Endocrine System

The endocrine system consists of glands widely separated from each other with no physical connections. Endocrine glands are groups of secretory cells surrounded by an extensive network of capillaries that facilitates diffusion of hormones (chemical messengers) from the secretory cells into the bloodstream. They are also referred to as ductless glands because hormones diffuse directly into the bloodstream. Hormones are then carried in the bloodstream to target tissues and organs that may be quite distant, where they influence cell growth and metabolism.

Homeostasis of the internal environment is maintained partly by the autonomic nervous system and partly by the endocrine system. The autonomic nervous system is concerned with rapid changes, while endocrine control is mainly involved in slower and more precise adjustments.

Although the hypothalamus is classified as a part of the brain rather than an endocrine gland, it controls the pituitary gland and indirectly influences many others. The ovaries and the testes secrete hormones associated with the reproductive system after puberty. The placenta that develops to nourish the developing fetus during pregnancy also has an endocrine function. In addition to the main endocrine glands many other organs and tissues also secrete hormones as a secondary function e.g. adipose tissue produces leptin, involved in the regulation of appetite; the heart secretes atrial natriuretic peptide that acts on the kidneys. Other hormones do not travel to remote organs but act locally e.g. prostaglandins.

Positions of the endocrine glands
Classification of endocrine glands

There are three general classes of hormones:

1. Proteins and polypeptides, including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others.

2. Steroids secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone).

3. Derivatives of the amino acid tyrosine, secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine). There are no known polysaccharides or nucleic acid hormones.

1. Proteins and polypeptides hormone

Polypeptide and protein hormones are stored in secretory vesicles until needed. Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 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 bloodstream by exocytosis.

2. Steroid Hormones

Steroid hormones 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.

3. **Amine Hormones**

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

**Mechanisms of Action of Hormones**

**Hormone Receptors and Their Activation**

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 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.

**Intracellular Signalling After Hormone Receptor Activation**

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects.

When a hormone arrives at its target cell, it binds to a specific receptor, where it acts as a switch influencing chemical or metabolic reactions inside the cell. Receptors for peptide hormones are situated on the cell membrane and those for lipid-based hormones are located inside cells. A hormone is released in response to a specific stimulus and usually its action reverses or negates the stimulus through a negative feedback mechanism. This may be controlled either indirectly through the release of hormones by the hypothalamus and the anterior pituitary gland, e.g. steroid and thyroid hormones, or directly by blood levels of the stimulus, e.g. insulin and glucagon and determined by plasma glucose levels.

The effect of a positive feedback mechanism is amplification of the stimulus and increasing release of the hormone until a particular process is complete and the stimulus ceases, e.g. release of oxytocin during labour.
Negative feedback regulation (Regulation of hormone)

Negative feedback prevents overactivity of hormone systems. Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through negative feedback mechanisms that ensure a proper level of 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 over secretion 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.
Pituitary gland and Hypothalamus

The pituitary gland and the hypothalamus act as a unit, regulating the activity of most of the other endocrine glands. The pituitary gland lies in the hypophyseal fossa of the sphenoid bone below the hypothalamus, to which it is attached by a stalk. It is the size of a pea, weighs about 500 mg and consists of two main parts that originate from different types of cells. The anterior pituitary (adenohypophysis) is an upgrowth of glandular epithelium from the pharynx and the posterior pituitary (neurohypophysis) a downgrowth of nervous tissue from the brain. There is a network of nerve fibres between the hypothalamus and the posterior pituitary.

Anterior pituitary

The anterior pituitary is supplied indirectly with arterial blood that has already passed through a capillary bed in the hypothalamus. This network of blood vessels forms part of the pituitary portal system, which transports blood from the hypothalamus to the anterior pituitary where it enters thin-walled sinusoids that are in close contact with the secretory cells. As well as providing oxygen and nutrients, this blood transports releasing and inhibiting hormones secreted by the hypothalamus. These hormones specifically influence secretion and release of other hormones formed in the anterior pituitary. Some of the hormones secreted by the anterior lobe stimulate or inhibit secretion by other endocrine glands (target glands) while others have a direct effect on target tissues.

Secretion of an anterior pituitary hormone follows stimulation of the gland by a specific releasing hormone produced by the hypothalamus and carried to the gland through the pituitary portal system. The whole system is controlled by a negative feedback mechanism. That is, when the level of a hormone in the blood supplying the hypothalamus is low it produces the appropriate releasing hormone that stimulates release of a trophic hormone by the anterior pituitary. This in turn stimulates the target gland to produce and release its hormone. As a result the blood level of that hormone rises and inhibits secretion of its releasing factor by the hypothalamus.
Structure of lobes of the pituitary gland and their relationship with the hypothalamus

**Hormones and functions of pituitary gland**

**Growth hormone (GH)**
This is the most abundant hormone synthesised by the anterior pituitary. It stimulates growth and division of most body cells but especially those in the bones and skeletal muscles. Body growth in response to the secretion of GH is evident during childhood and adolescence, and thereafter secretion of GH maintains the mass of bones and skeletal muscles. It also regulates aspects of metabolism in many organs, e.g. liver, intestines and pancreas; stimulates protein synthesis, especially tissue growth and repair; promotes breakdown of fats and increases blood glucose levels.

**Thyroid stimulating hormone (TSH)**
The release of this hormone is stimulated by thyrotrophin releasing hormone (TRH) from the hypothalamus. It stimulates growth and activity of the thyroid gland, which secretes the hormones thyroxine (T4) and tri-iodothyronine (T3). Release is lowest in the early evening and highest during the night. Secretion is regulated by a negative feedback mechanism, i.e. when the blood level of thyroid hormones is high, secretion of TSH is reduced, and vice versa.
**Adrenocorticotrophic hormone (ACTH, corticotrophin)**
Corticotrophin releasing hormone (CRH) from the hypothalamus promotes the synthesis and release of ACTH by the anterior pituitary. This increases the concentration of cholesterol and steroids within the adrenal cortex and the output of steroid hormones, especially cortisol.

**Prolactin**
This hormone is secreted during pregnancy to prepare the breasts for lactation (milk production) after childbirth. The blood level of prolactin is stimulated by prolactin releasing hormone (PRH) released from the hypothalamus and it is lowered by prolactin inhibiting hormone (PIH, dopamine) and by an increased blood level of prolactin. Prolactin, together with oestrogens, corticosteroids, insulin and thyroxine, is involved in initiating and maintaining lactation. Prolactin secretion is related to sleep, rising during any period of sleep, night or day.

**Gonadotrophins**
Just before puberty two gonadotrophins (sex hormones) are secreted in gradually increasing amounts by the anterior pituitary in response to luteinising hormone releasing hormone (LHRH), also known as gonadotrophin releasing hormone (GnRH). Rising levels of these hormones at puberty promotes mature functioning of the reproductive organs. In both males and females the hormones responsible are:
- Follicle stimulating hormone (FSH)
- Luteinising hormone (LH).

**In both sexes:** FSH stimulates production of gametes (ova or spermatozoa) by the gonads.

**In females:** LH and FSH are involved in secretion of the hormones oestrogen and progesterone during the menstrual cycle. As the levels of oestrogen and progesterone rise, secretion of LH and FSH is suppressed.

**In males:** LH, also called interstitial cell stimulating hormone (ICSH) stimulates the interstitial cells of the testes to secrete the hormone testosterone.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone (GH)</td>
<td>Regulates metabolism, promotes tissue growth especially of bones and muscles</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>Stimulates growth and activity of thyroid gland and secretion of T3 and T4</td>
</tr>
<tr>
<td>Adrenocorticotrophic hormone (ACTH)</td>
<td>Stimulates the adrenal cortex to secrete glucocorticoids</td>
</tr>
<tr>
<td>Prolactin (PRL)</td>
<td>Stimulates growth of breast tissue and milk production</td>
</tr>
<tr>
<td>Follicle stimulating hormone (FSH)</td>
<td>Stimulates production of sperm in the testes, stimulates secretion of oestrogen by the ovaries, maturation of ovarian follicles, ovulation</td>
</tr>
<tr>
<td>Luteinising hormone (LH)</td>
<td>Stimulates secretion of testosterone by the testes, stimulates secretion of progesterone by the corpus luteum</td>
</tr>
</tbody>
</table>

Summary of the hormones secreted by the anterior pituitary gland and their functions
Posterior pituitary

The posterior pituitary is formed from nervous tissue and consists of nerve cells surrounded by supporting glial cells called pituicytes. These neurones have their cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus and their axons form a bundle known as the hypothalamohypophyseal tract. Posterior pituitary hormones are synthesised in the nerve cell bodies, transported along the axons and stored in vesicles within the axon terminals in the posterior pituitary. Oxytocin and antidiuretic hormone (ADH, vasopressin) are the hormones released from axon terminals within the posterior pituitary. These hormones act directly on non-endocrine tissue.

Oxytocin

Oxytocin stimulates two target tissues during and after childbirth (parturition): uterine smooth muscle and the muscle cells of the lactating breast. During childbirth increasing amounts of oxytocin are released from the posterior pituitary into the bloodstream in response to increasing stimulation of sensory stretch receptors in the uterine cervix as the baby’s head progressively dilates it. Sensory impulses are generated and travel to the control centre in the hypothalamus, stimulating the posterior pituitary to release more oxytocin. In turn this stimulates more forceful uterine contractions and greater stretching of the uterine cervix as the baby’s head is forced further downwards. This is an example of a positive feedback mechanism which stops soon after the baby is delivered when distension of the uterine cervix is greatly reduced.

The process of milk ejection also involves a positive feedback mechanism. Suckling generates sensory impulses that are transmitted from the breast to the hypothalamus. The impulses trigger release of oxytocin from the posterior pituitary. On reaching the lactating breast, oxytocin stimulates contraction of the milk ducts and myoepithelial cells around the glandular cells, ejecting milk. Suckling also inhibits the release of prolactin inhibiting hormone (PIH), prolonging prolactin secretion and lactation.

Antidiuretic hormone (ADH, vasopressin)

The main effect of antidiuretic hormone is to reduce urine output (diuresis is the production of a large volume of urine). ADH acts on the distal convoluted tubules and collecting ducts of the nephrons of the kidneys. It increases their permeability to water and more of the glomerular filtrate is reabsorbed. ADH secretion is determined by the osmotic pressure of the blood circulating to the osmoreceptors in the hypothalamus.
As osmotic pressure rises, for example as a result of dehydration, secretion of ADH increases. More water is therefore reabsorbed and the urine output is reduced. This means that the body retains more water and the rise in osmotic pressure is reversed. Conversely, when the osmotic pressure of the blood is low, for example after a large fluid intake, secretion of ADH is reduced, less water is reabsorbed and more urine is produced.

**Thyroid gland**

The thyroid gland is situated in the neck in front of the larynx and trachea at the level of the 5th, 6th and 7th cervical and 1st thoracic vertebrae. It is a highly vascular gland that weighs about 25 g and is surrounded by a fibrous capsule. It resembles a butterfly in shape, consisting of two lobes, one on either side of the thyroid cartilage and upper cartilaginous rings of the trachea. The lobes are joined by a narrow isthmus, lying in front of the trachea. The lobes are roughly cone shaped, about 5 cm long and 3 cm wide.

The arterial blood supply to the gland is through the superior and inferior thyroid arteries. The superior thyroid artery is a branch of the external carotid artery and the inferior thyroid artery is a branch of the subclavian artery. The venous return is by the thyroid veins, which drain into the internal jugular veins.

The recurrent laryngeal nerves pass upwards close to the lobes of the gland and, especially on the right side, lie near the inferior thyroid artery.
The gland is composed of largely spherical follicles formed from cuboidal epithelium. These secrete and store colloid, a thick sticky protein material. Between the follicles are other cells found singly or in small groups: parafollicular cells, also called C-cells, which secrete the hormone calcitonin.

**Thyroxine and tri-iodothyronine**

Iodine is essential for the formation of the thyroid hormones, thyroxine (T4) and tri-iodothyronine (T3), so numbered as these molecules contain four and three atoms of the element iodine respectively. The main dietary sources of iodine are seafood, vegetables grown in iodine-rich soil and iodinated table salt. The thyroid gland selectively takes up iodine from the blood, a process called iodine trapping.

Thyroid hormones are synthesised as large precursor molecules called thyroglobulin, the major constituent of colloid. The release of T3 and T4 into the blood is stimulated by thyroid stimulating hormone (TSH) from the anterior pituitary.

Negative feedback regulation of the secretion of thyroxine (T4) and tri-iodothyronine (T3)
**Regulation and functions of Thyroid hormone**

Secretion of TSH is stimulated by thyrotrophin releasing hormone (TRH) from the hypothalamus and secretion of TRH is stimulated by exercise, stress, malnutrition, low plasma glucose levels and sleep. TSH secretion depends on the plasma levels of T3 and T4 because it is these hormones that control the sensitivity of the anterior pituitary to TRH. Through the negative feedback mechanism, increased levels of T3 and T4 decrease TSH secretion and vice versa. Dietary iodine deficiency greatly increases TSH secretion causing proliferation of thyroid gland cells and enlargement of the gland (goitre).

Thyroid hormones enter the cell nucleus and regulate gene expression, i.e. they increase or decrease protein synthesis. They enhance the effects of other hormones, e.g. adrenaline (epinephrine) and noradrenaline (norepinephrine). T3 and T4 affect most cells of the body by:

- Increasing the basal metabolic rate and heat production
- Regulating metabolism of carbohydrates, proteins and fats.

T3 and T4 are essential for normal growth and development, especially of the skeleton and nervous system. Most other organs and systems are also influenced by thyroid hormones. Physiological effects of T3 and T4 on the heart, skeletal muscles, skin, digestive and reproductive systems are more evident when there is underactivity or overactivity of the thyroid gland and can be profound in childhood.

**Calcitonin**

This hormone is secreted by the parafollicular or C-cells in the thyroid gland (Fig. 9.9). Calcitonin lowers raised blood calcium (Ca2+) levels. It does this by acting on:

- Bone cells promoting their storage of calcium
- Kidney tubules inhibiting the reabsorption of calcium.

Its effect is opposite to that of parathyroid hormone, the hormone secreted by the parathyroid glands. Release of calcitonin is stimulated by increased blood calcium levels. This hormone is important during childhood when bones undergo considerable changes in size and shape.
Parathyroid glands

There are four small parathyroid glands, each weighing around 50 g, two embedded in the posterior surface of each lobe of the thyroid gland. They are surrounded by fine connective tissue capsules that contain spherical cells arranged in columns with sinusoids containing blood in between them.

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.
Functions

Effect of Parathyroid Hormone on Calcium and Phosphate Concentrations in the Extracellular Fluid: Parathyroid Hormone Increases Calcium and Phosphate 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.

Rapid Phase of Calcium and Phosphate Absorption—Osteolysis: When large quantities of PTH are injected, the calcium ion concentration in the blood begins to rise within minutes, long before any new bone cells can be developed. Histological and physiologic studies have shown that PTH causes removal of bone salts from two areas in the bone: (1) from the bone matrix in the vicinity of the osteocytes lying within the bone itself and (2) in the vicinity of the osteoblasts along the bone surface.

Parathyroid Hormone Decreases Calcium Excretion and Increases Phosphate 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. Parathyroid hormone increases intestinal absorption of calcium and phosphate at this point.

These glands secrete parathyroid hormone (PTH, parathormone). Secretion is regulated by blood calcium levels. When they fall, secretion of PTH is increased and vice versa. The main function of PTH is to increase blood calcium levels. This is achieved by increasing the calcium absorption from the small intestine and reabsorption from the renal tubules. If these sources provide inadequate supplies then PTH stimulates osteoclasts (bone-destroying cells) and calcium is released from bones into the blood.
Parathormone and calcitonin from the thyroid gland act in a complementary manner to maintain blood calcium levels within the normal range. This is needed for:

- Muscle contraction
- Transmission of nerve impulses
- Blood clotting
- Normal action of many enzymes.

**Control of Parathyroid Secretion by Calcium 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 rickets, in which the level of calcium is usually depressed only a small amount; also, they become greatly enlarged in pregnancy, even though the decrease in calcium ion concentration in the mother’s extracellular fluid is hardly measurable; and they are greatly enlarged 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, and (3) bone absorption caused by factors other than PTH (for example, bone absorption caused by disuse of the bones).

**Disorders of Parathyroid Hormone**

**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.

**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.

**Osteoporosis—Decreased Bone Matrix**

Osteoporosis is the most common of all bone diseases in adults, especially in old age. It is different from osteo-malacia 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 cause of the diminished bone is excess osteoclastic activity.

**Disorders of Pituitary Hormone**

**Hypersecretion of anterior pituitary hormones**

**Gigantism and acromegaly**

The most common cause is prolonged hypersecretion of growth hormone (GH), usually by a hormone-secreting pituitary tumour. The conditions are occasionally due to excess growth hormone releasing hormone (GHRH) secreted by the hypothalamus. As the tumour increases in size, compression of nearby structures may lead to hyposecretion of other pituitary hormones (from both lobes) and damage to the optic nerves, causing visual disturbances. The effects of excess GH include:

- Excessive growth of bones
- Enlargement of internal organs
- Formation of excess connective tissue
- Enlargement of the heart and raised blood pressure
- Reduced glucose tolerance and a predisposition to diabetes mellitus.

**Gigantism:** This occurs in children when there is excess GH while epiphyseal cartilages of long bones are still growing, i.e. before ossification of bones is complete. It is evident mainly in the bones of the limbs, and affected individuals may grow to heights of 2.1 to 2.4 m, although body proportions remain normal.

**Acromegaly:** This means ‘large extremities’ and occurs in adults when there is excess GH after ossification is complete. The bones become abnormally thick and there is also thickening of the soft tissues. These changes are most noticeable as coarse facial features.
(especially excessive growth of the lower jaw), an enlarged tongue and excessively large hands and feet.

**Hyperprolactinaemia**

This is caused by a tumour that secretes large amounts of prolactin. It causes galactorrhoea (inappropriate milk secretion), amenorrhoea (cessation of menstruation) and sterility in women and impotence in men.

**Ischaemic necrosis**

**Simmond’s disease** is hypofunction of the anterior pituitary gland, which only rarely affects the posterior lobe. The arrangement of the blood supply makes the gland unusually susceptible to a fall in systemic BP. Severe hypotensive shock may cause ischaemic necrosis. The effects include deficient stimulation of target glands and hypofunction of all or some of the thyroid, adrenal cortex and gonads. The outcome depends on the extent of pituitary necrosis and hormone deficiency.

In severe cases, glucocorticoid deficiency may be life threatening or fatal. When this condition is associated with severe haemorrhage during or after childbirth it is known as postpartum necrosis (Sheehan’s syndrome), and in this situation the other effects are preceded by failure of lactation.

**Pituitary dwarfism (Lorain–Lévi syndrome)**

This is caused by severe deficiency of GH, and possibly of other hormones, in childhood. The individual is of small stature but is normally proportioned and cognitive development is not affected. Puberty is delayed and there may be episodes of hypoglycaemia. The condition may be due to genetic abnormality or a tumour.

**Diabetes insipidus**

This is a relatively rare condition usually caused by hyposecretion of ADH due to damage to the hypothalamus by, for example, trauma, tumour or encephalitis. Occasionally it occurs when the renal tubules fail to respond to ADH. Water reabsorption by the renal tubules is impaired, leading to excretion of excessive amounts of dilute urine, often more than 10 litres daily, causing dehydration and extreme thirst (polydipsia). Water balance is disturbed unless fluid intake is greatly increased to compensate for excess losses.
**Disorders of the thyroid gland**

These fall into three main categories:

- Abnormal secretion of thyroid hormones (T3 and T4) causing hyperthyroidism or hypothyroidism
- Goitre – enlargement of the thyroid gland

Abnormal thyroid function may arise not only from thyroid disease but also from disorders of the pituitary or hypothalamus; in addition, insufficient dietary iodine impairs thyroid hormone production. The main effects are caused by an abnormally high or low basal metabolic rate.

**Hyperthyroidism**

This syndrome, also known as thyrotoxicosis, arises as the body tissues are exposed to excessive levels of T3 and T4. The main effects are due to increased basal metabolic rate.

In older adults, cardiac failure is another common consequence as the ageing heart must work harder to deliver more blood and nutrients to the hyperactive body cells.

The main causes are:

- Graves’ disease
- Toxic nodular goitre
- Adenoma (a benign tumour)

**Graves’ disease**

Sometimes called Graves’ thyroiditis, this condition accounts for 75% of cases of hyperthyroidism. It affects more women than men and may occur at any age, being most common between the ages of 30 and 50 years. It is an autoimmune disorder in which an antibody that mimics the effects of TSH is produced, causing:

- Increased release of T3 and T4 and signs of hyperthyroidism
- Goitre (visible enlargement of the gland) as the antibody stimulates thyroid growth
- Exophthalmos in many cases.

**Exophthalmos**: This is protrusion of the eyeballs that gives the appearance of staring, which is due to the deposition of excess fat and fibrous tissue behind the eyes; it is often present in **Graves’ disease**. Effective treatment of hyperthyroidism does not completely reverse exophthalmos, although it may lessen after 2–3 years. In severe cases the eyelids become retracted and may not completely cover the eyes during blinking and sleep, leading to drying of the conjunctiva and predisposing to infection. It does not occur in other forms of hyperthyroidism.
Toxic nodular goitre
In this condition one or two nodules of a gland that is already affected by goitre become active and secrete excess T3 and T4 causing the effects of hyperthyroidism. It is more common in women than men and after middle age. As this condition affects an older age group than Graves’ disease, arrhythmias and cardiac failure are more common. Exophthalmos does not occur in this condition.

Hypothyroidism
This condition is prevalent in older adults and is five times more common in females than males. Deficiency of T3 and T4 in adults results in an abnormally low metabolic rate and other effects. There may be accumulation of mucopolysaccharides in the subcutaneous tissues causing swelling (non-pitting oedema), especially of the face, hands, feet and eyelids (myxoedema). The commonest causes are autoimmune thyroiditis, severe iodine deficiency (see goitre) and healthcare interventions, e.g. antithyroid drugs, surgical removal of thyroid tissue or ionising radiation.

Autoimmune thyroiditis: The most common cause of acquired hypothyroidism is Hashimoto’s disease. It is more common in women than men and, like Graves’ disease, an organ-specific autoimmune condition. Autoantibodies that react with thyroglobulin and thyroid gland cells develop and prevent synthesis and release of thyroid hormones causing hypothyroidism. Goitre is sometimes present.

Congenital hypothyroidism: This is a profound deficiency or absence of thyroid hormones that becomes evident a few weeks or months after birth. Hypothyroidism is endemic in parts of the world where the diet is severely deficient in iodine and contains insufficient for synthesis of T3 and T4. Absence of thyroid hormones results in profound impairment of growth and cognitive development. Unless treatment begins early in life, cognitive impairment is permanent and the individual typically has disproportionately short limbs, a large protruding tongue, coarse dry skin, poor abdominal muscle tone and, often, an umbilical hernia.

Simple goitre
This is enlargement of the thyroid gland without signs of hyperthyroidism. It is caused by a relative lack of T3 and T4 and the low levels stimulate secretion of TSH resulting in hyperplasia of the thyroid gland. Sometimes the extra thyroid tissue is able to maintain normal hormone levels but if not, hypothyroidism develops. Causes are:
- Persistent iodine deficiency. In parts of the world where there is dietary iodine deficiency, this is a common condition known as endemic goitre.
- Genetic abnormality affecting synthesis of t3 and t4.
- Iatrogenic, e.g. Antithyroid drugs, surgical removal of excess thyroid tissue.

The enlarged gland may cause pressure damage to adjacent tissues, especially if it lies in an abnormally low position, i.e. behind the sternum. The structures most commonly affected are the oesophagus, causing dysphagia; the trachea, causing dyspnoea; and the recurrent laryngeal nerve, causing hoarseness.
**Adrenal glands**

The two adrenal (suprarenal) glands are situated on the upper pole of each kidney enclosed within the renal fascia. They are about 4 cm long and 3 cm thick. The arterial blood supply is by branches from the abdominal aorta and renal arteries. The venous return is by suprarenal veins. The right gland drains into the inferior vena cava and the left into the left renal vein.

The glands are composed of two parts which have different structures and functions. The outer part is the cortex and the inner part the medulla. The adrenal cortex is essential to life but the medulla is not.

**Adrenal cortex**

The adrenal cortex produces three groups of steroid hormones from cholesterol. They are collectively called adrenocorticocoids (corticosteroids). The groups are:

- Glucocorticoids
- Mineralocorticoids
- Sex hormones (androgens).

The hormones in each group have different characteristic actions but as they are structurally similar their actions may overlap.
Glucocorticoids

Cortisol (hydrocortisone) is the main glucocorticoid but small amounts of corticosterone and cortisone are also produced. Commonly these are collectively known as ‘steroids’; they are essential for life, regulating metabolism and responses to stress.

Secretion is controlled through a negative feedback system involving the hypothalamus and anterior pituitary. It is stimulated by ACTH from the anterior pituitary and by stress. Cortisol secretion shows marked circadian variation peaking between 4 a.m. and 8 a.m. and being lowest between midnight and 3 a.m. When the sleeping waking pattern is changed, e.g. night shift working, it takes several days for ACTH/cortisol secretion to readjust. Glucocorticoid secretion increases in response to stress, including infection and surgery.

Glucocorticoids have widespread metabolic effects generally concerned with catabolism (breakdown) of protein and fat that makes glucose and other substances available for use. These include:

- Hyperglycaemia (raised blood glucose levels) caused by breakdown of glycogen and gluconeogenesis (formation of new sugar from, for example, protein)
- Lipolysis (breakdown of triglycerides into fatty acids and glycerol for energy production) raising circulating levels of free fatty acids
- Stimulating breakdown of protein, releasing amino acids, and increasing blood levels. Amino acids are then used for synthesis of other proteins, e.g. Enzymes, or for energy production.
- Promoting absorption of sodium and water from renal tubules (a weak mineralocorticoid effect).

In pathological and pharmacological quantities glucocorticoids also have other effects including:

- Anti-inflammatory actions
- Suppression of immune responses
- Delayed wound healing.

When corticosteroids are administered in the treatment of common disorders, e.g. asthma, the high circulating levels exert a negative feedback effect on the hypothalamus and pituitary and can completely suppress natural secretion of CRH and ACTH respectively.
Regulation of glucocorticoid secretion

**Mineralocorticoids (aldosterone)**

Aldosterone is the main mineralocorticoid. It is involved in maintaining water and electrolyte balance. Through a negative feedback system it stimulates the reabsorption of sodium (Na+) by the renal tubules and excretion of potassium (K+) in the urine. Sodium reabsorption is also accompanied by retention of water and therefore aldosterone is involved in the regulation of blood volume and blood pressure too.

Blood potassium levels regulate aldosterone secretion by the adrenal cortex. When blood potassium levels rise, more aldosterone is secreted. Low blood potassium has the opposite effect. Angiotensin also stimulates the release of aldosterone.

**Renin–angiotensin–aldosterone system:** When renal blood flow is reduced or blood sodium levels fall, the enzyme renin is secreted by kidney cells. Renin converts the plasma protein angiotensinogen, produced by the liver, to angiotensin 1. Angiotensin converting enzyme (ACE), formed in small quantities in the lungs, proximal kidney tubules and other tissues, converts angiotensin 1 to angiotensin 2, which stimulates secretion of aldosterone. Angiotensin 2 causes vasoconstriction and increases blood pressure closing the negative feedback loop.
Sex hormones
Sex hormones secreted by the adrenal cortex are mainly androgens (male sex hormones) although the amounts produced are insignificant compared with those secreted by the testes and ovaries in late puberty and adulthood.

Adrenal medulla
The medulla is completely surrounded by the adrenal cortex. It develops from nervous tissue in the embryo and is part of the sympathetic nervous system. When stimulated by extensive sympathetic nerve supply, the glands release the hormones adrenaline (epinephrine, 80%) and noradrenaline (norepinephrine, 20%).

Adrenaline (epinephrine) and noradrenaline (norepinephrine)
Noradrenaline is the postganglionic neurotransmitter of the sympathetic division of the autonomic nervous system. Adrenaline and some noradrenaline are released into the blood from the adrenal medulla during stimulation of the sympathetic nervous system. The action of these hormones prolongs and augments stimulation of the sympathetic nervous system. Structurally they are very similar, which explains their similar effects. Together they potentiate the fight or flight response by:

- Increasing heart rate
- Increasing blood pressure
- Diverting blood to essential organs, including the heart, brain and skeletal muscles, by dilating their blood vessels and constricting those of less essential organs, such as the skin
- Increasing metabolic rate
- Dilating the pupils.

Adrenaline has a greater effect on the heart and metabolic processes whereas noradrenaline has more influence on blood vessel diameter.
When the body is under stress homeostasis is disturbed. To restore it and, in some cases, to maintain life there are immediate and, if necessary, longer-term responses. Stressors include exercise, fasting, fright, temperature changes, infection, disease and emotional situations. The immediate response is sometimes described as preparing for ‘fight or flight’. This is mediated by the sympathetic nervous system.

In the longer term, ACTH from the anterior pituitary stimulates the release of glucocorticoids and mineralocorticoids from the adrenal cortex providing a more prolonged response to stress.
Disorders of the adrenal cortex

Hypersecretion of glucocorticoids (Cushing’s syndrome)

Cortisol is the main glucocorticoid hormone secreted by the adrenal cortex. Causes of hypersecretion include:

- Hormone-secreting adrenal tumours
- Hypersecretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary
- Abnormal secretion of acth by a non-pituitary tumour, e.g. Bronchial or pancreatic tumour.

Prolonged therapeutic use of systemic ACTH or glucocorticoids is another cause of Cushing’s syndrome where high blood levels arise from drug therapy.

Hypersecretion of cortisol exaggerates its physiological effects. These include:

- Adiposity of the face (moon face), neck and abdomen
- Excessive tissue protein breakdown, causing thinning of subcutaneous tissue and muscle wasting, especially of the limbs
- Diminished protein synthesis
- Suppression of growth hormone secretion preventing normal growth in children
- Osteoporosis and kyphosis if vertebral bodies are involved
- Pathological fractures caused by calcium loss from bones
- Excessive gluconeogenesis resulting in hyperglycaemia and glycosuria which can precipitate diabetes mellitus
- Atrophy of lymphoid tissue and depression of the immune response susceptibility to infection due to reduced febrile response, depressed immune and inflammatory responses
- Impaired collagen production, leading to capillary fragility, cataract and striae
- Insomnia, excitability, euphoria, depression or psychosis
- Hypertension due to salt and water retention
- Menstrual disturbances
- Formation of renal calculi
- Peptic ulceration.

Hyposecretion of glucocorticoids

Inadequate cortisol secretion causes diminished gluconeogenesis, low blood glucose levels, muscle weakness and pallor. This may be primary, i.e. due to disease of the adrenal cortex, or secondary due to deficiency of ACTH from the anterior pituitary. In primary deficiency there
is also hyposcretion of aldosterone but in secondary deficiency, aldosterone secretion is not usually affected because aldosterone release is controlled by the renin–angiotensin–aldosterone system.

**Hypersecretion of mineralocorticoids**

Excess aldosterone affects kidney function, with consequences elsewhere:

- Excessive reabsorption of sodium chloride and water, causing increased blood volume and hypertension
- Excessive excretion of potassium, causing hypokalaemia, which leads to cardiac arrhythmias, alkalosis, syncope and muscle weakness.

Primary hyperaldosteronism is due to excessive secretion of mineralocorticoids, independent of the renin–angiotensin–aldosterone system. It is usually caused by a tumour affecting only one adrenal gland.

Secondary hyperaldosteronism is caused by overstimulation of normal glands by the excessively high blood levels of renin and angiotensin that result from low renal perfusion or low blood sodium.

**Hyposecretion of mineralocorticoids**

Hypoaldosteronism results in failure of the kidneys to regulate sodium, potassium and water excretion, leading to:

- Blood sodium deficiency (hyponatraemia) and potassium excess (hyperkalaemia)
- Dehydration, low blood volume and low blood pressure.

There is usually hyposecretion of other adrenal cortical hormones, as in Addison’s disease.

**Chronic adrenocortical insufficiency (Addison’s disease)**

This is due to destruction of the adrenal cortex that results in hyposcretion of glucocorticoid and mineralocorticoid hormones. The most common causes are development of autoantibodies to cortical cells, metastasis (secondary tumours) and infections. Autoimmune disease of other glands can be associated with Addison’s disease, e.g. diabetes mellitus, thyrotoxicosis and hypoparathyroidism. The most important effects are:

- Muscle weakness and wasting
- Gastrointestinal disturbances, e.g. Vomiting, diarrhoea, anorexia
- Increased skin pigmentation, especially of exposed areas
- Listlessness and tiredness
- Hypoglycaemia
Endocrine System

- Confusion
- Menstrual disturbances and loss of body hair in women electrolyte imbalance, including hyponatraemia, low blood chloride levels and hyperkalaemia
- Chronic dehydration, low blood volume and hypotension.

The adrenal glands have a considerable tissue reserve and Addison’s disease is not usually severely debilitating unless more than 90% of cortical tissue is destroyed, but this condition is fatal without treatment.

**Acute adrenocortical insufficiency (Addisonian crisis)**

This is characterised by sudden severe nausea, vomiting, diarrhoea, hypotension, electrolyte imbalance (hyponatraemia and hyperkalaemia) and, in severe cases, circulatory collapse. It is precipitated when an individual with chronic adrenocortical insufficiency is subjected to stress, e.g. an acute infection.

**Disorders of the adrenal medulla**

**Tumours**

Hormone-secreting tumours are the most common problem. The effects of excess adrenaline (epinephrine) and noradrenaline (norepinephrine) include:

- Hypertension
- Weight loss
- Nervousness and anxiety
- Headache
- Excessive sweating and alternate flushing and blanching of the skin
- Hyperglycaemia and glycosuria
- Constipation.

**Phaeochromocytoma**

This is usually a benign tumour, occurring in one or both glands. Hormone secretion may be constantly elevated or in intermittent bursts, often precipitated by raised intraabdominal pressure, e.g. coughing or defaecation.

**Neuroblastoma**

This is a rare and malignant tumour, occurring in infants and children. Tumours that develop early tend to be highly malignant but there may be spontaneous regression.
**Pancreatic islets**

The pancreas is a pale grey gland weighing about 60 grams. It is about 12–15 cm long and is situated in the epigastric and left hypochondriac regions of the abdominal cavity. It consists of a broad head, a body and a narrow tail. The head lies in the curve of the duodenum, the body behind the stomach and the tail lies in front of the left kidney and just reaches the spleen. The abdominal aorta and the inferior vena cava lie behind the gland.

The pancreas is both an exocrine and endocrine gland.

**The exocrine pancreas**

This consists of a large number of lobules made up of small acini, the walls of which consist of secretory cells. Each lobule is drained by a tiny duct and these unite eventually to form the pancreatic duct, which extends along the whole length of the gland and opens into the duodenum. Just before entering the duodenum the pancreatic duct joins the common bile duct to form the hepatopancreatic ampulla. The duodenal opening of the ampulla is controlled by the hepatopancreatic sphincter (of Oddi) at the duodenal papilla.

The function of the exocrine pancreas is to produce pancreatic juice containing enzymes, some in the form of inactive precursors that digest carbohydrates, proteins and fats. As in the alimentary tract, parasympathetic stimulation increases the secretion of pancreatic juice and sympathetic stimulation depresses it.

**The endocrine pancreas**

Distributed throughout the gland are groups of specialised cells called the pancreatic islets (of Langerhans). The islets have no ducts so the hormones diffuse directly into the blood. The endocrine pancreas secretes the hormones insulin and glucagon, which are principally concerned with control of blood glucose levels.
The endocrine pancreas consists of clusters of cells, known as the pancreatic islets (islets of Langerhans), scattered throughout the gland. Pancreatic hormones are secreted directly into the bloodstream and circulate throughout the body. This is in contrast to the exocrine pancreas and its associated ducts. There are three main types of cells in the pancreatic islets:

- α (alpha) cells, which secrete glucagon
- β (beta) cells, which are the most numerous, secrete insulin
- δ (delta) cells, which secrete somatostatin (GHRIH)

The normal blood glucose level is between 3.5 and 8 mmol/litre (63 to 144 mg/100 mL). Blood glucose levels are controlled mainly by the opposing actions of insulin and glucagon:

- Glucagon increases blood glucose levels
- Insulin reduces blood glucose levels.

**Insulin**

Insulin is a polypeptide consisting of about 50 amino acids. Its main function is to lower raised blood nutrient levels, not only glucose but also amino acids and fatty acids. These effects are described as anabolic, i.e. they promote storage of nutrients. When nutrients, especially glucose, are in excess of immediate needs insulin promotes their storage by:

- Acting on cell membranes and stimulating uptake and use of glucose by muscle and connective tissue cells
- Increasing conversion of glucose to glycogen (glycogenesis), especially in the liver and skeletal muscles
- Accelerating uptake of amino acids by cells, and the synthesis of protein
- Promoting synthesis of fatty acids and storage of fat in adipose tissue (lipogenesis)
- Decreasing glycogenolysis (breakdown of glycogen into glucose)
- Preventing the breakdown of protein and fat, and gluconeogenesis (formation of new sugar from, e.g., protein).

Secretion of insulin is stimulated by increased blood glucose levels, for example after eating a meal, and to a lesser extent by parasympathetic stimulation, raised blood amino acid and fatty acid levels, and gastrointestinal hormones, e.g. gastrin, secretin and cholecystokinin. Secretion is decreased by sympathetic stimulation, glucagon, adrenaline, cortisol and somatostatin (GHRIH), which is secreted by the hypothalamus and pancreatic islets.

**Glucagon**

Glucagon increases blood glucose levels by stimulating:

- Conversion of glycogen to glucose in the liver and skeletal muscles (glycogenolysis)
Gluconeogenesis.
Secretion of glucagon is stimulated by low blood glucose levels and exercise, and decreased by somatostatin and insulin.

**Somatostatin (GHRH)**
This hormone, also produced by the hypothalamus, inhibits the secretion of both insulin and glucagon in addition to inhibiting the secretion of GH from the anterior pituitary.

**Disorders of the pancreatic islets**

**Diabetes mellitus (DM)**
This is the most common endocrine disorder; the primary sign is hyperglycaemia which is accompanied by varying degrees of disruption of carbohydrate and fat metabolism. DM is caused by complete absence of, relative deficiency of or resistance to the hormone insulin. Primary DM is categorised as type 1 or type 2. In secondary DM, the disorder arises as a result of other conditions, and gestational diabetes develops in pregnancy. The incidence of types 1 and 2 DM, especially type 2, is rapidly increasing worldwide.

**Type 1 diabetes mellitus**
Previously known as insulin-dependent diabetes mellitus (IDDM), this occurs mainly in children and young adults; the onset is usually sudden and can be life threatening. There is severe deficiency or absence of insulin secretion due to destruction of β-islet cells of the pancreas. Treatment with injections of insulin is required. There is usually evidence of an autoimmune mechanism that destroys the β-islet cells. Genetic predisposition and environmental factors, including viral infections, are also implicated.

**Type 2 diabetes mellitus**
Previously known as non-insulin-dependent diabetes mellitus (NIDDM), this is the most common form of diabetes, accounting for about 90% of cases. The causes are multifactorial and predisposing factors include:

- Obesity
- Sedentary lifestyle
- Increasing age: predominantly affecting middle-aged and older adults
- Genetic factors.

Its onset is gradual, often over many years, and it frequently goes undetected until signs are found on routine investigation or a complication occurs. Insulin secretion may be below or above normal. Deficiency of glucose inside body cells occurs despite hyperglycaemia and a
high insulin level. This may be due to insulin resistance, i.e. changes in cell membranes that block the insulin-assisted movement of glucose into cells. Treatment involves diet and/or drugs, although sometimes insulin injections are required.

**Pathophysiology of DM**

**Raised plasma glucose level**

After eating a carbohydrate-rich meal the plasma glucose level remains high because:

- Cells are unable to take up and use glucose from the bloodstream, despite high plasma levels
- Conversion of glucose to glycogen in the liver and muscles is diminished
- There is gluconeogenesis from protein, in response to deficiency of intracellular glucose.

**Glycosuria and polyuria**

The concentration of glucose in the glomerular filtrate is the same as in the blood and, although diabetes raises the renal threshold for glucose, it is not all reabsorbed by the tubules. The glucose remaining in the filtrate raises its osmotic pressure, water reabsorption is reduced and the volume of urine is increased (polyuria). This results in electrolyte imbalance and excretion of urine of high specific gravity. Polyuria leads to dehydration, extreme thirst (polydipsia) and increased fluid intake.

**Weight loss**

The cells are essentially starved of glucose because, in the absence of insulin, they are unable to extract it from the bloodstream, leading to derangement of energy metabolism as cells must use alternative pathways to produce the energy they need. This results in weight loss due to:

- Gluconeogenesis from amino acids and body protein, causing muscle wasting, tissue breakdown and further increases in blood glucose
- Catabolism of body fat, releasing some of its energy and excess production of ketone bodies.

This is very common in type 1 DM and sometimes occurs in type 2 DM.

**Ketosis and ketoacidosis**

This nearly always affects people with type 1 DM. In the absence of insulin to promote normal intracellular glucose metabolism, alternative energy sources must be used instead and increased breakdown of fat occurs. This leads to excessive production of weakly acidic ketone bodies, which can be used for metabolism by the liver. Normal buffering systems
Endocrine System

maintain pH balance so long as the levels of ketone bodies are not excessive. Ketosis develops as ketone bodies accumulate. Excretion of ketones is via the urine (ketonuria) and/or the lungs giving the breath a characteristic smell of acetone or ‘pear drops’.

Ketoacidosis develops owing to increased insulin requirement or increased resistance to insulin due to some added stress, such as pregnancy, infection, infarction, or cerebrovascular accident. It may occur when insufficient insulin is administered during times of increased requirement. Severe and dangerous ketoacidosis may occur without loss of consciousness. When worsening ketosis swamps the compensatory buffer systems, control of acid–base balance is lost; the blood pH falls and ketoacidosis occurs. The consequences if untreated are:

- Increasing acidosis (↓ blood ph) due to accumulation of ketoacids
- Increasing hyperglycaemia
- Hyperventilation as the lungs excrete excess hydrogen ions as CO2
- Acidification of urine – the result of kidney buffering
- Polyuria as the renal threshold for glucose is exceeded
- Dehydration and hypovolaemia (↓ BP and ↑ pulse) – caused by polyuria
- Disturbances of electrolyte balance accompanying fluid loss, hyponatraemia (↓ plasma sodium) and hypokalaemia (↓ plasma potassium)
- Confusion, coma and death.
**Pineal gland**

The pineal gland is a small body attached to the roof of the third ventricle and is connected to it by a short stalk containing nerves, many of which terminate in the hypothalamus. The pineal gland is about 10 mm long, reddish brown in colour and surrounded by a capsule. The gland tends to atrophy after puberty and may become calcified in later life.

**Functions**

For as long as the pineal gland has been known to exist, myriad functions have been ascribed to it, including its

- Being the seat of the soul,
- Enhancing sex,
- Staving off infection,
- Promoting sleep,
- Enhancing mood, and
- Increasing longevity (as much as 10 to 25 per cent).

It is known from comparative anatomy that the pineal gland is a vestigial remnant of what was a third eye located high in the back of the head in some lower animals. Many physiologists have been content with the idea that this gland is a nonfunctional remnant, but others have claimed for many years that it plays important roles in the control of sexual activities and reproduction, functions that still others said were nothing more than the fanciful imaginings of physiologists preoccupied with sexual delusions.

**Melatonin**

This is the main hormone secreted by the pineal gland. Secretion is controlled by daylight and darkness; levels fluctuate during each 24-hour period, the being highest at night and the lowest around midday. Secretion is also influenced by the number of daylight hours, i.e. there may be seasonal variations. Although its functions are not fully understood, melatonin is believed to be associated with:

- Coordination of the circadian and diurnal rhythms of many tissues, possibly by influencing the hypothalamus
- Inhibition of growth and development of the sex organs before puberty, possibly by preventing synthesis or release of gonadotrophins.

The pineal gland is controlled by the amount of light or “time pattern” of light seen by the eyes each day. For instance, in the hamster, greater than 13 hours of darkness each day activates the pineal gland, whereas less than that amount of darkness fails to activate it, with a
critical balance between activation and nonactivation. The nervous pathway involves the passage of light signals from the eyes to the suprachiasmal nucleus of the hypothalamus and then to the pineal gland, activating pineal secretion.

Second, the pineal gland secretes melatonin and several other, similar substances. Either melatonin or one of the other substances is believed to pass either by way of the blood or through the fluid of the third ventricle to the anterior pituitary gland to decrease gonadotropic hormone secretion. Thus, in the presence of pineal gland secretion, gonadotropic hormone secretion is suppressed in some species of animals, and the gonads become inhibited and even partly involuted. This is what presumably occurs during the early winter months when there is increasing darkness. But after about 4 months of dysfunction, gonadotropic hormone secretion breaks through the inhibitory effect of the pineal gland and the gonads become functional once more, ready for a full springtime of activity.

**Disorders**

**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.

Much more common than the interstitial Leydig cell tumors are tumors of the germinal epithelium. Because germinal cells are capable of differentiating into almost any type of cell, many of these tumors contain multiple tissues, such as placental tissue, hair, teeth, bone, skin, and so forth, all found together in the same timorous mass called a teratoma. These tumors often secrete few hormones, but if a significant quantity of placental tissue develops in the tumor, it may secrete large quantities of hCG with functions similar to those of LH. Also, estrogenic hormones are sometimes secreted by these tumors and cause the condition called gynecomastia (overgrowth of the breasts).
Thymus gland

The thymus gland lies in the upper part of the mediastinum behind the sternum and extends upwards into the root of the neck. It weighs about 10 to 15 g at birth and grows until puberty, when it begins to atrophy. Its maximum weight, at puberty, is between 30 and 40 g and by middle age it has returned to approximately its weight at birth.

Organs associated with the thymus

- Anteriorly: sternum and upper four costal cartilages
- Posteriorly: aortic arch and its branches, brachiocephalic veins, trachea
- Laterally: lungs
- Superiorly: structures in the root of the neck
- Inferiorly: heart

Structure

The thymus consists of two lobes joined by areolar tissue. The lobes are enclosed by a fibrous capsule which dips into their substance, dividing them into lobules that consist of an irregular branching framework of epithelial cells and lymphocytes.

Function

Lymphocytes originate from stem cells in red bone marrow. Those that enter the thymus develop into activated T-lymphocytes. Thymic processing produces mature T-lymphocytes that can distinguish ‘self’ tissue from foreign tissue, and also provides each T-lymphocyte with the ability to react to only one specific antigen from the millions it will encounter. T-
lymphocytes then leave the thymus and enter the blood. Some enter lymphoid tissues and others circulate in the bloodstream. T-lymphocyte production, although most prolific in youth, probably continues throughout life from a resident population of thymic stem cells. The maturation of the thymus and other lymphoid tissue is stimulated by thymosin, a hormone secreted by the epithelial cells that form the framework of the thymus gland. Shrinking of the gland begins in adolescence and, with increasing age, the effectiveness of the T-lymphocyte response to antigens declines.

**Cell-mediated immunity**

T-cells that have matured in the thymus gland are released into the circulation. When they encounter their antigen for the first time, they become sensitised to it. If the antigen has come from outside the body, it needs to be ‘presented’ to the T-cell on the surface of an antigen-presenting cell. There are different types of antigen-presenting cell, including macrophages. Macrophages are part of the non-specific defences, because they engulf and digest antigens indiscriminately, but they are a crucial ‘link’ cell between initial non-specific defences and the immune system. After digesting the antigen they transport the most antigenic fragment to their own cell membrane and display it on their surface. They display (present) this antigen to the T-cell that has been processed to target that particular antigen, activating the T-cell.

If the antigen is an abnormal body cell, such as a cancer cell, it too will be displaying foreign (non-self) material on its cell membrane that will stimulate the T-cell. Whichever way the antigen is presented to the T-cell, it stimulates it to divide and proliferate (clonal expansion). Four main types of specialised T-cell are produced, each of which is still directed against the original antigen, but which will tackle it in different ways.

**Diseases of the thymus gland**

Enlargement of the gland is associated with some autoimmune diseases, such as thyrotoxicosis and Addison’s disease.

Tumours are rare, although pressure caused by enlargement of the gland may damage or interfere with the functions of adjacent structures, e.g. the trachea, oesophagus or veins in the neck.

In myasthenia gravis, most patients have either thymic hyperplasia (the majority) or thymoma (a minority).