Endocrine Physiology

Lec.1 **Dr. Latief Fayadh**

Coordination of Body Functions

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

***1. Neurotransmitters** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.*

***2. Endocrine hormones** are released by glands or specialized cells into the circulating blood and influence the function of cells at another location in the body.*

***3. Neuroendocrine hormones** are secreted by neurons into the circulating blood and influence the function of cells at another location in the body.*

***4. Paracrines** are secreted by cells into the extracellular fluid and affect neighboring cells of a different type.*

***5. Autocrines** are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them by binding to cell surface receptors.*

***6. Cytokines** are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the interleukins and other lymphokines that are secreted by helper cells and act on other cells of the immune system Cytokine hormones (e.g., leptin) produced by adipocytes are sometimes called adipokines.*

Endocrine hormones.

In the next few lectures, we discuss mainly the endocrine hormone systems, keeping in mind that many of the body's chemical messenger systems interact with one another to maintain homeostasis. For example, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including antidiuretic hormone (ADH), oxytocin, and hypophysiotropic hormones, which control the secretion of anterior pituitary hormones.

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

Other hormones affect only specific target tissues, because only these tissues have receptors for the hormone. For example, adrenocorticotropic hormone (ACTH) from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the ovarian hormones have specific effects on the female sex organs as well as on the secondary sexual characteristics of the female body The multiple hormone systems play a key role in regulating almost all body functions, including metabolism, growth and development, water and electrolyte balance, reproduction, and behavior. For instance, without growth hormone, a person would be a dwarf. Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body would become sluggish, and the person would become sluggish as well. Without insulin from the pancreas, the body's cells could use little of the food carbohydrates for energy. And without the sex hormones, sexual development and sexual functions would be absent.

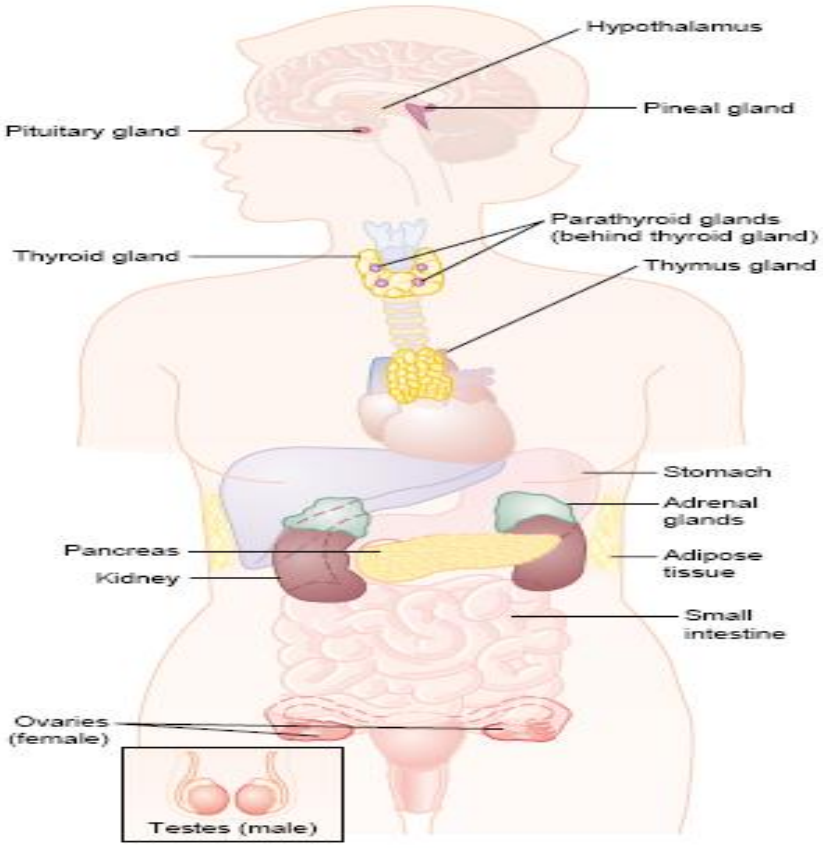


Figure 74–1

Anatomical loci of the principal endocrine glands and tissues of the body.

Classification of hormones:

There are three general classes of hormone according to the chemical structure and synthesis of hormones:

1. Polypeptide and protein hormones:-

Including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others. They are stored in secretory vesicles until needed. Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 3 amino acids (thyrotropin-releasing hormone) to proteins with almost 200 amino acids (growth hormone and prolactin). In general, polypeptides with 100 or more amino acids are called proteins, and those with fewer than 100 amino acids are referred to as peptides.

Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells, in the same fashion as most other proteins. They are usually synthesized first as larger proteins that are not biologically active (preprohormones) and are cleaved to form smaller prohormones in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the blood stream by exocytosis.

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

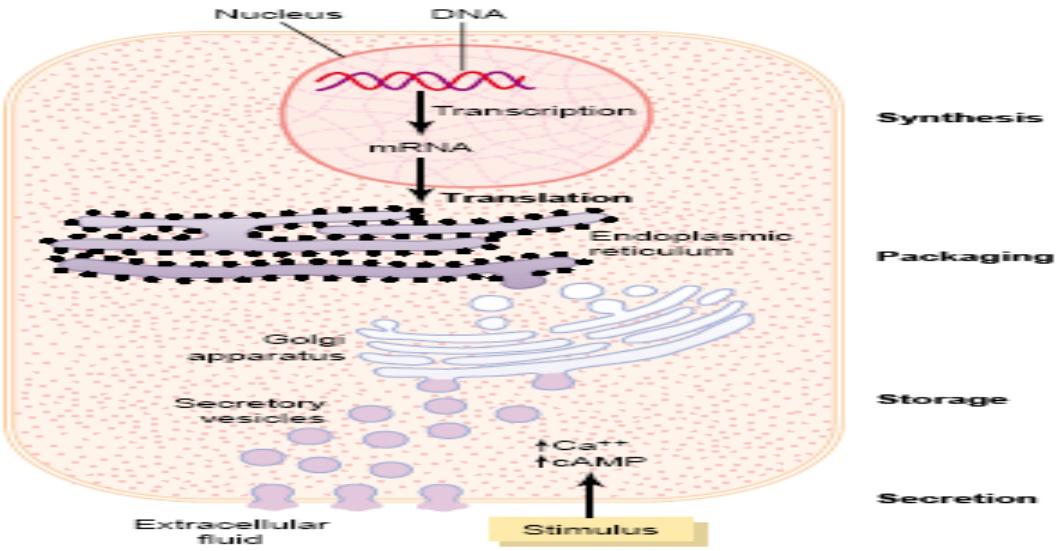


Figure 74–2

Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell.

2. Steroid hormones:-

Secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone). They are usually synthesized from cholesterol and are not stored. The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances they are synthesized from cholesterol itself they are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell Membrane and enter the interstitial fluid and then the blood.

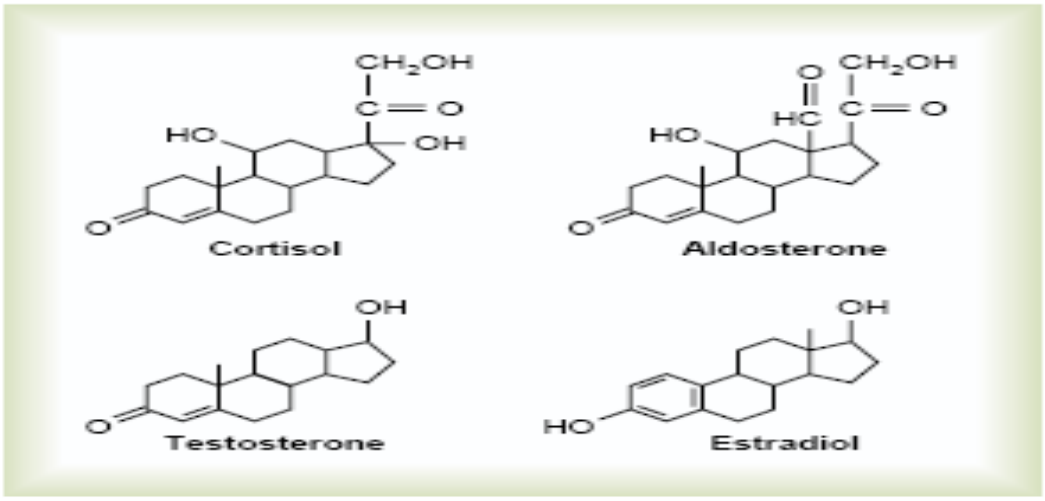


Figure 74–3

Chemical structures of several steroid hormones.

3. Amine hormones:-

Secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine Are derived from Tyrosine. The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein thyroglobulin, which is stored in large follicles

within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin, and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormones combine with plasma proteins, especially thyroxine- binding globulin, which slowly releases the hormones to the target tissues. Epinephrine and norepinephrine are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by exocytosis. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

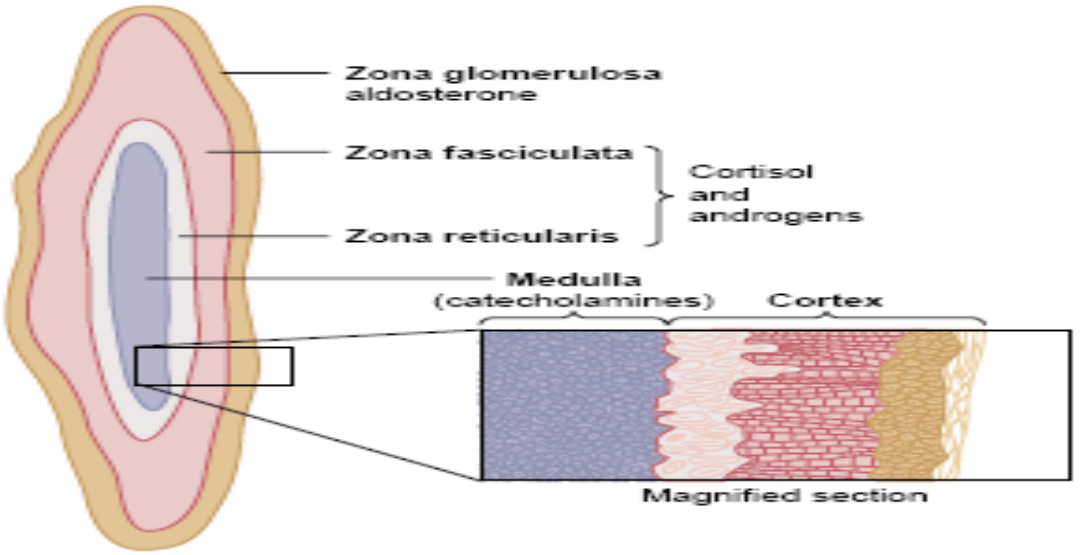


Figure 77–1

Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.

Feedback control of hormone secretion

Negative feedback prevents over activity of hormone systems.

Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through negative feedback mechanisms that ensure a proper level of hormone activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue. The controlled variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones.

Surges of hormones can occur with positive feedback.

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

Hormone secretion, transport, and clearance.

Some hormones, such as norepinephrine and epinephrine, are secreted within seconds after the gland is stimulated, and they may develop full action within another few seconds to minutes; the actions of other hormones, such as thyroxine or growth hormone, may require months for full effect. Thus, each of the different hormones has its own characteristic onset and duration of action—each tailored to perform its specific control function.

Concentrations of hormones in the circulating blood.

The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small. Their concentrations in the blood range from as little as 1 picogram (which is one millionth of one millionth of a gram) in each milliliter of blood up to at most a few micrograms (a few millionths of a gram) per milliliter of blood. Similarly, the rates of secretion of the various hormones are extremely small, usually measured in micrograms or milligrams per day.

Transport of hormones in the blood.

Water-soluble hormones (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells. Steroid and thyroid hormones, in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 per cent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 per cent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their target cells and are therefore biologically inactive until they dissociate from plasma proteins. The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Binding of hormones to plasma proteins greatly slows their clearance from the plasma.

Clearance of hormones from the blood.

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the ***metabolic clearance rate****. This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures****:***

(1) *The rate of disappearance of the hormone from the plasma per minute.*

(2) *The concentration of the hormone in each milliliter of plasma.*

Then, the metabolic clearance rate is calculated by the following formula:

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

The usual procedure for making this measurement is the following: A purified solution of the hormone to be measured is tagged with a radioactive substance then the radioactive hormone is infused at a constant rate into the blood stream until the radioactive concentration in the plasma becomes steady. At this time, the rate of disappearance of the radioactive hormone from the plasma equals the rate at which it is infused, which gives one the rate of disappearance. At the same time, the plasma concentration of the radioactive hormone is measured using a standard radioactive counting procedure. Then, using the formula just cited, the metabolic clearance rate is calculated. Hormones are "cleared" from the plasma in several ways, including:

(1) Metabolic destruction by the tissues.

(2) Binding with the tissues.

(3) Excretion by the liver into the bile.

(4) Excretion by the kidneys into the urine*.*

For certain hormones, a decreased metabolic clearance rate may cause an excessively high concentration of the hormone in the circulating body fluids. For instance, this occurs for several of the steroid hormones when the liver is diseased, because these hormones are conjugated mainly in the liver and then "cleared" into the bile. Hormones are sometimes degraded at their target cells by enzymatic processes that cause

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

Mechanisms of action of hormones:-

The first step of a hormone's action is to bind to specific receptors at the target cell. Cells that lack receptors for the hormones do not respond. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect. Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors. The locations for the different types of hormone receptors are generally the following:

***1. In or on the surface of the cell membrane**.*

The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.

***2. In the cell cytoplasm**.*

The primary receptors for the different steroid hormones are found mainly in the cytoplasm.

***3. In the cell nucleus**.*

The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

The number and sensitivity of hormone receptors are regulated.

*The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute. The receptor proteins themselves are often inactivated or destroyed during the course of their function, and at other times they are reactivated or new ones are manufactured by the protein-manufacturing mechanism of the cell. For instance, increased hormone concentration and increased binding with its target cell receptors sometimes cause the number of active receptors to decrease. This **down-regulation** of the receptors can occur as a result of:*

(1) Inactivation of some of the receptor molecules.

(2) Inactivation of some of the intracellular protein signaling molecules.

(3) Temporary sequestration of the receptor to the inside of the cell, away from the site of action of hormones that interact with cell membrane receptors.

(4) Destruction of the receptors by lysosomes after they are internalized.

(5) Decreased production of the receptors.

In each case, receptor down-regulation decreases the target tissue's responsiveness to the hormone.

*Some hormones cause **up-regulation** of receptors and intracellular signaling proteins; that is, the stimulating hormone induces greater than normal formation of receptor or intracellular signaling molecules by the protein-manufacturing machinery of the target cell, or greater availability of the receptor for interaction with the hormone. When this occurs, the target tissue becomes progressively more sensitive to the stimulating effects of the hormone.*

Measurement of hormone concentrations in the blood.

Most hormones are present in the blood in extremely minute quantities; some concentrations are as low as one billionth of a milligram (1 picogram) per milliliter. Therefore, it was very difficult to measure these concentrations by the usual chemical means. An extremely sensitive method, however, was developed several years ago that revolutionized the measurement of hormones, their precursors, and their metabolic end products. This method is called ***radioimmunoassay.***

Lec.2 ***Dr. Latief fayadh***

Pituitary Gland Hormones

Pituitary gland of two distinct parts, the anterior and posterior lobes. The pituitary gland also called the hypophysis, is a small gland about 1 centimeter in diameter and 0.5 to 1 gram in weight that lies in the sella turcica, a bony cavity at the base of the brain, and is connected to the hypothalamus by the pituitary stalk. Physiologically, the pituitary gland as shown in the figure below is divisible into two distinct portions: the anterior pituitary, also known as the ***adenohypophysis****, and the posterior pituitary, also known as the* ***neurohypophysis****. Between these is a small, relatively avascular zone called the* ***pars intermedia****, which is almost absent in the human being but is much larger and much more functional in some lower animals.*

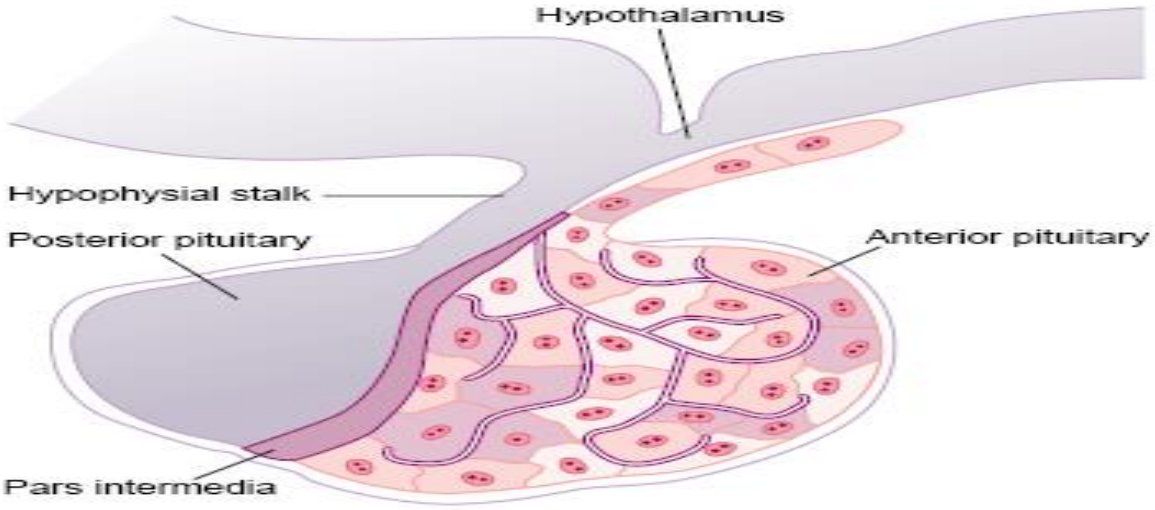


Figure 75–1

Pituitary gland.

Pituitary gland hormones.

Six important peptide hormones plus several less important ones are secreted by the anterior pituitary, and two important peptide hormones are secreted by the posterior pituitary. The hormones of the anterior pituitary play major roles in the control of metabolic functions throughout the body as shown in the following figure.

A- Anterior pituitary gland hormones.

1• Growth hormone.

Promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.

2• Adrenocorticotropin (corticotropin).

Controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats.

3• Thyroid-stimulating hormone.

Thyrotropin controls the rate of secretion of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body.

4• Prolactin.

Promotes mammary gland development and milk production.

5•** Two separate **gonadotropic hormones.

Follicle-stimulating hormone and luteinizing hormone, control growth of the ovaries and testes, as well as their hormonal and reproductive activities.

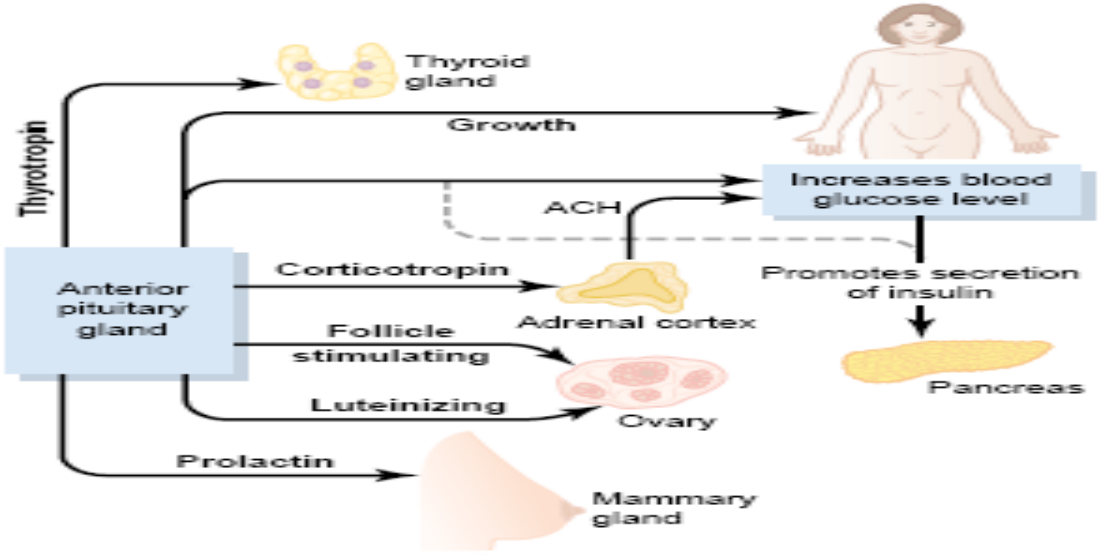


Figure 75–2

Metabolic functions of the anterior pituitary hormones. ACH, adrenal corticosteroid hormones.

B- Posterior pituitary gland hormones.

The two hormones secreted by the posterior pituitary play other roles.

1• Antidiuretic hormone *(also called vasopressin).*

Controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids.

2• Oxytocin

Helps express milk from the glands of the breast to the nipples during suckling and possibly helps in the delivery of the baby at the end of gestation.

Cell types of anterior pituitary gland that secretes hormones.

Usually, there is one cell type for each major hormone formed in anterior pituitary gland. With special stains attached to high-affinity antibodies that bind with the distinctive hormones, at least five cell types can be differentiated these five cell types are:

1. Somatotropes*—human growth hormone (hGH).*

2. Corticotropes*—adrenocorticotropin (ACTH).*

3. Thyrotropes*—thyroid-stimulating hormone (TSH).*

4. Gonadotropes*—gonadotropic hormones, which include both luteinizing hormone (LH) and follicle stimulating hormone (FSH).*

5. Lactotropes*—prolactin (PRL).*

The following Table provides a summary of these cell types, the hormones they produce, and their physiological actions.

Table 75–1

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Actions
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production
IGF, insulin-like growth factor			

About 30 to 40 per cent of the anterior pituitary cells are somatotropes that secrete growth hormone, and about 20 per cent are corticotropes that secrete ACTH.

Each of the other cell types accounts for only 3 to 5 per cent of the total; nevertheless, they secrete powerful hormones for controlling thyroid function, sexual functions, and milk secretion by the breasts. Somatotropes stain strongly with acid dyes and are therefore called acidophils. Thus, pituitary tumors that secrete large quantities of human growth hormone are called acidophilic tumors.

Posterior pituitary hormones synthesis.

Posterior pituitary hormones are synthesized by cell bodies in the Hypothalamus. The bodies of the cells that secrete the posterior pituitary hormones are not located in the pituitary gland itself but are large neurons, called magnocellular neurons, located in the supraoptic and paraventricular nuclei of the hypothalamus. The hormones are then transported in the axoplasm of the neurons' nerve fibers passing from the hypothalamus to the posterior pituitary gland.

Hypothalamic releasing and inhibitory hormones control anterior pituitary secretion.

The function of the releasing and inhibitory hormones is to control secretion of the anterior Pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control. The major hypothalamic releasing and inhibitory hormones are summarized in the following:

***1. Thyrotropin-releasing hormone** (TRH), which causes release of thyroid-stimulating hormone.*

***2. Corticotropin-releasing hormone** (CRH), which causes release of adrenocorticotropin.*

***3. Growth hormone–releasing hormone** (GHRH), which causes release of growth hormone, and growth hormone inhibitory hormone (GHIH), also called somatostatin, which inhibits release of growth hormone.*

***4. Gonadotropin-releasing hormone** (GnRH), which causes release of the two gonadotropic hormones, luteinizing hormone and follicle-stimulating hormone.*

***5. Prolactin inhibitory hormone** (PIH), which causes inhibition of prolactin secretion.*

There are some additional hypothalamic hormones, including one that stimulates prolactin secretion and perhaps others that inhibit release of the anterior pituitary hormones.

Physiological functions of growth hormone.

All the major anterior pituitary hormones, except for growth hormone, exert their principal effects by stimulating target glands, including thyroid gland, adrenal cortex, ovaries, testicles, and mammary glands. The functions of each of these pituitary hormones are so intimately concerned with the functions of the respective target glands that, except for growth hormone, their functions is not function through a target gland but exerts its effects directly on all or almost all tissues of the body.

Growth hormone promotes growth of many body tissues.

Growth hormone, also called somatotropic hormone or somatotropin, is a small protein molecule that contains 191 amino acids in a single chain It causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

Figure below shows typical weight charts of two growing littermate rats, one of which received daily injections of growth hormone and the other of which did not receive growth hormone. This figure shows marked enhancement of growth in the rat given growth hormone—in the early days of life and even after the two rats reached adulthood. In the early stages of development, all organs of the treated rat increased proportionately in size; after adulthood was reached, most of the bones stopped lengthening, but many of the soft tissues continued to grow. This result from the fact that once the epiphyses of the long bones have united with the shafts, further lengthening of bone cannot occur, even though most other tissues of the body can continue to grow throughout life.

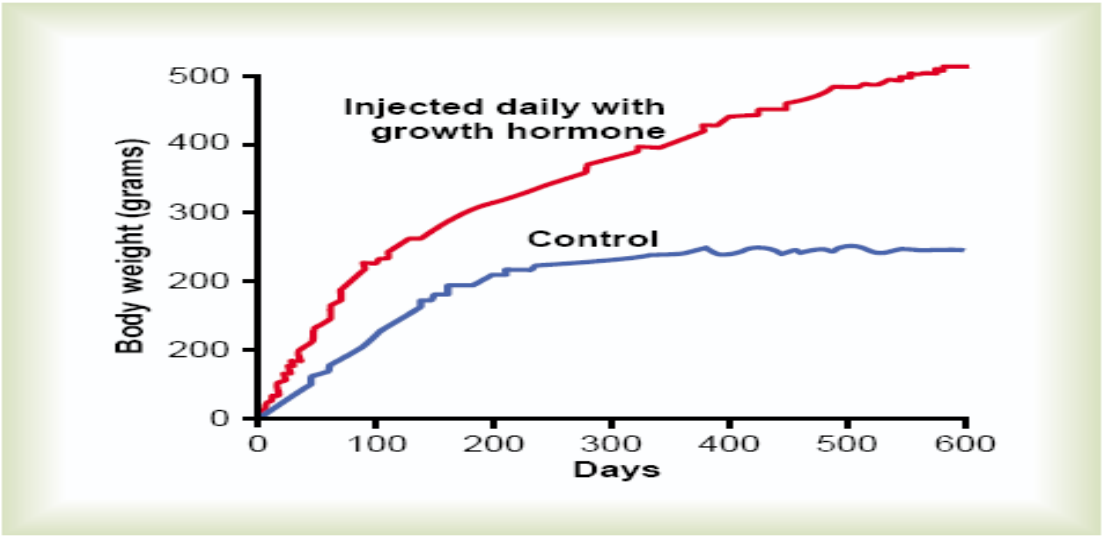


Figure 75–5

Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

Hormone secretion.

For many years it was believed that growth hormone was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue. After adolescence, secretion decreases slowly with aging, finally falling to about 25per cent of the adolescent level in very old age.

Growth hormone is secreted in a pulsatile pattern, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stresses are known to stimulate secretion:

***(1) Starvation**, especially with severe protein deficiency*

(2) Hypoglycemia or low concentration of fatty acids in the blood

(3) Exercise

(4) Excitement

***(5) Trauma**.*

Growth hormone also characteristically increases during the first 2 hours of deep sleep, as shown in following figure.

Figure 75–6

Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Table below summarizes some of the factors that are known to influence growth hormone secretion.

Factors That Stimulate or Inhibit Secretion of Growth Hormone

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Starvation or fasting, protein deficiency	Aging
Trauma, stress, excitement	Obesity
Exercise	Growth hormone inhibitory hormone (somatostatin)
Testosterone, estrogen	Growth hormone (exogenous)
Deep sleep (stages II and IV)	Somatomedins (insulin-like growth factors)
Growth hormone–releasing hormone	

Abnormalities of growth hormone secretion.

1. Panhypopituitarism.

This term means decreased secretion of all the anterior pituitary hormones. The decrease in secretion may be congenital (present from birth), or it may occur suddenly or slowly at any time during life, most often resulting from a pituitary tumor that destroys the pituitary gland.

2. Dwarfism.

Most instances of dwarfism result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood. In general, all the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child aged 4 to 5 years, and the same person at age 20 years may have the bodily development of a child aged 7 to 10 years. A person with panhypopituitary dwarfism does not pass through puberty and never secretes sufficient quantities of gonadotropic hormones to develop adult sexual functions. In one third of such dwarfs, however, only growth hormone is deficient; these persons do mature sexually and occasionally reproduce.

3. Gigantism.

Occasionally, the acidophilic, growth hormone–producing cells of the anterior pituitary gland become excessively active, and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones. If the condition

occurs before adolescence, before the epiphyses of the long bones have become fused with the shafts, height increases so that the person becomes a giant— up to 8 feet tall.

The giant ordinarily has hyperglycemia, and the beta cells of the islets of Langerhans in the pancreas are prone to degenerate because they become overactive owing to the hyperglycemia. Consequently, in about 10 per cent of giants, full-blown diabetes mellitus eventually develops. In most giants, panhypopituitarism eventually develops if they remain untreated, because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed. This eventual general deficiency of pituitary hormones usually causes death in early adulthood. However, once gigantism is diagnosed, further effects can often be blocked by microsurgical removal of the tumor or by irradiation of the pituitary gland.

4. Acromegaly.

If an acidophilic tumor occurs after adolescence— that is, after the epiphyses of the long bones have fused with the shafts—the person cannot grow taller, but the bones can become thicker and the soft tissues can continue to grow. This condition is known as acromegaly. Enlargement is especially marked in the bones of the hands and feet and in the membranous bones, including the cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone, and portions of the vertebrae, because their growth does not cease at adolescence. Consequently, the lower jaw protrudes forward, sometimes as much as half an inch, the forehead slants forward because of excess development of the supraorbital ridges, the nose increases to as much as twice normal size , and the fingers become extremely thickened so that the hands are almost twice normal size. In addition to these effects, changes in the vertebrae ordinarily cause a hunched back, which is known clinically as kyphosis. Finally, many soft tissue organs, such as the tongue, the liver, and especially the kidneys, become greatly enlarged.

Lec.3 ***Dr. Latief fayadh***

Posterior Pituitary Gland Hormones

The posterior pituitary gland, also called the neurohypophysis, is composed mainly of glial-like cells called pituicytes. The pituicytes do not secrete hormones; they act simply as a supporting structure for large numbers of terminal nerve fibers and terminal nerve endings from nerve tracts that originate in the supraoptic and paraventricular nuclei of the hypothalamus these tracts pass to the neurohypophysis through the pituitary stalk .The nerve endings are bulbous knobs that contain many secretory granules. These endings lie on the surfaces of capillaries, where they secrete their hormones.

Posterior pituitary hormones:

There are two hormones:

***(1) Antidiuretic hormone** (ADH), also called vasopressin.*

***(2) Oxytocin**.*

If the pituitary stalk is cut above the pituitary gland but the entire hypothalamus is left intact, the posterior pituitary hormones continue to be secreted normally, after a transient decrease for a few days; they are then secreted by the cut ends of the fibers within the hypothalamus and not by the nerve endings in the posterior pituitary. The reason for this is that the hormones are initially synthesized in the cell bodies of the supraoptic and paraventricular nuclei and are then transported in combination with "carrier" proteins down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

ADH is formed primarily in the supraoptic nuclei, whereas oxytocin is formed primarily in the paraventricular nuclei. Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone. When nerve impulses are transmitted downward along the fibers from the supraoptic or paraventricular nuclei, the hormone is immediately released from the secretory granules in the nerve endings by the usual secretory mechanism of exocytosis and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they are only loosely bound to each other, the hormone separates almost immediately. The neurophysin has no known function after leaving the nerve terminals.

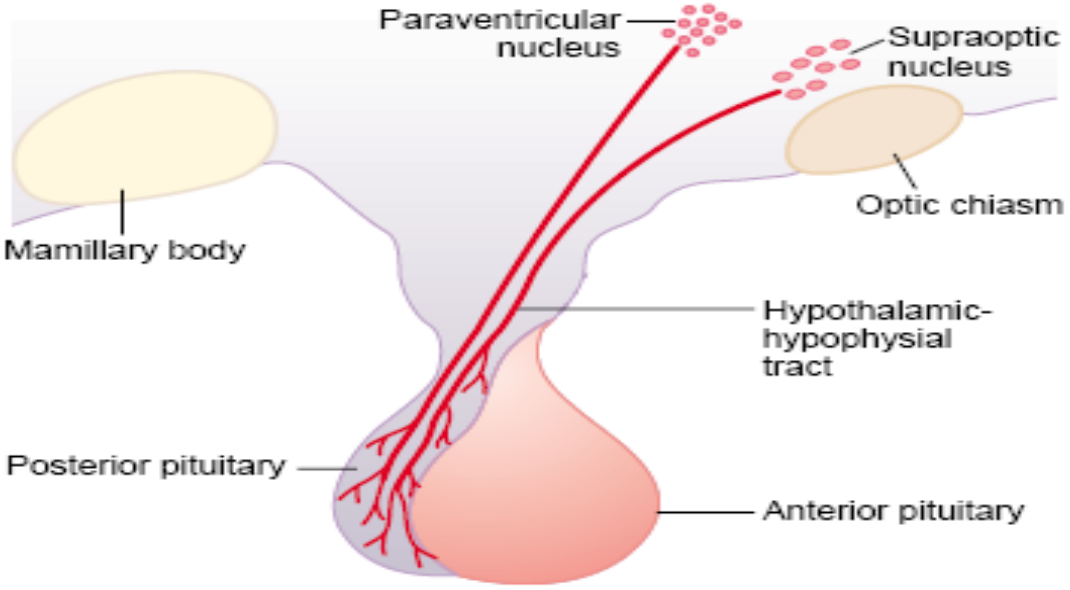


Figure 75–9

Hypothalamic control of the posterior pituitary.

Physiological functions of ADH.

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

*The precise mechanism by which ADH acts on the collecting ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells of the collecting ducts are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water permeable pores called **aquaporins**. When ADH acts on*

the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. All this occurs within 5 to 10 minutes. Then, in the absence of ADH, the entire process reverses in another 5 to 10 minutes. Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid through the tubular epithelial cells and into the renal interstitial fluid. Water is then absorbed from the collecting tubules and ducts by osmosis, in relation to the urine-concentrating mechanism of the kidneys.

Oxytocin hormone.

- Oxytocin causes contraction of the pregnant uterus.

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

(1) In a hypophysectomized animal, the duration of labor is prolonged, indicating a possible effect of oxytocin during delivery.

(2) The amount of oxytocin in the plasma increases during labor, especially during the last stage.

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

- Oxytocin aids in milk ejection by the breasts.

Oxytocin also plays an especially important role in lactation—a role that is far better understood than its role in delivery. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it by suckling.

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

Thyroid Metabolic Hormones

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults. The thyroid secretes two major hormones, ***thyroxine*** *and* ***triiodothyronine****, commonly called T4 and T3, respectively. Both of these hormones profoundly increase the metabolic rate of the body. Complete lack of thyroid secretion usually causes the basal metabolic rate to fall 40 to 50 per cent below normal, and extreme excesses of thyroid secretion can increase the basal metabolic rate to 60 to 100 per cent above normal. Thyroid secretion is controlled primarily by thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. The thyroid gland also secretes* ***calcitonin****, an important hormone for calcium metabolism which is discussed in the next lecture.*

Basal metabolic rate (BMR).

Even when a person is at complete rest, considerable energy is required to perform all the chemical reactions of the body. This minimum level of energy required to exist is called the basal metabolic rate (BMR) and accounts for about 50 - 70 % of the daily energy expenditure in most sedentary individuals.

Because the level of physical activity is highly variable among different individuals, measurement of the BMR provides a useful means of comparing one person's metabolic rate with that of another.

Measurement of BMR.

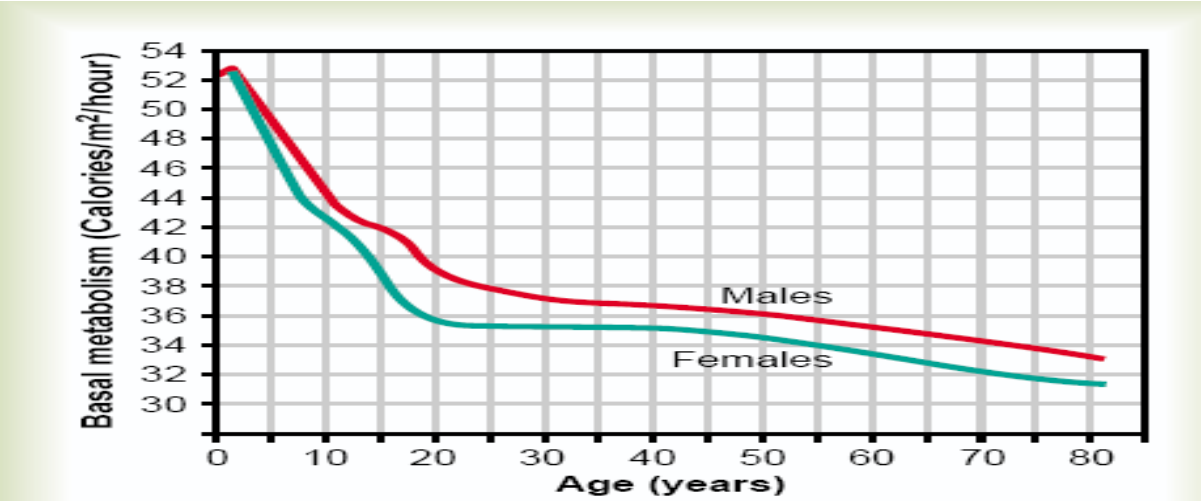
The usual method for determining BMR is to measure the rate of oxygen utilization over a given period of time under the following conditions:

1. The person must not have eaten food for at least 12 hours.
2. The BMR is determined after a night of restful sleep.
3. No strenuous activity is performed for at least 1 hour before the test.
4. All psychic and physical factors that cause excitement must be eliminated.
5. The temperature of the air must be comfortable and between 68° and 80°F.
6. No physical activity is permitted during the test.

The BMR normally averages about 65 to 70 Calories per hour in an average 70-kilogram man. Although much of the BMR is accounted for by essential activities of the central nervous system, heart, kidneys, and other organs, the variations in BMR among different individuals are related mainly to differences in the amount of skeletal muscle and body size. Skeletal muscle, even under resting conditions, accounts for 20 to 30 per cent of the BMR. For this reason, BMR is usually corrected for differences in body size by expressing it as Calories per hour per square meter of body surface area, calculated from height and weight. The average values for males and females of different ages are shown in figure below. Much of the decline in BMR with increasing age is probably related to loss of muscle mass and replacement of muscle with adipose tissue, which has a lower rate of metabolism. Likewise, slightly lower BMRs in women, compared with men, are due partly to their lower percentage of muscle mass and higher percentage of adipose tissue.

Factors alter the basal metabolic rate.

1. *Thyroid hormone increases BMR.*
2. *Male sex hormone increase BMR.*
3. *Growth hormone increases BMR.*
4. *Fever increases BMR.*
5. *Sleep decreases BMR.*
6. *Malnutrition decreases BMR.*



Synthesis and secretion of the thyroid metabolic hormones.

About 93 % of the metabolically active hormones secreted by the thyroid gland is thyroxine, and 7 % triiodothyronine. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

Physiologic anatomy of the thyroid gland.

The thyroid gland is composed of large numbers of closed follicles filled with a secretory substance called colloid and lined with cubical epithelial cells that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein thyroglobulin, which contains the thyroid hormones within its molecule. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex.

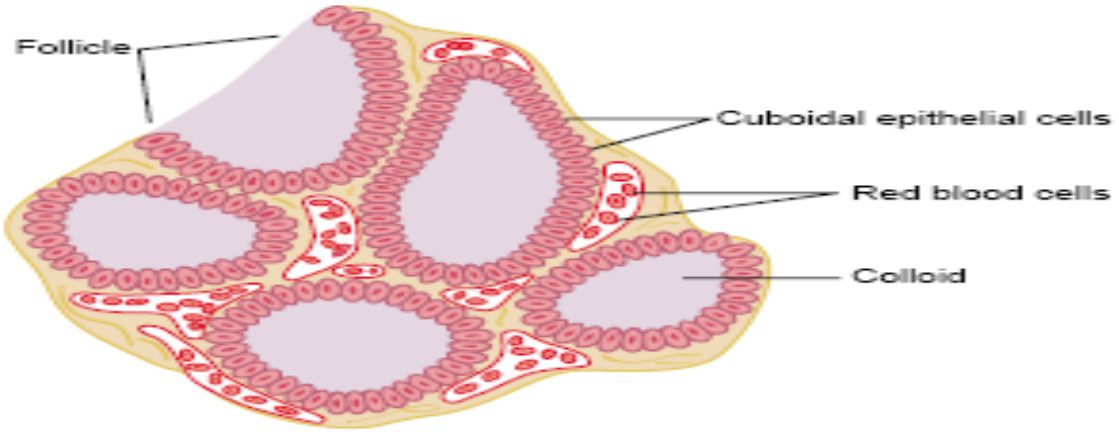


Figure 76–1

Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

Iodine is required for formation of thyroxin.

To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

- Fate of Ingested Iodides.

Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides. Normally, most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.

- Iodide pump (Iodide Trapping).

The first stage in the formation of thyroid hormones, shown in figure below, is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called ***iodide trapping****. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells.*

Formation and secretion of thyroglobulin by the thyroid cells.

The thyroid cells are typical protein-secreting glandular cells, as shown in figure below. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin, with a molecular weight of about 335,000. Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones

formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.

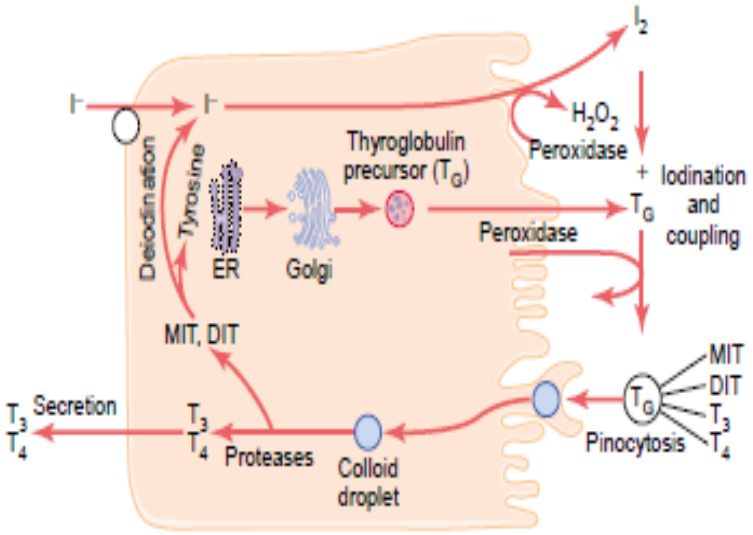


Figure 76–2

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.

Storage of Thyroglobulin.

The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

Release of T3 and T4 from the thyroid gland.

Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form pinocytic vesicles that enter the apex of the thyroid cell. Then lysosomes in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple proteases among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood.

About three quarters of the iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remains monoiodotyrosine and diiodotyrosine. During the digestion of the thyroglobulin molecule to cause release of thyroxine and triiodothyronine, these iodinated tyrosines also are freed from the thyroglobulin molecules. However, they are not secreted into the blood. Instead, their iodine is cleaved from them by a ***deiodinase enzyme*** *that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine-deficient because of failure of this recycling process.*

Thyroid Metabolic Hormones

Transport of thyroxine and triiodothyronine to tissues.

- Thyroxine and triiodothyronine are bound to plasma proteins.

On entering the blood, over 99 per cent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with thyroxine-binding globulin and much less so with thyroxine-binding prealbumin and albumin.

- Thyroxine and triiodothyronine are released slowly to tissue cells.

Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances— in particular, thyroxine are released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine—because of its lower affinity—is released to the cells in about 1 day.

On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks.

- Thyroid hormones have slow onset and long duration of action.

After injection of a large quantity of thyroxine into a human being, essentially no effect on the metabolic rate can be discerned for 2 to 3 days, thereby demonstrating that there is a long latent period before thyroxine activity begins. Once activity does begin, it increases progressively and reaches a maximum in 10 to 12 days, as shown in figure below. Thereafter, it decreases with a half-life of about 15 days. Some of the activity persists for as long as 6 weeks to 2 months.

The actions of triiodothyronine occur about four times as rapidly as those of thyroxine, with a latent period as short as 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days. Most of the latency and prolonged period of action of these hormones are probably caused by their binding with proteins both in the plasma and in the tissue cells, followed by their slow release.

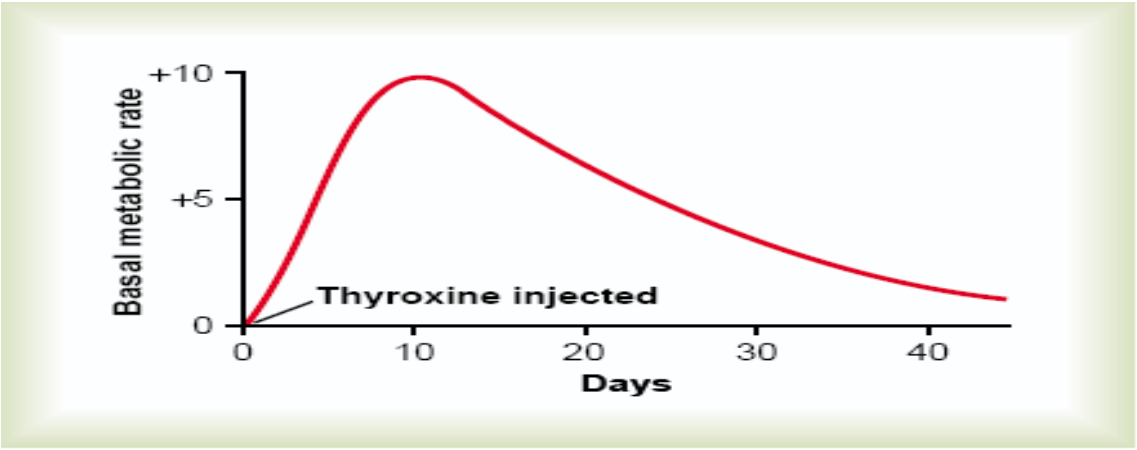


Figure 76–4

Approximate prolonged effect on the basal metabolic rate caused by administering a single large dose of thyroxine.

Thyroid hormones increase cellular metabolic activity.

The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 per cent above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated. Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased. The growth rate of young people is greatly accelerated. The mental processes are excited, and the activities of most of the other endocrine glands are increased.

Thyroid hormones increase the number and activity of mitochondria.

When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the animal's body increase in size as well as number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, one of the principal functions of thyroxine might be simply to increase the number and activity of mitochondria, which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. However, the increase in the number and activity of mitochondria could be the result of increased activity of the cells as well as the cause of the increase.

Thyroid hormones increase active transport of ions through cell membranes.

One of the enzymes that increases its activity in response to thyroid hormone is Na+-K+- ATPase. This in turn increases the rate of transport of both sodium and potassium ions through the cell membranes of some tissues. Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms by which thyroid hormone increases the body's metabolic rate. In fact, thyroid hormone also causes the cell membranes of most cells to become leaky to sodium ions, which further activates the sodium pump and further increases heat production.

Physiologic functions of the thyroid hormones.

1. Thyroid hormones increase the generalized functional activity throughout the body.

2. Thyroid hormones activate nuclear receptors.

3. Thyroid hormones increase cellular metabolic activity; the thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 per cent above normal when large quantities of the hormones are secreted.

4. Thyroid hormones increase the number and activity of mitochondria.

5. Thyroid hormones increase active transport of ions through cell membranes.

6. Effect of thyroid hormone on growth and development of body and brain during intrauterine life.

7. Effects of thyroid hormone on specific bodily mechanisms include:

A) Stimulation of carbohydrate metabolism.

B) Stimulation of fat metabolism.

C) Effect on plasma and liver fats. Increased thyroid hormone decreases the concentrations of cholesterol, phospholipids, and triglycerides in the plasma,
D) Increased requirement for vitamins.
E) Increased basal metabolic rate.
F) Decreased body weight. Greatly increased thyroid hormone almost always decreases the body weight, and greatly decreased hormone almost always increases the body weight.
G) Effect of thyroid hormones on the cardiovascular system.
H) Increased respiration.
I) Increased gastrointestinal motility.
J) Excitatory effects on the central nervous system.
K) Effect on the function of the muscles.
L) Muscle tremor.
M) Effect on sleep.
N) Effect on other endocrine glands.
O) Effect of thyroid hormone on sexual function.

Regulation of thyroid hormone secretion

To maintain normal levels of metabolic activity in the body, precisely the right amount of thyroid hormone must be secreted at all times; to achieve this, specific feedback mechanisms operate through the hypothalamus and anterior pituitary gland to control the rate of thyroid secretion. These mechanisms are as follows.

TSH Increases thyroid secretion.

TSH, also known as thyrotropin, is an anterior pituitary hormone this hormone increases the secretion of thyroxine and triiodothyronine by the thyroid gland. Its specific effects on the thyroid gland are as follows:
1. Increased proteolysis of the thyroglobulin that has already been stored in the follicles, with resultant release of the thyroid hormones into the circulating blood and diminishment of the follicular substance itself.
2. Increased activity of the iodide pump, which increases the rate of "iodide trapping" in the glandular cells, sometimes increasing the ratio of intracellular to extracellular iodide concentration in the glandular substance to as much as eight times normal.
3. Increased iodination of tyrosine to form the thyroid hormones.
4. Increased size and increased secretory activity of the thyroid cells.
5. Increased number of thyroid cells.
In summary, TSH increases all the known secretory activities of the thyroid glandular cells. The most important early effect after administration of TSH is to initiate proteolysis of the thyroglobulin, which causes release of thyroxine and triiodothyronine into the blood within 30 minutes. The other effects require hours or even days and weeks to develop fully.

Effects of cold and other neurogenic stimuli on TRH and TSH secretion.

One of the best-known stimuli for increasing the rate of TRH secretion by the hypothalamus, and therefore TSH secretion by the anterior pituitary gland, is exposure of an animal to cold. This effect almost certainly results from excitation of the hypothalamic centers for body temperature control. Exposure of rats for several weeks to severe cold increases the output of thyroid hormones sometimes to more than 100 per cent of normal and can increase the basal metabolic rate as much as 50 per cent. Indeed, persons moving to arctic regions have been known to develop basal metabolic rates 15 to 20 per cent above normal.
Various emotional reactions can also affect the output of TRH and TSH and therefore indirectly affect the secretion of thyroid hormones. Excitement and anxiety—conditions that greatly stimulate the sympathetic nervous system—cause an acute decrease in secretion of TSH, perhaps because these states increase the metabolic rate and body heat and therefore exert an inverse effect on the heat control center. Neither these

emotional effects nor the effect of cold is observed after the hypophysial stalk has been cut, demonstrating that both of these effects are mediated by way of the hypothalamus.

Feedback effect of thyroid hormone to decrease secretion of TSH.

Increased thyroid hormone in the body fluids decreases secretion of TSH by the anterior pituitary. When the rate of thyroid hormone secretion rises to about 1.75 times normal, the rate of TSH secretion falls essentially to zero. Almost all this feedback depressant effect occurs even when the anterior pituitary has been separated from the hypothalamus. Therefore, as shown in figure below it is probable that increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by a direct effect on the anterior pituitary gland itself. Regardless of the mechanism of the feedback, its effect is to maintain an almost constant concentration of free thyroid hormones in the circulating body fluids.

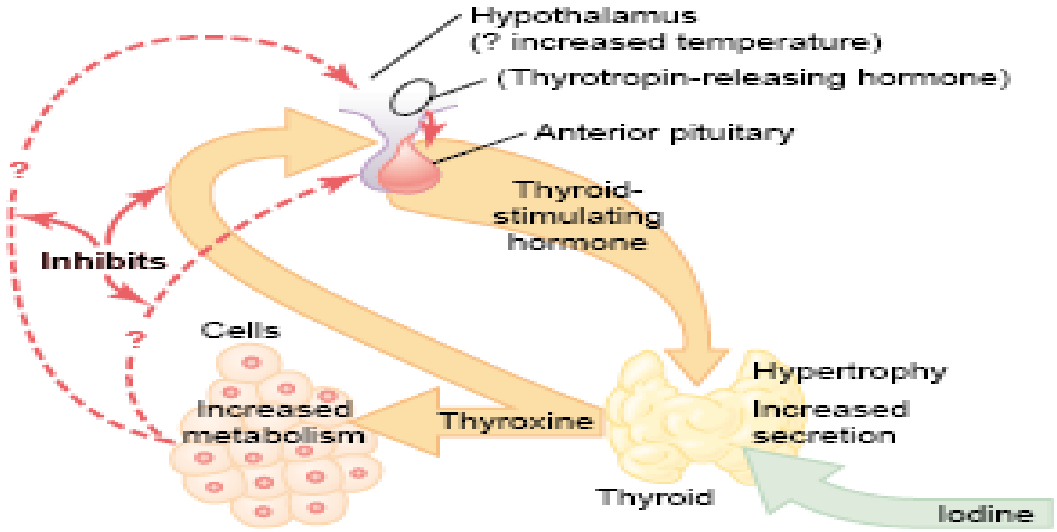


Figure 76–7

Regulation of thyroid secretion.

Diseases of the Thyroid:

1. Hyperthyroidism (Toxic Goiter, Thyrotoxicosis, Graves' disease).

Most effects of hyperthyroidism are obvious from the various physiologic effects of thyroid hormone However, some specific effects is mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism.

- Causes of Hyperthyroidism

Thyroid gland is increased to two to three times normal size, with tremendous hyperplasia and infolding of the follicular cell lining into the follicles, so that the number of cells is increased greatly. Also, each cell increases its rate of secretion severalfold; radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates 5 to15 times normal. The changes in the thyroid gland in most instances are similar to those caused by excessive TSH. However, plasma TSH concentrations are less than normal rather than enhanced in almost all patients and often are essentially zero.

- Symptoms of Hyperthyroidism

The symptoms of hyperthyroidism are:

(1) High state of excitability.
(2) Intolerance to heat.
(3) Increased sweating.
(4) Mild to extreme weight loss.
(5) Varying degrees of diarrhea.
(6) Muscle weakness.

(7) Nervousness or other psychic disorders.
(8) Extreme fatigue but inability to sleep.
(9) Tremor of the hands.
(10) Exophthalmos. Most people with hyperthyroidism develop some degree of protrusion of the eyeballs.

2. Hypothyroidism:

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism, but there are a few physiologic mechanisms peculiar to hypothyroidism. Hypothyroidism, like hyperthyroidism, probably is initiated by autoimmunity against the thyroid gland, but immunity that destroys the gland rather than stimulates it. The thyroid glands of most of these patients first have autoimmune "thyroiditis," which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called thyroid goiter.

3. Cretinism

*Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood. This condition is characterized especially by failure of body growth and by mental retardation. It results from congenital lack of a thyroid gland (**congenital cretinism**), from failure of the thyroid gland to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (**endemic cretinism**). The severity of endemic cretinism varies greatly, depending on the amount of iodine in the diet. A neonate without a thyroid gland may have normal appearance and function because it was supplied with some (but usually not enough) thyroid hormone by the mother while in utero, but a few weeks after birth, the neonate's movements become sluggish and both physical and mental growth begin to be greatly retarded. Treatment of the neonate with cretinism at any time with adequate iodine or thyroxine usually causes normal return of physical growth, but unless the cretinism is treated within a few weeks after birth, mental growth remains permanently retarded.*
Skeletal growth in the child with cretinism is characteristically more inhibited than is soft tissue growth. As a result of this disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the child with cretinism an obese, stocky, and short appearance. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the child.

4. Myxedema.

Myxedema develops in the patient with almost total lack of thyroid hormone function. The patient, developing bagginess under the eyes and swelling of the face. In this condition, for reasons not explained, greatly increased quantities of hyaluronic acid and chondroitin sulfate bound with protein form excessive tissue gel in the interstitial spaces and this causes the total quantity of interstitial fluid to increase. Because of the gel nature of the excess fluid, it is mainly immobile, and the edema is the non pitting type.

Calcium, Phosphate and Vitamin D Metabolism

The physiology of calcium and phosphate metabolism, formation of bone and teeth, and regulation of vitamin D, parathyroid hormone (PTH), and calcitonin are all closely intertwined. Extracellular calcium ion concentration, for example, is determined by the interplay of calcium absorption from the intestine, renal excretion of calcium, and bone uptake and release of calcium, each of which is regulated by the hormones just noted. Because phosphate homeostasis and calcium homeostasis are closely associated, they are discussed together.

Overview of Ca and Ph regulation in the E.C.F. and plasma:

Extracellular fluid calcium concentration normally is regulated very precisely, seldom rising or falling more than a few per cent from the normal value. This precise control is essential, because calcium plays a key role in many physiologic processes, including contraction of skeletal, cardiac, and smooth muscles; blood clotting; and transmission of nerve impulses, to name just a few. Excitable cells, such as neurons, are very sensitive to changes in calcium ion concentrations, and increases in calcium ion concentration above normal (hypercalcemia) cause progressive depression of the nervous system; conversely, decreases in calcium concentration (hypocalcemia) cause the nervous system to become more excited.

An important feature of extracellular calcium regulation is that only about 0.1 % of the total body calcium is in the extracellular fluid, about 1 % is in the cells, and the rest is stored in bones. Therefore, the bones can serve as large reservoirs, releasing calcium when extracellular fluid concentration decreases and storing excess calcium. Approximately 85 % of the body's phosphate is stored in bones, 14 to 15 % is in the cells, and less than 1 per cent is in the extracellular fluid. Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.

Calcium in the plasma and interstitial fluid.

The calcium in the plasma is present in three forms:

(1) About 41 %) of the calcium is combined with the plasma proteins and in this form is non diffusible through the capillary membrane.

(2) About 9 %of the calcium is diffusible through the capillary membrane but is combined with anionic substances of the plasma and interstitial fluids (citrate and phosphate, for instance) in such a manner that it is not ionized.

(3) The remaining 50 % of the calcium in the plasma is both diffusible through the capillary membrane and ionized. Thus, the plasma and interstitial fluids have a normal calcium ion concentration of about 1.2 mol/L, a level only one half the total plasma calcium concentration. This ionic calcium is the form that is important for most functions of calcium in the body, including the effect of calcium on the heart, the nervous system, and bone formation.

Inorganic phosphate in the extracellular fluids.

Inorganic phosphate in the plasma is mainly in two forms: $HPO4^{-}$ and $H2PO4^{-}$. The concentration of $HPO4^{-}$ is about 1.05 mmol/L, and the concentration of $H2PO4^{-}$ is about 0.26 mmol/L. When the total quantity of phosphate in the extracellular fluid rises, so does the quantity of each of these two types of phosphate ions. Furthermore, when the pH of the extracellular fluid becomes more acidic, there is a relative increase in $H2PO4^{-}$ and a decrease in $HPO4^{-}$, whereas the opposite occurs when the extracellular fluid becomes alkaline. Because it is difficult to determine chemically the exact quantities of

$HPO4^-$ and $H2PO4^-$ in the blood, ordinarily the total quantity of phosphate is expressed in terms of milligrams of phosphorus per deciliter (100 ml) of blood. The average total quantity of inorganic phosphorus represented by both phosphate ions is about 4 mg/dl, varying between normal limits of 3 to 4 mg/dl in adults and 4 to 5 mg/dl in children.

Physiologic effects of altered Ca and Ph concentrations in the body fluids.

Changing the level of phosphate in the extracellular fluid from far below normal to two to three times normal does not cause major immediate effects on the body. In contrast, even slight increases or decreases of calcium ion in the extracellular fluid can cause extreme immediate physiologic effects. In addition, chronic hypocalcemia or hypophosphatemia greatly decreases bone mineralization.

- Hypocalcemia causes nervous system excitement and tetany.

When the extracellular fluid concentration of calcium ions falls below normal, the nervous system becomes progressively more excitable, because this causes increased neuronal membrane permeability to sodium ions, allowing easy initiation of action potentials. At plasma calcium ion concentrations about 50 per cent below normal, the peripheral nerve fibers become so excitable that they begin to discharge spontaneously, initiating trains of nerve impulses that pass to the peripheral skeletal muscles to elicit tetanic muscle contraction. Consequently, hypocalcemia causes tetany. It also occasionally causes seizures because of its action of increasing excitability in the brain.

Figure below shows tetany in the hand, which usually occurs before tetany develops in most other parts of the body. This is called ***"carpopedal spasm."*** *Tetany ordinarily occurs when the blood concentration of calcium falls from its normal level of 9.4 mg/dl to about 6 mg/dl, which is only 35 per cent below the normal calcium concentration, and it is usually lethal at about 4 mg/dl.*

In laboratory animals, in which calcium can gradually be reduced beyond the usual lethal levels, very extreme hypocalcemia can cause other effects that are seldom evident in patients, such as marked dilatation of the heart, changes in cellular enzyme activities, increased membrane permeability in some cells (in addition to nerve cells), and impaired blood clotting.

- Hypercalcemia depresses nervous system and muscle activity.

When the level of calcium in the body fluids rises above normal, the nervous system becomes depressed and reflex activities of the central nervous system are sluggish. Also, increased calcium ion concentration decreases the QT interval of the heart and causes lack of appetite and constipation, probably because of depressed contractility of the muscle walls of the gastrointestinal tract.

These depressive effects begin to appear when the blood level of calcium rises above about 12 mg/dl, and they can become marked as the calcium level rises above 15 mg/dl. When the level of calcium rises above about 17 mg/dl in the blood, calcium phosphate crystals are likely to precipitate throughout the body.

Absorption and excretion of Ca and Ph.

- Intestinal absorption and fecal excretion of Ca and Ph.

The usual rates of intake are about 1000 mg/day each for calcium and phosphorus, about the amounts in 1 liter of milk. Normally, divalent cations such as calcium ions are poorly absorbed from the intestines. However, vitamin D promotes calcium absorption by the intestines, and about 35 per cent (350 mg/day) of the ingested calcium is usually absorbed; the calcium remaining in the intestine is excreted in the feces. An additional 250 mg/day of calcium enters the intestines via secreted gastrointestinal juices and sloughed mucosal cells. Thus, about 90 per cent (900 mg/day) of the daily intake of calcium is excreted in the feces (Figure below).

Intestinal absorption of phosphate occurs very easily. Except for the portion of phosphate that is excreted in the feces in combination with non-absorbed calcium, almost all the dietary phosphate is absorbed into the blood from the gut and later excreted in the urine.

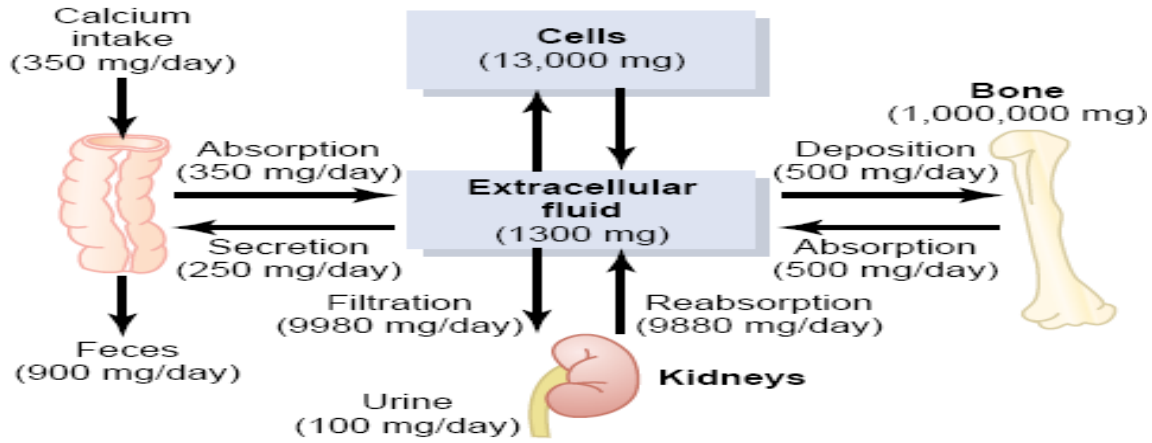


Figure 79–3

Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

- Renal excretion of Ca and Ph.

Approximately 10 per cent (100 mg/day) of the ingested calcium is excreted in the urine. About 41 per cent of the plasma calcium is bound to plasma proteins and is therefore not filtered by the glomerular capillaries. The rest is combined with anions such as phosphate (9 per cent) or ionized (50 per cent) and is filtered through the glomeruli into the renal tubules. Normally, the renal tubules reabsorb 99 per cent of the filtered calcium, and about 100 mg/day is excreted in the urine. When calcium concentration is low, this reabsorption is great, so that almost no calcium is lost in the urine. Conversely, even a minute increase in blood calcium ion concentration above normal increases calcium excretion markedly.

*Renal phosphate excretion is controlled by an **overflow mechanism**, That is, when phosphate concentration in the plasma is below the critical value of about 1 mmol/L, all the phosphate in the glomerular filtrate is reabsorbed and no phosphate is lost in the urine. But above this critical concentration, the rate of phosphate loss is directly proportional to the additional increase. Thus, the kidneys regulate the phosphate concentration in the extracellular fluid by altering the rate of phosphate excretion in accordance with the plasma phosphate concentration and the rate of phosphate filtration by the kidneys. However, PTH can greatly increase phosphate excretion by the kidneys, thereby playing an important role in the control of plasma phosphate concentration as well as calcium concentration.*

Bone and its relation to extracellular Ca and Ph.

Bone is composed of a tough organic matrix that is greatly strengthened by deposits of calcium salts. Average compact bone contains by weight about 30 % matrix and 70 % salts. Newly formed bone may have a considerably higher percentage of matrix in relation to salts.

-Organic matrix of bone.

The organic matrix of bone is 90 to 95 % collagen fibers, and the remainder is a homogeneous gelatinous medium called ground substance. The collagen fibers extend primarily along the lines of tensional force and give bone its powerful tensile strength. The ground substance is composed of extracellular fluid plus proteoglycans, especially chondroitin sulfate and hyaluronic acid. The precise function of each of these is not known, although they do help to control the deposition of calcium salts.

-Bone salts.

The crystalline salts deposited in the organic matrix of bone are composed principally of calcium and phosphate. Magnesium, sodium, potassium, and carbonate ions are also present among the bone salts, although x-ray diffraction studies fail to show definite crystals formed by them. Therefore, they are believed to be conjugated to the hydroxyapatite crystals rather than organized into distinct crystals of their own. This ability of many types of ions to conjugate to bone crystals extends to many ions normally foreign to bone, such as strontium, uranium, plutonium, the other transuranic elements, lead, gold, other heavy metals, and at least 9 of 14 of the major radioactive products released by explosion of the hydrogen bomb. Deposition of radioactive substances in the bone can cause prolonged irradiation of the bone tissues, and if a sufficient amount is deposited, an osteogenic sarcoma (bone cancer) eventually develops in most cases.

Calcium exchange between bone and extracellular fluid.

If soluble calcium salts are injected intravenously, the calcium ion concentration may increase immediately to high levels. However, within 30 minutes to 1 hour or more, the calcium ion concentration returns to normal. Likewise, if large quantities of calcium ions are removed from the circulating body fluids, the calcium ion concentration again returns to normal within 30 minutes to about 1 hour. These effects result in great part from the fact that the bone contains a type of exchangeable calcium that is always in equilibrium with the calcium ions in the extracellular fluids.

A small portion of this exchangeable calcium is also the calcium found in all tissue cells, especially in highly permeable types of cells such as those of the liver and the gastrointestinal tract. However, most of the exchangeable calcium is in the bone. It normally amounts to about 0.4 to 1 per cent of the total bone calcium. This calcium is deposited in the bones in a form of readily mobilizable salt such as CaHPO4 and other amorphous calcium salts. The importance of exchangeable calcium is that it provides a rapid buffering mechanism to keep the calcium ion concentration in the extracellular fluids from rising to excessive levels or falling to very low levels under transient conditions of excess or decreased availability of calcium.

Deposition and absorption of bone—remodeling of bone

- Deposition of bone by the osteoblasts.

Bone is continually being deposited by osteoblasts, and it is continually being absorbed where osteoclasts are active (Figure below). Osteoblasts are found on the outer surfaces of the bones and in the bone cavities. A small amount of osteoblastic activity occurs continually in all living bones (on about 4 per cent of all surfaces at any given time in an adult), so that at least some new bone is being formed constantly.

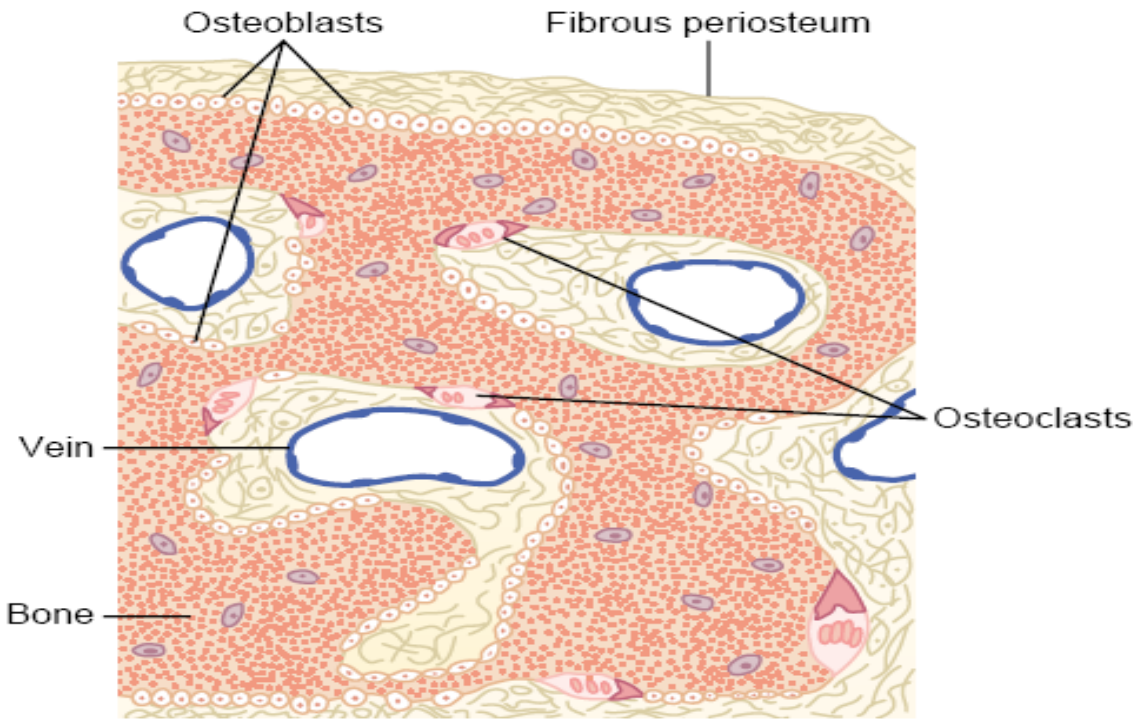


Figure 79–4

Osteoblastic and osteoclastic activity in the same bone.

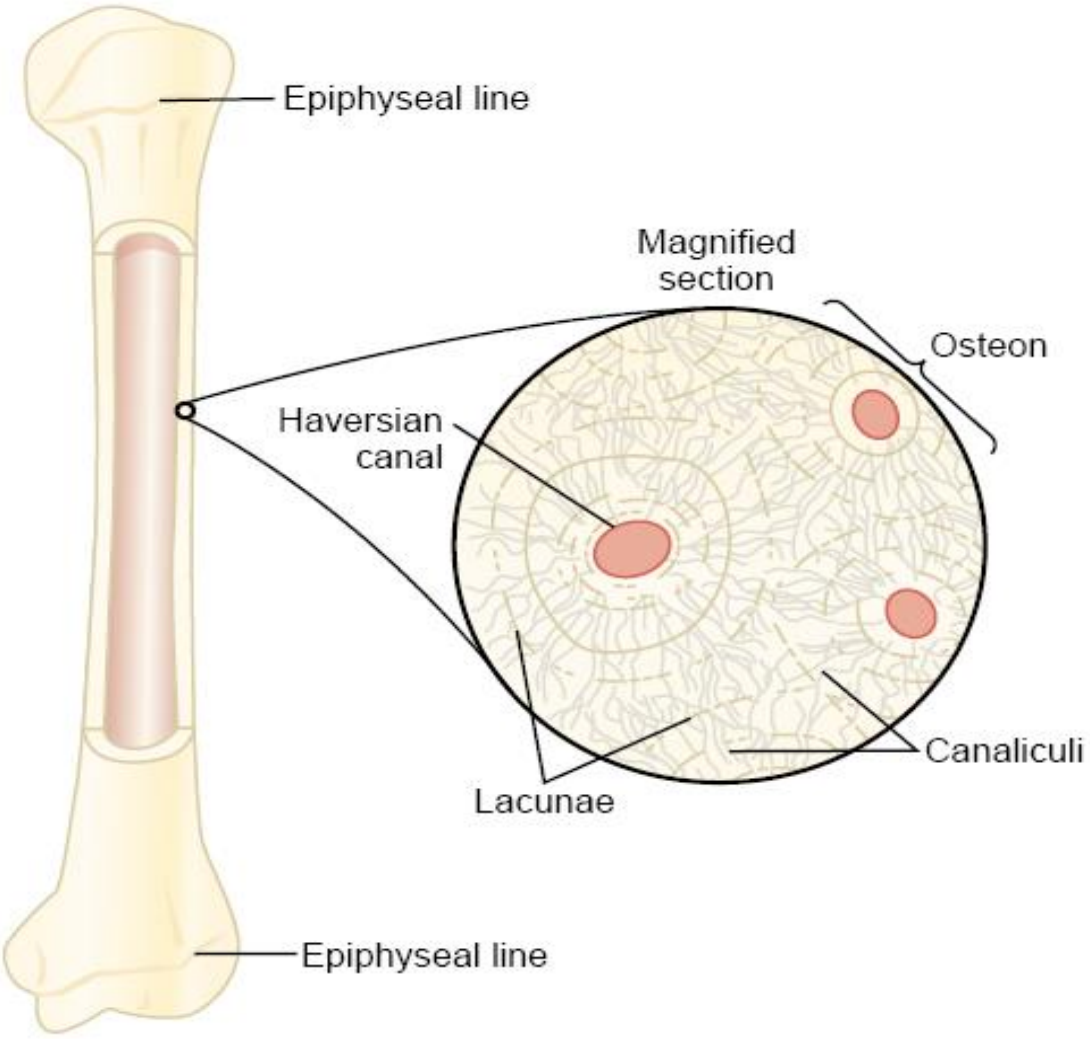
- *Absorption of bone—function of the osteoclasts.*

Bone is also being continually absorbed in the presence of osteoclasts, which are large phagocytic, multinucleated cells (as many as 50 nuclei). The osteoclasts are normally active on less than 1 per cent of the bone surfaces of an adult. Later we see that PTH controls the bone absorptive activity of osteoclasts.

Histologically, bone absorption occurs immediately adjacent to the osteoclasts. The mechanism of this absorption is believed to be by the secretion of proteolytic enzymes and several acids including citric and lactic acids. The enzymes digest or dissolve the organic matrix of the bone, and the acids cause solution of the bone salts. The osteoclastic cells also imbibe by phagocytosis minute particles of bone matrix and crystals, eventually also dissoluting these and releasing the products into the blood.

- *Bone deposition and absorption are normally in equilibrium.*

Normally, except in growing bones, the rates of bone deposition and absorption are equal to each other, so that the total mass of bone remains constant. Osteoclasts usually exist in small but concentrated masses, and once a mass of osteoclasts begins to develop, it usually eats away at the bone for about 3 weeks, creating a tunnel that ranges in diameter from 0.2 to 1 millimeter and is several millimeters long. At the end of this time, the osteoclasts disappear and the tunnel is invaded by osteoblasts instead; then new bone begins to develop. Bone deposition then continues for several months, the new bone being laid down in successive layers of concentric circles (lamellae) on the inner surfaces of the cavity until the tunnel is filled. Deposition of new bone ceases when the bone begins to encroach on the blood vessels supplying the area. The canal through which these vessels run, called the ***haversian canal****, is all that remains of the original cavity. Each new area of bone deposited in this way is called an* ***osteon****.*


Epiphyseal line
Magnified section
Osteon
Haversian canal
Canaliculi
Lacunae
Epiphyseal line

Value of continual bone remodeling.

The continual deposition and absorption of bone have several physiologically important functions.

1. Bone ordinarily adjusts its strength in proportion to the degree of bone stress. Consequently, bones thicken when subjected to heavy loads.

2. Even the shape of the bone can be rearranged for proper support of mechanical forces by deposition and absorption of bone in accordance with stress patterns.

3. Because old bone becomes relatively brittle and weak, new organic matrix is needed as the old organic matrix degenerates. In this manner, the normal toughness of bone is maintained. Indeed, the bones of children, in whom the rates of deposition and absorption are rapid, show little brittleness in comparison with the bones of the elderly, in whom the rates of deposition and absorption are slow.

- Control of the rate of bone deposition by bone "Stress."

Bone is deposited in proportion to the compressional load that the bone must carry. For instance, the bones of athletes become considerably heavier than those of non-athletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30 per cent decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified. Therefore, continual physical stress stimulates osteoblastic deposition and calcification of bone. Bone stress also determines the shape of bones under certain circumstances. For instance, if a long bone of the leg breaks in its center and then heals at an angle, the compression stress on the inside of the angle causes increased deposition of bone, and increased absorption occurs on the outer side of the angle where the bone is not compressed. After many years of increased deposition on the inner side of the angulated bone and absorption on the outer side, the bone can become almost straight, especially in children because of the rapid remodeling of bone at younger ages.

- Repair of a fracture activates osteoblasts.

Fracture of a bone in some way maximally activates all the periosteal and intraosseous osteoblasts involved in the break. Also, immense numbers of new osteoblasts are formed almost immediately from osteoprogenitor cells, which are bone stem cells in the surface tissue lining bone, called the "bone membrane." Therefore, within a short time, a large bulge of osteoblastic tissue and new organic bone matrix, followed shortly by the deposition of calcium salts, develops between the two broken ends of the bone. This is called a ***callus.***

Many bone surgeons use the phenomenon of bone stress to accelerate the rate of fracture healing. This is done by use of special mechanical fixation apparatuses for holding the ends of the broken bone together so that the patient can continue to use the bone immediately. This causes stress on the opposed ends of the broken bones, which accelerates osteoblastic activity at the break and often shortens convalescence.

Vitamin D

Vitamin D has a potent effect to increase calcium absorption from the intestinal tract; it also has important effects on both bone deposition and bone absorption, however, vitamin D itself is not the active substance that actually causes these effects. Instead, vitamin D must first be converted through a succession of reactions in the liver and the kidneys to the final active product, 1, 25-dihydroxycholecalciferol, also called 1, 25$(OH)_2D_3$. The succession of steps that lead to the formation of this substance from vitamin D is as follows:

1. Cholecalciferol (Vitamin D3) is formed in the skin.

Several compounds derived from vitamin D family, and they all perform more or less the same functions. Vitamin D3 (also called cholecalciferol) is the most important of these and is formed in the skin as a result of irradiation of 7-dehydrocholesterol, a substance normally in the skin, by ultraviolet rays from the sun. Consequently, appropriate exposure to the sun prevents vitamin D deficiency. The additional vitamin D

compounds that we ingest in food are identical to the cholecalciferol formed in the skin, except for the substitution of one or more atoms that do not affect their function.

2. Cholecalciferol is converted to 25-Hydroxycholecalciferol in the liver.

The first step in the activation of cholecalciferol is to convert it to 25-hydroxycholecalciferol; this occurs in the liver. The process is a limited one, because the 25-hydroxycholecalciferol has a feedback inhibitory effect on the conversion reactions. This feedback effect is extremely important for two reasons.

First, *the feedback mechanism precisely regulates the concentration of 25-hydroxycholecalciferol in the plasma, the intake of vitamin D3 can increase many times and yet the concentration of 25-hydroxycholecalciferol remains nearly normal. This high degree of feedback control prevents excessive action of vitamin D when intake of vitamin D3 is altered over a wide range.*

Second, *this controlled conversion of vitamin D3 to 25-hydroxycholecalciferol conserves the vitamin D stored in the liver for future use. Once it is converted, it persists in the body for only a few weeks, whereas in the vitamin D form, it can be stored in the liver for many months.*

3. Formation of 1, 25-Dihydroxycholecalciferol in the kidneys.

The conversion in the proximal tubules of the kidneys of 25-hydroxycholecalciferol to 1, 25-dihydroxycholecalciferol, which is the most active form of vitamin D. The conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol requires PTH. In the absence of PTH, almost none of the 1,25-dihydroxycholecalciferol is formed. Therefore, PTH exerts a potent influence in determining the functional effects of vitamin D in the body.

4. Ca ion concentration controls the formation of 1, 25-Dihydroxycholecalciferol.

The plasma concentration of 1, 25-dihydroxycholecalciferol is inversely affected by the concentration of calcium in the plasma. There are two reasons for this.

1. The calcium ion itself has a slight effect in preventing the conversion of 25-hydroxycholecalciferol to 1, 25-dihydroxycholecalciferol.

2. The rate of secretion of PTH is greatly suppressed when the plasma calcium ion concentration rises above 9 to 10 mg/100 ml. Therefore, at calcium concentrations below this level, PTH promotes the conversion of 25- hydroxycholecalciferol to 1,25-dihydroxycholecalciferol in the kidneys.

When the plasma calcium concentration is already too high, the formation of 1,25-dihydroxycholecalciferol is greatly depressed. Lack of this in turn decreases the absorption of calcium from the intestines, the bones, and the renal tubules, thus causing the calcium ion concentration to fall back toward its normal level.

Actions of vitamin D

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

1. Hormonal effect of vitamin D to promote intestinal calcium absorption.

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

2. Vitamin D promotes phosphate absorption by the intestines.

Although phosphate is usually absorbed easily, phosphate flux through the gastrointestinal epithelium is enhanced by vitamin D. It is believed that this results from a direct effect of 1,25-dihydroxycholecalciferol,

but it is possible that it results secondarily from this hormone's action on calcium absorption, the calcium in turn acting as a transport mediator for the phosphate.

3. Vitamin D decreases renal calcium and phosphate excretion.

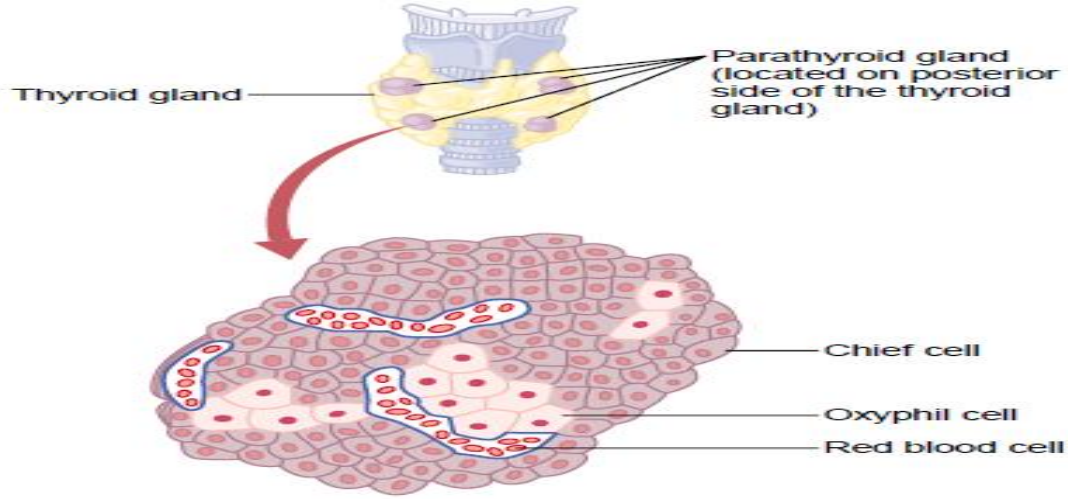
Vitamin D also increases calcium and phosphate absorption by the epithelial cells of the renal tubules, thereby tending to decrease excretion of these substances in the urine. However, this is a weak effect and probably not of major importance in regulating the extracellular fluid concentration of these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

4. Effect of vitamin D on bone and its relation to parathyroid hormone activity.

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

Parathyroid Hormone

Parathyroid hormone provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating intestinal reabsorption, renal excretion, and exchange between the extracellular fluid and bone of these ions. Excess activity of the parathyroid gland causes rapid absorption of calcium salts from the bones, with resultant hypercalcemia in the extracellular fluid; conversely, hypofunction of the parathyroid glands causes hypocalcemia, often with resultant tetany.



Physiologic anatomy of the parathyroid glands.

Normally there are four parathyroid glands in humans; they are located immediately behind the thyroid gland one behind each of the upper and each of the lower poles of the thyroid. Each parathyroid gland is about 6 millimeters long, 3 millimeters wide, and 2 millimeters thick and has a macroscopic appearance of dark brown fat. The parathyroid glands are difficult to locate during thyroid operations because they often look like just another lobule of the thyroid gland. For this reason, before the importance of these glands was generally recognized, total or subtotal thyroidectomy frequently resulted in removal of the parathyroid glands as well. Removal of half the parathyroid glands usually causes no major physiologic abnormalities. However, removal of three of the four normal glands causes transient hypoparathyroidism. But even a small quantity of remaining parathyroid tissue is usually capable of hypertrophying satisfactorily to perform the function of all the glands. The parathyroid gland of the adult human being, shown in Figure above, contains mainly chief cells and a small to moderate number of oxyphil cells, but oxyphil cells are absent in many animals and in young humans. The chief cells are believed to secrete most, if not all, of the PTH. The function of the oxyphil cells is not certain, but they are believed to be modified or depleted chief cells that no longer secrete hormone.

Chemistry of parathyroid hormone.

PTH has been isolated in a pure form. It is first synthesized on the ribosomes in the form of a preprohormone, a polypeptide chain of 110 amino acids. This is cleaved first to a prohormone with 90 amino acids, then to the hormone itself with 84 amino acids by the endoplasmic reticulum and Golgi apparatus, and finally is packaged in secretory granules in the cytoplasm of the cells. The final hormone has a molecular weight of about 9500. Smaller compounds with as few as 34 amino acids adjacent to the N terminus of the molecule have also been isolated from the parathyroid glands that exhibit full PTH activity. In fact, because the kidneys rapidly remove the whole 84-amino acid hormone within minutes but fail to remove many of the fragments for hours, a large share of the hormonal activity is caused by the fragments.

Effect of PTH on Ca and Ph concentrations in the E.C.F.

Figure below shows the approximate effects on the blood calcium and phosphate concentrations caused by suddenly infusing PTH into an animal and continuing this for several hours. Note that at the onset of infusion the calcium ion concentration begins to rise and reaches a plateau in about 4 hours. The phosphate concentration, however, falls more rapidly than the calcium rises and reaches a depressed level within 1 or 2 hours. The rise in calcium concentration is caused principally by two effects:

(1) An effect of PTH to increase calcium and phosphate absorption from the bone.

(2) A rapid effect of PTH to decrease the excretion of calcium by the kidneys.

The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.

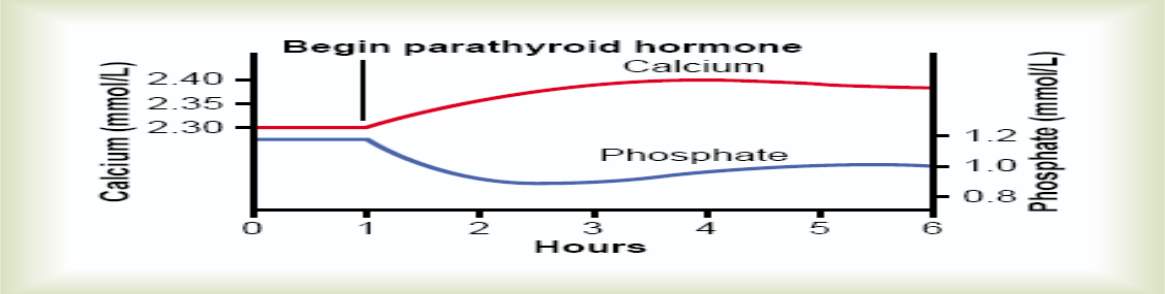


Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

A. PTH increases Ca and Ph absorption from the bone.

PTH has two effects on bone in causing absorption of calcium and phosphate. One is a rapid phase that begins in minutes and increases progressively for several hours. This phase results from activation of the already existing bone cells (mainly the osteocytes) to promote calcium and phosphate absorption. The second phase is a much slower one, requiring several days or even weeks to become fully developed; it results from proliferation of the osteoclasts, followed by greatly increased osteoclastic reabsorption of the bone itself, not merely absorption of the calcium phosphate salts from the bone.

B. PTH decreases Ca excretion and increases Ph excretion by the kidneys.

Administration of PTH causes rapid loss of phosphate in the urine owing to the effect of the hormone to diminish proximal tubular reabsorption of phosphate ions. PTH also increases renal tubular reabsorption of

calcium at the same time that it diminishes phosphate reabsorption. Moreover, it increases the rate of reabsorption of magnesium ions and hydrogen ions while it decreases the reabsorption of sodium, potassium,

and amino acid ions in much the same way that it affects phosphate. The increased calcium absorption occurs mainly in the late distal tubules, the collecting tubules, the early collecting ducts, and possibly the ascending loop of Henle to a lesser extent. Were it not for the effect of PTH on the kidneys to increase

calcium reabsorption, continual loss of calcium into the urine would eventually deplete both the extracellular fluid and the bones of this mineral.

Control of parathyroid secretion by ion concentration.

Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes; if the decreased calcium concentration persists, the glands will hypertrophy, sometimes fivefold or more. For instance, the parathyroid glands become greatly enlarged in:

(1) Rickets, in which the level of calcium is usually depressed only a small amount.

(2) Pregnancy, even though the decrease in calcium ion concentration in the mother's extracellular fluid is hardly measurable.

(3) During lactation because calcium is used for milk formation.

Conversely, conditions that increase the calcium ion concentration above normal cause decreased activity and reduced size of the parathyroid glands. Such conditions include

(1) Excess quantities of calcium in the diet.

(2) Increased vitamin D in the diet.

(3) Bone absorption caused by factors other than PTH (for example, bone absorption caused by disuse of the bones).

Calcitonin

Calcitonin secreted by the thyroid gland, tends to decrease plasma calcium concentration and, in general, has effects opposite to those of PTH. However, the quantitative role of calcitonin is far less than that of PTH in regulating calcium ion concentration. Synthesis and secretion of calcitonin occur in the parafollicular cells, or C cells, lying in the interstitial fluid between the follicles of the thyroid gland. These cells constitute only about 0.1 % of the human thyroid gland and are the remnants of the ultimo brachial glands of lower animals such as fish, amphibians, reptiles, and birds. Calcitonin is a 32-amino acid peptide with a molecular weight of about 3400.

Increased plasma calcium concentration stimulates calcitonin secretion.

The primary stimulus for calcitonin secretion is increased plasma calcium ion concentration. This contrasts with PTH secretion, which is stimulated by decreased calcium concentration. In young animals, but much less so in older animals and in humans, an increase in plasma calcium concentration of about 10 per cent causes an immediate twofold or more increase in the rate of secretion of calcitonin. This provides a second hormonal feedback mechanism for controlling the plasma calcium ion concentration, but one that is relatively weak and works in a way opposite that of the PTH system.

Lec.7 **Dr.latief fayadh**

Pathophysiology of parathyroid hormone, vitamin D, and bone disease.

A. Hypoparathyroidism

When the parathyroid glands do not secrete sufficient PTH, the osteocytic reabsorption of exchangeable calcium decreases and the osteoclasts become almost totally inactive. As a result, calcium reabsorption from the bones is so depressed that the level of calcium in the body fluids decreases. Yet, because calcium and phosphates are not being absorbed from the bone, the bone usually remains strong. When the parathyroid glands are suddenly removed, the calcium level in the blood falls from the normal of 9.4 mg/dl to 6 to 7 mg/dl within 2 to 3 days, and the blood phosphate concentration may double. When this low calcium level is reached, the usual signs of tetany develop. Among the muscles of the body especially sensitive to tetanic spasm are the laryngeal muscles. Spasm of these muscles obstructs respiration, which is the usual cause of death in tetany unless appropriate treatment is applied.

Treatment of hypoparathyroidism with PTH and Vitamin D.

PTH is occasionally used for treating hypoparathyroidism. However, because of the expense of this hormone, because its effect lasts for a few hours at most, and because the tendency of the body to develop antibodies against it makes it progressively less and less effective, hypoparathyroidism is usually not treated with PTH administration. In most patients with hypothyroidism, the administration of extremely large quantities of vitamin D, to as high as 100,000 units per day, along with intake of 1 to 2 grams of calcium, keeps the calcium ion concentration in a normal range. At times, it might be necessary to administer 1, 25-dihydroxycholecalciferol instead of the nonactivated form of vitamin D because of its much more potent and much more rapid action. This can also cause unwanted effects, because it is sometimes difficult to prevent overactivity by this activated form of vitamin D.

B. Primary hyperparathyroidism

In primary hyperparathyroidism, an abnormality of the parathyroid glands causes inappropriate, excess PTH secretion. The cause of primary hyperparathyroidism ordinarily is a tumor of one of the parathyroid glands; such tumors occur much more frequently in women than in men or children, mainly because pregnancy and lactation stimulate the parathyroid glands and therefore predispose to the development of such a tumor. Hyperparathyroidism causes extreme osteoclastic activity in the bones. This elevates the calcium ion concentration in the extracellular fluid while usually depressing the concentration of phosphate ions because of increased renal excretion of phosphate.

- Formation of kidney stones in hyperparathyroidism

Most patients with mild hyperparathyroidism show few signs of bone disease and few general abnormalities as a result of elevated calcium, but they do have an extreme tendency to form kidney stones. The reason is that the excess calcium and phosphate absorbed from the intestines or mobilized from the bones in hyperparathyroidism must eventually be excreted by the kidneys, causing a proportionate increase in the concentrations of these substances in the urine. As a result, crystals of calcium phosphate tend to precipitate in the kidney, forming calcium phosphate stones. Also, calcium oxalate stones develop because even normal levels of oxalate cause calcium precipitation at high calcium levels. Because the solubility of most renal stones is slight in alkaline media, the tendency for formation of renal calculi is considerably greater in alkaline urine than in acid urine. For this reason, acidotic diets and acidic drugs are frequently used for treating renal calculi.

C. Secondary hyperparathyroidism

In secondary hyperparathyroidism, high levels of PTH occur as a compensation for hypocalcemia rather than as a primary abnormality of the parathyroid glands. This contrasts with primary hyperparathyroidism, which is associated with hypercalcemia. Secondary hyperparathyroidism can be caused by vitamin D deficiency or chronic renal disease in which the damaged kidneys are unable to produce sufficient amounts of the active form of vitamin D, the vitamin D deficiency leads to osteomalacia (inadequate mineralization of the bones), and high levels of PTH cause absorption of the bones.

D. Rickets—vitamin D deficiency

Rickets occurs mainly in children. It results from calcium or phosphate deficiency in the extracellular fluid, usually caused by lack of vitamin D. If the child is adequately exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementation in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

- Treatment of rickets.

The treatment of rickets depends on supplying adequate calcium and phosphate in the diet and, equally important, on administering large amounts of vitamin D. If vitamin D is not administered, little calcium and phosphate are absorbed from the gut.

- Osteomalacia "Adult Rickets".

Adults seldom have a serious dietary deficiency of vitamin D or calcium because large quantities of calcium are not needed for bone growth as in children. However, serious deficiencies of both vitamin D and calcium occasionally occur as a result of steatorrhea (failure to absorb fat) because vitamin D is fat-soluble and calcium tends to form insoluble soaps with fat; consequently, in steatorrhea, both vitamin D and calcium tend to pass into the feces. Under these conditions, an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, although this almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

- Osteomalacia and rickets caused by renal disease." Renal rickets"

A type of osteomalacia that results from prolonged kidney damage. The cause of this condition is mainly failure of the damaged kidneys to form, the active form of vitamin D. In patients whose kidneys have been removed or destroyed and who are being treated by hemodialysis, the problem of renal rickets is often a severe one.

E. Osteoporosis (decreased bone Matrix).

Osteoporosis is the most common of all bone diseases in adults, especially in old age. It is different from osteomalacia and rickets because it results from diminished organic bone matrix rather than from poor bone calcification. In osteoporosis the osteoblastic activity in the bone usually is less than normal, and consequently the rate of bone osteoid deposition is depressed. But occasionally, as in hyperparathyroidism, the causes of the osteoporosis are:

(1) Lack of physical stress on the bones because of inactivity.

(2) Malnutrition to the extent that sufficient protein matrix cannot be formed.

(3) Lack of vitamin C, which is necessary for the secretion of intercellular substances by all cells, including formation of osteoid by the osteoblasts.

(4) Postmenopausal lack of estrogen secretion because estrogens decrease the number and activity of osteoclasts.

(5) Old age, in which growth hormone and other growth factors diminish greatly, plus the fact that many of the protein anabolic functions also deteriorate with age, so that bone matrix cannot be deposited satisfactorily

(6) Cushing's syndrome because massive quantities of glucocorticoids secreted in this disease cause decreased deposition of protein throughout the body and increased catabolism of protein and have the specific effect of depressing osteoblastic activity. Thus, many diseases of deficiency of protein metabolism can cause osteoporosis.

Physiology of the Teeth

The teeth cut, grind, and mix the food eaten. To perform these functions, the jaws have powerful muscles capable of providing an occlusive force between the front teeth of 50 to 100 pounds and for the jaw teeth, 150 to 200 pounds. Also, the upper and lower teeth are provided with projections and facets that interdigitate, so that the upper set of teeth fits with the lower. This fitting is called occlusion, and it allows even small particles of food to be caught and ground between the tooth surfaces.

Function of the different parts of the teeth.

Figure below shows a sagittal section of a tooth, demonstrating its major functional parts: the enamel, dentin, cementum, and pulp. The tooth can also be divided into the crown, which is the portion that protrudes out from the gum into the mouth, and the root, which is the portion within the bony socket of the jaw. The collar between the crown and the root where the tooth is surrounded by the gum is called the neck.

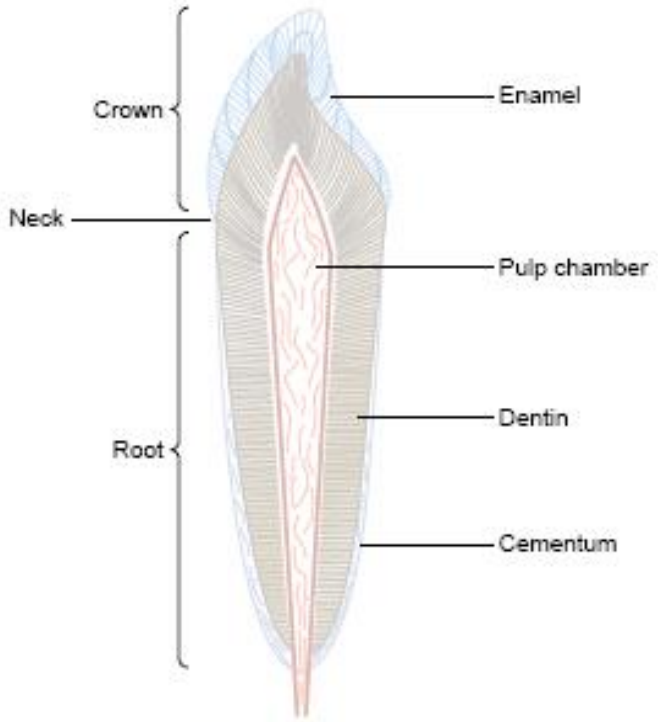


Figure 79–12

Functional parts of a tooth.

1. Enamel.

The outer surface of the tooth is covered by a layer of enamel that is formed before eruption of the tooth by special epithelial cells called ameloblasts. Once the tooth has erupted, no more enamel is formed. Enamel is composed of very large and very dense crystals of hydroxyapatite with adsorbed carbonate, magnesium, sodium, potassium, and other ions imbedded in a fine meshwork of strong and almost insoluble protein fibers that are similar in physical characteristics (but not chemically identical) to the keratin of hair. The crystalline structure of the salts makes the enamel extremely hard-much harder than the dentin. Also, the special protein fiber meshwork, although constituting only about 1 per cent of the enamel mass, makes enamel resistant to acids, enzymes, and other corrosive agents because this protein is one of the most insoluble and resistant proteins known.

2. Dentin.

The main body of the tooth is composed of dentin, which has a strong, bony structure. Dentin is made up principally of hydroxyapatite crystals similar to those in bone but much more dense. These crystals are imbedded in a strong meshwork of collagen fibers. In other words, the principal constituents of dentin are very much the same as those of bone. The major difference is its histological organization, because dentin does not contain any osteoblasts, osteocytes, osteoclasts, or spaces for blood vessels or nerves. Instead, it is deposited and nourished by a layer of cells called odontoblasts, which line its inner surface along the wall of the pulp cavity. The calcium salts in dentin make it extremely resistant to compressional forces, and the collagen fibers make it tough and resistant to tensional forces that might result when the teeth are struck by solid objects.

3. Cementum.

Cementum is a bony substance secreted by cells of the periodontal membrane, which lines the tooth socket. Many collagen fibers pass directly from the bone of the jaw, through the periodontal membrane, and then into the cementum. These collagen fibers and the cementum hold the tooth in place. When the teeth are exposed to excessive strain, the layer of cementum becomes thicker and stronger. Also, it increases in thickness and strength with age, causing the teeth to become more firmly seated in the jaws by adulthood and later.

4. Pulp.

The pulp cavity of each tooth is filled with pulp, which is composed of connective tissue with an abundant supply of nerve fibers, blood vessels, and lymphatics. The cells lining the surface of the pulp cavity are the odontoblasts, which, during the formative years of the tooth, lay down the dentin but at the same time encroach more and more on the pulp cavity, making it smaller. In later life, the dentin stops growing and the pulp cavity remains essentially constant in size. However, the odontoblasts are still viable and send projections into small dentinal tubules that penetrate all the way through the dentin; they are of importance for exchange of calcium, phosphate, and other minerals with the dentin.

Dentition:

Humans and most other mammals develop two sets of teeth during a lifetime. The first teeth are called the deciduous teeth, or milk teeth, and they number 20 in humans. They erupt between the 7th month and the 2nd year of life, and they last until the 6th to the 13th year. After each deciduous tooth is lost, a permanent tooth replaces it, and an additional 8 to 12 molars appear posteriorly in the jaws, making the total number of permanent teeth 28 to 32, depending on whether the four wisdom teeth finally appear, which does not occur in everyone.

Eruption of teeth.

During early childhood, the teeth begin to protrude outward from the bone through the oral epithelium into the mouth. The cause of "eruption"is unknown, although several theories have been offered in an attempt to explain this phenomenon. The most likely theory is that growth of the tooth root as well as of the bone underneath the tooth progressively shoves the tooth forward.

Development of the permanent teeth.

During embryonic life, a tooth-forming organ also develops in the deeper dental lamina for each permanent tooth that will be needed after the deciduous teeth are gone. These tooth-producing organs slowly form the permanent teeth throughout the first 6 to 20 years of life. When each permanent tooth becomes fully formed, it, like the deciduous tooth, pushes outward through the bone. In so doing, it erodes the root of the deciduous tooth and eventually causes it to loosen and fall out. Soon thereafter, the permanent tooth erupts to take the place of the original one.

Metabolic factors influence development of the teeth.

The rate of development and the speed of eruption of teeth can be accelerated by both thyroid and growth hormones. Also, the deposition of salts in the early forming teeth is affected considerably by various factors of metabolism, such as the availability of calcium and phosphate in the diet, the amount of vitamin D present, and the rate of PTH secretion. When all these factors are normal, the dentin and enamel will be correspondingly healthy, but when they are deficient, the calcification of the teeth also may be defective, so that the teeth will be abnormal throughout life.

Dental abnormalities

The two most common dental abnormalities are caries and malocclusion. Caries refers to erosion of the teeth, whereas malocclusion is failure of the projections of the upper and lower teeth to interdigitate properly.

1. Caries and the role of bacteria and ingested carbohydrates.

It is generally agreed that caries result from the action of bacteria on the teeth, the most common of which is Streptococcus mutans. The first event in the development of caries is the deposit of plaque, a film of precipitated products of saliva and food, on the teeth. Large numbers of bacteria inhabit this plaque and are readily available to cause caries. These bacteria depend to a great extent on carbohydrates for their food. When carbohydrates are available, their metabolic systems are strongly activated and they multiply. In addition, they form acids (particularly lactic acid) and proteolytic enzymes. The acids are the major culprit in causing caries because the calcium salts of teeth are slowly dissolved in a highly acidic medium. And once the salts have become absorbed, the remaining organic matrix is rapidly digested by the proteolytic enzymes. The enamel of the tooth is the primary barrier to the development of caries. Enamel is

far more resistant to demineralization by acids than is dentin, primarily because the crystals of enamel are dense, but also because each enamel crystal is about 200 times as large in volume as each dentin crystal. Once the carious process has penetrated through the enamel to the dentin, it proceeds many times as rapidly because of the high degree of solubility of the dentin salts. Because of the dependence of the caries bacteria on carbohydrates for their nutrition, it has frequently been taught that eating a diet high in carbohydrate content will lead to excessive development of caries. However, it is not the quantity of carbohydrate ingested but the frequency with which it is eaten that is important. If carbohydrates are eaten in many small parcels throughout the day, such as in the form of candy, the bacteria are supplied with their preferential metabolic substrate for many hours of the day, and the development of caries is greatly increased.

- Role of fluorine in preventing caries.

Teeth formed in children who drink water that contains small amounts of fluorine develop enamel that is more resistant to caries than the enamel in children who drink water that does not contain fluorine. Fluorine does not make the enamel harder than usual, but fluorine ions replace many of the hydroxyl ions in the hydroxyapatite crystals, which in turn makes the enamel several times less soluble. Fluorine may also be toxic to the bacteria. Finally, when small pits do develop in the enamel, fluorine is believed to promote deposition of calcium phosphate to "heal" the enamel surface. Regardless of the precise means by which fluorine protects the teeth, it is known that small amounts of fluorine deposited in enamel make teeth about three times as resistant to caries as teeth without fluorine.

2. Malocclusion.

Malocclusion is usually caused by a hereditary abnormality that causes the teeth of one jaw to grow to abnormal positions. In malocclusion, the teeth do not interdigitate properly and therefore cannot perform their normal grinding or cutting action adequately. Malocclusion occasionally also results in abnormal displacement of the lower jaw in relation to the upper jaw, causing such undesirable effects as pain in the mandibular joint and deterioration of the teeth. The orthodontist can usually correct malocclusion by applying prolonged gentle pressure against the teeth with appropriate braces. The gentle pressure causes absorption of alveolar jaw bone on the compressed side of the tooth and deposition of new bone on the tensional side of the tooth. In this way, the tooth gradually moves to a new position as directed by the applied pressure.

Pancreatic Hormones

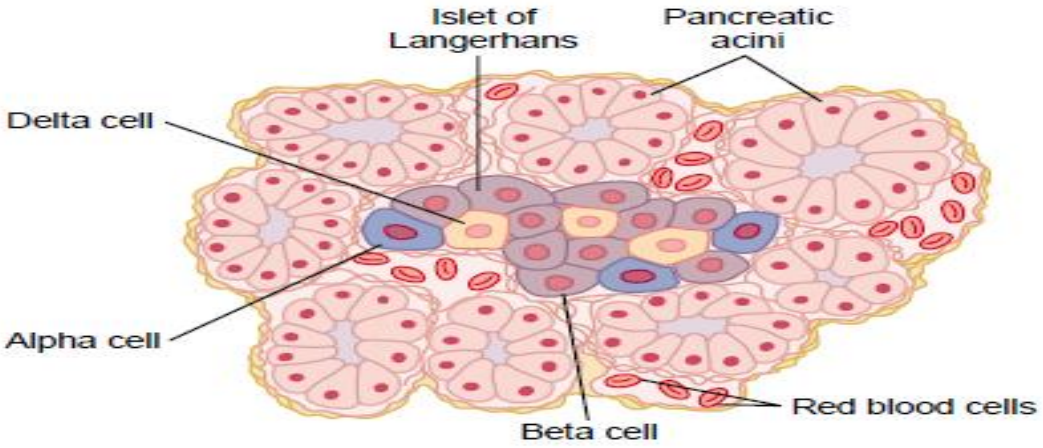
The pancreas, in addition to its digestive functions, secretes two important hormones, insulin and glucagon, that are crucial for normal regulation of glucose, lipid, and protein metabolism. Although the pancreas secretes other hormones, such as amylin, somatostatin, and pancreatic polypeptide, their functions are not as well established.

Physiologic anatomy of the pancreas.

The pancreas is composed of two major types of tissues, as shown in figure below:

(1) The acini, which secrete digestive juices into the duodenum.

(2) The islets of Langerhans, which secrete insulin and glucagon directly into the blood. The human pancreas has 1 to 2 million islets of Langerhans, each only about 0.3 millimeter in diameter and organized around small capillaries into which its cells secrete their hormones. The islets contain three major types of cells, alpha, beta, and delta cells, which are distinguished from one another by their morphological and staining characteristics. The beta cells, constituting about 60 per cent of all the cells of the islets, lie mainly in the middle of each islet and secrete insulin and amylin, a hormone that is often secreted in parallel with insulin, although its function is unclear. The alpha cells, about 25 per cent of the total, secrete glucagon. And the delta cells, about 10 per cent of the total, secrete somatostatin. In addition, at least one other type of cell, the PP cell, is present in small numbers in the islets and secretes a hormone of uncertain function called pancreatic polypeptide. The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, insulin inhibits glucagon secretion, amylin inhibits insulin secretion, and somatostatin inhibits the secretion of both insulin and glucagon.



Insulin and its metabolic effects.

Insulin was first isolated from the pancreas in 1922 by Banting and Best, and almost overnight the outlook for the severely diabetic patient changed from one of rapid decline and death to that of a nearly normal person. Historically, insulin has been associated with "blood sugar," and true enough, insulin has profound effects on carbohydrate metabolism. Yet it is abnormalities of fat metabolism, causing such conditions as acidosis and arteriosclerosis, that are the usual causes of death in diabetic patients. Also, in patients with prolonged diabetes, diminished ability to synthesize proteins leads to wasting of the tissues as well as many cellular functional disorders. Therefore, it is clear that insulin affects fat and protein metabolism almost as much as it does carbohydrate metabolism.

Insulin is a hormone associated with energy abundance.

It will become apparent that insulin secretion is associated with energy abundance. That is, when there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin is secreted in great quantity. In turn, the insulin plays an important role in storing the excess energy. In the case of excess carbohydrates, it causes them to be stored as glycogen mainly in the liver and muscles. Also, all the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in the adipose tissue. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. In addition, it inhibits the breakdown of the proteins that are already in the cells.

A. Effect of insulin on carbohydrate metabolism

Immediately after a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin, The insulin in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body, but especially by the muscles, adipose tissue, and liver.

- Insulin promotes muscle glucose uptake and metabolism

During much of the day, muscle tissue depends not on glucose for its energy but on fatty acids. The principal reason for this is that the normal resting muscle membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.

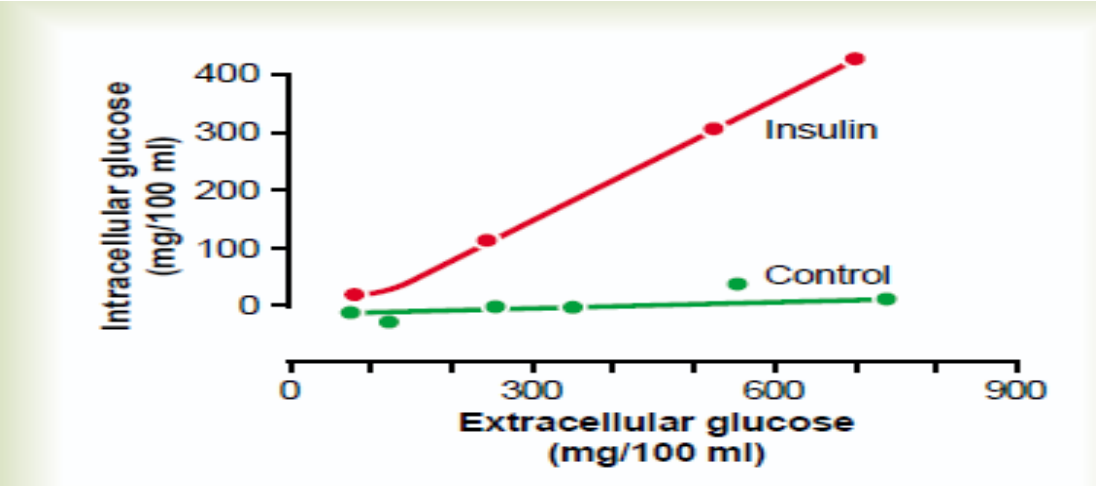
However, under two conditions the muscles do use large amounts of glucose. ***One*** *of these is during moderate or heavy exercise. This usage of glucose does not require large amounts of insulin, because exercising muscle fibers become more permeable to glucose even in the absence of insulin because of the contraction process itself.* ***The second*** *condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin. The extra insulin causes rapid transport of glucose into the muscle cells. This causes the muscle cell during this period to use glucose preferentially over fatty acids.*

- Storage of glycogen in muscle.

If the muscles are not exercising after a meal and yet glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of muscle glycogen instead of being used for

energy, up to a limit of 2 to 3 per cent concentration. The glycogen can later be used for energy by the muscle.

The quantitative effect of insulin to facilitate glucose transport through the muscle cell membrane is demonstrated by the experimental results shown in figure below. The lower curve labeled "control" shows the concentration of free glucose measured inside the cell, demonstrating that the glucose concentration remained almost zero despite increased extracellular glucose concentration up to as high as 750 mg/100 ml. In contrast, the curve labeled "insulin" demonstrates that the intracellular glucose concentration rose to as high as 400 mg/100 ml when insulin was added. Thus, it is clear that insulin can increase the rate of transport of glucose into the resting muscle cell by at least 15-fold.



- Lack of effect of insulin on glucose uptake and usage by the brain

The brain is quite different from most other tissues of the body in that insulin has little effect on uptake or use of glucose. Instead, the brain cells are permeable to glucose and can use glucose without the intermediation of insulin. The brain cells are also quite different from most other cells of the body in that they normally use only glucose for energy and can use other energy substrates, such as fats, only with difficulty. Therefore, it is essential that the blood glucose level always be maintained above a critical level, which is one of the most important functions of the blood glucose control system. When the blood glucose falls too low, into the range of 20 to 50 mg/100 ml, symptoms of hypoglycemic shock develop, characterized by progressive nervous irritability that leads to fainting, seizures, and even coma.

B. Effect of insulin on fat metabolism

Although not quite as visible as the acute effects of insulin on carbohydrate metabolism, insulin's effects on fat metabolism are, in the long run, equally important. Especially dramatic is the long-term effect of insulin lack in causing extreme atherosclerosis, often leading to heart attacks, cerebral strokes, and other vascular accidents. Insulin has several effects that lead to fat storage in adipose tissue. First, insulin increases the utilization of glucose by most of the body's tissues, which automatically decreases the utilization of fat, thus functioning as a fat sparer. However, insulin also promotes fatty acid synthesis. This is especially true when more carbohydrates are ingested than can be used for immediate energy, thus providing the substrate for fat synthesis. Almost all this synthesis occurs in the liver cells, and the fatty acids are then transported from the liver by way of the blood lipoproteins to the adipose cells to be stored.

C. Effect of Insulin on Protein Metabolism and on Growth

During the few hours after a meal when excess quantities of nutrients are available in the circulating blood, not only carbohydrates and fats but proteins as well are stored in the tissues; insulin is required for this to occur. The manner in which insulin causes protein storage is not as well understood as the mechanisms for both glucose and fat storage. Some of the facts follow.

1. Insulin stimulates transport of many of the amino acids into the cells.

2. Insulin increases the translation of messenger RNA, thus forming new proteins.

3. Insulin inhibits the catabolism of proteins, thus decreasing the rate of amino acid release from the cells.

4. In the liver, insulin depresses the rate of gluconeogenesis.

In summary, insulin promotes protein formation and prevents the degradation of proteins.

Glucagon and its functions

Glucagon, a hormone secreted by the alpha cells of the islets of Langerhans when the blood glucose concentration falls, has several functions that are diametrically opposed to those of insulin. Most important of these functions is to increase the blood glucose concentration, an effect that is exactly the opposite that of insulin. Like insulin on injection of purified glucagon into an animal, a profound hyperglycemic effect occurs. Only 1 mg/kg of glucagon can elevate the blood glucose concentration about 20 mg/100 ml of blood (a 25 per cent increase) in about 20 minutes. For this reason, glucagon is also called the hyperglycemic hormone.

The major effects of glucagon on glucose metabolism are

(1) Breakdown of liver glycogen (glycogenolysis).

(2) Increased gluconeogenesis in the liver.

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

Regulation of glucagon secretion

A. Increased blood glucose inhibits glucagon secretion.

The blood glucose concentration is by far the most potent factor that controls glucagon secretion. Note specifically, however, that the effect of blood glucose concentration on glucagon secretion is in exactly the opposite direction from the effect of glucose on insulin secretion.

This is demonstrated in figure below, showing that a decrease in the blood glucose concentration from its normal fasting level of about 90 mg/100 ml of blood down to hypoglycemic levels can increase the plasma concentration of glucagon severalfold. Conversely, increasing the blood glucose to hyperglycemic levels decreases plasma glucagon. Thus, in hypoglycemia, glucagon is secreted in large amounts; it then greatly increases the output of glucose from the liver and thereby serves the important function of correcting the hypoglycemia.

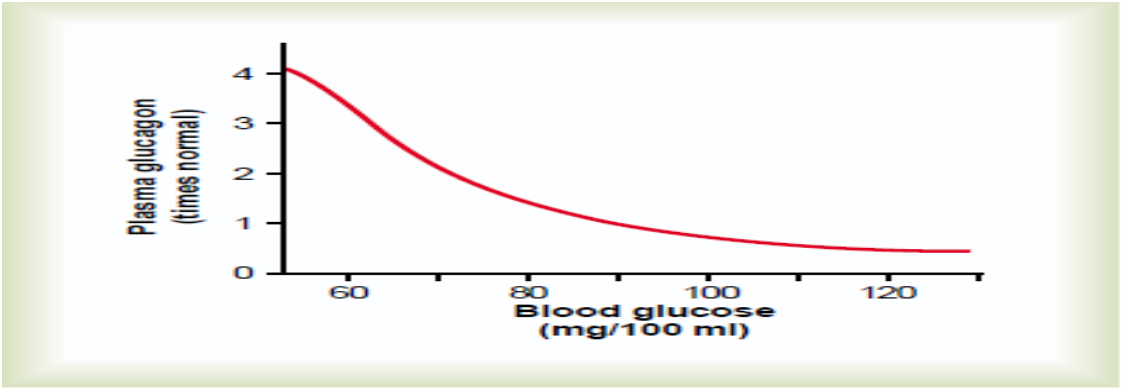


Figure 78–10

Approximate plasma glucagon concentration at different blood glucose levels.

B. Increased blood amino acids stimulate glucagon secretion.

High concentrations of amino acids, as occur in the blood after a protein meal stimulate the secretion of glucagon. This is the same effect that amino acids have in stimulating insulin secretion. Thus, in this instance, the glucagon and insulin responses are not opposites. The importance of amino acid stimulation of glucagon secretion is that the glucagon then promotes rapid conversion of the amino acids to glucose, thus making even more glucose available to the tissues.

C. Exercise stimulates glucagon secretion.

In exhaustive exercise, the blood concentration of glucagon often increases fourfold to fivefold. What causes this is not understood, because the blood glucose concentration does not necessarily fall. A beneficial effect of the glucagon is that it prevents a decrease in blood glucose. One of the factors that might increase glucagon secretion in exercise is increased circulating amino acids. Other factors, such as β-adrenergic stimulation of the islets of Langerhans, may also play a role.

Somatostatin inhibits glucagon and insulin secretion.

The delta cells of the islets of Langerhans secrete the hormone somatostatin, which has an extremely short half-life of only 3 minutes in the circulating blood. Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include

(1) Increased blood glucose.

(2) Increased amino acids.

(3) Increased fatty acids.

(4)Increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake. In turn, somatostatin has multiple inhibitory effects as follows:

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.

2. Somatostatin decreases the motility of the stomach, duodenum, and gallbladder.

3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to depress insulin and glucagons secretion decreases the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time. It should also be recalled that somatostatin is the same chemical substance as growth hormone inhibitory hormone, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

Diabetes Mellitus

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus:

1. Type I diabetes, also called insulin-dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion.

2. Type II diabetes, also called non–insulin-dependent diabetes mellitus (NIDDM), is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called ***insulin resistance****. In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and proteins increases.*

Type I diabetes—lack of insulin production by beta cells of the pancreas

Injury to the beta cells of the pancreas or diseases that impair insulin production can lead to type I diabetes. Viral infections or autoimmune disorders may be involved in the destruction of beta cells in many patients with type I diabetes, although heredity also plays a major role in determining the susceptibility of the beta cells to destruction by these insults. In some instances, there may be a hereditary tendency for beta cell degeneration even without viral infections or autoimmune disorders. The usual onset of type I diabetes occurs at about 14 years of age in the United States, and for this reason it is often called ***juvenile diabetes mellitus****. Type I diabetes may develop very abruptly, over a period of a few days or weeks, with three principal sequelae:*

(1) Increased blood glucose.

(2) Increased utilization of fats for energy and for formation of cholesterol by the liver.

(3) Depletion of the body's proteins.

Type II diabetes—resistance to the metabolic effects of insulin

Type II diabetes is far more common than type I, accounting for about 90 per cent of all cases of diabetes mellitus. In most cases, the onset of type II diabetes occurs after age 30, often between the ages of 50 and 60 years, and the disease develops gradually. Therefore, this syndrome is often referred to as ***adult-onset diabetes****. In recent years, however, there has been a steady increase in the number of younger individuals, some less than 20 years old, with type II diabetes. This trend appears to be related mainly to the increasing prevalence of obesity, the most important risk factor for type II diabetes in children as well as in adults.*

Lec.9 **Dr.latief fayadh**

Pancreatic Hormones

Physiology of diagnosis of diabetes mellitus

Table below compares some of clinical features of type I and type II diabetes mellitus. The usual methods for diagnosing diabetes are based on various chemical tests of the urine and the blood.

1. Urinary glucose.

Simple office tests or more complicated quantitative laboratory tests may be used to determine the quantity of glucose lost in the urine. In general, a normal person loses undetectable amounts of glucose, whereas a person with diabetes loses glucose in small to large amounts, in proportion to the severity of disease and the intake of carbohydrates.

2. Fasting blood glucose and insulin levels.

The fasting blood glucose level in the early morning is normally 80 to 90 mg/100 ml, and 110 mg/100 ml is considered to be the upper limit of normal. A fasting blood glucose level above this value often indicates diabetes mellitus or at least marked insulin resistance. In type I diabetes, plasma insulin levels are very low or undetectable during fasting and even after a meal. In type II diabetes, plasma insulin concentration may be several fold higher than normal and usually increases to a greater extent after ingestion of a standard glucose blood during a glucose tolerance test.

Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 years	Usually >30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

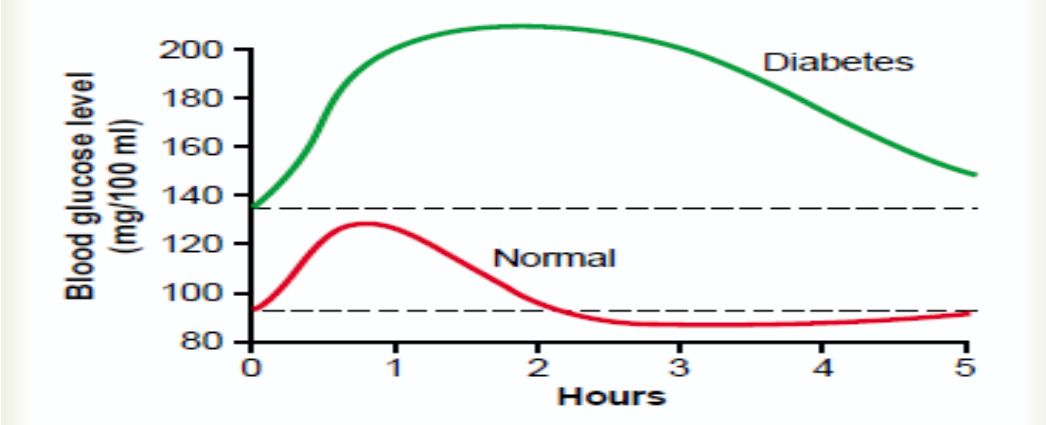
3. Glucose tolerance test.

As demonstrated by the bottom curve in figure below, called a "glucose tolerance curve," when a normal, fasting person ingests 1 gram of glucose per kilogram of body weight, the blood glucose level rises from about 90 mg/100 ml to 120 to 140 mg/100 ml and falls back to below normal in about 2 hours. In a person with diabetes, the fasting blood glucose concentration is almost always above 110 mg/100 ml and often above 140 mg/100 ml. Also, the glucose tolerance test is almost always abnormal. On ingestion of glucose, these people exhibit a much greater than normal rise in blood glucose level, as demonstrated by the upper curve in figure below, and the glucose level falls back to the control value only after 4 to 6 hours; furthermore, it fails to fall below the control level. The slow fall of this curve and its failure to fall below the control level demonstrate that either:

(1) The normal increase in insulin secretion after glucose ingestion does not occur.

(2) There is decreased sensitivity to insulin.

A diagnosis of diabetes mellitus can usually be established on the basis of such a curve, and type I and type II diabetes can be distinguished from each other by measurements of plasma insulin, with plasma insulin being low or undetectable in type I diabetes and increased in type II diabetes.



4. Acetone breath.

Small quantities of acetoacetic acid is preents in the blood, which increase greatly in severe diabetes, are converted to acetone. This is volatile and vaporized into the expired air. Consequently, one can frequently make a diagnosis of type I diabetes mellitus simply by ***smelling acetone*** *on the breath of a patient. Also, keto acids can be detected by chemical means in the urine, and their quantitation aids in determining the severity of the diabetes. In the early stages of type II diabetes, however, keto acids are usually not produced in excess amounts. However, when insulin resistance becomes very severe and there is greatly increased utilization of fats for energy, keto acids are then produced in persons with type II diabetes.*

Insulinoma (Hyperinsulinism).

Although much rarer than diabetes, excessive insulin production occasionally occurs from an adenoma of an islet of Langerhans. About 10 to 15 per cent of these adenomas are malignant, and occasionally metastases from the islets of Langerhans spread throughout the body, causing tremendous production of insulin by both the primary and the metastatic cancers. Indeed, more than 1000 grams of glucose have had to be administered every 24 hours to prevent hypoglycemia in some of these patients.

Insulin shock and hypoglycemia.

The central nervous system normally derives essentially all its energy from glucose metabolism, and insulin is not necessary for this use of glucose. However, if high levels of insulin cause blood glucose to fall to low values, the metabolism of the central nervous system becomes depressed. Consequently, in patients with insulin-secreting tumors or in patients with diabetes who administer too much insulin to themselves, the syndrome called ***insulin shock*** *may occur as follows.*

As the blood glucose level falls into the range of 50 to 70 mg/100 ml, the central nervous system usually becomes quite excitable, because this degree of hypoglycemia sensitizes neuronal activity. Sometimes various forms of hallucinations result, but more often the patient simply experiences extreme nervousness,

trembles all over, and breaks out in a sweat. As the blood glucose level falls to 20 to 50 mg/100 ml, clonic seizures and loss of consciousness are likely to occur. As the glucose level falls still lower, the seizures cease and only a state of coma remains. Indeed, at times it is difficult by simple clinical observation to distinguish between diabetic coma as a result of insulin-lack acidosis and coma due to hypoglycemia caused by excess insulin. The acetone breath and the rapid, deep breathing of diabetic coma are not present in hypoglycemic coma.

Proper treatment for a patient who has hypoglycemic shock or coma is immediate intravenous administration of large quantities of glucose. This usually brings the patient out of shock within a minute or more. If treatment is not effected immediately, permanent damage to the neuronal cells of the central nervous system often occurs.

Adrenocortical Hormones

The two adrenal glands, each of which weighs about 4 grams, lie at the superior poles of the two kidneys. As shown in figure below, each gland is composed of two distinct parts, the adrenal medulla and the adrenal cortex. The adrenal medulla, the central 20 per cent of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones epinephrine and norepinephrine in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body. These hormones and their effects are discussed in related to the sympathetic nervous system. The adrenal cortex secretes an entirely different group of hormones, called ***corticosteroids****. These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.*

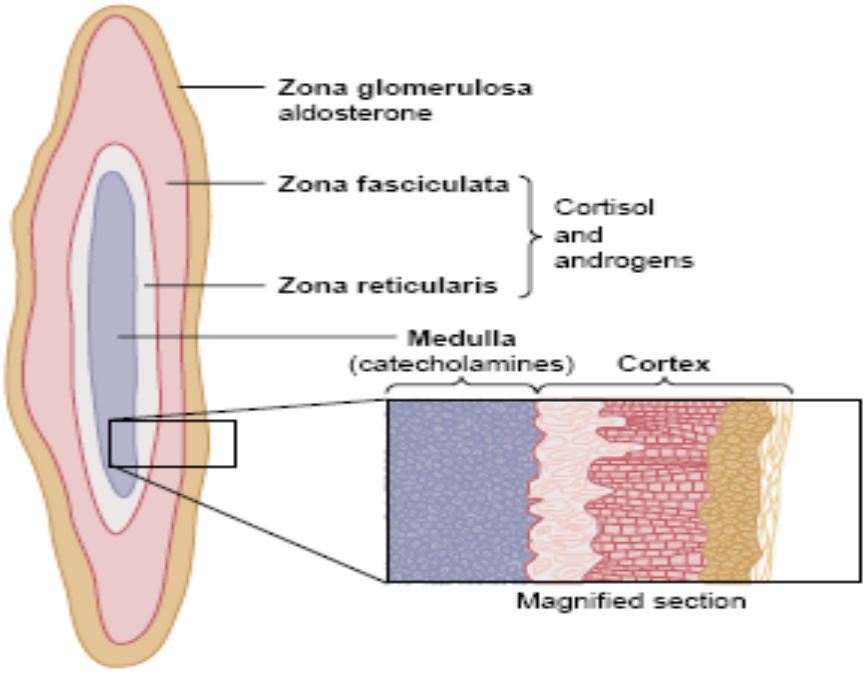


Figure 77–1

Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.

Corticosteroids Mineralocorticoids, Glucocorticoids, and Androgens.

Two major types of adrenocortical hormones, the mineralocorticoids and the glucocorticoids, are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially androgenic hormones, which exhibit about the same effects in the body as the male sex hormone testosterone. They are normally of only slight importance, although in certain abnormalities of the adrenal

cortices, extreme quantities can be secreted and can result in masculinizing effects. The mineralocorticoids have gained this name because they especially affect the electrolytes (the "minerals") of the extracellular fluids-sodium and potassium, in particular. The glucocorticoids have gained their name because they exhibit important effects that increase blood glucose concentration. They have additional effects on both protein and fat metabolism that are equally as important to body function as their effects on carbohydrate metabolism. More than 30 steroids have been isolated from the adrenal cortex, but two are of exceptional importance to the normal endocrine function of the human body: aldosterone, which is the principal mineralocorticoid, and cortisol, which is the principal glucocorticoid.

Synthesis and secretion of adrenocortical hormones

The adrenal cortex has three distinct layers. Figure above shows that the adrenal cortex is composed of three relatively distinct layers:

1. The zona glomerulosa, a thin layer of cells that lies just underneath the capsule, constitutes about 15 per cent of the adrenal cortex. These cells are the only ones in the adrenal gland capable of secreting significant amounts of aldosterone because they contain the enzyme aldosterone synthase which is necessary for synthesis of aldosterone. The secretion of these cells is controlled mainly by the extracellular fluid concentrations of angiotensin II and potassium, both of which stimulate aldosterone secretion.

2. The zona fasciculata, the middle and widest layer, constitutes about 75 per cent of the adrenal cortex and secretes the glucocorticoids cortisol and corticosterone, as well as small amounts of adrenal androgens and estrogens. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via adrenocorticotropic hormone (ACTH).

3. The zona reticularis, the deep layer of the cortex, secretes the adrenal androgens dehydroepiandrosterone (DHEA) and androstenedione, as well as small amounts of estrogens and some glucocorticoids. ACTH also regulates secretion of these cells, although other factors such as cortical androgen-stimulating hormone, released from the pituitary, may also be involved. The mechanisms for controlling adrenal androgen production, however, are not nearly as well understood as those for glucocorticoids and mineralocorticoids.

Mineralocorticoids

- *Aldosterone (very potent, accounts for about 90 per cent of all mineralocorticoid activity)*
- *Desoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted)*
- *Corticosterone (slight mineralocorticoid activity)*
- *9α-Fluorocortisol (synthetic, slightly more potent than aldosterone)*
- *Cortisol (very slight mineralocorticoid activity, but large quantity secreted)*
- *Cortisone (synthetic, slight mineralocorticoid activity)*

Glucocorticoids

- *Cortisol (very potent, accounts for about 95 per cent of all glucocorticoid activity)*
- *Corticosterone (provides about 4 per cent of total glucocorticoid activity, but much less potent than cortisol)*
- *Cortisone (synthetic, almost as potent as cortisol)*
- *Prednisone (synthetic, four times as potent as cortisol)*
- *Methylprednisone (synthetic, five times as potent as cortisol)*
- *Dexamethasone (synthetic, 30 times as potent as cortisol)*

It is clear from this list that some of these hormones have both glucocorticoid and mineralocorticoid activities. It is especially significant that cortisol has a small amount of mineralocorticoid activity, because some syndromes of excess cortisol secretion can cause significant mineralocorticoid effects, along with its much more potent glucocorticoid effects.

The intense glucocorticoid activity of the synthetic hormone dexamethasone, which has almost zero mineralocorticoid activity, makes this an especially important drug for stimulating specific glucocorticoid activity.

Functions of the adrenal hormones:

A. Mineralocorticoids (aldosterone).

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

B. The glucocorticoids.

Even though mineralocorticoids can save the life of an acutely adrenalectomized animal, the animal still is far from normal. Instead, its metabolic systems for utilization of proteins, carbohydrates, and fats remain considerably deranged. Furthermore, the animal cannot resist different types of physical or even mental stress, and minor illnesses such as respiratory tract infections can lead to death. Therefore, the glucocorticoids have functions just as important to the ***long-continued life*** *of the animal as those of the mineralocorticoids. At least 95 per cent of the glucocorticoid activity of the adrenocortical secretions results from the secretion of cortisol, known also as hydrocortisone. In addition to this, a small but significant amount of glucocorticoid activity is provided by corticosterone.*

C. The adrenal androgens.

Several moderately active male sex hormones called adrenal androgens are continually secreted by the adrenal cortex, especially during fetal life, Also, progesterone and estrogens, which are female sex hormones, are secreted in minute quantities. Normally, the adrenal androgens have only weak effects in humans. It is possible that part of the early development of the male sex organs results from childhood secretion of adrenal androgens. The adrenal androgens also exert mild effects in the female, not only before puberty but also throughout life. Much of the growth of the pubic and axillary hair in the female results from the action of these hormones. In extra-adrenal tissues, some of the adrenal androgens are converted to testosterone, the primary male sex hormone, which probably accounts for much of their androgenic activity.

Abnormalities of adrenocortical secretion:

1. Hypoadrenalism (Addison's disease):

Addison's disease results from failure of the adrenal cortices to produce adrenocortical hormones, and this in turn is most frequently caused by primary atrophy of the adrenal cortices. In about 80 per cent of the cases, the atrophy is caused by autoimmunity against the cortices. Adrenal gland hypofunction is also frequently caused by tuberculous destruction of the adrenal glands or invasion of the adrenal cortices by cancer.

- Mineralocorticoid deficiency.

Lack of aldosterone secretion greatly decreases renal tubular sodium reabsorption and consequently allows sodium ions, chloride ions, and water to be lost into urine in great profusion. The net result is a greatly decreased extracellular fluid volume. Furthermore, hyponatremia, hyperkalemia, and mild acidosis develop because of failure of potassium and hydrogen ions to be secreted in exchange for sodium reabsorption.

As the extracellular fluid becomes depleted, plasma volume falls, red blood cell concentration rises markedly, cardiac output decreases, and the patient dies in shock, death usually occurring in the untreated patient 4 days to 2 weeks after cessation of mineralocorticoid secretion.

- Glucocorticoid deficiency.

Loss of cortisol secretion makes it impossible for a person with Addison's disease to maintain normal blood glucose concentration between meals because he or she cannot synthesize significant quantities of glucose by gluconeogenesis. Furthermore, lack of cortisol reduces the mobilization of both proteins and fats from the tissues, thereby depressing many other metabolic functions of the body. This sluggishness of energy mobilization when cortisol is not available is one of the major detrimental effects of glucocorticoid lack. Even when excess quantities of glucose and other nutrients are available; the person's muscles are weak, indicating that glucocorticoids are needed to maintain other metabolic functions of the tissues in addition to energy metabolism. Lack of adequate glucocorticoid secretion also makes a person with Addison's disease highly susceptible to the deteriorating effects of different types of stress, and even a mild respiratory infection can cause death.

- Melanin Pigmentation.

Another characteristic of most people with Addison's disease is melanin pigmentation of the mucous membranes and skin. This melanin is not always deposited evenly but occasionally is deposited in blotches, and it is deposited especially in the thin skin areas, such as the mucous membranes of the lips and the thin skin of the nipples.

The cause of the melanin deposition is believed to be the following: When cortisol secretion is depressed, the normal negative feedback to the hypothalamus and anterior pituitary gland is also depressed, therefore allowing tremendous rates of ACTH secretion as well as simultaneous secretion of increased amounts of MSH. Probably the tremendous amounts of ACTH cause most of the pigmenting effect because they can stimulate formation of melanin by the melanocytes in the same way that MSH does.

- Treatment of People with Addison's Disease.

An untreated person with total adrenal destruction dies within a few days to a few weeks because of weakness and usually circulatory shock. Yet such a person can live for years if small quantities of mineralocorticoids and glucocorticoids are administered daily.

- Addisonian Crisis.

Great quantities of glucocorticoids are occasionally secreted in response to different types of physical or mental stress. In a person with Addison's disease, the output of glucocorticoids does not increase during stress. Yet whenever different types of trauma, disease, or other stresses, such as surgical operations, supervene, a person is likely to have an acute need for excessive amounts of glucocorticoids and often must be given 10 or more times the normal quantities of glucocorticoids to prevent death. This critical need for extra glucocorticoids and the associated severe debility in times of stress is called an ***addisonian crisis.***

2. Hyperadrenalism (Cushing's syndrome):

Hypersecretion by the adrenal cortex causes a complex cascade of hormone effects called Cushing's syndrome. Most of the abnormalities of Cushing's syndrome are ascribable to abnormal amounts of cortisol, but excess secretion of androgens may also cause important effects. Hypercortisolism can occur from multiple causes, including:

(1) Adenomas of the anterior pituitary that secrete large amounts of ACTH, which then causes adrenal hyperplasia and excess cortisol secretion.

(2) Abnormal function of the hypothalamus that causes high levels of corticotropin-releasing hormone (CRH), which stimulates excess ACTH release.

(3) "Ectopic secretion" of ACTH by a tumor elsewhere in the body, such as an abdominal carcinoma.

(4) Adenomas of the adrenal cortex.

When Cushing's syndrome is secondary to excess secretion of ACTH by the anterior pituitary, this is referred to as ***Cushing's disease****.*

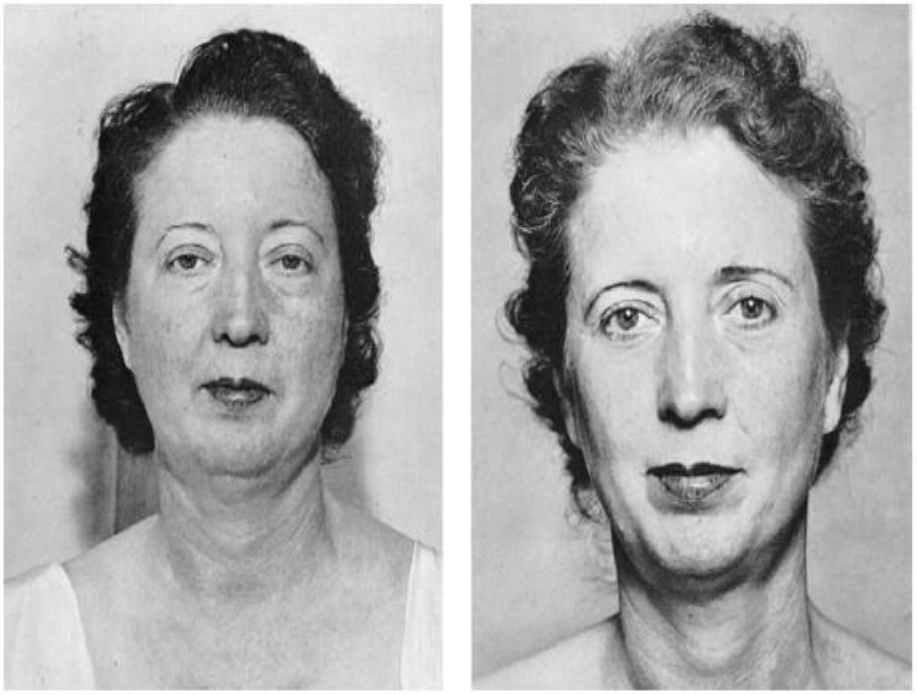


Figure 77–9

A person with Cushing's syndrome before (*left*) and after (*right*) subtotal adrenalectomy. (Courtesy Dr. Leonard Posey.)

3. Primary aldosteronism (Conn's syndrome):

Occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldosterone; the resulting condition is called ***"primary aldosteronism"*** *or* ***"Conn's syndrome."*** *Also, in a few instances, hyperplastic adrenal cortices secrete aldosterone rather than cortisol. The effects of the excess aldosterone are hypokalemia, slight increase in extracellular fluid volume and blood volume, very slight increase in plasma sodium concentration and, almost always, hypertension. Especially interesting in primary aldosteronism are occasional periods of muscle paralysis caused by the hypokalemia. The paralysis is caused by a depressant effect of low extracellular potassium concentration on action potential transmission by the nerve fibers. One of the diagnostic criteria of primary*

aldosteronism is a decreased plasma renin concentration. This results from feedback suppression of renin secretion caused by the excess aldosterone or by the excess extracellular fluid volume and arterial pressure resulting from the aldosteronism. Treatment of primary aldosteronism is usually surgical removal of the tumor or of most of the adrenal tissue when hyperplasia is the cause.

4. Adrenogenital syndrome:

An occasional adrenocortical tumor secretes excessive quantities of androgens that cause intense masculinizing effects throughout the body. If this occurs in a female, she develops virile characteristics, including growth of a beard, a much deeper voice, occasionally baldness if she also has the genetic trait for baldness, masculine distribution of hair on the body and the pubis, growth of the clitoris to resemble a penis, and deposition of proteins in the skin and especially in the muscles to give typical masculine characteristics. In the prepubertal male, a virilizing adrenal tumor causes the same characteristics as in the female plus rapid development of the male sexual organs, In the adult male, the virilizing characteristics of adrenogenital syndrome are usually obscured by the normal virilizing characteristics of the testosterone secreted by the testes. It is often difficult to make a diagnosis of adrenogenital syndrome in the adult male. In adrenogenital syndrome, the excretion of 17-ketosteroids (which are derived from androgens) in the urine may be 10 to 15 times normal. This finding can be used in diagnosing the disease.

Pineal Gland

*The small, cone-shaped **pineal gland** is located in the roof of the third ventricle of the diencephalon, where it is encapsulated by the meninges covering the brain. The pineal gland of a child weighs about 0.2 g and is 5 to 8 mm long and 9 mm wide. The gland begins to regress in size at about age 7 and in the adult appears as a thickened strand of fibrous tissue. Although the pineal gland lacks direct nervous connections to the rest of the brain, it is highly innervated by the sympathetic nervous system from the superior cervical ganglion. The principal hormone of the pineal gland is **melatonin.***

*Production and secretion of this hormone is stimulated by activity of the **suprachiasmatic nucleus (SCN)** in the hypothalamus of the brain via active action of sympathetic neurons to the pineal gland. The SCN is the primary center for **circadian rhythms** in the body: rhythms of physiological activity that follow a 24-hour pattern. The circadian activity of the SCN is automatic, but environmental light/dark changes are required to entrain (synchronize) this activity to a day/night cycle. Activity of the SCN, and thus secretion of melatonin, begins to increase with darkness and peaks by the middle of the night. During the day, neural pathways from the retina of the eyes to the hypothalamus act to depress the activity of the SCN, reducing sympathetic stimulation of the pineal and thus decreasing melatonin secretion.*

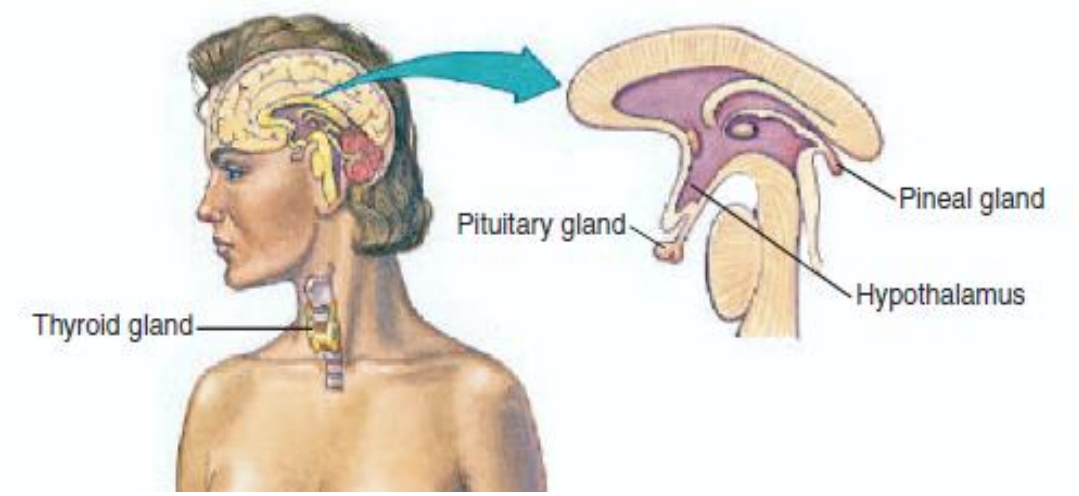
Physiological considerations:

The pineal gland has been implicated in a variety of physiological processes. One of the most widely studied is the ability of melatonin to inhibit the pituitary-gonad axis. Indeed, a decrease in melatonin secretion in many species is required for the maturation of the gonads during the reproductive season of seasonal breeders. Although there is evidence to support an antigonadotropic effect in humans, this possibility has not yet been proven. For example, excessive melatonin secretion in humans is associated with a delay in the onset of puberty. Research findings indicate that melatonin secretion is highest in children between the ages of 1 and 5 and decreases thereafter, reaching its lowest levels at the end of puberty, when concentrations are 75% lower than during early childhood. This suggests a role for melatonin in the onset of human puberty. However, because of much conflicting data, the importance of melatonin in human reproduction is still highly controversial.

- Melatonin pills.

The pattern of melatonin secretion is altered when a person works night shifts or flies across different time zones. There is evidence that exogenous melatonin (taken as a pill) may be beneficial in the treatment of

jet lag, but the optimum dosage is not currently known. Phototherapy using bright fluorescent lamps, which act like sunlight to inhibit melatonin secretion, has been used effectively in the treatment of seasonal affective disorder (SAD), or "winter depression. "Melatonin pills decrease the time required to fall asleep and increase the duration of rapid eye movement (REM) sleep; for these reasons, they may be useful in the treatment of insomnia. This is particularly significant for elderly people with insomnia, who have the lowest nighttime levels of endogenous melatonin secretion.



Thymus gland.

The thymus is a bilobed organ positioned in front of the aorta and behind the manubrium of the sternum. Although the size of the thymus varies considerably from person to person, it is relatively large in newborns and children, and sharply regresses in size after puberty. Besides decreasing in size, the thymus of adults becomes infiltrated with strands of fibrous and fatty connective tissue.

The thymus is the site of production of T cells (thymus dependent cells), which are the lymphocytes involved in cell mediated immunity. In addition to providing T cells, the thymus secretes a number of hormones that are believed to stimulate T cells after they leave the thymus.

Gastrointestinal tract hormones.

The stomach and small intestine secrete a number of hormones that act on the gastrointestinal tract itself and on the pancreas and gallbladder. These hormones, acting in concert with regulation by the autonomic nervous system, coordinate the activities of different regions of the digestive tract and the secretions of pancreatic juice and bile.

Lec.11 **Dr. Lateef Fayyad**

Reproductive and Hormonal Functions of the Male

The reproductive functions of the male can be divided into three major subdivisions:

(1) Spermatogenesis, which means simply the formation of sperm.

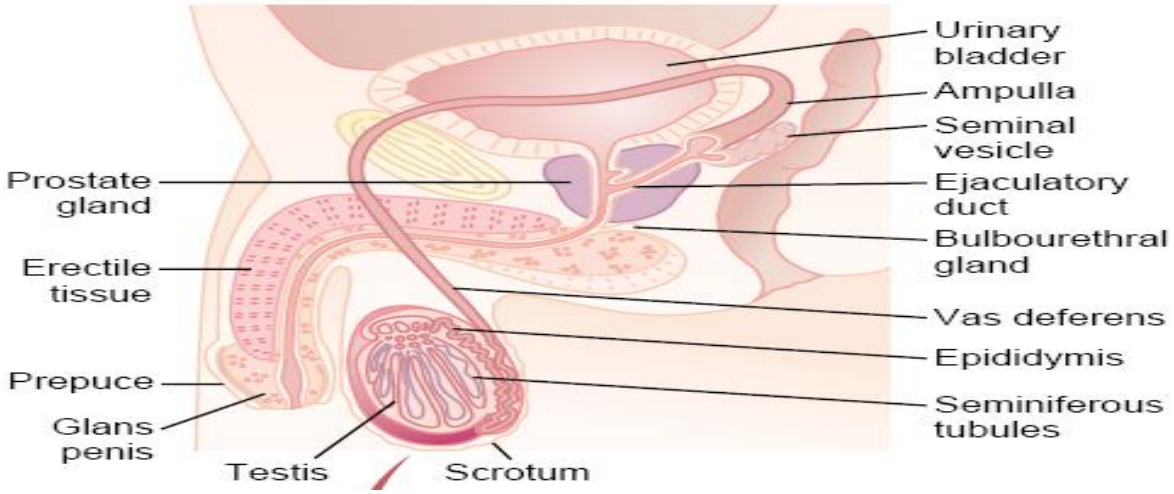
(2) Performance of the male sexual act.

(3) Regulation of male reproductive functions by the various hormones.

Associated with these reproductive functions are the effects of the male sex hormones on the accessory sexual organs, cellular metabolism, growth, and other functions of the body.

Physiologic anatomy of the male sexual organs.

The testis is composed of up to 900 coiled seminiferous tubules, each averaging more than one half meter long, in which the sperm are formed. The sperm then empty into the epididymis, another coiled tube about 6 meters long. The epididymis leads into the vas deferens, which enlarges into the ampulla of the vas deferens immediately before the vas enters the body of the prostate gland. Two seminal vesicles, one located on each side of the prostate, empty into the prostatic end of the ampulla, and the contents from both the ampulla and the seminal vesicles pass into an ejaculatory duct leading through the body of the prostate gland and then emptying into the internal urethra. Prostatic ducts, too, empty from the prostate gland into the ejaculatory duct and from there into the prostatic urethra. Finally, the urethra is the last connecting link from the testis to the exterior. The urethra is supplied with mucus derived from a large number of minute urethral glands located along its entire extent and even more so from bilateral bulbourethral glands (Cowper's glands) located near the origin of the urethra.



Spermatogenesis.

During formation of the embryo, the primordial germ cells migrate into the testes and become immature germ cells called spermatogonia which lie in two or three layers of the inner surfaces of the seminiferous tubules. The spermatogonia begin to undergo mitotic division, beginning at puberty, and continually proliferate and differentiate through definite stages of development to form sperm.

Steps of Spermatogenesis.

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior pituitary gonadotropic hormones, beginning at an average age of 13 years and continuing throughout most of the remainder of life but decreasing markedly in old age. In the first stage of spermatogenesis, the spermatogonia migrate among Sertoli cells toward the central lumen of the seminiferous tubule. The Sertoli cells are very large, with overflowing cytoplasmic envelopes that surround the developing spermatogonia all the way to the central lumen of the tubule.

Meiosis.

Spermatogonia that cross the barrier into the Sertoli cell layer become progressively modified and enlarged to form large primary spermatocytes. Each of these, in turn, undergoes meiotic division to form two secondary spermatocytes. After another few days, these too divide to form spermatids that are eventually modified to become spermatozoa (sperm).

During the change from the spermatocyte stage to the spermatid stage, the 46 chromosomes (23 pairs of chromosomes) of the spermatocyte are divided, so that 23 chromosomes go to one spermatid and the other 23 to the second spermatid. This also divides the chromosomal genes so that only one half of the genetic characteristics of the eventual fetus are provided by the father, while the other half are derived from the

oocyte provided by the mother. The entire period of spermatogenesis, from spermatogonia to spermatozoa, takes about 74 days.

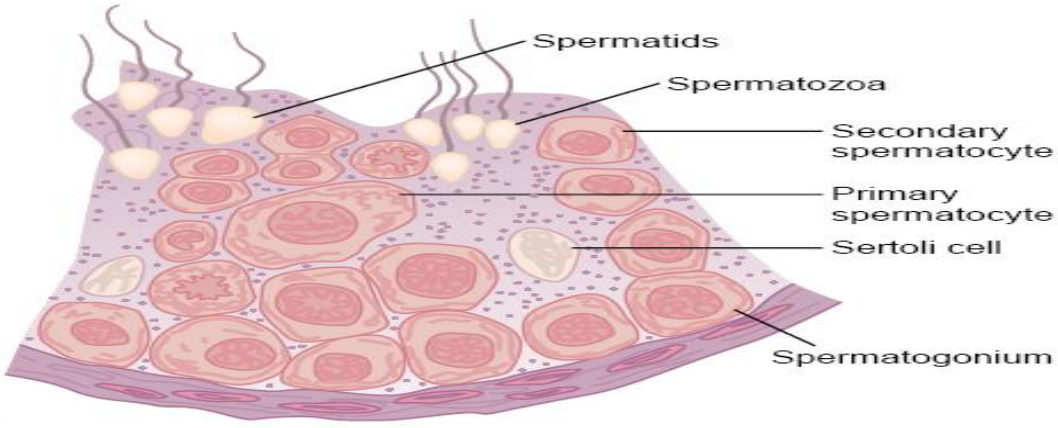


Figure 80–2

A, Cross section of a seminiferous tubule. *B*, Stages in the development of sperm from spermatogonia.

Sex chromosomes.

In each spermatogonium, one of the 23 pairs of chromosomes carries the genetic information that determines the sex of each eventual offspring. This pair is composed of one X chromosome, which is called the female chromosome, and one Y chromosome, the male chromosome. During meiotic division, the male Y chromosome goes to one spermatid that then becomes a male sperm, and the female X chromosome goes to another spermatid that becomes a female sperm. The sex of the eventual offspring is determined by which of these two types of sperm fertilizes the ovum.

Formation of sperm.

When the spermatids are first formed, they still have the usual characteristics of epithelioid cells, but soon they begin to differentiate and elongate into spermatozoa. As shown in Figure below, each spermatozoon is composed of a head and a tail. The head comprises the condensed nucleus of the cell with only a thin cytoplasmic and cell membrane layer around its surface. On the outside of the anterior two thirds of the head is a thick cap called the acrosome that is formed mainly from the Golgi apparatus. This contains a number of enzymes similar to those found in lysosomes of the typical cell, including hyaluronidase (which can digest proteoglycan filaments of tissues) and powerful proteolytic enzymes (which can digest proteins). These enzymes play important roles in allowing the sperm to enter the ovum and fertilize it.

The tail of the sperm, called the flagellum, has three major components:

(1) A central skeleton constructed of 11 microtubules, collectively called the axoneme— the structure of this is similar to that of cilia found on the surfaces of other types of cells.

(2) A thin cell membrane covering the axoneme.

(3) A collection of mitochondria surrounding the axoneme in the proximal portion of the tail (called the body of the tail).

Back-and-forth movement of the tail (flagellar movement) provides motility for the sperm. This movement results from a rhythmical longitudinal sliding motion between the anterior and posterior tubules that make up the axoneme. The energy for this process is supplied in the form of adenosine triphosphate that is synthesized by the mitochondria in the body of the tail. Normal sperm move in a fluid medium at a velocity of 1 to 4 mm/min. This allows them to move through the female genital tract in quest of the ovum.

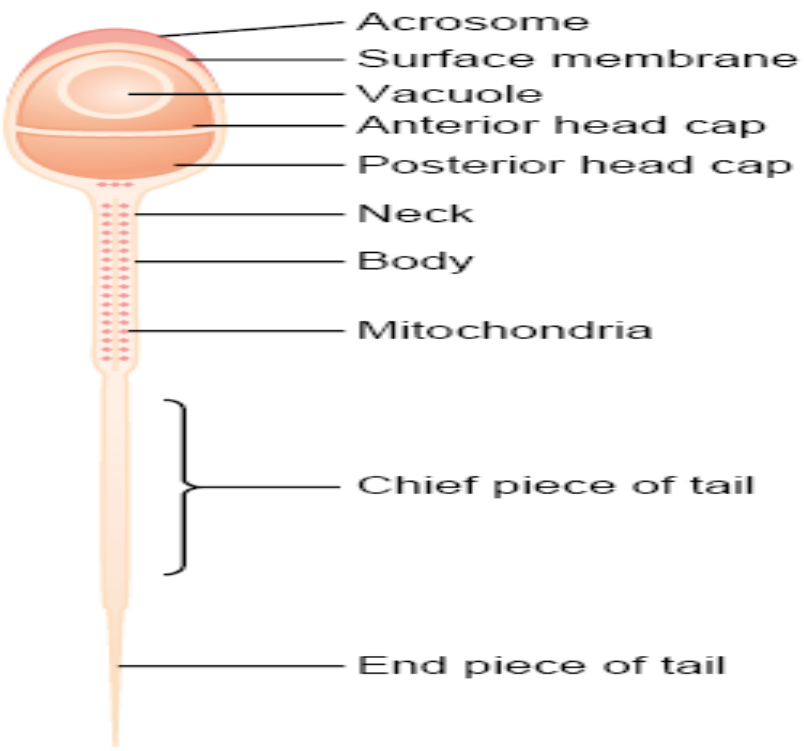


Figure 80–4

Structure of the human spermatozoon.

Hormonal factors that stimulate spermatogenesis.

Several hormones play essential roles in spermatogenesis. Some of these are as follows:

1. Testosterone, secreted by the Leydig cells located in the interstitium of the testis, is essential for growth and division of the testicular germinal cells, which is the first stage in forming sperm.

2. Luteinizing hormone, secreted by the anterior pituitary gland, stimulates the Leydig cells to secrete testosterone.

3. Follicle-stimulating hormone, also secreted by the anterior pituitary gland, stimulates the Sertoli cells; without this stimulation, the conversion of the spermatids to sperm will not occur.

4. Estrogens, formed from testosterone by the Sertoli cells when they are stimulated by follicle stimulating hormone, are probably also essential for spermiogenesis.

5. Growth hormone (as well as most of the other body hormones) is necessary for controlling background metabolic functions of the testes. Growth hormone specifically promotes early division of the spermatogonia themselves; in its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent, thus causing infertility.

Maturation of sperm in the epididymis.

After formation in the seminiferous tubules, the sperm require several days to pass through the 6-meter-long tubule of the epididymis. Sperm removed from the seminiferous tubules and from the early portions of the epididymis are nonmotile, and they cannot fertilize an ovum. However, after the sperm have been in the epididymis for some 18 to 24 hours, they develop the capability of motility, even though several inhibitory proteins in the epididymal fluid still prevent final motility until after ejaculation.

Storage of sperm.

The two testes of the human adult form up to 120 million sperm each day. A small quantity of these can be stored in the epididymis, but most are stored in the vas deferens. They can remain stored, maintaining their fertility, for at least a month. During this time, they are kept in a deeply suppressed inactive state by multiple inhibitory substances in the secretions of the ducts. Conversely, with a high level of sexual activity and ejaculations, storage may be no longer than a few days.

After ejaculation, the sperm become motile, and they also become capable of fertilizing the ovum, a process called maturation. The Sertoli cells and the epithelium of the epididymis secrete a special nutrient fluid that is ejaculated along with the sperm. This fluid contains hormones (including both testosterone and estrogens), enzymes, and special nutrients that are essential for sperm maturation.

Physiology of the mature sperm.

The normal motile, fertile sperm are capable of flagellated movement though the fluid medium at velocities of 1 to 4 mm/min. The activity of sperm is greatly enhanced in a neutral and slightly alkaline medium, as exists in the ejaculated semen, but it is greatly depressed in a mildly acidic medium. A strong acidic medium can cause

rapid death of sperm. The activity of sperm increases markedly with increasing temperature, but so does the rate of metabolism, causing the life of the sperm to be considerably shortened. Although sperm can live for many weeks in the suppressed state in the genital ducts of the testes, life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days.

Function of the seminal vesicles.

Each seminal vesicle is a tortuous, loculated tube lined with a secretory epithelium that secretes a mucoid material containing an abundance of fructose, citric acid, and other nutrient substances, as well as large quantities of prostaglandins and fibrinogen. During the process of emission and ejaculation, each seminal vesicle empties its contents into the ejaculatory duct shortly after the vas deferens empties the sperm. This adds greatly to the bulk of the ejaculated semen, and the fructose and other substances in the seminal fluid are of considerable nutrient value for the ejaculated sperm until one of the sperm fertilizes the ovum. Prostaglandins are believed to aid fertilization in two ways:

(1) By reacting with the female cervical mucus to make it more receptive to sperm movement.

(2) By possibly causing backward, reverse peristaltic contractions in the uterus and fallopian tubes to move the ejaculated sperm toward the ovaries (a few sperm reach the upper ends of the fallopian tubes within 5 minutes).

Function of the prostate gland.

The prostate gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting enzyme, and a profibrinolysin. During emission, the capsule of the prostate gland contracts simultaneously with the contractions of the vas deferens so that the thin, milky fluid of the prostate gland adds further to the bulk of the semen. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum, because the fluid of the vas deferens is relatively acidic owing to the presence of citric acid and metabolic end products of the sperm and, consequently, helps to inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (pH of 3.5 to 4.0). Sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 to 6.5. Consequently, it is probable that the slightly alkaline prostatic fluid helps to neutralize the acidity of the other seminal fluids during ejaculation, and thus enhances the motility and fertility of the sperm.

Semen.

Semen, which is ejaculated during the male sexual act, is composed of the fluid and sperm from the vas deferens (about 10 per cent of the total), fluid from the seminal vesicles (almost 60 per cent), fluid from the prostate gland (about 30 per cent), and small amounts from the mucous glands, especially the bulbourethral glands. Thus, the bulk of the semen is seminal vesicle fluid, which is the last to be ejaculated and serves to wash the sperm through the ejaculatory duct and urethra.

The average pH of the combined semen is about 7.5, the alkaline prostatic fluid having more than neutralized the mild acidity of the other portions of the semen. The prostatic fluid gives the semen a milky appearance, and fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency. Also, a clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that holds the semen in the deeper regions of the vagina where the uterine cervix lies. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed

from the prostatic profibrinolysin. In the early minutes after ejaculation, the sperm remain relatively immobile, possibly because of the viscosity of the coagulum.

As the coagulum dissolves, the sperm simultaneously become highly motile. Although sperm can live for many weeks in the male genital ducts, once they are ejaculated in the semen, their maximal life span is only 24 to 48 hours at body temperature. At lowered temperatures, however, semen can be stored for several weeks, and when frozen at temperatures below -100°C, sperm have been preserved for years.

Why does only one sperm enter the oocyte?

With as many sperm as there are, why does only one enter the oocyte? The reason is not entirely known, but within a few minutes after the first sperm penetrates the zona pellucida of the ovum, calcium ions diffuse inward through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off. Thus, almost never does more than one sperm enter the oocyte during fertilization.

Effect of temperature on spermatogenesis.

Increasing the temperature of the testes can prevent spermatogenesis by causing degeneration of most cells of the seminiferous tubules besides the spermatogonia. It has often been stated that the reason the testes are located in the dangling scrotum is to maintain the temperature of these glands below the internal temperature of the body, although usually only about 2°C below the internal temperature. On cold days, scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body to maintain this 2° differential. Thus, the scrotum theoretically acts as a cooling mechanism for the testes (but a controlled cooling), without which spermatogenesis might be deficient during hot weather.

Effect of sperm count on fertility.

The usual quantity of semen ejaculated during each coitus averages about 3.5 milliliters, and in each milliliter of semen is an average of about 120 million sperm, although even in "normal" males this can vary from 35 million to 200 million. This means an average total of 400 million sperm are usually present in the several milliliters of each ejaculate. When the number of sperm in each milliliter falls below about 20 million, the person is likely to be infertile. Thus, even though only a single sperm is necessary to fertilize the ovum, for reasons not understood, the ejaculate usually must contain a tremendous number of sperm for only one sperm to fertilize the ovum.

Effect of sperm morphology and motility on fertility.

Occasionally a man has a normal number of sperm but is still infertile. When this occurs, sometimes as many as one half the sperm are found to be abnormal physically, having two heads, abnormally shaped heads, or abnormal tails. At other times, the sperm appear to be structurally normal, but for reasons not understood, they are either entirely nonmotile or relatively nonmotile. Whenever the majority of the sperm are morphologically abnormal or are nonmotile, the person is likely to be infertile, even though the remainder of the sperm appear to be normal.

Lec.12 **Dr.Latief Fayadh**

Effect of testosterone on development of adult primary and secondary sexual characteristics.

After puberty, the increasing amounts of testosterone secretion cause the penis, scrotum, and testes to enlarge about eightfold before the age of 20 years. In addition, testosterone causes the secondary sexual characteristics of the male to develop, beginning at puberty and ending at maturity. These secondary

sexual characteristics, in addition to the sexual organs themselves, distinguish the male from the female as follows.

A. Effect on the distribution of body hair.

Testosterone causes growth of hair

(1) Over the pubis.

(2) Upward along the linea alba of the abdomen sometimes to the umbilicus and above.

(3) On the face.

(4) Usually on the chest.

(5) Less often on other regions of the body, such as the back. It also causes the hair on most other portions of the body to become more prolific.

B. Baldness.

Testosterone decreases the growth of hair on the top of the head; a man who does not have functional testes does not become bald. However, many virile men never become bald because baldness is a result of two factors: first, a genetic background for the development of baldness and, second, superimposed on this genetic background, large quantities of androgenic hormones. A woman who has the appropriate genetic background and who develops a long sustained androgenic tumor becomes bald in the same manner as does a man.

C. Effect on the voice.

Testosterone secreted by the testes or injected into the body causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects cause at first a relatively discordant, "cracking" voice, but this gradually changes into the typical adult masculine voice.

D. Testosterone increases skin thickness and development of acne.

Testosterone increases the thickness of the skin over the entire body and increases the ruggedness of the subcutaneous tissues. Testosterone also increases the rate of secretion by some or perhaps all the body's sebaceous glands. Especially important is excessive secretion by the sebaceous glands of the face, because this can result in acne. Therefore, acne is one of the most common features of male adolescence when the body is first becoming introduced to increased testosterone. After several years of testosterone secretion, the skin normally adapts to the testosterone in a way that allows it to overcome the acne.

E. Testosterone increases protein formation and muscle development.

One of the most important male characteristics is development of increasing musculature after puberty, averaging about a 50 per cent increase in muscle mass over that in the female. This is associated with increased protein in the nonmuscle parts of the body as well. Many of the changes in the skin are due to deposition of proteins in the skin, and the changes in the voice also result partly from this protein anabolic function of testosterone. Because of the great effect that testosterone and other androgens have on the body musculature, synthetic androgens are widely used by athletes to improve their muscular performance. This practice is to be severely deprecated because of prolonged harmful effects of excess androgens. Testosterone or synthetic androgens are also occasionally used in old age as a "youth hormone" to improve muscle strength and vigor, but with questionable results.

F. Testosterone increases bone matrix and causes calcium retention.

After the great increase in circulating testosterone that occurs at puberty (or after prolonged injection of testosterone), the bones grow considerably thicker and deposit considerable additional calcium salts. Thus, testosterone increases the total quantity of bone matrix and causes calcium retention. The increase in bone matrix is believed to result from the general protein anabolic function of testosterone plus deposition of calcium salts in response to the increased protein. Testosterone has a specific effect on the pelvis to

(1) Narrow the pelvic outlet.

(2) Lengthen it.

(3) Cause a funnel-like shape instead of the broad ovoid shape of the female pelvis.
(4) Greatly increase the strength of the entire pelvis for load-bearing.
In the absence of testosterone, the male pelvis develops into a pelvis that is similar to that of the female. Because of the ability of testosterone to increase the size and strength of bones, it is often used in older men to treat osteoporosis.

G. Testosterone increases basal metabolism.

Injection of large quantities of testosterone can increase the basal metabolic rate by as much as 15 per cent. Also, even the usual quantity of testosterone secreted by the testes during adolescence and early adult life increases the rate of metabolism some 5 to 10 per cent above the value that it would be were the testes not active. This increased rate of metabolism is possibly an indirect result of the effect of testosterone on protein anabolism, the increased quantity of proteins—the enzymes especially—increasing the activities of all cells.

H. Effect on red blood cells.

When normal quantities of testosterone are injected into a castrated adult, the number of red blood cells per cubic millimeter of blood increases 15 to 20 per cent. Also, the average man has about 700,000 more red blood cells per cubic millimeter than the average woman. This difference may be due partly to the increased metabolic rate that occurs after testosterone administration rather than to a direct effect of testosterone on red blood cell production.

I. Effect on electrolyte and water balance.

Many steroid hormones can increase the reabsorption of sodium in the distal tubules of the kidneys. Testosterone also has such an effect, but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5 to 10 per cent.

Control of male sexual functions by hormones from the hypothalamus and anterior pituitary gland.

A major share of the control of sexual functions in both the male and the female begins with secretion of gonadotropin-releasing hormone (GRH) by the hypothalamus. This hormone in turn stimulates the anterior pituitary gland to secrete two other hormones called gonadotropic hormones:
(1) Luteinizing hormone (LH) .
(2) Follicle-stimulating hormone (FSH). In turn, LH is the primary stimulus for the secretion of testosterone by the testes, and FSH mainly stimulates spermatogenesis.

Gonadotropic Hormones: LH and FSH.

Both of the gonadotropic hormones, LH and FSH, are secreted by the same cells, called gonadotropes, in the anterior pituitary gland. In the absence of GRH secretion from the hypothalamus, the gonadotropes in the pituitary gland secrete almost no LH or FSH. LH and FSH are glycoproteins. They exert their effects on their target tissues in the testes mainly by activating the cyclic adenosine monophosphate second messenger system, which in turn activates specific enzyme systems in the respective target cells.

Testosterone —regulation of its production by LH.

Testosterone is secreted by the interstitial cells of Leydig in the testes, but only when they are stimulated by LH from the anterior pituitary gland. Furthermore, the quantity of testosterone secreted increases approximately in direct proportion to the amount of LH available. Mature Leydig cells are normally found in a child's testes for a few weeks after birth but then disappear until after the age of about 10 years. However, either injection of purified LH into a child at any age or secretion of LH at puberty causes testicular interstitial cells that look like fibroblasts to evolve into functioning Leydig cells.

Inhibition of anterior pituitary secretion of LH and FSH by testosterone.

The testosterone secreted by the testes in response to LH has the reciprocal effect of inhibiting anterior pituitary secretion of LH. Most of this inhibition probably results from a direct effect of testosterone on the

hypothalamus to decrease the secretion of GRH. This in turn causes a corresponding decrease in secretion of both LH and FSH by the anterior pituitary, and the decrease in LH reduces the secretion of testosterone by the testes. Thus, whenever secretion of testosterone becomes too great, this automatic negative feedback effect, operating through the hypothalamus and anterior pituitary gland, reduces the testosterone secretion back toward the desired operating level. Conversely, too little testosterone allows the hypothalamus to secrete large amounts of GRH, with a corresponding increase in anterior pituitary LH and FSH secretion and consequent increase in testicular testosterone secretion.

Regulation of spermatogenesis by FSH and testosterone.

FSH binds with specific FSH receptors attached to the Sertoli cells in the seminiferous tubules. This causes these cells to grow and secrete various spermatogenic substances. Simultaneously, testosterone (and dihydrotestosterone) diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. Thus, to initiate spermatogenesis, both FSH and testosterone are necessary.

Male adult sexual life and male climacteric.

After puberty, gonadotropic hormones are produced by the male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death. Most men, however, begin to exhibit slowly decreasing sexual functions in their late 40s or 50s, and one study showed that the average age for terminating intersexual relations was 68, although the variation was great. This decline in sexual function is related to decrease in testosterone secretion. The decrease in male sexual function is called the ***male climacteric****. Occasionally the male climacteric is associated with symptoms of hot flashes, suffocation, and psychic disorders similar to the menopausal symptoms of the female. These symptoms can be abrogated by administration of testosterone, synthetic androgens, or even estrogens that are used for treatment of menopausal symptoms in the female.*

Abnormalities of male sexual function.

1. Prostate gland and its abnormalities

The prostate gland remains relatively small throughout childhood and begins to grow at puberty under the stimulus of testosterone. This gland reaches an almost stationary size by the age of 20 years and remains at this size up to the age of about 50 years. At that time, in some men it begins to involute, along with decreased production of testosterone by the testes. A benign prostatic fibroadenoma frequently develops in the prostate in many older men and can cause urinary obstruction. This hypertrophy is caused not by testosterone but instead by abnormal overgrowth of prostate tissue itself. Cancer of the prostate gland is a different problem and is a common cause of death, accounting for about 2 to 3 per cent of all male deaths. Once cancer of the prostate gland does occur, the cancerous cells are usually stimulated to more rapid growth by testosterone and are inhibited by removal of both testes so that testosterone cannot be formed. Prostatic cancer usually can be inhibited by administration of estrogens.

2. Hypogonadism in the Male

When the testes of a male fetus are nonfunctional during fetal life, none of the male sexual characteristics develop in the fetus. Instead, female organs are formed. The reason for this is that the basic genetic characteristic of the fetus, whether male or female, is to form female sexual organs if there are no sex hormones. But in the presence of testosterone, formation of female sexual organs is suppressed, and instead, male organs are induced. When a boy loses his testes before puberty, a state of eunuchism ensues in which he continues to have infantile sex organs and other infantile sexual characteristics throughout life. The height of an adult eunuch is slightly greater than that of a normal man because the bone epiphyses are slow to unite, although the bones are quite thin and the muscles are considerably weaker than those of a normal man. The voice is childlike, there is no loss of hair on the head, and the normal adult masculine hair distribution on the face and elsewhere does not occur.

When a man is castrated after puberty, some of his male secondary sexual characteristics revert to those of a child and others remain of adult masculine character. The sexual organs regress slightly in size but not

to a childlike state, and the voice regresses from the bass quality only slightly. Conversely, there is loss of masculine hair production, loss of the thick masculine bones, and loss of the musculature of the virile male. Also in a castrated adult male, sexual desires are decreased but not lost, provided sexual activities have been practiced previously.

Testicular tumors and hypergonadism in the male

Interstitial Leydig cell tumors develop in rare instances in the testes, but when they do develop, they sometimes produce as much as 100 times the normal quantities of testosterone. When such tumors develop in young children, they cause rapid growth of the musculature and bones but also cause early uniting of the epiphyses, so that the eventual adult height actually is considerably less than that which would have been achieved otherwise. Such interstitial cell tumors also cause excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics. In the adult male, small interstitial cell tumors are difficult to diagnose because masculine features are already present.

Female physiology and female hormones

Female reproductive functions can be divided into two major phases:

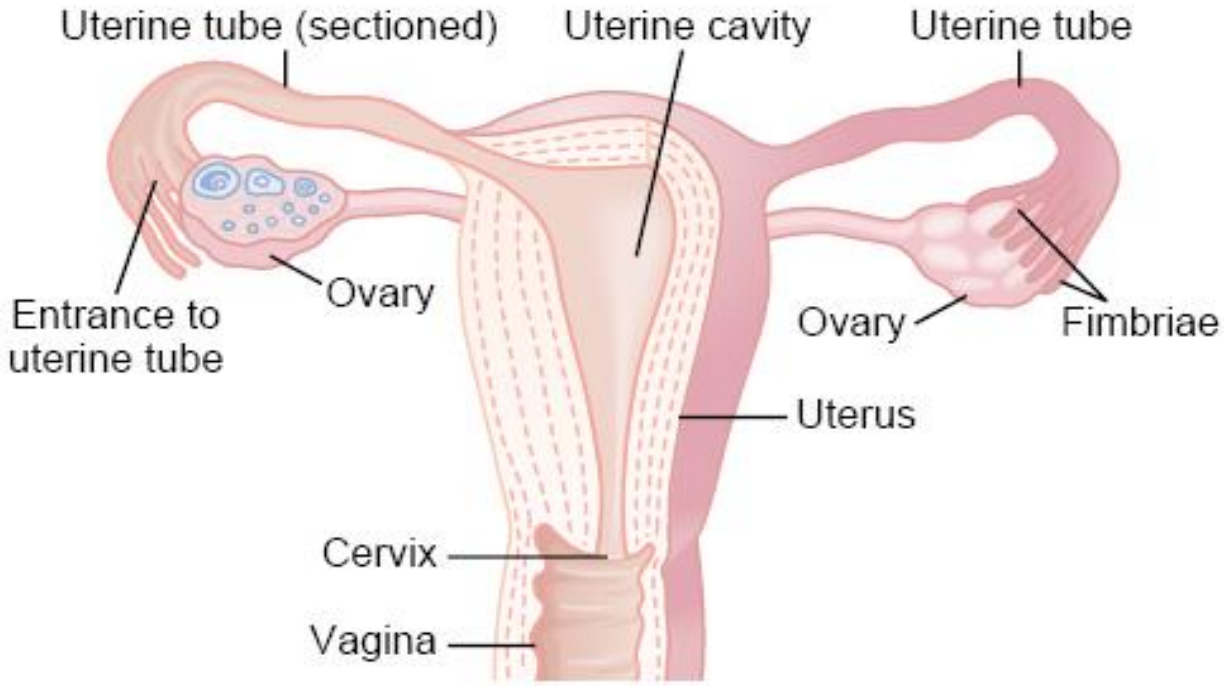
(1) Preparation of the female body for conception and pregnancy.

(2) The period of pregnancy itself. This lecture is concerned with preparation of the female body for pregnancy, and the physiology of pregnancy and childbirth.

Physiologic anatomy of the female sexual organs

Figure below show the principal organs of the human female reproductive tract, the most important of which are the ovaries, fallopian tubes, uterus, and vagina. Reproduction begins with the development of ova in the ovaries. In the middle of each monthly sexual cycle, a single ovum is expelled from an ovarian follicle into the abdominal cavity near the open fimbriated ends of the two fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus; if it has been fertilized by a sperm, it implants in the uterus, where it develops into a fetus, a placenta, and fetal membranes and eventually into a baby.

During fetal life, the outer surface of the ovary is covered by a germinal epithelium, as the female fetus develops; primordial ova differentiate from this germinal epithelium and migrate into the substance of the ovarian cortex. Each ovum then collects around it a layer of spindle cells from the ovarian stroma and causes them to take on epithelioid characteristics; they are then called granulosa cells. The ovum surrounded by a single layer of granulosa cells is called a primordial follicle. The ovum itself at this stage is still immature, requiring two more cell divisions before it can be fertilized by a sperm. At this time, the ovum is called a primary oocyte. During all the reproductive years of adult life, between about 13 and 46 years of age, 400 to 500 of the primordial follicles develop enough to expel their ova—one each month; the remainder degenerate. At the end of reproductive capability (at menopause), only a few primordial follicles remain in the ovaries, and even these degenerate soon thereafter.



Female hormonal system

The female hormonal system, like that of the male, consists of three hierarchies of hormones, as follows:

1. A hypothalamic releasing hormone, gonadotropin-releasing hormone (GRH)

2. The anterior pituitary sex hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both of which are secreted in response to the release of GRH from the hypothalamus.

3. The ovarian hormones, estrogen and progesterone, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland.

These various hormones are not secreted in constant amounts throughout the female monthly sexual cycle; they are secreted at drastically differing rates during different parts of the cycle. The amount of GRH released from the hypothalamus increases and decreases much less drastically during the monthly sexual cycle. It is secreted in short pulses averaging once every 90 minutes, as occurs in the male.

Monthly ovarian cycle; function of the gonadotropic hormones

The normal reproductive years of the female are characterized by monthly rhythmical changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. This rhythmical pattern is called the female monthly sexual cycle (or, less accurately, the menstrual cycle). The duration of the cycle averages 28 days. It may be as short as 20 days or as long as 45 days in some women, although abnormal cycle length is frequently associated with decreased fertility.

There are two significant results of the female sexual cycle.

1. Only a single ovum is normally released from the ovaries each month, so that normally only a single fetus will begin to grow at a time.

2. The uterine endometrium is prepared in advance for implantation of the fertilized ovum at the required time of the month.

Gonadotropic hormones and their effects on the ovaries

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, secreted by the anterior pituitary gland. In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted. At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years. This period of change is called puberty, and the time of the first menstrual cycle is called menarche. During each

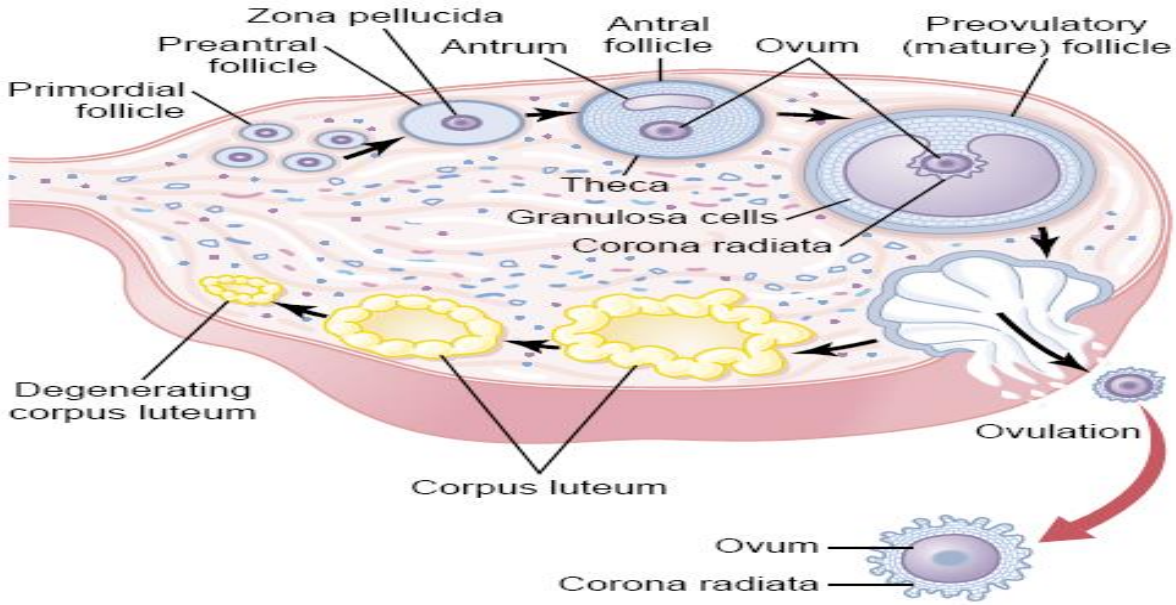
month of the female sexual cycle, there is a cyclical increase and decrease of both FSH and LH. These cyclical variations cause cyclical ovarian changes. Both FSH and LH stimulate their ovarian target cells by combining with highly specific FSH and LH receptors in the ovarian target cell membranes. In turn, the activated receptors increase the cells' rates of secretion and usually the growth and proliferation of the cells as well.

Ovarian follicle growth— "Follicular" phase of the ovarian cycle

Figure below shows the progressive stages of follicular growth in the ovaries. When a female child is born, each ovum is surrounded by a single layer of granulose cells; the ovum, with this granulosa cell sheath, is called a ***primordial follicle****, as shown in the figure. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an oocyte maturation-inhibiting factor that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division. Then, after*

puberty, when FSH and LH from the anterior pituitary gland begin to be secreted in significant quantities, the ovaries, together with some of the follicles within them, begin to grow.

The first stage of follicular growth is moderate enlargement of the ovum itself, which increases in diameter twofold to threefold. Then follows growth of additional layers of granulosa cells in some of the follicles; these follicles are known as ***primary follicles****.*



Development of antral and vesicular follicles.

During the first few days of each monthly female sexual cycle, the concentrations of both FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month. The initial effect is rapid proliferation of the granulosa cells, giving rise to many more layers of these cells. In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells called the theca. This is divided into two layers. In the ***theca interna****, the cells take on epithelioid characteristics similar to those of the granulose cells and develop the ability to secrete additional steroid sex hormones (estrogen and progesterone).*

The outer layer, the ***theca externa****, develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle. After the early proliferative phase of growth, lasting for a few days, the mass of granulosa cells secretes a follicular fluid that contains a high concentration of estrogen, one of the important female sex hormones. Accumulation of this fluid causes an antrum to appear within the mass of granulosa cells, as shown in figure above.*

Only one follicle fully matures each month, and the remainder undergo atresia.

After a week or more of growth— but before ovulation occurs—one of the follicles begins to outgrow all the others; the remaining 5 to 11 developing follicles involute (a process called atresia), and these follicles are said to become atretic. The cause of the atresia is unknown, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute.

This process of atresia is important, because it normally allows only one of the follicles to grow large enough each month to ovulate; this usually prevents more than one child from developing with each

pregnancy. The single follicle reaches a diameter of 1 to 1.5 centimeters at the time of ovulation and is called the mature follicle.

Ovulation

Ovulation in a woman who has a normal 28-day female sexual cycle occurs 14 days after the onset of menstruation. Shortly before ovulation, the protruding outer wall of the follicle swells rapidly, and a small area in the center of the follicular capsule, called the ***stigma****, protrudes like a nipple. In another 30 minutes or so, fluid begins to ooze from the follicle through the stigma, and about 2 minutes later, the stigma ruptures widely, allowing a more viscous fluid, which has occupied the central portion of the follicle, to evaginate outward. This viscous fluid carries with it the ovum surrounded by a mass of several thousand small granulosa cells, called the* ***corona radiata****.*

Surge of LH is necessary for ovulation.

LH is necessary for final follicular growth and ovulation. Without this hormone, even when large quantities of FSH are available, the follicle will not progress to the stage of ovulation. About 2 days before ovulation (for reasons that are not completely understood), the rate of secretion of LH by the anterior pituitary gland increases markedly, rising 6- to 10-fold and peaking about 16 hours before ovulation. FSH also increases about 2-fold to 3-fold at the same time, and the FSH and LH act synergistically to cause rapid swelling of the follicle during the last few days before ovulation. The LH also has a specific effect on the granulosa and theca cells, converting them mainly to progesterone-secreting cells. Therefore, the rate of secretion of estrogen begins to fall about 1 day before ovulation, while increasing amounts of progesterone begin to be secreted. It is in this environment of:

(1) Rapid growth of the follicle.

(2) Diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion.

(3) Initiation of secretion of progesterone that ovulation occurs.

Without the initial preovulatory surge of LH, ovulation will not take place.

Initiation of ovulation.

The initiation of ovulation, showing the role of the large quantity of LH secreted by the anterior pituitary gland. This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation:

(1) The theca externa (the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma.

(2) Simultaneously, there is rapid growth of new blood vessels into the follicle wall, and at the same time, prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues. These two effects cause plasma transudation into the follicle, which contributes to follicle swelling.

(3) Finally, the combination of follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum.

Corpus luteum—"Luteal" phase of the ovarian cycle

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into lutein cells. They enlarge in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance. This process is called luteinization, and the total mass of cells together is called the corpus luteum. A well-developed vascular supply also grows into the ***corpus luteum****. The granulosa cells in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones progesterone and estrogen. The theca cells form mainly the androgens androstenedione and testosterone rather than female sex hormones. However, most of these hormones are also converted by the granulosa cells into the female hormones.*

In the normal female, the corpus luteum grows to about 1.5 centimeters in diameter, reaching this stage of development 7 to 8 days after ovulation. Then it begins to involute and eventually loses its secretory function as well as its yellowish, lipid characteristic about 12 days after ovulation, becoming the ***corpus albicans****; during the ensuing few weeks, this is replaced by connective tissue and over months is absorbed.*

Involution of the corpus luteum and onset of the next ovarian cycle.

Estrogen in particular and progesterone to a lesser extent, secreted by the corpus luteum during the luteal phase of the ovarian cycle, have strong feedback effects on the anterior pituitary gland to maintain low secretory rates of both FSH and LH. In addition, the lutein cells secrete small amounts of the hormone ***inhibin****, the same as the inhibin secreted by the Sertoli cells of the male testes. This hormone inhibits secretion by the anterior pituitary gland, especially FSH secretion. Low blood concentrations of both FSH and LH result, and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called involution of the corpus luteum. Final involution normally occurs at the end of almost exactly 12 days of corpus luteum life, which is around the 26th day of the normal female sexual cycle, 2 days before menstruation begins. At this time, the sudden cessation of secretion of estrogen, progesterone, and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH initiate the growth of new follicles, beginning a new ovarian cycle. The paucity of secretion of progesterone and estrogen at this time also leads to menstruation by the uterus, as explained later.*

Summary

About every 28 days, gonadotropic hormones from the anterior pituitary gland cause about 8 to 12 new follicles to begin to grow in the ovaries. One of these follicles finally becomes "mature" and ovulates on the 14th day of the cycle. During growth of the follicles, mainly estrogen is secreted. After ovulation, the secretory cells of the ovulating follicle develop into a corpus luteum that secretes large quantities of both the major female hormones, progesterone and estrogen. After another 2 weeks, the corpus luteum degenerates, whereupon the ovarian hormones estrogen and progesterone decrease greatly, and menstruation begins. A new ovarian cycle then follows.

Functions of the ovarian hormones—Estradiol and Progesterone

The two types of ovarian sex hormones are the estrogens and the progestins. By far the most important of the estrogens is the hormone estradiol, and by far the most important progestin is progesterone. The estrogens mainly promote proliferation and growth of specific cells in the body that are responsible for the development of most secondary sexual characteristics of the female. The progestins function mainly to prepare the uterus for pregnancy and the breasts for lactation.

Chemistry of the sex hormones

A. Estrogens.

In the normal nonpregnant female, estrogens are secreted in significant quantities only by the ovaries, although minute amounts are also secreted by the adrenal cortices. During pregnancy, tremendous quantities of estrogens are also secreted by the placenta; only three estrogens are present in significant quantities in the plasma of the human female: b-estradiol, estrone, and estriol. The principal estrogen secreted by the ovaries is b-estradiol. Small amounts of estrone are also secreted, but most of this is formed in the peripheral tissues from androgens secreted by the adrenal cortices and by ovarian thecal cells. Estriol is a weak estrogen. The estrogenic potency of b-estradiol is 12 times that of estrone and 80 times that of estriol. Considering these relative potencies, one can see that the total estrogenic effect of b-estradiol is usually many times that of the other two together. For this reason, bestradiol is considered the major estrogen, although the estrogenic effects of estrone are not negligible.

B. Progestins.

By far the most important of the progestins is progesterone. However, small amounts of another progestin, 17-a-hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects. Yet, for practical purposes, it is usually reasonable to consider progesterone the only important progestin. In the normal nonpregnant female, progesterone is secreted in significant amounts only during the latter half of each ovarian cycle, when it is secreted by the corpus luteum. Large amounts of progesterone are also secreted by the placenta during pregnancy, especially after the fourth month of gestation.

Functions of the estrogens;

A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.

1. Effect of estrogens on the uterus and external female sex organs.

During childhood, estrogens are secreted only in minute quantities, but at puberty, the quantity secreted in the female under the influence of the pituitary gonadotropic hormones increases 20-fold or more. At this time, the female sex organs change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus, and vagina all increase several times in size. Also, the external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and enlargement of the labia minora. During the first few years after puberty, the size of the uterus increases twofold to threefold, but more important than the increase in uterus size are the changes that take place in the uterine endometrium under the influence of estrogens. Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands, which will later aid in providing nutrition to the implanted ovum.

2. Effect of estrogens on the fallopian tubes.

The estrogens' effect on the mucosal lining of the fallopian tubes is similar to that on the uterine endometrium. They cause the glandular tissues of this lining to proliferate; especially important, they cause the number of ciliated epithelial cells that line the fallopian tubes to increase. Also, activity of the cilia is considerably enhanced. These cilia always beat toward the uterus, which helps propel the fertilized ovum in that direction.

3. Effect of estrogens on the breasts.

The primordial breasts of females and males are exactly alike. In fact, under the influence of appropriate hormones, the masculine breast during the first 2 decades of life can develop sufficiently to produce milk in the same manner as the female breast. Estrogens caused development of the stromal tissues of the breasts, growth of an extensive ductile system and deposition of fat in the breasts.

The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin that cause the ultimate determinative growth and function of these structures. In summary, the estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast.

4. Effect of estrogens on the skeleton.

Estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth. At puberty, when the female enters her reproductive years, her growth in height becomes rapid for several years. However, estrogens have another potent effect on skeletal growth: They cause uniting of the epiphyses with the shafts of the long bones. This effect of estrogen in the female is much stronger than the similar effect of testosterone in the male. As a result, growth of the female usually ceases several years earlier than growth of the male.

5. Osteoporosis of the bones caused by estrogen deficiency in old age.

After menopause, almost no estrogens are secreted by the ovaries. This estrogen deficiency leads to

(1) Increased osteoclastic activity in the bones.

(2) Decreased bone matrix.

(3) Decreased deposition of bone calcium and phosphate.

In some women, this effect is extremely severe, and the resulting condition is osteoporosis. Because this can greatly weaken the bones and lead to bone fracture, especially fracture of the vertebrae, a large share of postmenopausal women are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

6. Effect of estrogens on protein deposition.

Estrogens cause a slight increase in total body protein, which is evidenced by a slight positive nitrogen balance when estrogens are administered. This mainly results from the growth-promoting effect of estrogen on the sexual organs, the bones, and a few other tissues of the body. The enhanced protein deposition caused by testosterone is much more general and many times as powerful as that caused by estrogens.

7. Effect of estrogens on body metabolism and fat deposition.

Estrogens increase the whole-body metabolic rate slightly, but only about one third as much as the increase caused by the male sex hormone testosterone. They also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in the female body is considerably greater than that in the male body, which contains more protein. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause the deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure.

8. Effect of estrogens on hair distribution.

Estrogens do not greatly affect hair distribution. However, hair does develop in the pubic region and in the axillae after puberty. Androgens formed in increased quantities by the female adrenal glands after puberty are mainly responsible for this.

9. Effect of estrogens on the skin.

Estrogens cause the skin to develop a texture that is soft and usually smooth, but even so, the skin of a woman is thicker than that of a child or a castrated female. Also, estrogens cause the skin to become more vascular; this is often associated with increased warmth of the skin and also promotes greater bleeding of cut surfaces than is observed in men.

10. Effect of estrogens on electrolyte balance.

The chemical similarity of estrogenic hormones to adrenocortical hormones has been pointed out. Estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. This effect of estrogens is normally slight and rarely of significance, but during pregnancy, the tremendous formation of estrogens by the placenta may contribute to body fluid retention.

Lec.14 **Dr.Latief Fayadh**

Functions of progesterone

1. Effect of progesterone on the uterus.

By far the most important function of progesterone is to promote secretory changes in the uterine endometrium during the latter half of the monthly female sexual cycle, thus preparing the uterus for implantation of the fertilized ovum. In addition to this effect on the endometrium, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.

2. Effect of progesterone on the fallopian tubes.

Progesterone also promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube before implantation.

3. Effect of progesterone on the breasts.

Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. However, progesterone does not cause the alveoli to secrete milk; milk is secreted only after the prepared breast is further stimulated by prolactin from the anterior pituitary gland. Progesterone also causes the breasts to swell. Part of this swelling is due to the

secretory development in the lobules and alveoli, but part also results from increased fluid in the subcutaneous tissue.

Monthly endometrial cycle and menstruation

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that operates through the following stages:

(1) Proliferation of the uterine endometrium. ***(Estrogen Phase)***

(2) Development of secretory changes in the endometrium. ***(Progestational Phase)***

(3) Desquamation of the endometrium, which is known as menstruation. The various phases of this endometrial cycle are shown in figure below.

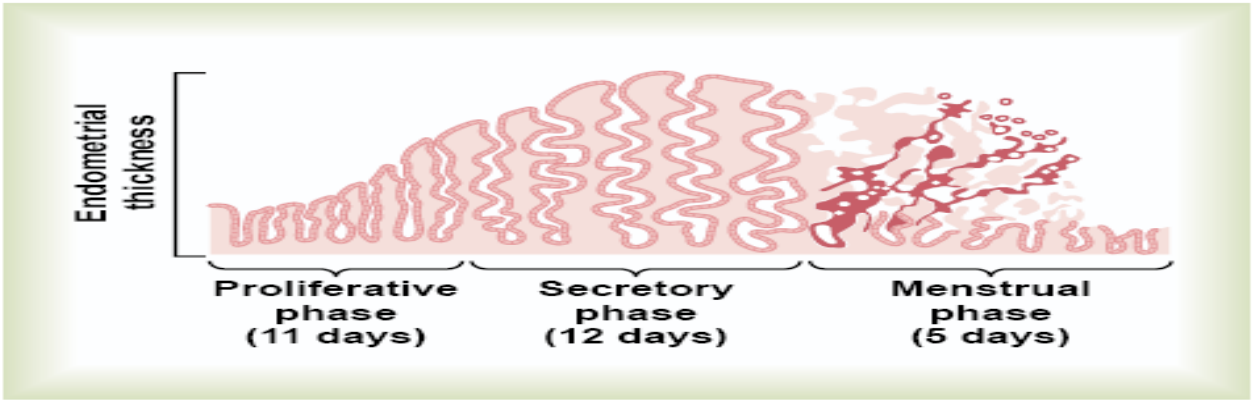


Figure 81–7

Phases of endometrial growth and menstruation during each monthly female sexual cycle.

1. Proliferative phase of the endometrial cycle, occurring before ovulation.

At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation. After menstruation, only a thin layer of endometrial stroma remains, and the only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium. Under the influence of estrogens, secreted in increasing quantities by the ovary during the first part of the monthly ovarian cycle, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is reepithelialized within 4 to 7 days after the beginning of menstruation. Then, during the next week and a half—that is, before ovulation occurs—the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells and to progressive growth of the endometrial glands and new blood vessels into the endometrium. At the time of ovulation, the endometrium is 3 to 5 millimeters thick. The endometrial glands, especially those of the cervical region, secrete thin, stringy mucus. The mucus strings actually align themselves along the length of the cervical canal, forming channels that help guide sperm in the proper direction from the vagina into the uterus.

2. Secretory phase of the endometrial cycle, occurring after ovulation.

During most of the latter half of the monthly cycle, after ovulation has occurred, progesterone and estrogen together are secreted in large quantities by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity; an excess of secretory substances accumulates in the glandular epithelial cells. Also, the cytoplasm of the stromal cells increases; and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters. The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a fertilized ovum during the latter half of the monthly cycle. From the time a fertilized ovum enters the uterine cavity from the fallopian tube until the time the ovum implants the uterine secretions, called "uterine milk," provide nutrition for the early dividing ovum.

3. Menstruation.

If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum in the ovary suddenly involutes, and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion, Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle. The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium itself to about 65 per cent of its previous thickness. Then, during the 24 hours preceding the onset of menstruation, the tortuous blood vessels leading to the mucosal layers of the endometrium become vasospastic, presumably because of some effect of involution, such as release of a vasoconstrictor material—possibly one of the vasoconstrictor types of prostaglandins that are present in abundance at this time.

During normal menstruation, approximately 40 milliliters of blood and an additional 35 milliliters of serous fluid are lost. The menstrual fluid is normally nonclotting because a fibrinolysin is released along with the necrotic endometrial material. If excessive bleeding occurs from the uterine surface, the quantity of fibrinolysin may not be sufficient to prevent clotting. The presence of clots during menstruation is often clinical evidence of uterine pathology. Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized.

Puberty and menarche

Puberty means the onset of adult sexual life, and menarche means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, , and usually culminating in the onset of puberty and menstruation between ages 11 and 16 years in girls (average, 13 years). In the female, as in the male, the infantile pituitary gland and ovaries are capable of full function if appropriately stimulated. However, as is also true in the male, and for reasons not understood, the hypothalamus does not secrete significant quantities of GRH during childhood. Experiments have shown that the hypothalamus itself is capable of secreting this hormone, but the appropriate signal from some other area of brain to cause the secretion is lacking. Therefore, it is now believed that the onset of puberty is initiated by some maturation process that occurs elsewhere in the brain, perhaps somewhere in the limbic system. Figure below shows:

(1) The increasing levels of estrogen secretion at puberty.

(2) The cyclical variation during the monthly sexual cycle.

(3) The further increase in estrogen secretion during the first few years of reproductive life.

(4) The progressive decrease in estrogen secretion toward the end of reproductive life, and, finally.

(5) Almost no estrogen or progesterone secretion beyond menopause.

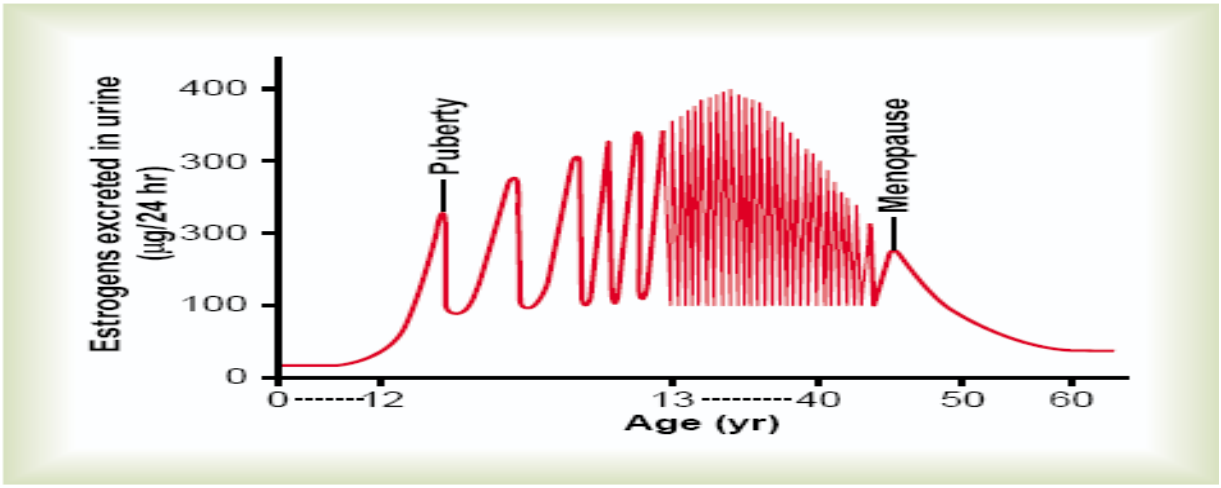


Figure 81–10

Estrogen secretion throughout the sexual life of the female human being.

Menopause.

At age 40 to 50 years, the sexual cycle usually becomes irregular, and ovulation often fails to occur. After a few months to a few years, the cycle ceases altogether, as shown in Figure above. The period during which the cycle ceases and the female sex hormones diminish to almost none is called menopause. The cause of menopause is "burning out" of the ovaries. Throughout a woman's reproductive life, about 400 of the primordial follicles grow into mature follicles and ovulate, and hundreds of thousands of ova degenerate. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH, and, as shown in Figure above the production of estrogens by the ovaries decreases as the number of primordial follicles approaches zero. At the time of menopause, a woman must readjust her life from one that has been physiologically stimulated by estrogen and progesterone production to one devoid of these hormones. The loss of estrogens often causes marked physiological changes in the function of the body, including:

(1) "Hot flushes" characterized by extreme flushing of the skin.

(2) Psychic sensations of dyspnea.

(3) Irritability.

(4) Fatigue.

(5) Anxiety.

(6) Occasionally various psychotic states.

(7) Decreased strength and calcification of bones throughout the body.

These symptoms are of sufficient magnitude in about 15 per cent of women to warrant treatment. If counseling fails, daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women can likely avoid severe symptoms.

Abnormalities of Secretion by the Ovaries

A. Hypogonadism.

Less than normal secretion by the ovaries can result from poorly formed ovaries, lack of ovaries, or genetically abnormal ovaries that secrete the wrong hormones because of missing enzymes in the secretory cells. When ovaries are absent from birth or when they become nonfunctional before puberty, female eunuchism occurs. In this condition, the usual secondary sexual characteristics do not appear, and the sexual organs remain infantile. Especially characteristic of this condition is prolonged growth of the long bones because the epiphyses do not unite with the shafts as early as they do in a normal woman. When the ovaries of a fully developed woman are removed, the sexual organs regress to some extent so that the uterus becomes almost infantile in size, the vagina becomes smaller, and the vaginal epithelium becomes thin and easily damaged. The breasts atrophy and become pendulous, and the pubic hair becomes thinner. The same changes occur in women after menopause.

B. Irregularity of menses, and amenorrhea caused by hypogonadism.

As pointed out in menopause, the quantity of estrogens produced by the ovaries must rise above a critical value in order to cause rhythmical sexual cycles. Consequently, in hypogonadism or when the gonads are secreting small quantities of estrogens, the ovarian cycle often does not occur normally. Instead, several months may elapse between menstrual periods, or menstruation may cease altogether (amenorrhea). Prolonged ovarian cycles are frequently associated with failure of ovulation, presumably because of insufficient secretion of LH at the time of the preovulatory surge of LH, which is necessary for ovulation.

C. Hypersecretion by the ovaries.

Extreme hypersecretion of ovarian hormones by the ovaries is a rare clinical entity, because excessive secretion of estrogens automatically decreases the production of gonadotropins by the pituitary, and this limits the production of ovarian hormones. Consequently, hypersecretion of feminizing hormones is usually recognized clinically only when a feminizing tumor develops. A rare granulosa cell tumor can develop in an ovary, occurring more often after menopause than before. These tumors secrete large quantities of estrogens, which exert the usual estrogenic effects, including hypertrophy of the uterine

endometrium and irregular bleeding from this endometrium. In fact, bleeding is often the first and only indication that such a tumor exists.

Female fertility

A. Fertile period of each sexual cycle.

The ovum remains viable and capable of being fertilized after it is expelled from the ovary probably no longer than 24 hours. Therefore, sperm must be available soon after ovulation if fertilization is to take place. A few sperm can remain fertile in the female reproductive tract for up to 5 days. Therefore, for fertilization to take place, intercourse must occur sometime between 4 and 5 days before ovulation up to a few hours after ovulation. Thus, the period of female fertility during each month is short, about 4 to 5 days.

B. Rhythm method of contraception.

One of the commonly practiced methods of contraception is to avoid intercourse near the time of ovulation. The difficulty with this method of contraception is predicting the exact time of ovulation. Yet the interval from ovulation until the next succeeding onset of menstruation is almost always between 13 and 15 days. Therefore, if the menstrual cycle is regular, with an exact periodicity of 28 days, ovulation usually occurs within 1 day of the 14^{th} day of the cycle. If, in contrast, the periodicity of the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. Finally, if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the 7th day of the cycle. Therefore, it is usually stated that avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward prevents conception.

C. Hormonal suppression of fertility—"The Pill."

It has long been known that administration of either estrogen or progesterone, if given in appropriate quantities during the first half of the monthly cycle, can inhibit ovulation. The reason for this is that appropriate administration of either of these hormones can prevent the preovulatory surge of LH secretion by the pituitary gland, which is essential in causing ovulation. The problem in devising methods for the hormonal suppression of ovulation has been in developing appropriate combinations of estrogens and progestins that suppress ovulation but do not cause other, unwanted effects. For instance, too much of either hormone can cause abnormal menstrual bleeding patterns. However, use of certain synthetic progestins in place of progesterone, along with small amounts of estrogens usually prevents ovulation yet allows an almost normal pattern of menstruation. Therefore, almost all "pills" used for the control of fertility consist of some combination of synthetic estrogens and synthetic progestins.