and granulosa cells of ovarian follicle, the corpus luteum and placenta. 2% of the circulating estradiol is free. The secreted estrogen during menstrual cycle is of ovarian origin with two peaks of secretion: one just before ovulation and the other in the mid–luteal phase. The effects of estrogens are:

**[A] Effects on female genitalia:**
[a] Estrogens facilitate growth of ovarian follicle.
[b] Increase motility of fallopian tubes
[c] Cyclic changes of endometrium, cervix and vagina as mentioned previously.
Al-Mustansiriya College of Medicine/ Endocrine Physiology

[d] Increases uterine blood flow.
[e] Increases the amount of uterine muscle and it’s content of contractile proteins.

The muscle becomes active and more excitable.
[f] Estrogen makes uterus more sensitive to oxytocin.
[g] Vaginal epithelium is changed from cuboidal to stratified columnar epith.

**B Effect on development of secondary sexual characters:**

[a] Female body configuration: Narrow shoulder, broad hip, converged thigh, diverged arm. Fat distribution in buttocks and breast.
[b] Larynx: Voice becomes high pitched.
[c] Skin: Soft, smooth, but thicker than childhood, more vascular, therefore, the skin is warm and bleed more than male, less body hair, more scalp hair, pubic hair is flat topped pattern (axillary and pubic hair is due to effect of adrenal androgen).
[d] Sebaceous glands secretions become more fluid so reduced acne formation.
[e] Breasts Become enlarged due to growth of stromal tissue, ductal system deposition of fat, pigmentation of areola and apperance of mature female breast.

**C Behavioral effects:** Estrogens are responsible for estrous behavior in animals and they increase libido in human due to effects on special neurons in hypothalamus.

**D Effect on skeleton:** Estrogen had osteoblastic activity so it causes increase in bone length but later causes early closure of epiphyseal plate so low estrogen levels lead to osteoporosis, decrease bone matrix and decrease bone Ca^+ and PO4^-.

**E Metabolic effects:**

- On proteins it causes protein anabolic effect on specific target organs like breast, skeleton, uterus and certain fatty areas. On fat it causes increase in BMR, increases deposition of fat in subcutaneous tissues and has significant plasma cholesterol lowering action (less atherosclerosis).

**F Other effects:**
- Mild Na and H_2O retention (significant in pregnancy only).
- Has positive and negative feedback effect on LH and FSH secretion.
- Increase size of pituitary.
- Increase secretion of angiotensinogen and thyroid binding protein.

**[2] Progesterone:** It is secreted mainly from corpus luteum, placenta and less by the follicle. Small amounts enter circulation from testes and adrenal cortex. About 2% of circulating progesterone is free, 80% is bound to albumin and 18% to corticosteroid binding protein. Plasma progesterone level in men is 1 nmol/L whereas in female is 3 nmol/L during follicular phase and 60 nmo/L in luteal phase. The effects of progesterone are:

**A On uterus:**

- Cyclic changes on vagina and cervix.
- Progestational changes on endometrium.
- Antiestrogenic effect on myometrium including decreasing excitability of myometrium cells and their spontaneous electrical activity by increasing their membrane potential, also decrease number of estrogen receptors in endometrium and increase conversion of estradiol to less active estrogen.

**B On fallopian tubes:** Promotes secretory changes in mucosal membrane which are necessary for nutrition of fertilized ovum.

**C On breast:** Stimulate the development of lobules and alveoli and increase fluid in subcutaneous tissue leading to breast swelling. It induces differentiation of estrogen-prepared ductal tissues and support the secretory function of breast during lactation.

**D On hypothalamus and pituitary:** High does of progesterone causes feedback effect and inhibit LH secretion and potentiate the inhibitory effect of estrogen preventing ovulation (the action of contraceptive pills).

**E Other effects:** Large doses produce natriuresis by blocking the action of aldosterone on the kidney. It has thermogenic effect causing rise in basal body temperature at time of ovulation. Progesterone causes stimulation of respiration and therefore, alveolar PaCO_2 falls as progesterone secretion rises. The hormone does not have a significant anabolic effect.
**[3] Relaxin:** Polypeptide hormone produced by corpus luteum, uterus, placenta and mammary glands in women and from prostate in man. During pregnancy it relaxes pubic symphysis and other pelvic joints and softens and dilates uterine cervix to facilitate delivery. It also inhibits uterine contractions and may play a role in the development of mammary glands. In non-pregnant woman it’s function is unknown. In men relaxin is found in semen and it may help to maintain sperm motility and aid sperm penetration to the ovum.

**[4] Inhibin:** A polypeptide produced by the granulosa cells and inhibits FSH secretion.

In Summary, the control of the Cycle

- Luteolysis starting 3-4 days before menses is the key to the menstrual cycle.
- When luteolysis occurs, progesterone and estrogen levels fall and the secretion of LH and FSH increases.
- A new group of follicles develop and as a result of FSH and LH, one follicle only becomes mature.
- Near mid cycle – Estrogen and Progesterone level from the follicle rise.
- This rise augments the responsiveness of pituitary to GnRH and triggers a burst of LH secretion.
- Ovulation results with formation of corpus luteum resulting in drop of estrogen secretion but later the levels of estrogen and progesterone rise together, along with inhibin.

**Contraception**

Many methods are commonly in use to prevent conception, one of these is hormonal method. Woman undergoing long term therapy with large dose of estrogen do not ovulate because of depressed levels of FSH, and multiple irregular bursts of LH secretion rather than single midcycle peak.

Contraceptive pills of combined estrogen and progesterone also leads to failure of ovulation because both FSH and LH are suppressed in addition progesterone makes the cervical mucus thick and unfavorable to sperm migration and may interfere with implantation.

The pills are given for 21 days then withdrawn for 5-7 days to allow menstrual flow started again.

**Puberty**

It is the period when the endocrine and gametogenic functions of the gonads have first developed to the point where reproduction is possible. Puberty is initiated by the onset of pulsatile GnRH release from the hypothalamus. FSH and LH are, in turn, secreted in pulsatile fashion. GnRH up-regulates its own receptor in the anterior pituitary. In girls occurs at 8 – 13 years, starts by development of breasts (thelarche) then by development of axillary and pubic hair (pubarche) and followed by the first menstrual period appearance (menarche). The initial periods are anovulatory, and regular ovulatory cycles appears about a year later. In males puberty started at age of 9 – 14 years. In addition, at the time of puberty there is an increase in secretion of adrenal androgens (adenarche). It occurs at age of 8 – 10 years without any change in the cortisol or ACTH levels.

- In childhood, hormone levels are lowest and FSH is more than LH.
- At puberty and during the reproductive years, hormone level increase and LH is more than FSH.
- In senescence, hormone levels are highest and FSH is more than LH.

**Menopause**

Cessation of menstrual cycles at age of 45 – 55 years is called menopause. The physiological changes include:-

1. Unresponsiveness of ovaries to FSH and LH due to decline in number of primordial cells.
2. Ovaries do not secrete estrogen and progesterone.
3. FSH and LH secretion and plasma levels are increased due to cessation of the – ve feedback.

Clinical symptoms of low estrogen levels are experienced.

**Menstrual abnormalities**

Anovulatory cycles: Some women who are infertile have anovulatory cycles, they fail to ovulate but their cycles are regular. Since no ovulation occurs, progesterone is not secreted as there is no corpus luteum and no effects of progesterone on endometrium. Endometrium still affected by estrogen (thick proliferation phase) lead to variable increase in duration and amount of bleeding.

Amenorrhoea: absence of menstrual cycle.
Dysmenorrhoea: Painful menstruation common in young women which disappears after pregnancy.
Premenstrual syndrome: Some women develop symptoms such as irritability, headache, depression, low concentration, emotional changes, edema, and constipation in 7-10 days of their menstrual cycles.
Menorrhagia: Refer to profuse heavy vaginal flow during regular periods.
Metrorrhagia: Is vaginal bleeding between the periods.
Oligomenorrhoea: Reduced frequency of periods.
Pregnancy

It is characterized by steadily increasing levels of estrogen and progesterone, which maintain the endometrium for the fetus, suppress ovarian follicular function (by inhibiting FSH and LH secretion), and stimulate development of the breast.

Fertilization and implantation: In humans fertilization of the ovum by the sperm usually occurs in the mid portion of uterine tube. There is an evidence that the humans ovum secretes an attractant or chemotactic factor that attracts sperm to the ovum. 50-100 sperms reach the ovum and many of these contacts to zona pellucida. Sperms bind to a sperm receptor called ZP3 in the zona. This is followed by acrosomal reaction during which the acrosome (the lysosomes like organel in the head of sperm) breakdown and release of acrosin (a trypsin like protease) aids the penetration of sperm through zona pellucida and reach to the ovum membrane. The fusion is mediated by a fertilin which is a protein found in the head of the sperm. The fusion provides:

1. The signal that initiate development.
2. Reduction in membrane potential of the ovum that prevent polyspermy. This transient potential change is followed by structural changes in zona pellucid a that provides protection against polyspermy on a more long term basis. The developing embryo is called blastocyst which moves down to the uterus (3 days duration) and reaches the 8 or 16-cells stage. Once reaching endometrium the blastocyst becomes surrounded by an outer layer of syncytiotrophoblast and inner layer called cytотrophoblast. The syncytiotrophoblast erodes the endometrium and the blastocyst burrow into it (implantation), placenta then develops. Although the fetus and the mother are two genetically distinct individuals, rejection does not occur because the placental trophoblast does not express the major histocompatibility complex genes (MHC) I and II responsible for rejection and instead it express HLA-G (human Leukocyte antigen G) which is a nonpolymorphic gene. Therefore antibodies against fetal proteins do not develop in addition there is a decrease in maternal antibody production during pregnancy.

Hormones secreted from placenta:

[1] Human Chorionic gonadotropin (hCG): hCG is a glycoprotein secreted by the syncytiotrophoblast, made up of α and β subunits. The α subunit has similar structure of α chain of FSH, LH and TSH and acts on same receptors of LH. It appears in blood 6 days after conception and in urine after 14 days (so used as pregnancy test). It is secreted by the kidney and liver of fetus in small amounts. The rate of secretion reaches maximum about 10 – 12 weeks of gestation and decrease to much lower value by 16-20 week, and continues at this level for the rest of pregnancy.

Functions of hCG:

a. hCG stimulates corpus luteum to continue secretes estrogen and progesterone until the 6th week of gestation after that the placenta secrete estrogen and progesterone. The function of Corpus luteum begins to decline after 8 weeks of pregnancy but it persist throughout pregnancy.

b. hCG exerts an interstitial cell stimulating effect on the testes thus resulting in production of testosterone in male fetus until the time of birth.

[2] Human Chorionic somatomammotropin (hCS, or human placental lactogen): Secreted by syncytiotrophoblasts. The amount of hCS secreted is proportional to the size of placenta, which normally weights 116 of fetal weight. Therefore, low hCS levels indicates placental insufficiency. Large quantities of hCS are found in maternal blood but very little amounts reaches the fetus.

Functions of hCS are:

a. Has Lactogenic effect with slight increase in breast development.

b. It has most actions of GH (due to similar structure) but less potent than GH. It causes retention of nitrogen, K+ and Ca++. Secretion of GH from maternal pitutary is reduced by the hCS.

c. Causes reduced insulin sensitivity and decrease utilization of glucose in maternal tissues thus making large quantities of glucose available to the fetus.
[3] **Estrogen**: It is formed by corpus luteum in early pregnancy and by placenta in late pregnancy. It differs from the estrogen secreted by the ovaries by:

a. Most of this estrogen is estriol (very weak type).

b. It is not secreted purely from placenta but interaction between placenta and fetal Adrenal cortex (fetoplacental unit).

Functions of estrogen in pregnancy are:

A. Development of maternal uterus, breasts and external genitilia.

B. Relaxes various pelvic ligaments.

C. Affects general aspects of fetal development as the rate of cell reproduction of early embryo.

---

![Interaction between the placenta and the fetal adrenal cortex in the production of steroids.](image)

**Interaction between the placenta and the fetal adrenal cortex in the production of steroids.**

- **DHEAS** = dehydroepiandrosterone sulfate
- **16-OHDHEAS** = 16-hydroxydehydroepiandrosterone sulfate

---

[4] **Progesterone**: Secreted by corpus luteum in early pregnancy or by placenta in late pregnancy.

The functions of progesterone during pregnancy are:

a. Development of decidual cells in utrine endometrium which are important for nutrition of embryo in early stages.

b. Decreases contractility of gravid uterus and prevent abortion.

c. Increases the section of fallopian tubes and uterus to provide appropriate nutritive matter for the developing morula and blastocyst.

[5] **Other Placental Hormones**: Hormones secreted by the placenta also include: Pro-opiomelarocartin (POMC), melanocyte stimulating hormone, B-endrophin, dynorphin, GnRH and inhibin (which stimulates and inhibits hCG), also prolactin and prorenin hormones.

During the first trimester of pregnancy (i.e., during the first 12 weeks of gestation), the corpus luteum (stimulated by hCG) is responsible for the production of estradiol and progesterone. During
second and third trimesters, progesterone is produced by the placenta while estrogens are produced by the interplay of the fetal adrenal gland and the placenta.

**Endocrinial changes during Pregnancy:**

1. Pituitary gland: Increase in size, increased secretion of ACTH, TSH and prolactin. In addition, decreased levels of FSH and LH.
2. Adrenal glands: Increased secretion of glucocorticoids, aldosterone and estrogen causes water and Na\(^+\) retention.
3. Thyroid gland: Increased size of the gland with increased thyroxin due to the thyrotropic effect of hCG and human chorionic thyrotropin (from placenta).
4. Parathyroid gland: Increase in the size of the gland. Increase PTH during pregnancy and lactation to meet the increased Ca\(^+\) demand of the fetus.
5. Relaxin: Secreted by corpus luteum and then by the placenta. It helps to relax the pelvic joints.

**Parturition (delivery of the baby or labour)**

The duration of pregnancy in humans averages 270 days from fertilization (284 days from the first day of menestral period before conception. In the last month of pregnancy irregular uterine contractions increases in frequency. This is due to:

1. The number and sensitivity of oxytocin receptors in myometrium and decidua increases more than 100 folds during pregnancy and reach a peak during early labour. This is due to estrogen and uterine distention in late pregnancy which increases the formation of oxytocin receptors.
2. Mechanical factors increases uterine contractions are:
   - A- Stretch of uterine musculature caused by fetal movements.
   - B- Stretch of cervix, leads to increase in oxytocin secretion. As plasma oxytocin level rises, more oxytocin acts on uterus, and positive feedback loop is established that aids delivery and is terminated when products of conception are expelled.

Oxytocin increases uterine contractions by:
1. Acts directly on uterine smooth muscles.
2. Stimulation of PG formation in decidua. the PG enhances the oxytocin – induced contractions.

**Development of breasts and lactation**

1. During puberty: Estrogen are primarily responsible for proliferation of mammary ducts while progesterone is necessary for development of lobules. Other hormones like insulin, GH and prolactin are necessary for mammary development but by themselves do not cause breast growth.
2. During pregnancy: Enlargement of breast occur due to high circulating levels of estrogen, progesterone, prolactin and hCG. Milk is secreted as early as the Fifth month but in small amounts.

**Hormonal control of milk Production and secretion**

1. Oxytocin as mentioned before.
2. Prolactin: Prolactin is secreted from anterior pituitary gland. It is tonically inhibited by hypothalamic prolactin–inhibiting hormone (PIH). It causes milk production and inhibits gonadotropin in females and causes impotence in males.


   Each time the mother nurses her baby, nervous signals from the nipple to hypothalamus causes increase prolactin secretion and hence milk production is increased. When nursing is stopped, the PIH is secreted so prolactin level is reduced and milk production also decrease. So prolactin level increases in cycles during the period of nursing.
**Milk ejection reflex:** It is a neuroendocrine reflex, initiated by by touching the touch receptors at areolas (the area around the nipples) and nipples, stimulated by sucking the mother nipples by the baby. Impulses generated in these receptors are then relayed to the suproptic and paraventricular nuclei. Discharge of the oxytocin-containing neurons causes secretion of oxytocin from the posterior pituitary gland. Oxytocin causes contraction of myoepithelial cells lining the duct walls leading to milk ejection.

Suckling not only evokes reflex oxytocin release and milk ejection, it also maintains and augments the secretion of milk because of prolactin stimulation as well.

**Effect of lactation on menstrual cycles**

Women who do not nurse their infants usually have their 1st mense 6 weeks after delivery. Women regularly nursing have their 1st cycle 25-30 weeks after delivery. Prolactin stimulated by nursing inhibits GnRH secretion ➔ inhibition of gonadotropin of pituitary gland ➔ antagonize the action of gonadotropin on ovary ➔ ovulation is inhibited ➔ inactive ovaries ➔ estrogen and progesteron levels fall to low values. Only 5-10 % of women become pregnant again during suckling period also 50 % of the cycles in the first 6 months after return of menses are anovulatery cycles.

**Other organs of endocrine function:**

[1] **The kidney:** The kidney produces three hormones, 1-25 dihydroxycholecalciferol, renin and erythropoietin

**The renin-angiotensin system:** The renin is an enzyme secreted by the kidney to convert angiotensinogen to angiotensin I. The prorenin is secreted by juxtaglomerular cells and ovaries but only the secretory granules of juxtaglomerular cells are capable of converting prorenin to renin. The circulating angiotensinogen is found in the α2 globulin fraction of the plasma, formed in the liver and it’s level in the plasma is increased by glucocorticoids, thyroid hormones, estrogen, several cytokines and angiotensin II.

**Angiotensin converting enzyme (ACE):** ACE is an enzyme that converts angiotensin I to angiotensin II, it also inactivates bradykinin. Most of the converting enzyme is found in the endothelial cells. The conversion occurs mainly in the lungs as blood passes through it, and in other parts of the body conversion occur also but to a lower extent. The half life of Angiotensin II is 1-2 minutes then is converted by angiotensinase (aminopeptidase) to Angiotensin III. This enzyme is also capable of converting Angiotensin I to Angiotensin III directly. The angiotensinase is present mainly in red blood cells and many tissues. Angiotensin III has 40 % pressor activity of Angiotensin II, but has 100 % of aldosterone stimulating activity. It is suggested that Angiotensin II is the blood pressure regulating peptide while Ang III is the Aldosterone stimulating activity peptide.

**Actions of Angiotensins :**

1- Angiotensin I: has no known action.

2- Angiotensin II:

[A] **Effect on blood pressure:** It causes increase in systolic and diastolic blood pressure through the following mechanisms:

1- **Smooth muscles of blood vesseles:** It causes vasoconstriction of arterioles, it is one of most potent vasoconstrictor, it is 4-8 times as active as norepinephrine.

2- **Brain:** Angiotensin II act on the area prostrema in the brain to increase BP, and on subfornical organ to increase water intake and increases secretion of vasopressin and ACTH. It does not penetrate the blood brain barrier, but produce the response by acting on circumventricular organ.

3- **Peripheral autonomic nervous system:** It facilitates sympathetic transmission by acting on adrenergic nerves and increase release of epinephrine and norepinephrine from adrenal medulla and stimulate autonomic ganglia.
4. **Heart:** Angiotensin II has direct positive inotropic action on the heart. Its pressor activity is decreased in Na+ depleted persons and in cirrhotic patients due to increased circulating Angiotensin II down regulates the Angiotensin II receptors in vasclar smooth muscles.  

**[B] Effect on adrenal cortex:** It acts directly on adrenal cortex to increase biosynthesis of corticosterone and aldosterone. The renin-angiotensin system is a major regulator of aldosterone secretion.  

**[C] Effect on the kidney:** It decreases GFR by causing contraction of mesangial cells, vasoconstriction of efferent arterioles and increase tubular sodium reabsorption.

**Angiotensin Receptors:** It is of 2 kinds, angiotensin receptors I and II. Excess of Ang II down regulates the vascular receptor, but up regulates the adrenocorticoid receports making the gland more sensitive to aldosterone stimulating effect of the peptid.

**Regulation of renin secretion:**  
1. Intrarenal baroreceptor mechanism: As arteriolar pressure at the level of JG cells increases, it inhibits renin secretion and vice versa.  
2. Macula densa mechanism: Renin secretion is inversly proportional to rate of transport of Na+ and Cl across this portion of the tubule. The macula densa effect on renin secretion is mediated by NO.  
3. Prostaglandins espically prostacyclin stimulate renin secretion by direct action on JG cells.  
4. Angiotensin II feedback to cause inhibition of renin secretion by direct effect on JG cells.  
5. Vasopressin also inhibits renin secretion.  
6. Increased sympathetic nervous system actvity increases renin secretion by (a) increased circulating catecholamines and (b) by renal sympathetic nerves.

**[2] The heart:** The heart secretes the atrial natriuretic peptide (ANP) by atrial muscle cells secretory granules that increases in number when NaCl intake is increased and extracellular fluid expand. ANP secretion is proportional to degree of stretch of atria as in increased central venous pressure, increased ECF volume, immersion in water up to neck, by ingestion of high sidum diet. A small decrease in ANP secretion occur on rising from supine to the standing position due to decreased in central venous pressure.

**Actions of ANP:**  
1. **Natriuresis:** ANP causes relaxation of mesengial cells in glomeruli so increases the effective surface area available for filtration so increases GFR causing natriuresis.  
2. **Lowering of Blood Pressure:** by  
   - Decreasing responsivness of vascular smooth muscles to many vasoconstrictor substances.  
   - Decreasing responsivness of zona glomerulosa to stimuli that increases aldosterone secretion and inhibits secretion of vasopressin.

**The pineal gland:** Melatonin is synthesized by pineal paranchymal cells and secreted to blood and cebrospinal fluid. The synthesis and secretion has diurnal rhythm as melatonin is increased during dark period of the day and maintained to low level during daylight hours. This diurnal change is due to norepinephrine secreted by postgangilionic sympathetic nerves that innervate the pineal gland.

The diurnal changes in melatonin secretion function as some sort of timing signal of light - dark cycle in the environment especially in seasonally breeding animals. So melatonin may have some effects on gonadal function. In human it is of unknown physiological action.