chapter 7:

DISORDERS OF THE ENDOCRINE SYSTEM

OBJECTIVES

After studying this chapter you should be able to:

- list the different types of hormones and give examples;
- outline the structure and roles of the endocrine system;
- describe general mechanisms underlying hormone actions;
- explain how disorders of the endocrine system occur;
- discuss the causes, investigation and management of some endocrine disorders.

7.1 INTRODUCTION

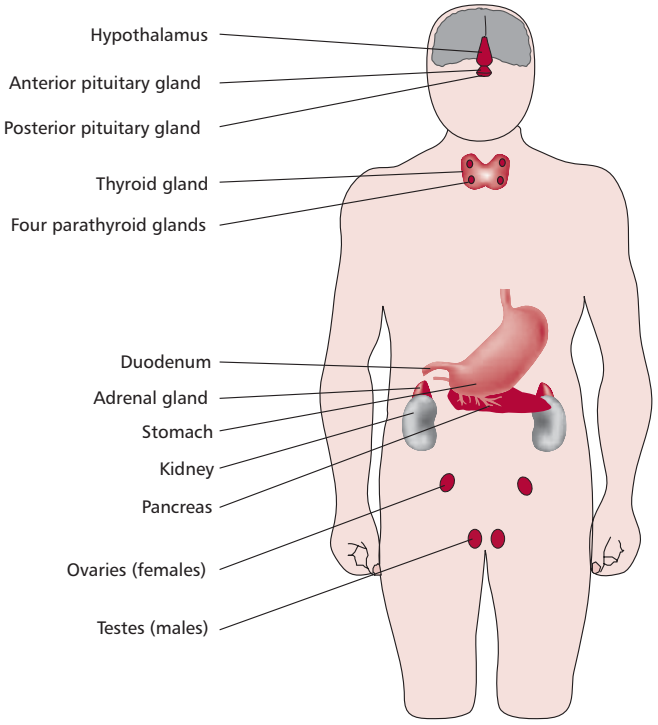
The endocrine system is one of two major control systems in the body, the other being the nervous system, that help control the activities of the body. It consists of a number of ductless glands (*Figure 7.1*) that produce hormones. Hormones are molecules that circulate in the blood and excite or inhibit the metabolic activity of target tissues or organs. These responses maintain and regulate body functions, such as growth and development, responses to stress and injury, reproduction, homeostasis and energy metabolism (*Figure 7.2*).

Hormones can be divided into three chemical groups: amines, peptides and proteins, and steroids (*Table 7.1*). Many amine hormones, such as adrenaline (epinephrine) and those produced by the thyroid gland, are derivatives of tyrosine. The majority of hormones are peptides and proteins, examples being insulin and growth hormone. A number of protein hormones, for example thyroid stimulating hormone, are glycoproteins in that they have carbohydrate groups covalently attached to them. All steroid hormones are derivatives of cholesterol and include cortisol and testosterone. *Figure 7.3* shows examples of each type of hormones.

Class	Examples	Associated glands
Amines	adrenaline noradrenaline thyroid hormones T_3 and T_4	adrenal medulla thyroid gland
Peptides and proteins	insulin, growth hormone	islets of Langerhans anterior pituitary
Steroids	cortisol aldosterone testosterone	adrenal cortex

Table 7.1 A structural classification of hormones with selected examples

Figure 7.1 The major endocrine glands of the body.



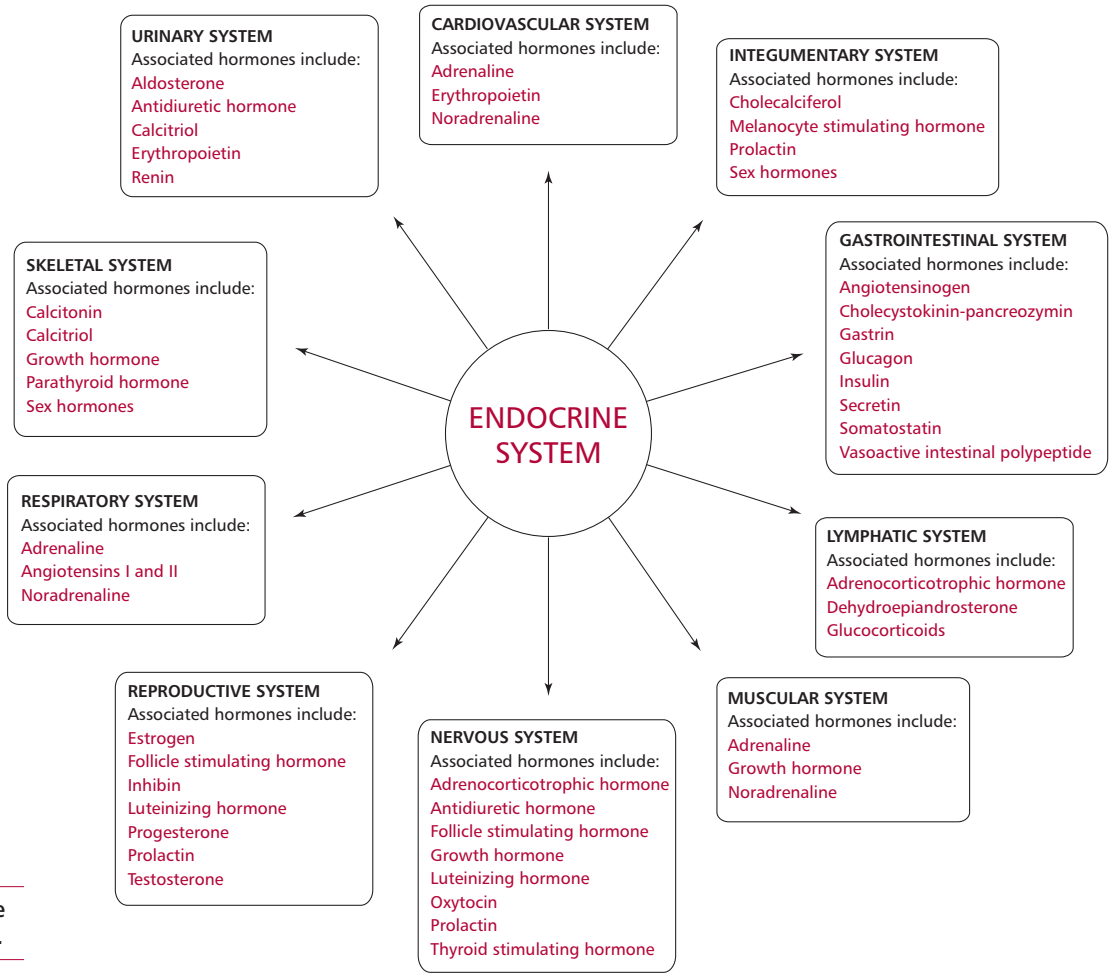


Figure 7.2 Effects of endocrine glands on other body systems.

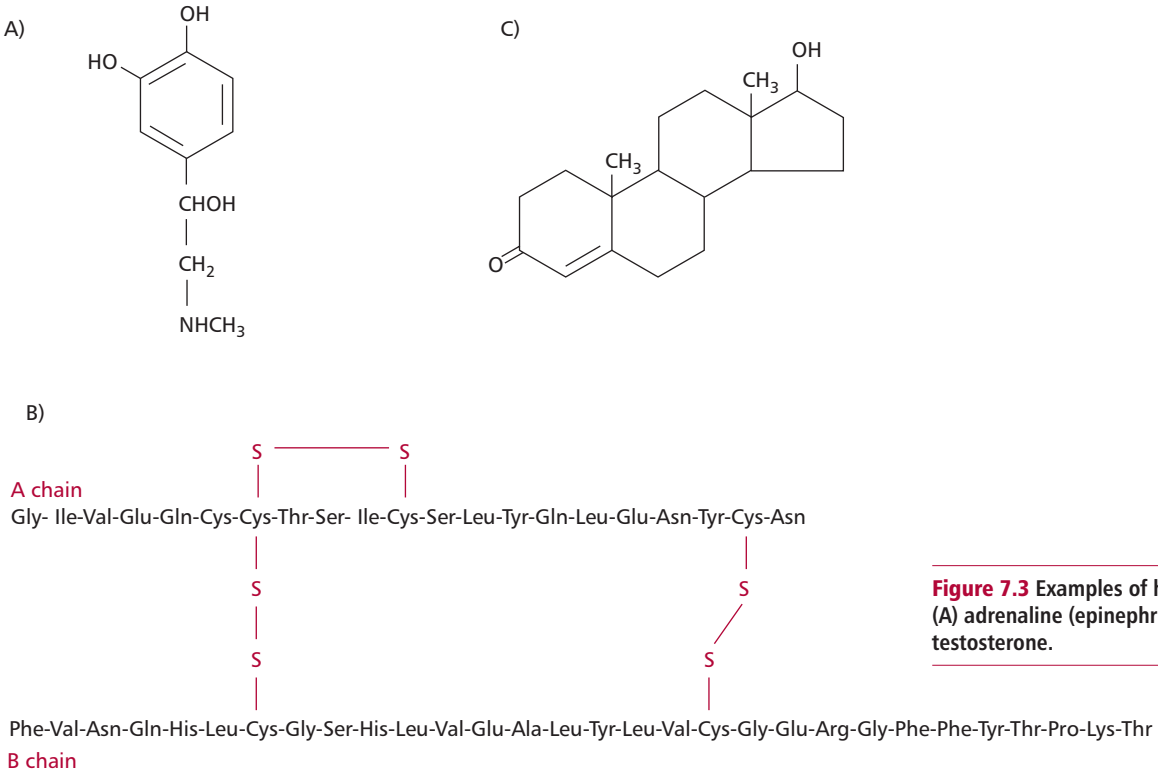


Figure 7.3 Examples of hormones. (A) adrenaline (epinephrine), (B) insulin and (C) testosterone.

7.2 HORMONE PRODUCTION

Amine hormones include adrenaline, noradrenaline (also called epinephrine and norepinephrine respectively) and thyroid hormones. Their synthesis involves a series of enzyme-catalyzed reactions in the cytoplasm of endocrine cells. For example, thyroid hormones (*Section 7.7*) are synthesized by iodination of tyrosine residues in the protein thyroglobulin found in the thyroid. Most peptide hormones are synthesized as large inactive prohormones, which are subsequently cleaved by enzymes to produce the active hormone. Sometimes a number of hormones may be derived from the same prohormone. Steroid hormones are synthesized by a sequence of enzymatic reactions using cholesterol as a common precursor. The enzymes responsible for conversion of cholesterol to hormone are located in the smooth endoplasmic reticulum and mitochondria of cells. The presence or absence of particular enzymes determines the type of steroid hormone synthesized by that specific cell.

Amine hormones, such as adrenaline and noradrenaline, are stored in secretory granules within the cytoplasm, but thyroid hormones are stored within the thyroid follicles as components of thyroglobulin. Peptide hormones are usually stored in membrane-bound vesicles within the cytoplasm of the endocrine cell. Steroid hormones are not usually stored but are released upon synthesis. However, lipid droplets may be found in the cytoplasm containing precursor material for these hormones.

Hormones are released in response to nervous, hormonal or metabolic stimuli. Hormones stored in granules are released when the granules move and fuse with the plasma membrane. Some hormones, for example thyroxine, are released continuously whereas others show diurnal variation and their release varies during the day. For example, cortisol shows diurnal variation with levels being high in the morning but low at night. The concentrations of hormones in the plasma must be kept within narrow ranges for optimum function. A

BOX 7.1 The pineal gland

The pineal gland or body is an appendage of the posterior end of the roof of the third ventricle in the brain (*Figure 7.4*). It is shaped like a pinecone, hence its name, weighs 100 to 150 mg and is only 8 to 10 mm long. It is composed largely of pinealocytes and glial cells. In older animals, the pineal often contains calcium deposits, sometimes referred to as brain sand! Descartes (1596–1650) regarded the pineal gland as 'the seat of the soul', because he believed it was unique in the human brain in being the only structure not duplicated on the right and left sides. This observation is not strictly true, however, since it is finely divided into two hemispheres that can be observed with a microscope.

The physiological function of the pineal gland in humans is poorly understood. However, pinealocytes are known to produce the hormone, melatonin (5-methoxy-*N*-acetyltryptamine), from tryptophan by acetylating serotonin (*Figure 7.5*). Melatonin has a relatively simple structure yet communicates information about environmental lighting to physiological systems of the body. This light-transducing ability has led some to call the pineal gland the 'third eye'. Melatonin, therefore, helps regulate the internal 'clock' of the body affecting biological rhythms and, in particular, patterns of sleeping and waking and possibly the onset of puberty. It may also function as a free radical scavenger and reduce oxidative damage. Most melatonin is synthesized during the night and can be secreted directly into the blood because the capillaries of the pineal gland are permeable and do not form part of the normal blood–brain barrier (*Figure 3.4*). In a normal environment in healthy humans the release of melatonin usually starts at 21.00 to 22.00 h and ends between 07.00 to 09.00 h, with peak levels of 60 to 70 pg cm^{-3} occurring in the plasma of adults between 02.00 and 04.00 h. The activity of the usual rate-limiting enzyme, serotonin-*N*-acetyltransferase (NAT), increases 7–150 fold during peak production. In daylight the activity of NAT, and therefore melatonin production, is reduced. The rhythm is endogenously synchronized to 24 h by the suprachiasmatic nucleus of the hypothalamus, an area of the brain known to coordinate biological clock signals, but can be entrained to values between 23 and 27 h primarily by the environmental light–dark cycle acting through the retina. When the retina is exposed to light, nervous impulses are relayed to the suprachiasmatic nucleus. Nerve fibers from the hypothalamus descend to the spinal cord, from where postganglionic fibers ascend back to the pineal gland. Thus the pineal gland can measure day length and adjust its secretion of melatonin appropriately.

Small cysts are commonly seen within the pineal region although their discovery is frequently incidental to radiographic investigations. However, they are benign and nonprogressive and should be treated conservatively. The pineal gland is also subject to numerous types of malignant tumors, for example teratomas, germinomas, choriocarcinomas, endodermal sinus tumors, mixed germ cell tumors, pineoblastoma and pineocytoma, and gliomas. Fortunately, all are rare and collectively account for less than 1% of intracranial space-occupying lesions. With the exception of parenchymal cell tumors, pineoblastoma and pineocytoma, they occur mainly in patients below the age of 20 years. Germinomas and teratomas occur predominantly in males. The commonest symptoms are secondary to hydrocephalus, such as headaches, vomiting, and drowsiness, with visual problems, diabetes insipidus, and reproductive abnormalities. In children, pineal tumors of the region are often associated with abnormal pubertal development. Some evidence suggests that precocious puberty is due to the production of human chorionic gonadotrophin (hCG) by germ cell tumors of the pineal gland. Delayed puberty has also been associated with pineal tumors.

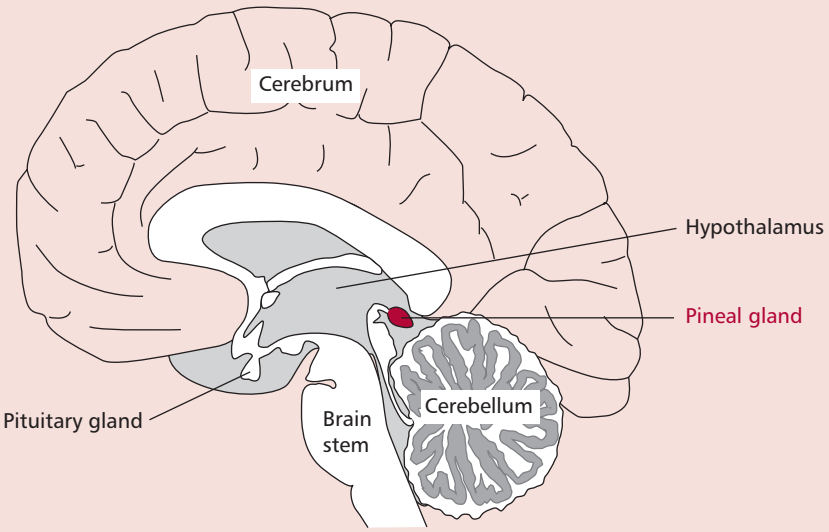
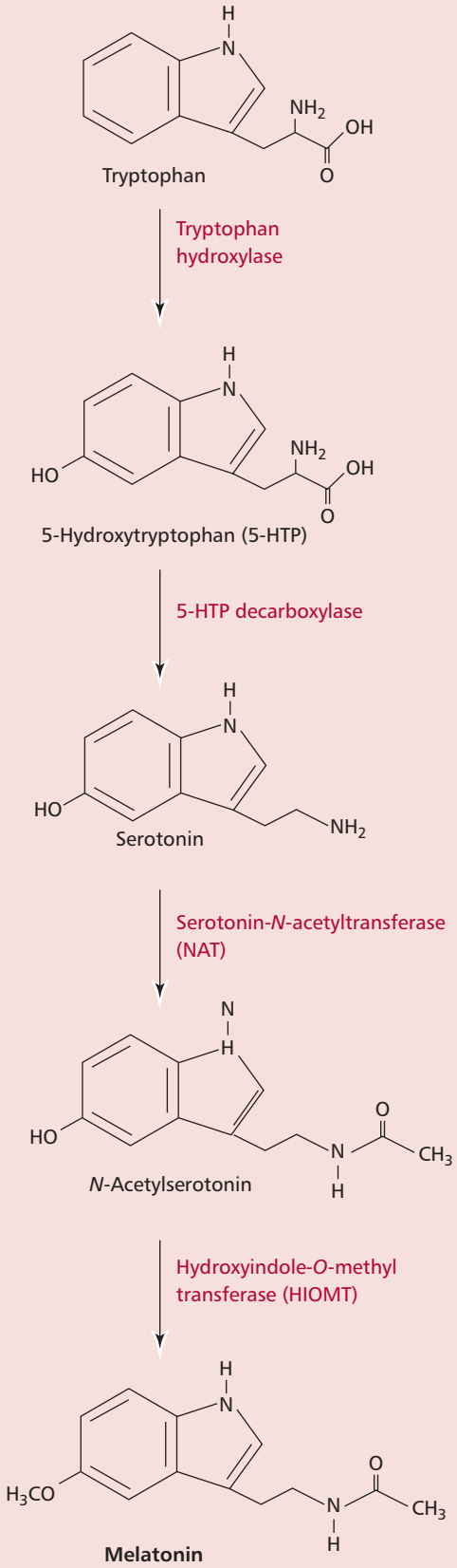


Figure 7.4 Schematic showing the location and structure of the pineal gland.

BOX 7.1 continued



Pineal tumors can be diagnosed from the symptoms, physical examination and tests for tumor markers in samples of cerebrospinal fluid (CSF), such as α fetoprotein and hCG, together with CSF cytology. Computer aided tomography (CAT) or magnetic resonance imaging (MRI) (*Chapter 18*) can aid in differential diagnosis. Germinomas respond well to radiation therapy, whereas surgery is usually the choice for other types. There have been significant improvements in prognosis, with 62% surviving germinomas for over five years, although survival is only 14% for other malignant tumors.

Given that melatonin affects normal sleep patterns, there is interest in using it, possibly combined with **phototherapy**, to treat sleep disorders. Phototherapy, more properly called full spectrum bright light therapy, is a repeated exposure to 3 to 6 h of artificial light that is as bright as sunlight. The use of melatonin in shift workers, who often find it difficult to adjust to working at night and sleeping during the day, unfortunately has not shown promise. Melatonin therapy does not appear to help their condition and appears not to be as effective as phototherapy. However, melatonin therapy appears to be modestly beneficial in elderly insomniacs who have lower concentrations compared with matched noninsomniacs. Jet lag also involves the disruption of circadian rhythms where melatonin therapy seems to be of use. During long distance air travel, taking melatonin close to the bedtime of the destination appears to reduce the symptoms associated with jet lag. The greatest benefits occur when jet lag would be expected to be greatest, that is, on journeys that cross many time zones.

The production and secretion of melatonin is related to the length of the night: the longer the night, the more produced over a longer secretion time. Also, melatonin profiles show a seasonal phase, with an earlier secretion in summer than in winter. The condition **seasonally affective disorder (SAD)** or **winter depression** is characterized by changes of moods and eating and sleeping patterns. It appears to develop in people living at high latitudes in winter when sunlight is lacking. The increased release of melatonin in winter has been suggested as a possible cause of SAD but at present there is no consensus as to its causes. The assumption that melatonin duration is a seasonal signal in humans led to the treatment of SAD with bright light in an attempt to induce advancement of the melatonin rhythm. It appears to be somewhat more efficient when given in the morning, although there is a large placebo effect. However, other mechanisms are also possible; indeed, many pharmacological antidepressant treatments stimulate melatonin secretion.

Figure 7.5 The synthesis of melatonin.

number of factors control hormone production by the endocrine glands. The secretion of pituitary hormones is under the influence of peptides released from the hypothalamus and, this in turn, is influenced by signals from the central nervous system (CNS). Most hormones released from endocrine glands are controlled by a negative feedback effect, such as for thyroid hormones (*Section 7.7*) and cortisol (*Section 7.9*). Finally, changes in the amounts of materials regulated by hormones themselves may influence the release of that hormone, as is the case for insulin. Target cells and the liver contain enzymes that degrade hormones. Hormones of low M_r are removed from the circulation by the kidneys and excreted in urine.

The half-lives of hormones vary from a few seconds to weeks. Many small or water insoluble hormones form complexes with large plasma transport proteins. The kidneys cannot filter out these large complexes and so their rapid loss is prevented. In addition, these complexes protect the hormone from degradation by enzymes and release the hormone slowly. The bound and free hormones are in equilibrium and it is only the free fraction that is biologically active.

7.3 MECHANISMS OF HORMONAL ACTION

Hormones act by binding to specific receptors of target cells to form a complex (*Figure 7.6*) that elicits a cellular response. Only the target tissue will express the receptor for a given hormone and be able to respond to it. Hormone receptors may be located on the surface of the cell or within the cell respectively. Hormones that bind to the former function through what are called second messenger systems, the hormone being the primary or first messenger. Second messengers are small M_r water-soluble molecules and ions that are generally able to move freely throughout the cell. The most common secondary messengers are cyclic adenosine monophosphate (cAMP), the structurally related cyclic guanosine monophosphate (cGMP), Ca^{2+}, inositol triphosphate (IP_3), and diacylglycerol (DAG) whose structures are shown in *Figure 7.7*.

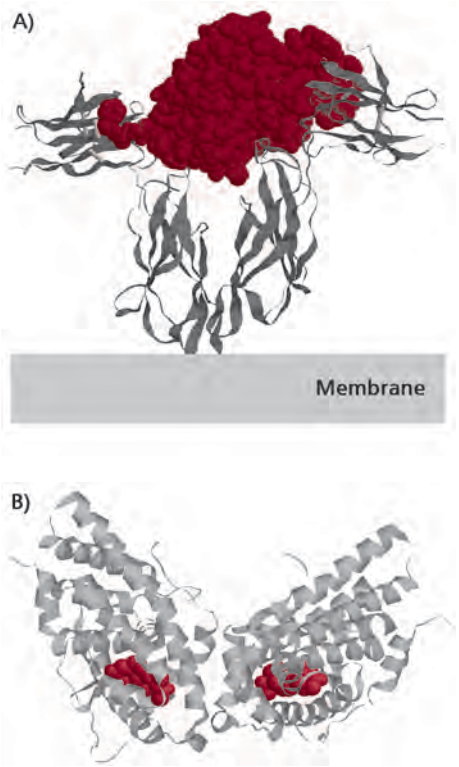


Figure 7.6 (A) Molecular model of human growth hormone (red) bound to the extracellular portion of its receptor (black). PDB file 3HHR. The gray bar represents the surface of the target cell. (B) Molecular model of a dimer of the steroid hormone progesterone (red) bound to its intracellular receptor. PDB file 1A28.

Extracellular receptors are transmembrane proteins that have an extracellular and an intracellular portion joined by a transmembrane domain. Binding of the hormone to the extracellular portion changes the conformation or shape of the complex, such that the intracellular part can catalyze changes to the concentration of the second messenger in the cytosol and amplify the initial signal, that is the binding of the hormone, to produce marked changes in the activities of existing proteins in the target cell.

Amine and peptide and protein hormones are water soluble and cannot easily cross the lipid layer of the plasma membrane. These hormones bind to surface receptors on the plasma membrane (*Figure 7.8*). G-protein-coupled receptors are the most common cell surface receptors and binding to these results in the activation of adenylate kinase, through a number of proteins whose conformations are changed in turn. Activated adenylate kinase catalyzes the conversion of ATP to the secondary messenger cAMP, whose concentration in the cytoplasm therefore increases.

$$ATP + H_2O \longrightarrow cAMP + PP_i$$

Cyclic AMP, in turn, stimulates protein kinase which then catalyzes the phosphorylation of specific enzymes in the cytosol. Depending on the enzyme, phosphorylation can cause an increase or decrease in activity. A phosphodiesterase inactivates cAMP by hydrolyzing it to AMP and prevents its accumulation in the cytoplasm.

Hormones that recognize intracellular receptors function in an entirely different fashion. Such hormones are able directly to enter the cell where

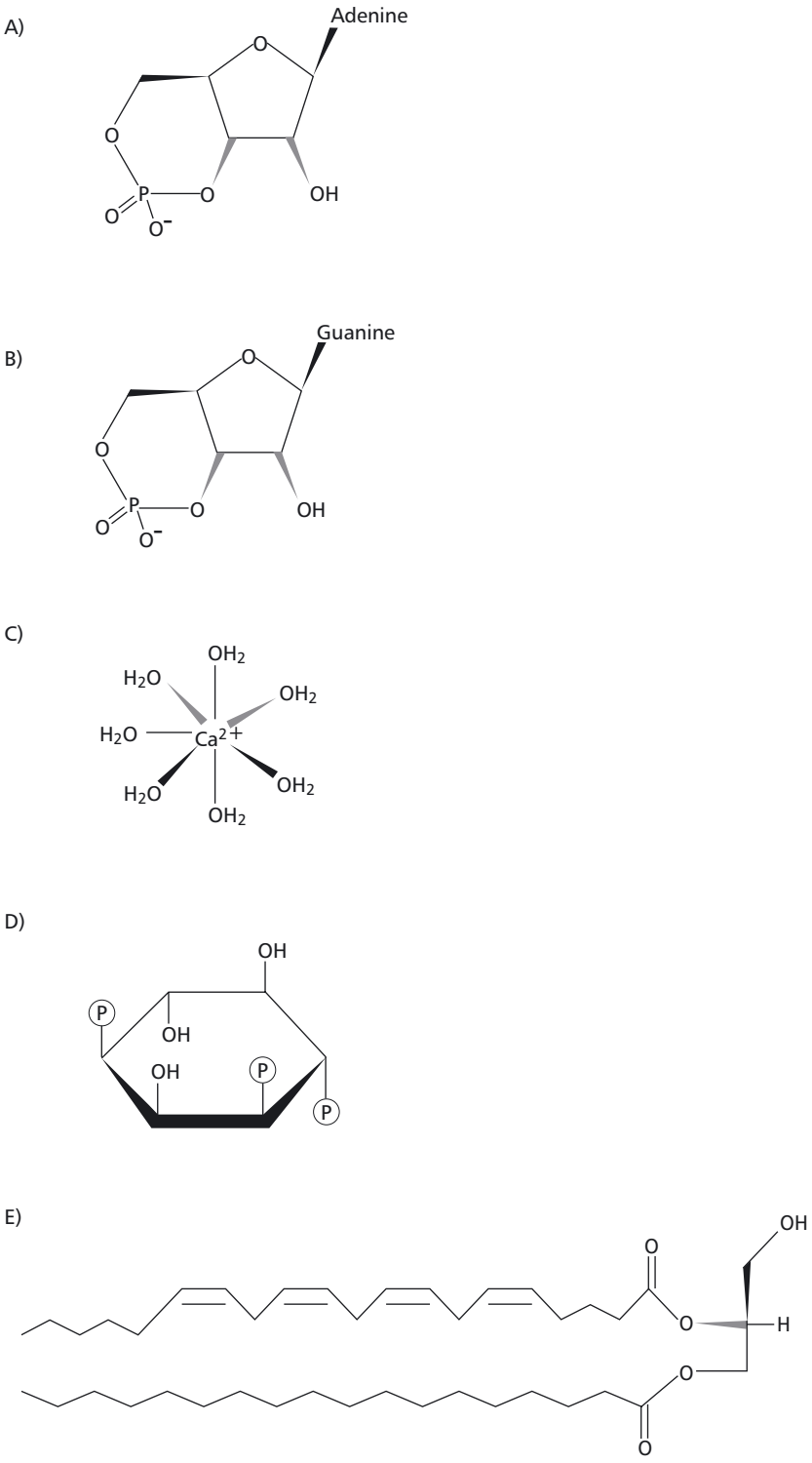


Figure 7.7 Examples of hormone secondary messengers. (A) cAMP, (B) cGMP, (C) a hydrated Ca^{2+}, (D) inositol triphosphate (IP_3) and (E) a diacylglycerol (DAG).

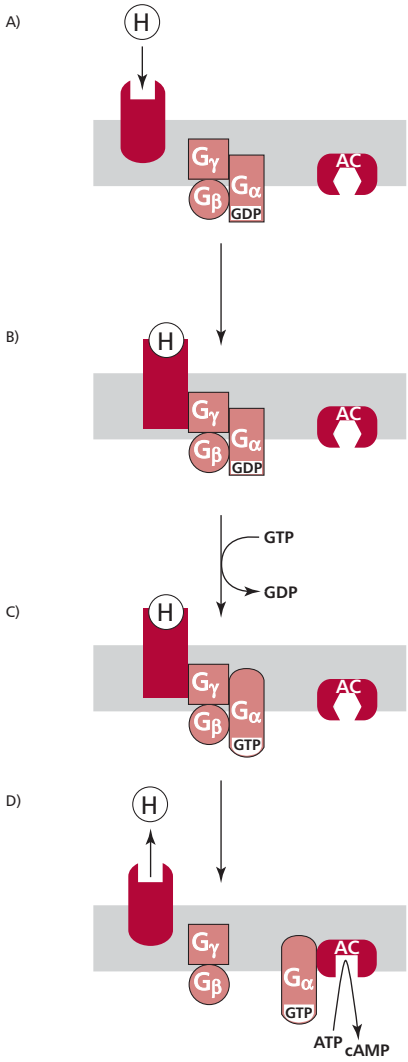


Figure 7.8 Mechanism of action of a hormone that acts through the second messenger, cAMP. Note the conformational changes that are shown schematically as (A) the hormone binds to its receptor, (B) and (C) to the trimeric G protein as GDP and GTP are exchanged and to the (D) adenylate cyclase (AC) as it is activated by the Gα-GTP complex.

Margin Note 7.1 G proteins

G proteins are so called because they bind the guanyl nucleotides, GDP and GTP. They are a diverse group, ranging from small soluble monomers to large multisubunit membrane proteins. Their functions are also wide ranging, from the activities associated with numerous hormones, to sense perception and the nucleocytoplasmic transport described in *Chapter 16*. However, all are GTPases that can hydrolyze their bound GTP to GDP

GTP protein
+
H_2O
↓
GDP protein*
+
P_i

The GDP portion can be exchanged for a GTP. This alteration of the nucleotide between the GTP–GDP forms allows the protein to switch between two conformations (*Figure 7.9*). The form with a bound GTP is active (functional); the other has GDP bound and is nonactive. Thus G proteins provide on–off switches in physiological systems as they oscillate between the two forms.

*indicates a change in the conformation of the protein (see also *Figure 7.9*)

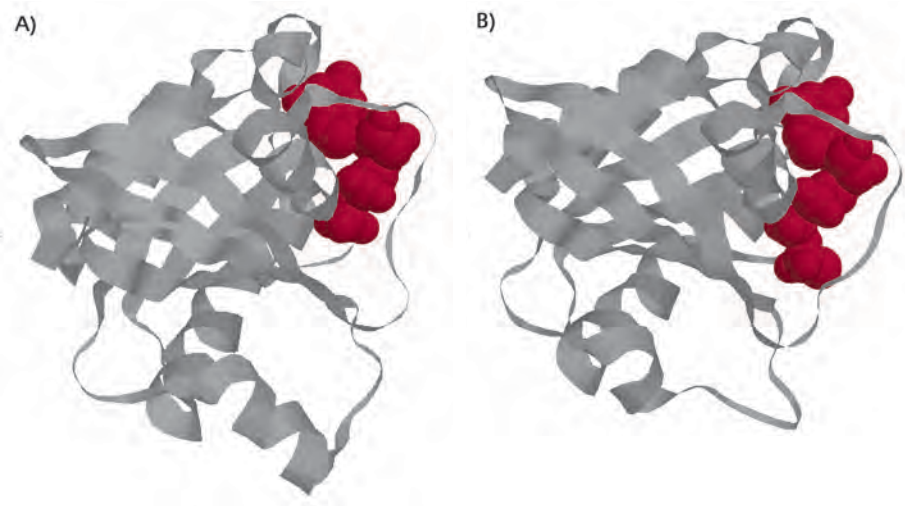


Figure 7.9 A small soluble G protein with bound (A) GDP and (B) GTP. In both cases the nucleotide is shown in red. Note the difference in conformation between the two forms. PDB files 1OIV and 1OIW respectively.

they regulate the synthesis of proteins. For example, steroid hormones are hydrophobic and lipid soluble and so diffuse directly through the plasma membrane into the cytoplasm of target cells. Thyroid hormones enter their target cells by facilitated diffusion. In the cytoplasm, steroid and thyroid hormones bind to intracellular receptors forming hormone–receptor complexes (*Figure 7.10*). The complex then interacts with the DNA of specific genes in the nucleus to switch their transcription on or off, allowing or preventing the production of appropriate mRNA molecules respectively. Thus the cell's production of proteins, such as enzymes, is regulated to produce a physiological response to the hormone.

7.4 CAUSES OF ENDOCRINE DISORDERS

Endocrine disorders arise because a disruption to the endocrine system causes decreased (hypofunction) or increased (hyperfunction) hormonal activity or resistance to hormone action. There may be defects in synthesis of the hormone due to an inherited deficiency of an enzyme required for its synthesis. Inappropriate stimuli may impair the release of the hormone or certain drugs may stimulate hormone release. Defects in the negative feedback mechanism may cause abnormal hormone secretion. Faulty inactivation or excretion of hormones in liver or renal diseases respectively can increase hormone levels. Excessive hormone secretion can occur ectopically from a nonendocrine source, such as a tumor. Even if correctly synthesized and released, the target tissues may not recognize the hormone because of a lack of receptors or because the receptors themselves are nonfunctional. Disorders will also occur if the target cells do recognize the hormone but there is a defect in the secondary messenger system responsible for converting the hormonal signal to a physiological action.

In some autoimmune diseases (*Chapter 5*), antibodies are produced that stimulate or destroy endocrine glands, as in Grave's disease and autoimmune thyroiditis respectively. The various causes underlying endocrine disorders are summarized in *Figure 7.11*. A considerable number of endocrine disorders have been described including disorders associated with the pituitary, thyroid, pancreas, adrenal glands and the reproductive systems.

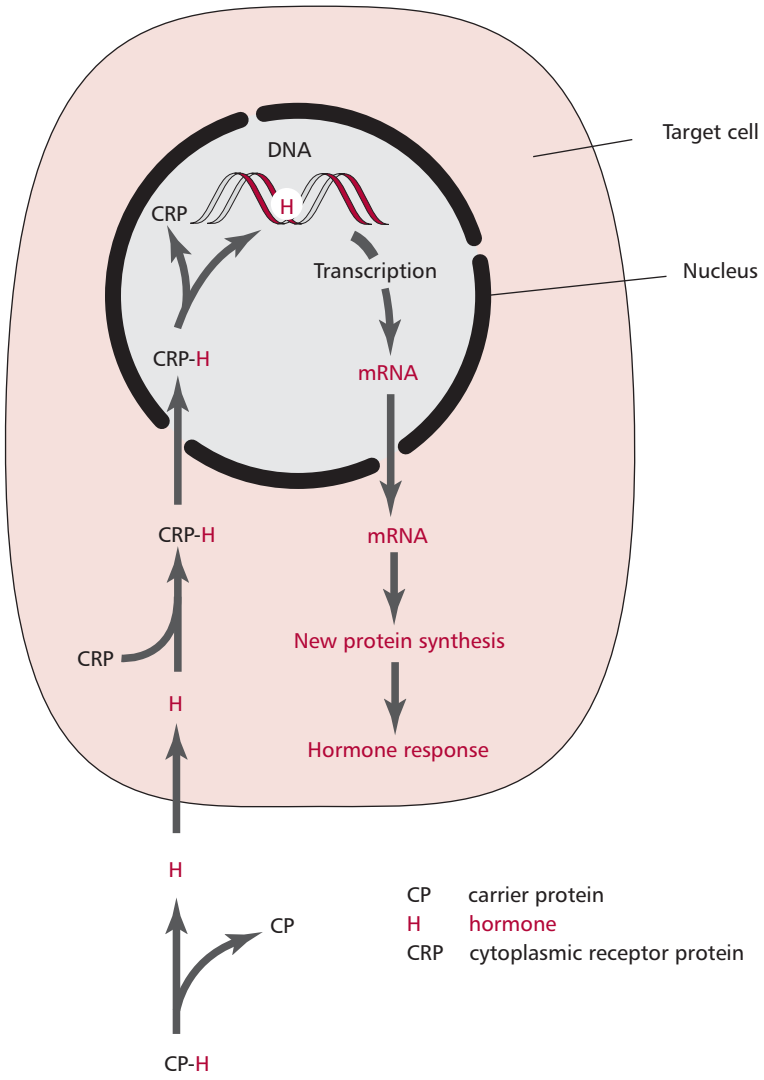


Figure 7.10 Mechanism of action of a hormone that binds to an intracellular receptor. See text for details.

7.5 THE PITUITARY GLAND

The pituitary gland is often referred to as 'the master gland' given that its secretions regulate the activities of many of the other hormone-producing glands. Despite its crucial role, it weighs only about 0.5 g. The pituitary is found in a bony cavity at the base of the skull and is connected to the hypothalamus by a pituitary stalk composed of blood vessels and nerve fibers. It is composed of two lobes, an anterior pituitary or adenohypophysis and a posterior pituitary or neurohypophysis (*Figure 7.12*).

The anterior pituitary secretes a number of hormones (*Figure 7.13*) that are regulated by the release of peptides from the hypothalamus with stimulatory or inhibitory effects on the anterior pituitary. The principal peptides released by the hypothalamus reach the anterior pituitary by a portal blood circulation. These peptides include thyrotrophin releasing hormone (TRH), growth hormone releasing hormone (GHRH), gonadotrophin releasing hormone (GnRH), corticotrophin releasing hormone (CRH) and dopamine. With the exception of dopamine, all are stimulatory, controlling the release of thyroid stimulating hormone (TSH), growth hormone (GH), follicle stimulating hormone (FSH) together with luteinizing hormone (LH) and adrenocorticotrophic hormone (ACTH) respectively. Thyroid stimulating hormone targets the thyroid gland causing it to release thyroid hormones.

Figure 7.11 Overview of the causes of endocrine disorders.

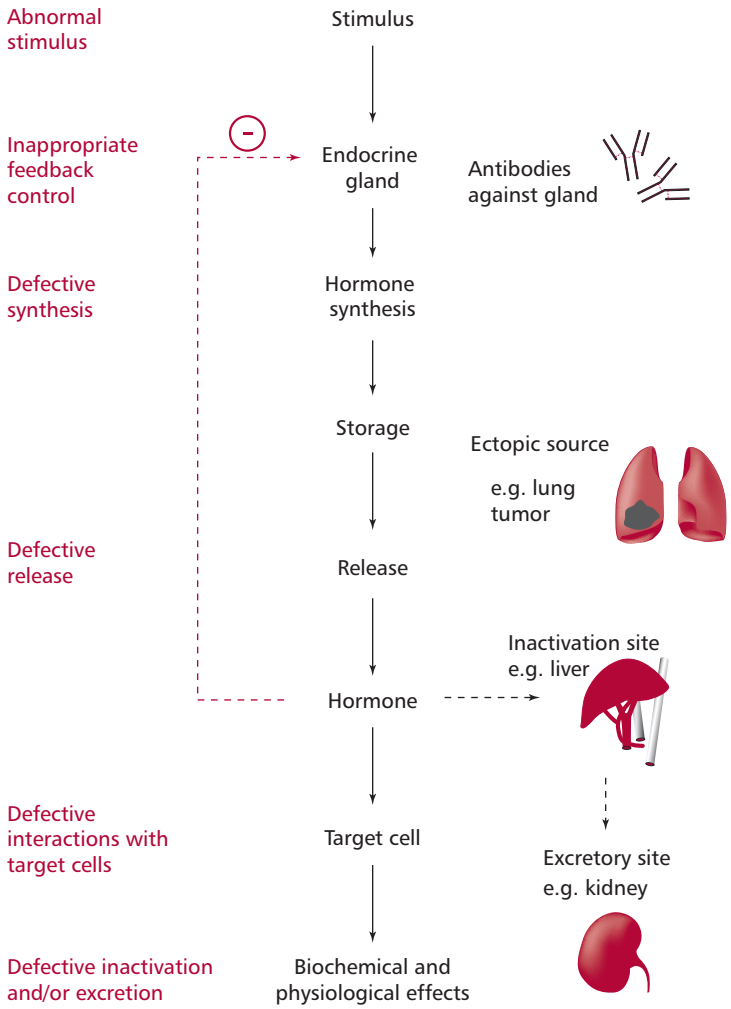
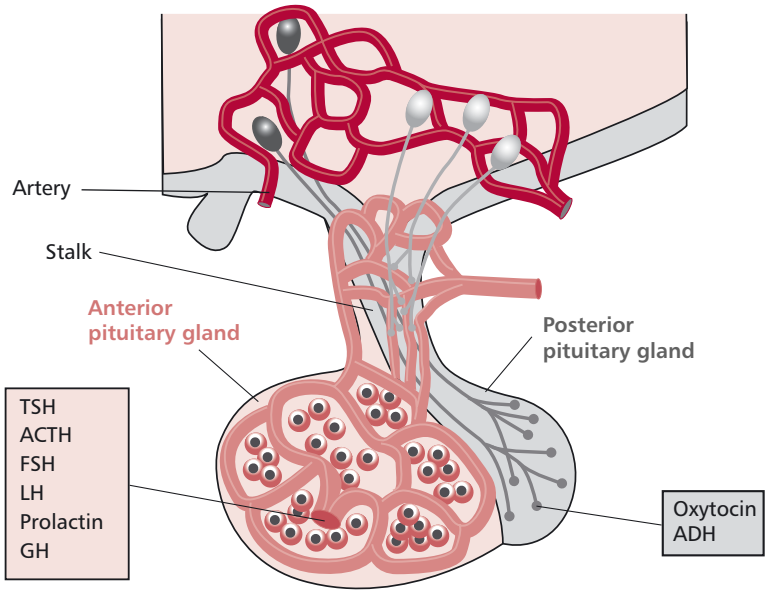


Figure 7.12 Structure of the pituitary gland, with the secreted hormones indicated.



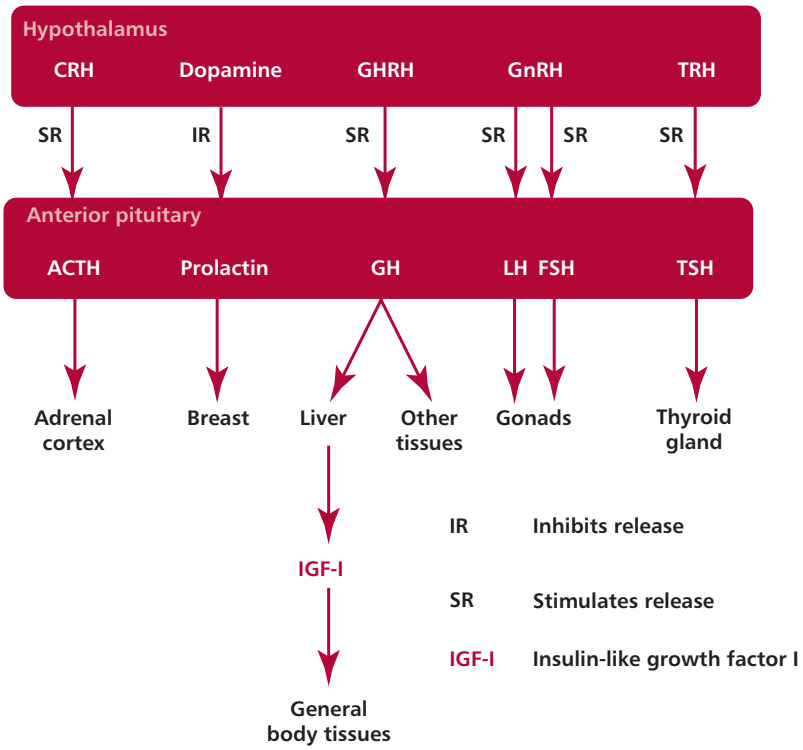


Figure 7.13 Hypothalamic factors that regulate anterior pituitary function.

Growth hormone acts on general body tissues to promote growth and development. Follicle stimulating hormone and LH, collectively referred to as gonadotrophins, act on the testes and ovaries and are essential for reproduction. Adrenocorticotrophic hormone acts on the adrenal cortex and stimulates release of cortisol. Prolactin stimulates the female mammary glands to control lactation. The release of prolactin is inhibited by dopamine.

The posterior pituitary is composed of a collection of nerve fibers originating in the hypothalamus. It secretes two main hormones, antidiuretic hormone (ADH) or vasopressin, and oxytocin although both are made in the hypothalamus and reach the posterior pituitary in the nerve fibers of the stalk. The former stimulates the kidneys to conserve water (*Chapter 8*), whereas the latter promotes uterine contractions during childbirth and stimulates the release of milk in breast feeding.

DISORDERS OF PITUITARY FUNCTION

The majority of disorders in pituitary function are caused by tumors of the gland although some pituitary diseases can lead to underproduction of its hormones. Approximately 80% of pituitary tumors are functional, that is they cause an excessive secretion of hormones. The most common secrete prolactin, and account for 50% of functional tumors. The incidence of

tumors affecting other hormones is 15% GH, 10% ACTH, 4% FSH/LH with less than 1% promoting TSH secretion. Large pituitary tumors may also exert pressure on nerves, causing headaches and visual disturbances. Radiological investigations such as X-rays, computer-aided tomography (CAT) scans and magnetic resonance imaging (MRI), outlined in *Chapter 18*, are important in locating tumors and estimating their sizes.

Prolactin secreting tumors, prolactinomas, cause hyperprolactinemia that, in turn, can lead to infertility in both males and females. Nonprolactin secreting tumors or pituitary stalk section by surgery, which block the dopaminergic inhibition of prolactin secretion, also result in hyperprolactinemia. Hyperprolactinemia abolishes menstruation (**amenorrhea**) and causes an inappropriate release of breast milk (**galactorrhea**) and impotence and breast development (**gynecomastia**) in males. Other causes of hyperprolactinemia include drugs, for example phenothiazines, that block dopamine receptors, or methyldopa that reduces the level of dopamine in the brain.

Investigating a patient with a possible prolactinoma includes assessing the concentrations of prolactin in the plasma (*Table 7.2*) following stimulation with TRH, although this test is not commonly used in most hospitals. In addition to TRH, prolactin is also secreted in response to stress and estrogens. Patients with a prolactinoma have plasma prolactin concentrations in excess of 2000 mU dm^{-3}. These high values are generally not affected by TRH stimulation in individuals with prolactinomas. The first line of treatment is with a dopamine antagonist, such as bromocriptine, although surgical removal of the tumor may be necessary in cases which do not respond to drug therapy.

Disorders of oxytocin are uncommon and have little clinical significance. However, ADH release is essential for life and disorders of its release are well recognized. The release of ADH is stimulated by increased osmolality of the plasma and a decrease in blood volume detected by hypothalamic osmoreceptors and cardiac baroreceptors respectively. The role of ADH in fluid regulation is outlined in *Chapter 8*. A decreased output of ADH gives rise to diabetes insipidus, characterized by excessive production of dilute urine (polyuria). Patients are constantly thirsty (**polydipsia**), have hypernatremia and a plasma osmolality in excess of 295 mmol kg^{-1}.

[Prolactin] / mU dm^{-3}	Interpretation
Males < 381	normal
Females < 629	normal
Males 381–1000	repeat test; does not usually indicate a serious problem
Females 629–1000	repeat test; does not usually indicate a serious problem
1000–2000	repeat test; the increased [prolactin] may be secondary to stress, drug use, hypothalamic disorders, acromegaly, primary hyperthyroidism or chronic renal failure
2000–4000	possible microprolactinoma or a hypothalamic disorder
4000–6000	prolactinoma probably present, although the possibilities of a hypothalamic disorder or pregnancy should be investigated
> 6000	virtually always indicates the presence of a macroprolactinoma

Table 7.2 Interpretation of serum prolactin concentrations in the diagnosis of hyperprolactinemia

Cranial diabetes insipidus may be caused by brain tumors, meningitis, trauma and following surgery, but can be idiopathic. Nephrogenic diabetes insipidus occurs when the kidneys fail to respond to ADH. The lack of response may be caused by drugs, such as lithium, chronic renal disease, hypercalcemia or it may be congenital. Patients with suspected diabetes insipidus are investigated by performing a fluid deprivation test in which the patient is deprived of fluid intake for a period of 8 h. In normal individuals, this results in concentrated urine with a plasma osmolality below 295 mmol kg^{-1}. However, in patients with diabetes insipidus, the urine does not become concentrated and the plasma osmolality increases. At the end of the 8 h period, the patient is allowed to drink water and given desmopressin, a synthetic analog of ADH, after which the urine is collected hourly for a further 4 h. In cranial diabetes insipidus the urine becomes concentrated, but with nephrogenic diabetes insipidus this does not occur as the kidneys are insensitive to ADH (or desmopressin in this case). Hence the test discriminates between cranial and nephrogenic diabetes insipidus.

Patients suffering from diabetes insipidus require access to rehydrating fluids but, in each case, the underlying cause must be treated. Patients with cranial diabetes insipidus are often given desmopressin in a nasal spray or chloropropamide which increases renal sensitivity to ADH. The use of the latter drug requires careful monitoring since it can lead to hypoglycemia. Individuals with nephrogenic diabetes insipidus do not respond to analogs of ADH and often there is no suitable treatment. Especial attention to adequate water intake is essential.

A number of patients present with hypopituitarism, which is a failure to secrete one or more pituitary hormones, although this is a relatively uncommon complaint. Hypopituitarism may result from a tumor, infarction, infections, trauma affecting the pituitary or may be secondary to disorders of the hypothalamus. The clinical presentation of hypopituitarism often depends on the age of the affected individual. A decreased release of GH is often an early feature, leading to dwarfism in children (*Section 7.6*). Inadequate secretion of gonadotrophins may cause amenorrhea (see above) and infertility in adult females, and loss of secondary sexual characteristics in males. Elderly patients with hypopituitarism may complain of symptoms, such as hypoglycemia and hypothermia, relating to ACTH and TSH deficiencies respectively. In most cases, GH and gonadotrophin deficiencies tend to present before that of ACTH. Hyposecretion is assessed by stimulatory tests where the ability of the anterior pituitary to secrete the hormone in question is assessed following stimulation of the patient with the hypothalamic peptide or its analog. A failure to respond would suggest hypopituitarism.

7.6 GROWTH HORMONE DISORDERS

Growth hormone (GH) or somatotrophin promotes linear growth and the maintenance of tissues by stimulating the uptake of amino acids by cells, protein synthesis, increasing blood glucose concentration and fat metabolism and promoting epiphyseal bone growth. These effects are mediated by locally acting effectors called somatomedins that are synthesized by many tissues but particularly liver. Somatomedins stimulate cell proliferation and/or differentiation. They include insulin-like growth factors-I and II (IGF-I and IGF-II). Insulin-like growth factor-I is the most significant physiologically and, indeed, its concentration correlates with that of GH.

Growth hormone is a polypeptide 191 amino acid residues long (*Figure 7.14 (A)*). Approximately 70% of plasma GH is bound to growth hormone binding protein. Growth hormone is synthesized in the anterior pituitary gland in

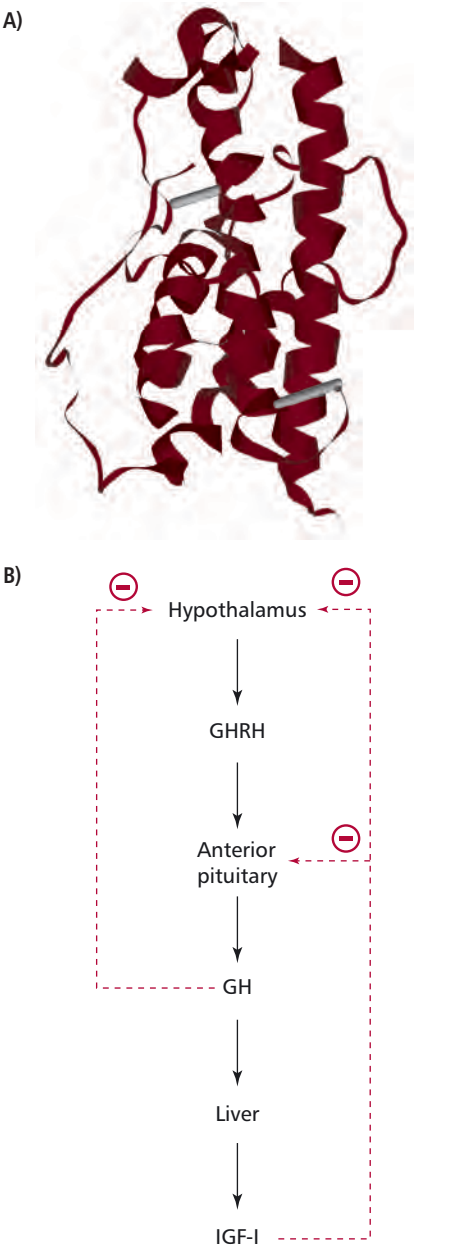


Figure 7.14 (A) Structure of human growth hormone. PDB file 1HGU. (B) The regulation of the secretion of GH.

an inactive form called preprogrowth hormone that is hydrolyzed in several enzyme-catalyzed reactions to give active GH prior to its secretion. A number of factors, such as sleep, amino acids, exercise and stress stimulate GHRH release from the hypothalamus and that, in turn, stimulates GH secretion. Hyperglycemia stimulates the secretion of somatostatin from the hypothalamus and this inhibits the secretion of GH. Increasing concentrations of serum GH and IGF-I exert a negative feedback effect that prevents further release of GH (*Figure 7.14 (B)*). The rate of adult secretion varies but is generally about 1.4 mg daily and occurs in pulses with the largest amounts being released during sleep.

The clinical features resulting from an excess or deficiency of GH depend on the age of the person. A deficiency during childhood leads to a stunted growth called dwarfism (*Figure 7.15 (A)*) and therefore requires early detection. However, GH deficiency is a rare cause of dwarfism and other causes, for example thyroid deficiency or inadequate nutrition, need to be excluded first. The commonest causes of GH deficiency are nonendocrine tumors that affect the pituitary gland or hypothalamus. Growth hormone deficiency may also be a consequence of generalized pituitary disease or a congenital defect leading to a deficient production of GHRH. Whatever the cause, the major clinical feature is stunted growth, well below that expected for a child of comparable age, with a short height, immature face and skeleton as revealed by radiological investigations. Clinical signs of other anterior pituitary hormone deficiencies may be evident.

The most common cause of excessive GH release is a GH secreting pituitary tumor or adenoma (*Chapter 17*). Although these are benign, they are not subject to normal control and continually release large amounts of GH. The

Figure 7.15 Photographs showing one of the authors beside (A) a dwarf and (B) a person with combined gigantism and acromegaly.

causes of these tumors are unknown but a genetic basis has been suggested. Ectopic GH secretion is extremely rare but has been reported in patients with bronchial carcinoma.

Excessive GH release causes gigantism in children and acromegaly in adults. Children with GH excess grow as much as 6 inches per year to abnormal heights, often in excess of 8 feet. Muscle weakness is seen in longstanding cases. Acromegaly has an insidious onset and may take years for its clinical features, enlargement of bones of hands, feet and face, thickening of soft tissues causing coarse facial features, enlarged tongue and lips, prognathism or protruding jaw, increased sweating and enlargement of internal organs, such as liver, spleen and heart, to become apparent. Additionally, acromegalics suffer from paresthesia of the hands and feet due to entrapment of nerves by thickened bone and subcutaneous tissue, headaches/vision disorders due to the growing pituitary tumor and sensory nerve entrapment, impaired glucose tolerance or diabetes mellitus and increased incidences of coronary heart disease and stroke (*Chapter 14*). Individuals affected by excessive GH secretion throughout life show features of both gigantism and acromegaly (*Figure 7.15 (B)*). The prognosis for both gigantism and acromegaly depends on how far the disorder has advanced. Gigantism is rarely life threatening and prognosis is usually good. However, an individual with advanced acromegaly will develop serious complications, such as coronary heart disease, cerebrovascular disease and diabetes mellitus.

DIAGNOSIS AND TREATMENT OF GROWTH HORMONE DISORDERS

A variety of tests are used to assess GH deficiency. Random measurements of serum GH are of limited value due to fluctuations in plasma GH levels in normal individuals. Urinary GH excretion is low in deficiency but obtaining an accurately timed collection of urine is difficult. Most tests rely on demonstrating that the hormone does not increase in concentration following a stimulus. Growth hormone increases after exercise and this has been used as a preliminary screening test. In the exercise test, the patient is subjected to hard physical exercise until they have a pulse rate greater than 150 beats per min (*Chapter 14*). Blood is collected at 0, 2 and 20 min after stopping exercise. In normal individuals, the plasma concentration of GH increases by 20 mU dm^{-3} above the initial value. Growth hormone release increases during sleep, hence high values in a nocturnal sample may exclude deficiency. Blood samples are collected using a venous catheter at 30 min intervals for 3 to 4 h after the onset of sleep. A peak of at least 10 mU dm^{-3} occurs in normal individuals but not in patients with GH deficiency. Clonidine is a potent stimulator of GH secretion and is used in a definitive test for GH deficiency. Growth hormone from genetically engineered sources is used in treatment but must be continued until longitudinal growth is completed. In cases where deficiency is due to low levels of GHRH, analogs of this peptide, for example hexarelin, have been used.

A diagnosis of excess GH is made on clinical grounds supported by biochemical and radiological investigations. Photographs taken of the patient when younger are particularly useful when making a diagnosis. Basal serum concentrations of GH are increased in GH excess but, because release is influenced by so many factors, the result of a single sample is unreliable.

The concentration of IGF-I in serum is raised in patients with acromegaly and is of diagnostic significance. The oral glucose tolerance test (OGTT) is used to confirm a diagnosis of acromegaly and is similar to that used for diagnosis of diabetes mellitus (*Section 7.8*) except that levels of plasma GH are also determined. In a healthy individual, the glucose load suppresses GH release to below 2 mU dm^{-3} by stimulating the release of somatostatin. In patients with acromegaly, this suppression is not seen.

Figure 7.16 The histological structure of the thyroid gland. Courtesy of Dr A.L. Bell, University of New England, College of Osteopathic Medicine, USA.

The management of GH excess cannot reverse any clinical changes that have taken place prior to treatment. However, management is important because it improves survival and reduces deaths due to heart disease or stroke. Growth hormone secreting tumors are treated in one of three ways, the clinical decision depending on severity of disease, the age of the patient and the response to treatment. Surgical removal of the pituitary tumor may be attempted depending on its size and location with steps taken to minimize damage to the anterior pituitary. If GH levels do not normalize, other treatments must be considered. Radiotherapy is usually performed over a 4–6 week period by external irradiation using a cobalt source. Its effects are slow and, in some cases, hyposecretion of other pituitary hormones may occur. Drugs, such as bromocriptine, suppress GH release in acromegalics and are often used in patients too old to undergo surgery or radiotherapy. Somatostatin analogs, for example octeotride, have also been used to inhibit GH release. Some patients require all three modes of treatment but are not always successfully treated. To detect recurrence, serum IGF-I needs to be monitored at regular intervals.

7.7 THYROID HORMONE DISORDERS

The thyroid gland is the largest endocrine gland in the body, weighing about 20 g. It is a bilobular organ that consists of microscopic spherical follicles with secretory cells (*Figure 7.16*) that synthesize the thyroid hormones. Thyroid hormones (*Figure 7.17 (A)* and *(B)*) consist of triiodothyronine (T_3) and thyroxine (T_4). Triiodothyronine is the most active, four times that of T_4, and has a half-life of 1.5 days compared with 9 days for T_4. However in most tissues, particular the liver, T_4 can be readily converted to T_3. More than 99% of T_3 and T_4 are transported in the serum as complexes: 70% to thyroxine binding globulin (TBG) and about 20% to albumin and around 10% to prealbumin. The remaining small free portion is the metabolically active fraction.

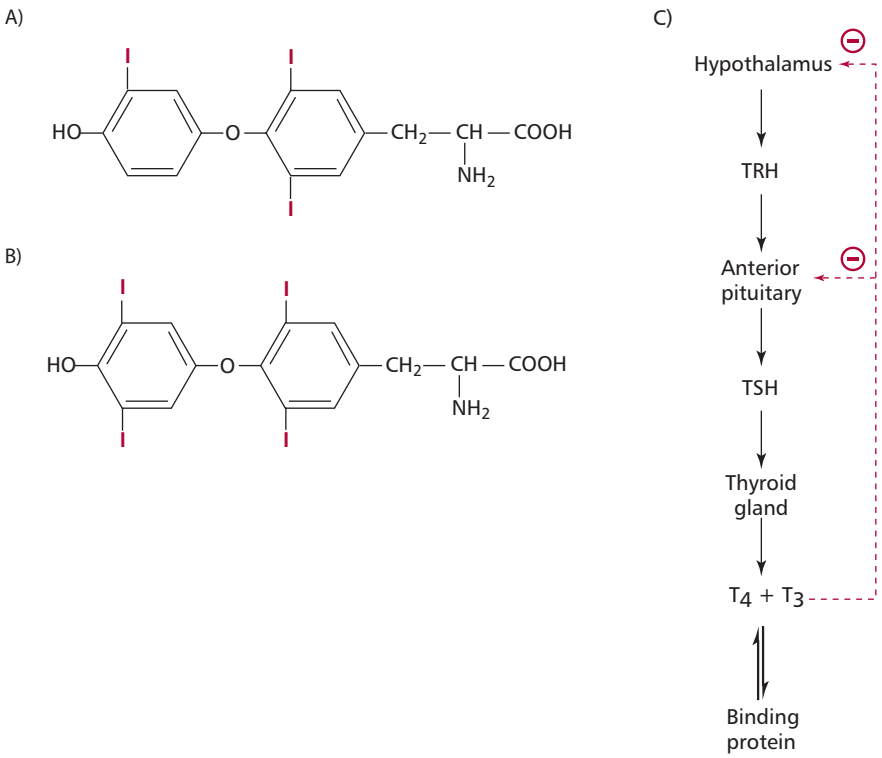


Figure 7.17 The major thyroid hormones (A) T_3, (B) T_4 and (C) the regulation of the secretion of T_4 and T_3 by a negative feedback mechanism.

The effects of thyroid hormones are to increase heat production, oxygen consumption, the metabolism of proteins, fats and carbohydrates and to promote normal growth. They are also necessary for the normal functioning of the CNS. Levels of plasma T_4 and T_3 are regulated by the release of thyroid stimulating hormone (TSH) from the anterior pituitary that, in turn, is controlled by the release of thyrotrophin releasing hormone (TRH) from the hypothalamus. Increasing concentrations of free T_4 and T_3 inhibit further release of TSH and TRH by a negative feedback effect (*Figure 7.17 (C)*).

The most serious disorder of thyroid function is hyperthyroidism caused by an excessive production of thyroid hormones. The clinical syndrome resulting from hyperthyroidism is thyrotoxicosis (*Figure 7.18*). Its clinical features are weight loss, sweating, heat intolerance, anxiety, hyperkinesis, increased appetite, osteoporosis, menorrhagia, tachycardia and pretibial edema.

The commonest cause of hyperthyroidism is Grave's disease, which can occur at any age but particularly in 20- to 40-year-old females. Patients with Grave's disease suffer from **exophthalmos** or protrusion of the eyeballs, in addition to clinical features of hyperthyroidism. It is an autoimmune disease (*Chapter 5*), characterized by the presence of thyroid stimulating antibodies in the blood that bind to TSH receptors in thyroid cells and stimulate them in a similar manner to TSH. Toxic nodules are the second main cause of hyperthyroidism and tend to be found in elderly patients. They may occur singly or as multiples in a nodular goiter and are autonomous (self-governing) secretors of thyroid hormones. An excessive intake of thyroxine in individuals who are treated for hypothyroidism can cause hyperthyroidism. Rare causes of hyperthyroidism include ectopic thyroid tissue and tumors that secrete TSH although the latter are very uncommon.

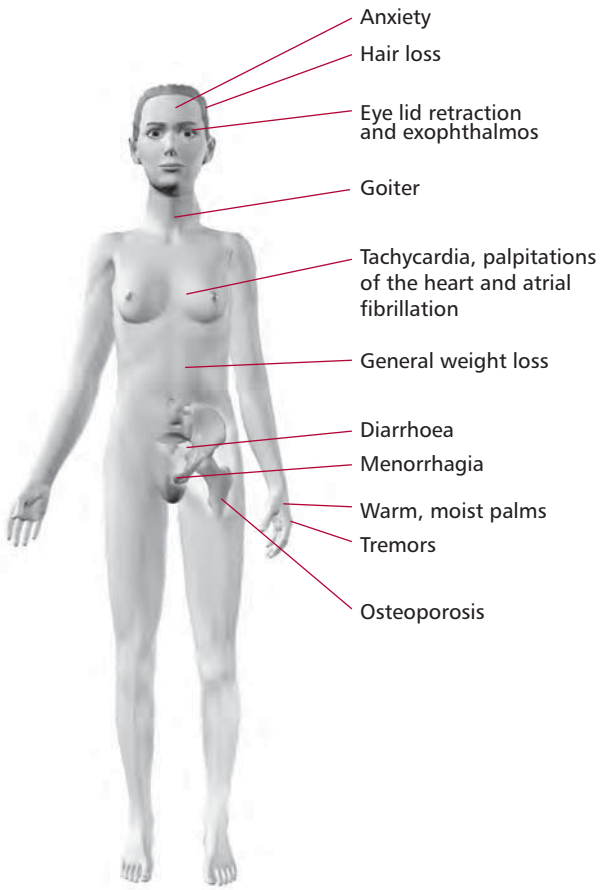


Figure 7.18 Schematic to show the clinical features of thyrotoxicosis.

Hypothyroidism (myxodema) is most common in women of 30–60 years of age (*Figure 7.19*). Its clinical features include psychosis, diminished sweating, hypokinesis, weight gain, muscle weakness, constipation, dry, cold skin and dry hair, ischemic heart disease, bradycardia and menstrual irregularities. The primary cause of hypothyroidism is a defect in the secretion of thyroid hormones by the thyroid gland. In, for example, Hashimoto's thyroiditis, an autoimmune disease, there is destruction of thyroid tissue by antibodies (*Chapters 4* and *5*) produced against the thyroid. Hypothyroidism may also occur after surgery (postthyroidectomy) and following treatment with antithyroid drugs. Congenital hypothyroidism occurs because of the failure of the thyroid gland to develop normally during embryonic growth. If untreated, this condition results in **cretinism** where the child suffers from mental retardation, muscle weakness, short stature, neurological signs and is often dumb and mute. Hypothyroidism may also arise due to iodine deficiency in certain parts of the world. Secondary causes of hypothyroidism are linked to the pituitary or the hypothalamus with defective secretions of TSH and TRH respectively.

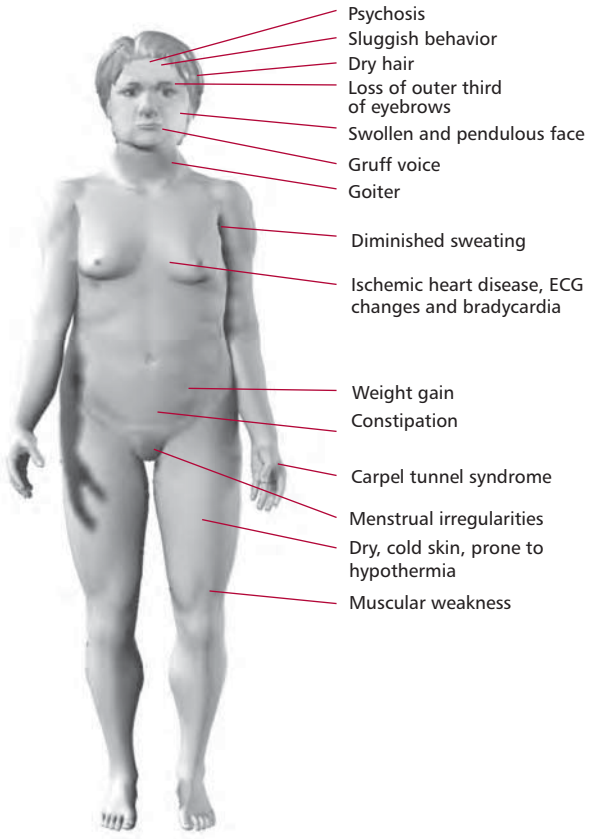


Figure 7.19 Schematic to show the clinical features of myxodema.

DIAGNOSIS AND TREATMENT OF THYROID DISORDERS

Investigating thyroid abnormalities involves measurements of serum TSH as a first line test for thyroid function. Some laboratories also include measurement of free T_4 and/or free or total T_3 in their first line screen. Sensitive assays for measurement of TSH are readily available. Thyroid stimulating hormone levels are increased in primary hypothyroidism, normal in euthyroid individuals (those without thyroid disease) and low or undetectable in hyperthyroidism.

Total T_4 and T_3 measurements were once used widely in pathology laboratories but have the disadvantage that their values are dependent on plasma TBG levels, which can give misleading results. When TBG levels increase, for example in pregnancy or in females receiving estrogen-containing oral contraceptives, then total T_4 and total T_3 are also increased even though the individual is not hyperthyroid. Decreases in TBG concentrations occur in malnutrition, protein loss, severe illness and malabsorption (*Chapters 10* and *11*) and causes a reduction in total T_4 and T_3. There has been some controversy on the validity of free thyroid hormone measurements, but most laboratories now determine free T_4 and T_3, rather than the total concentration. Free T_4 and particularly free T_3, are usually increased in hyperthyroidism. Free T_4 is low in hypothyroidism and is the preferred measurement for its detection because free T_3 can be normal in hypothyroidism due to an increase in its peripheral formation from T_4. In a few patients with hyperthyroidism, free T_4 is within the reference range but free T_3 is increased and TSH is nearly always undetectable. This form of hyperthyroidism is referred to as T_3 toxicosis.

In any systemic illness, such as myocardial infarction, fever or liver disease, the normal metabolism of thyroid hormones is disturbed, reducing the concentrations of T_4 and T_3 in the plasma because T_4 is converted to an inactive isomer called reverse T_3 or rT_3 (*Figure 7.20*) and T_3 is not replenished from T_4. Thyroid stimulating hormone levels may be normal or reduced and concentrations of TBG, albumin and prealbumin may also decline. Patients may have reduced T_4, T_3 and TSH, although there is no thyroid dysfunction. For this reason, thyroid function tests should not be performed on sick patients until they recover. *Table 7.3* outlines the results of tests used in thyroid disorders. The TRH test is rarely used now in the diagnosis of thyroid disease. It is almost exclusively used in the diagnosis of patients with pituitary disease and to assess the capacity of the pituitary to secrete TSH. The patient is given 200 µg of TRH intravenously and the serum TSH is measured after 0, 20 and 60 min. A normal response involves a three- to fivefold increase in TSH above the basal level. A slow rise in TSH (where the 60-min concentration is greater than the one at 20 min) together with low basal levels of TSH and thyroid hormones suggests hypothalamic disease, while a lack of response is suggestive of pituitary hypothyroidism or hyperthyroidism (*Figure 7.21*).

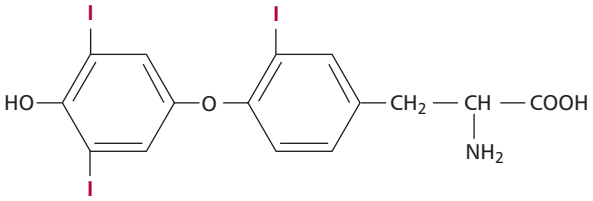


Figure 7.20 Reverse T_3 (rT_3). Compare its structure with those shown in *Figure 7.17*.

Test	Hyperthyroidism	Hypothyroidism	Developing hypothyroidism	T_3 toxicosis	Nonthyroidal illness
TSH	decreased	increased	increased	increased	decreased or normal
Free T_4	increased	decreased	normal	normal	decreased
Free T_3	considerable increase	decreased or normal	decreased or normal	considerable increase	decreased

Table 7.3 Interpretation of results for thyroid function tests

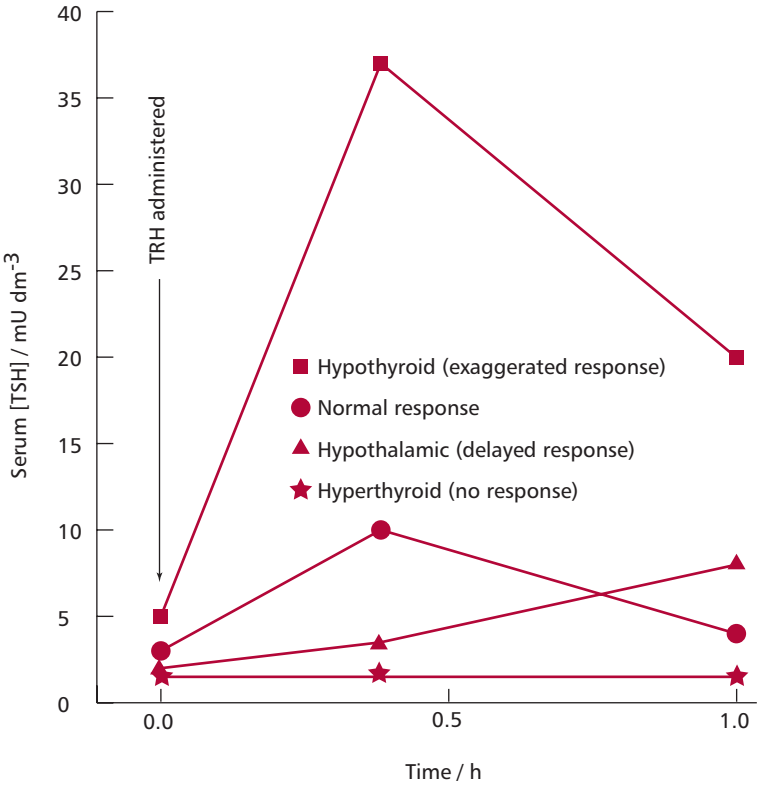


Figure 7.21 Potential results from a TRH test. See text for details.

Other techniques for investigating thyroid function include administration of isotopes, such as ^{99m}Tc-pertechnetate, and determining their distribution using a camera that detects γ radiation. This technique distinguishes between active and inactive thyroid nodules and can distinguish between Grave's disease, multinodular goiter or an adenoma affecting the thyroid gland. A thyroid biopsy involves aspirating tissue from the affected region of the thyroid using a syringe and fine needle. The collected cells are examined microscopically for evidence of thyroid nodules. Often thyroid disease has an autoimmune basis and measurement of antibodies can aid diagnosis. Antiperoxidase and antithyroglobulin antibodies are found in patients affected by Hashimoto's thyroiditis and often in those with Grave's disease. However, the detection of antibodies is not always diagnostic, as low levels of these antibodies can occur in older people who are euthyroid.

The management of hyperthyroidism includes using antithyroid drugs, for example, carbimazole. This is useful in young patients and acts by reducing the production of thyroid hormones. Other forms of treatment include radioiodine therapy with ^{131}I, although this is normally used in older patients, and partial or complete surgical removal of the thyroid gland (thyroidectomy). Some patients develop hypothyroidism, often as a consequence of treatment, and may have to be placed on thyroxine therapy. In this regard it is important to monitor TSH levels to detect developing hypothyroidism. Management of hypothyroidism involves replacement therapy with thyroxine, often for life. Thyroxine is readily available, safe and inexpensive. The treatment is monitored at regular intervals by measurement of serum concentrations of TSH to ensure they are kept within its reference range.

7.8 REGULATION OF BLOOD GLUCOSE

Adequate concentrations of glucose in the blood are necessary for brain cells as they cannot metabolize substances other than glucose and ketone bodies as energy sources nor can they store or synthesize glucose. After a meal, any released glucose is absorbed by the gastrointestinal tract (*Chapter 11*) enters the bloodstream and is delivered to the peripheral tissues where it may be metabolized to allow ATP production. Surplus glucose is converted to glycogen and stored in the liver and skeletal muscles or converted to triacylglycerols and stored in adipose tissue. During fasting, the liver produces glucose by glycogenolysis or gluconeogenesis and this is used to maintain blood glucose concentration (*Figure 7.22*).

The concentration of glucose in plasma is regulated by the hormones insulin and glucagon. Insulin is synthesized as preproinsulin in the β cells of the islets of Langerhans in the pancreas but during its secretion is enzymatically converted to active insulin (*Figures 7.3 (B)* and *7.23*). Insulin has a number of functions. It inhibits glycogenolysis, gluconeogenesis, lipolysis, ketogenesis

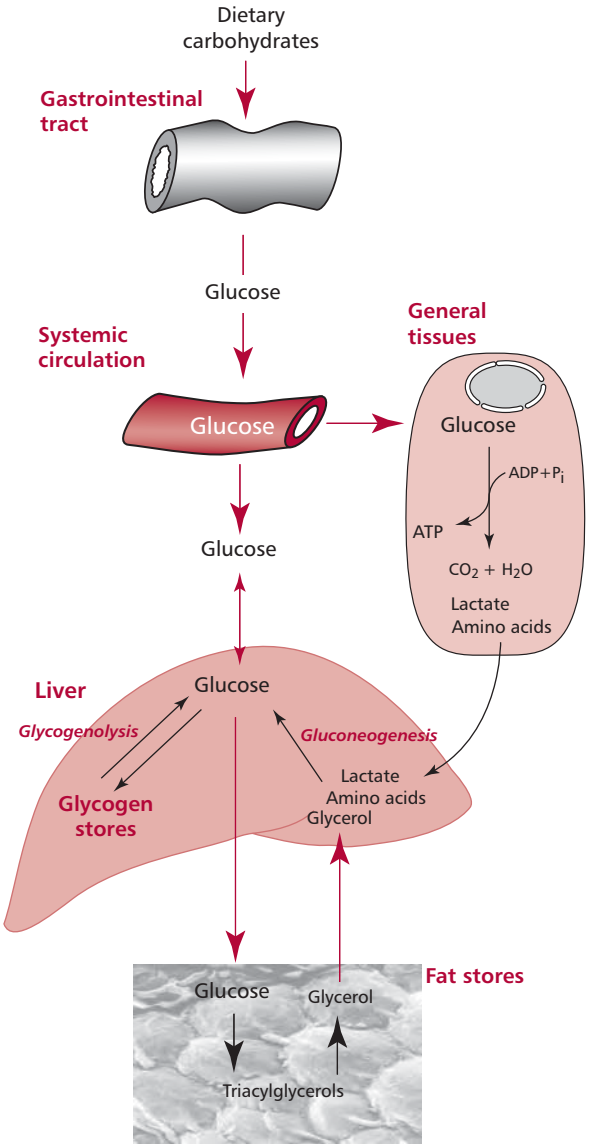


Figure 7.22 Overview of glucose homeostasis. See text for details.

Margin Note 7.2 Sanger and sequences

Sanger determined the complete sequences of the amino acid residues, the primary structures, of both chains of insulin in the early 1950s. This was the first unequivocal demonstration that proteins have strictly defined primary structures. With the techniques of chemistry and molecular biology available at that time, this was an incredible achievement and Sanger was awarded the 1958 Nobel Prize in Chemistry. Nowadays, sequencing a protein as small as insulin would be a trivial task. The sequences of smallish peptides are easily determined by mass spectrometry and it is relatively easy to determine the base sequence of a gene (DNA) and then interpret it in terms of the amino acid order of the encoded protein. Indeed, complete genome sequences of numerous organisms, including those of human beings and a number of human pathogens and parasites, are known and are widely available in various websites. Incredibly, the major method for sequencing DNA, the dideoxy method, was also devised by Sanger in 1977, when he and coworkers published the complete sequence of the genome of the virus, φX174. Sanger was awarded the Nobel Prize in Chemistry in 1980 for this work. Sanger thus belongs to the tiny elite group of people to have received two Nobel Prizes.

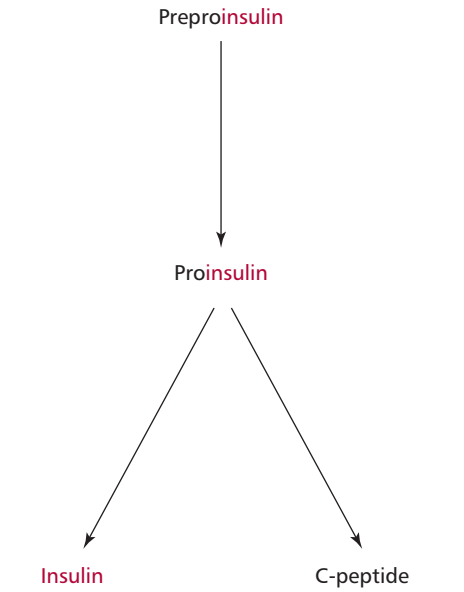


Figure 7.23 The conversion of preproinsulin to active insulin. See also *Figure 7.3 (B)*.

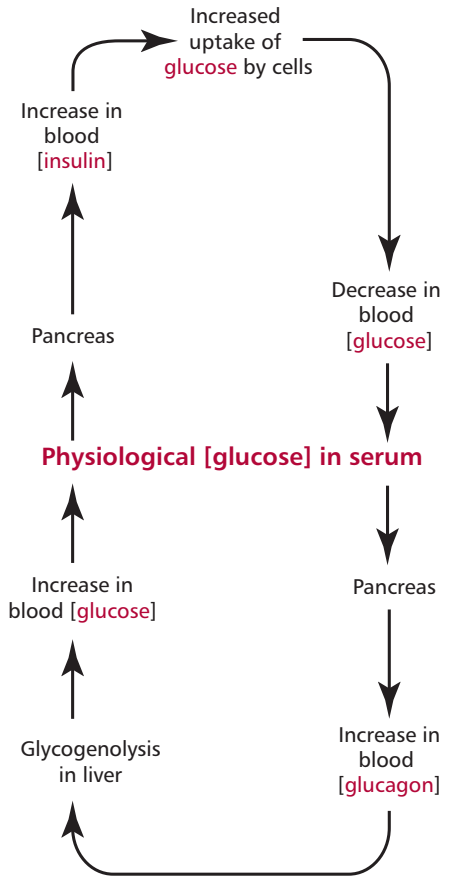


Figure 7.24 Regulation of blood glucose concentration by insulin and glucagon.

and proteolysis and stimulates glucose uptake by muscle and adipose tissues, glycolysis, glycogenesis, protein synthesis and uptake of K^+ and P_i. Glucagon is released by the α cells of the pancreas. Its effects are antagonistic to those of insulin. An increase in blood glucose stimulates the pancreas to produce insulin which, in turn, promotes the uptake and utilization of glucose by cells lowering its concentration. A reduction in blood glucose stimulates release of glucagon that promotes glycogenolysis in the liver thereby increasing blood glucose levels (*Figure 7.24*). Disorders of insulin release or activity can cause an increase in blood glucose, hyperglycemia, or its reduction, hypoglycemia.

DIABETES MELLITUS

Diabetes mellitus is a syndrome characterized by hyperglycemia due to an absolute or relative deficiency of, and/or resistance to, insulin. This is the commonest endocrine disorder, affecting about 2% of the world's population. Diabetes can be primary when caused directly by malfunction of one or more of the systems regulating blood glucose concentration, or secondary as a result of another disease. Primary diabetes is divided into types 1 and 2. In type 1 diabetes, also known as insulin dependent diabetes mellitus (IDDM), there is a decrease or absence of insulin production. It occurs in 15% of all diabetics and typically presents acutely during childhood or adolescence, although it can occur at any age. Patients have marked weight loss and ketoacidosis (*see below*) can occur readily. Type 1 diabetes mellitus is an autoimmune disease (*Chapter* ***5***) and antibodies that react with β cells of the islets of Langerhans in the pancreas have been demonstrated in over 90% of patients. It also has a strong association with certain histocompatibility antigens such as HLA-DR3, DR4 and certain DQ alleles (*Chapters 4* and *6*). Many cases of type 1 diabetes may develop after a viral infection, such as with Coxsackie B, which initiates an autoimmune reaction that destroys the β cells of the pancreas. Type 2 diabetes is also known as noninsulin dependent diabetes mellitus (NIDDM), where insulin secretion tends to be normal or even elevated. It accounts for about 85% of all cases of diabetes, has a gradual onset and tends to occur in middle-aged and elderly individuals. Patients are less likely to develop ketoacidosis. The etiology of type 2 diabetes is still unclear but has a strong association with obesity. The disease may arise because an abnormal insulin, not recognized by its receptor, is produced, lack of insulin receptors, the presence of defective receptors or by a defective secondary messenger system linking the insulin receptor to the glucose transporter in the plasma membrane. Type 2 diabetes has a strong familial incidence. For example, if an identical twin develops type 2 diabetes there is a strong likelihood that the other twin will become diabetic.

Secondary diabetes mellitus is uncommon and is a consequence of other disorders that involve excess secretion of hormones antagonistic to insulin, such as cortisol in Cushing's syndrome and GH in acromegaly. Damage to the pancreas following, for example, chronic pancreatitis or pancreatic surgery, may result in secondary diabetes.

Patients with diabetes mellitus suffer from a number of symptoms, including polydipsia, the production of large volumes of urine (**polyuria**), unexplained weight loss, blurred vision, tiredness and an increased susceptibility to infections. Diabetic patients are also susceptible to acute and chronic complications.

Acute complications of diabetes mellitus include diabetic ketoacidosis (DKA), hyperosmolar nonketotic (HONK) coma and hypoglycemia. Diabetic ketoacidosis occurs most commonly in patients with uncontrolled type 1 diabetes mellitus as a result of their failure to comply with insulin therapy or it can also be precipitated by infections, such as the common cold, when the body responds by releasing more glucose into the bloodstream and by

reducing the action of insulin. The pathogenesis of DKA is outlined in *Figure 7.25*. In DKA, glucose uptake by cells decreases whereas gluconeogenesis and glycogenolysis are both stimulated, causing severe hyperglycemia. Increased breakdown of proteins occurs and the released amino acids enter gluconeogenesis or are degraded to form urea. As a result of insulin deficiency, there is a shift of both K^+ and P_i from the intracellular to the extracellular compartments causing hyperkalemia and hyperphosphatemia respectively (*Chapter 8*). The insulin deficiency also stimulates lipolysis producing free fatty acids (FFAs) and glycerol. In the liver, FFAs are converted to acetyl CoA which is then converted to acetoacetate and finally acetone and β-hydroxybutyrate. Acetoacetate, acetone and β-hydroxybutyrate are called **ketone bodies** even though β-hydroxybutyrate is not a ketone. The liver cannot utilize ketone bodies and they accumulate in the blood (**ketonemia**) and may be excreted in the urine (**ketonuria**). The ketone bodies in the blood are moderately strong acids, $H^+Ketone^-$, and react with buffers, such as $NaHCO_3$ (*Chapter 9*),

$$H^+Ketone^- + NaHCO_3 \longrightarrow Na^+Ketone^- + H_2CO_3$$

decreasing the concentration of hydrogen carbonate but increasing that of carbonic acid producing an acidosis. The carbonic acid dissociates to CO_2 and H_2O and the blood PCO_2 increases. Thus the lung ventilation rate increases as the body attempts to remove the excess CO_2. The ketonemia is believed to be responsible for the abdominal pain, vomiting and acidosis associated with DKA. Severe hyperglycemia in DKA exerts a high osmotic pressure causing water to move out of the cells leading to cellular dehydration. Blood volume rises and the kidneys respond with polyuria. If blood glucose levels exceed the renal threshold, glucose is lost in the urine causing glycosuria. Eventually an osmotic diuresis may occur with loss of water and electrolytes. The blood volume therefore declines further (**hypovolemia**) reducing the glomerular

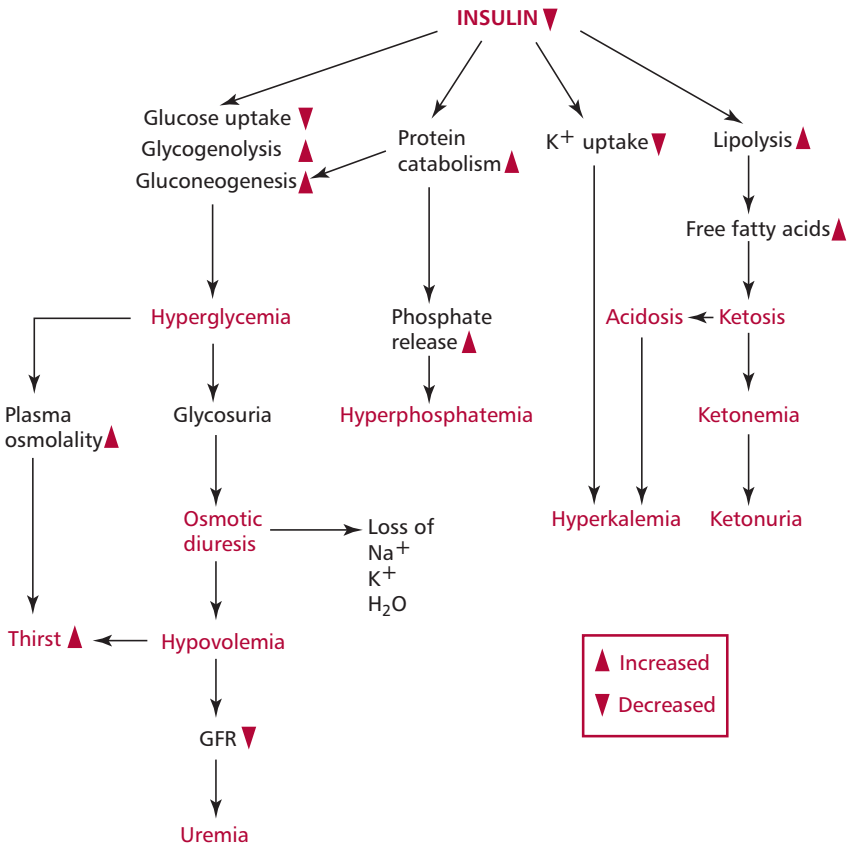


Figure 7.25 An overview of the factors causing diabetic ketoacidosis (DKA). See text for details.

filtration rate (GFR) and causing uremia. Dehydration and hypovolemia may stimulate the thirst center and the patient may suffer polydipsia.

Diabetic ketoacidosis is a medical emergency and is fatal in about 10% of adults and 5% of children if untreated. Death in untreated cases of DKA is due to poor tissue perfusion, acidosis and cardiovascular failure. The following approaches are taken to correct the metabolic disturbance. Isotonic saline and insulin are administered to correct the dehydration and hyperglycemia respectively. Following administration of insulin, K^+ enters the cells and this may cause hypokalemia therefore it may be necessary to administer K^+ supplements. In the past, severe cases of acidosis were treated by infusion of hydrogen carbonate although this approach is rarely adopted nowadays. Finally, if the DKA was precipitated by an infection, then it is necessary to identify and treat this infection.

Patients with uncontrolled type 2 diabetes mellitus may enter a HONK coma. This tends to occur in the elderly and develops over a period of days or even weeks. In these patients, the levels of insulin are sufficient to prevent ketosis but they often have severe hyperglycemia, characterized by blood glucose concentration above 35 and often in excess of 50 mmol dm^{-3}, together with severe dehydration and high serum osmolality. A HONK coma is usually precipitated by severe illness, diuretics, dehydration and glucocorticoid therapy. Its treatment is similar to that for DKA, except that the patient is rehydrated at a slower rate and insulin requirements are lower than those for a patient with DKA.

The chronic complications of diabetes mellitus include retinopathy, cataract, atherosclerosis, nephropathy and neuropathy. Diabetics with poor blood glucose control are most susceptible to these chronic complications. It is generally accepted that increased protein glycation and the accumulation of tissue advanced glycation end products (*Chapter 18*) are involved in the pathogenesis of chronic complications.

Diagnosis and treatment of diabetes mellitus

Investigation of diabetes is made on the basis of clinical features and laboratory investigations. A preliminary screening test may identify the presence of urinary glucose, although this is not diagnostic of diabetes mellitus. A patient presenting with symptoms of diabetes mellitus must have a venous blood specimen taken and its glucose concentration determined. A patient is diagnosed as diabetic if the fasting plasma glucose concentration is equal to or greater than 7.0 or the random concentration is greater than 11.1 mmol dm^{-3}. Diabetes mellitus is excluded if the fasting or random plasma glucose concentrations are less than 6.1 or 7.8 mmol dm^{-3} respectively. If the individual under investigation lacks the typical symptoms of diabetes then diagnosis cannot be confirmed by a single glucose determination but reconfirmed by at least one additional positive test on another day or investigated using the oral glucose tolerance test (OGTT). During the OGTT, the patient is kept on a normal diet for three days prior to the test and then fasts overnight prior to the test. A basal (fasting) venous blood sample is taken for glucose determination before the patient drinks 75 g of anhydrous glucose dissolved in a small volume of water. Blood specimens are collected after one and two hours and plasma glucose determined. Plasma glucose values greater than or equal to 7.0 mmol dm^{-3} for the basal sample or 11.1 mmol dm^{-3} for the 2 h samples are diagnostic of diabetes mellitus. Individuals with plasma glucose concentrations less than 7.0 for the basal sample or between 7.8 and 11.1 mmol dm^{-3} for the 2h samples are categorized as having impaired glucose tolerance (IGT). This group has an increased risk of developing cardiovascular disease (*Chapter 14*). Patients with plasma glucose concentrations of 6.1 to 7.0 mmol dm^{-3} for the basal samples or less than 7.8 mmol dm^{-3} for the 2 h

samples are categorized as having impaired fasting glucose (IFG) and are at risk of developing diabetes. The values given relate to venous plasma samples and are different from those for whole blood samples.

The management of diabetes mellitus aims to provide relief from symptoms and reduce the chances of developing acute and chronic complications. This includes educating the patient that diabetes is a life-long disease and affected individuals must be responsible for their own treatment. Regular clinical and laboratory assessment of the patient is required to ensure that treatment is effective, to detect early signs of treatable complications so as to reduce their progression and ensure compliance with treatment. Management involves the dietary restriction of simple sugars and of saturated fats and cholesterol and the use of complex carbohydrate and fibers. Dietary control is often accompanied by use of injected insulin or oral hypoglycemic drugs, such as sulfonylureas, in patients with type 1 and type 2 diabetes respectively. Occasionally, it may be necessary to use insulin in patients with type 2 diabetes to control blood glucose effectively. Hypoglycemic drugs act by increasing the sensitivity of β cells to glucose therefore stimulating insulin release or by increasing sensitivity of target cells to insulin. Both effects will reduce blood glucose levels. Some hypoglycemic drugs act to reduce the absorption of glucose by the GIT or reduce glycogenolysis in the liver. Diabetic patients on treatment are monitored regularly to ensure that blood glucose is kept in control. Most patients measure their own blood glucose at home regularly using kit methods based on reagent strips and a portable glucose meter (*Figure 7.26*) and adjust insulin dosage according to needs, perhaps following a change in diet, during illness or after exercise. The amount of glycated hemoglobin (*Figure 1.14*) in a patient is determined regularly to assess therapy compliance because its presence is an indicator of average glycemia over the previous 6–8 weeks. The amount of glycated hemoglobin tends to be less than 6% in nondiabetics but may exceed 10% in uncontrolled diabetes. Diabetic patients with high values have poor blood glucose control and their treatment or compliance must be reviewed.

HYPOGLYCEMIA

Hypoglycemia is defined as a blood glucose concentration less than 2.2 mmol dm^{-3} in a random specimen collected into a tube containing an inhibitor of glycolysis. Hypoglycemia occurs because of an imbalance between glucose intake, endogenous glucose production and glucose

Figure 7.26 A blood glucose meter.

utilization. Its clinical features are mainly due to abnormal function of the CNS (neuroglycopenia) and can be acute or chronic. Acute features include tiredness, confusion, hunger, dizziness, blurred vision, convulsions, coma, anxiety, profuse sweating and tachycardia. The typical signs and symptoms are more likely to occur if blood glucose falls rapidly: in children and young adults the symptoms often present when the glucose concentration is less than 2.2 whereas neonates develop symptoms only when it is less than 1.5 mmol dm^{-3}. Acute hypoglycemia is usually associated with diabetics who have taken too much insulin. Its chronic features include personality changes, memory loss and dementia and are generally observed in patients with insulin secreting tumors.

Most cases of hypoglycemia occur in patients with type 1 diabetes mellitus because of insufficient carbohydrate, too high a dose of insulin, inappropriate use of hypoglycemic drugs, excessive alcohol intake and strenuous exercise. Hypoglycemia can occur during fasting if the individual has an insulin secreting tumor or insulinoma which is a primary tumor of the β cells of the islets of Langerhans. These tumors produce excessive amounts of insulin or secrete insulin when it is not required. Nonpancreatic tumors, especially carcinomas of the liver and sarcomas, may cause hypoglycemia by increasing cellular uptake of glucose but this is unlikely to be the sole cause. Many of these tumors secrete IGF-II which has insulin-like effects and is capable of causing hypoglycemia.

Hypoglycemia in children is particularly dangerous because of the high risk of permanent brain damage. Its diagnosis is especially necessary in the first few months of life. A fetus exposed to maternal hyperglycemia will have pancreatic islet cell hyperplasia and elevated insulin levels. Following birth, the neonate has hyperinsulinism and may develop hypoglycemia now the high glucose supply from the mother has been removed. In addition, these babies are larger than average in size since insulin promotes growth.

Diagnosis and treatment of hypoglycemia

An initial assessment of a patient with frequent episodes of hypoglycemia involves a thorough clinical evaluation with an emphasis on the patient's drug history, relationship of symptoms to meals, presence/history of endocrine disease and an investigation of a possible nonpancreatic tumor. Laboratory tests can confirm the diagnosis of hypoglycemia by demonstrating a low blood glucose concentration. To confirm that the clinical features are due to hypoglycemia, the patient can be given glucose by mouth or parenterally as appropriate. Symptoms that are due to acute neuroglycopenia resolve immediately whereas those due to chronic neuroglycopenia often persist. Measurement of plasma insulin concentration can help in the diagnosis or exclusion of an insulinoma. An insulinoma is likely if the patient has fasting hypoglycemia together with high serum insulin levels that are greater than 10 mU dm^{-3} and raised C-peptide levels (*Figure 7.23*). Insulin secretion in an insulin-treated diabetic cannot be determined for obvious reasons. However, insulin and the C-peptide are secreted by islet cells in equimolar amounts and therefore a measurement of C-peptide together with insulin can differentiate between hypoglycemia due to an insulinoma, which will have a high C-peptide concentration, from that due to exogenous insulin, which will have relatively low amounts of C-peptide.

Hypoglycemia can be fatal and patients must be treated urgently. The aim in comatose patients is to rapidly correct the hypoglycemia using intravenous dextrose or intramuscular glucagon. If a patient is conscious and can swallow, then they are given sweet drinks, sweets or glucose tablets. The underlying cause of hypoglycemia needs to be identified and rectified; an insulinoma, for example, requires surgical removal.

7.9 DISORDERS OF THE ADRENAL CORTEX

Adrenal glands each weigh about 5 g and are found on the upper surfaces of the kidneys. They consist of an outer cortex and an inner medulla. The cortex consists of three layers: the zona glomerulosa, zona fasciculata and zona reticularis (*Figure 7.27*). The adrenal cortex is essential for life since it produces three groups of steroid hormones. The glucocorticoids, such as cortisol, and adrenal androgens, for example testosterone, are produced by the zona reticularis and zona fasciculata and mineralocorticoids, such as aldosterone, from the zona glomerulosa. Adrenal cortex cells have many low density lipoprotein receptors on their surfaces enabling them to take up precursor cholesterol rapidly from the plasma.

Cortisol (*Figure 7.28 (A)*) is released in response to adrenocorticotrophic hormone (ACTH) from the anterior pituitary that, in turn, is controlled by the release of corticotrophin releasing factor (CRF) from the hypothalamus. Cortisol exerts a negative feedback effect on the anterior pituitary and hypothalamus (*Figure 7.28 (B)*). The secretion of cortisol shows a diurnal variation: highest in the morning, lowest at night. Cortisol stimulates an increase in protein catabolism, hepatic glycogenolysis and gluconeogenesis and a redistribution of adipose tissue but suppresses inflammation. About 90% of blood cortisol is bound to a cortisol binding globulin called transcortin whilst the remaining 10% is free.

The major mineralocorticoid, aldosterone (*Figure 7.29 (A)*), is released in response to hypotension, Na^+ depletion or hyperkalemia (*Chapter 8*). A group of cells in the kidneys called juxtaglomerular cells detect a fall in blood pressure and secrete renin which circulates in the blood and catalyzes the conversion of the plasma protein angiotensinogen to angiotensin I. A converting enzyme in the lungs converts angiotensin I to angiotensin II that stimulates the release of aldosterone from the adrenal cortex and ADH from the posterior pituitary (*Figure 7.29 (B)*). Aldosterone stimulates the retention of Na^+ in exchange for K^+ and H^+ in the kidney tubules increasing the osmolality of the ECF and the retention of water raising the blood pressure or the ECF volume back to

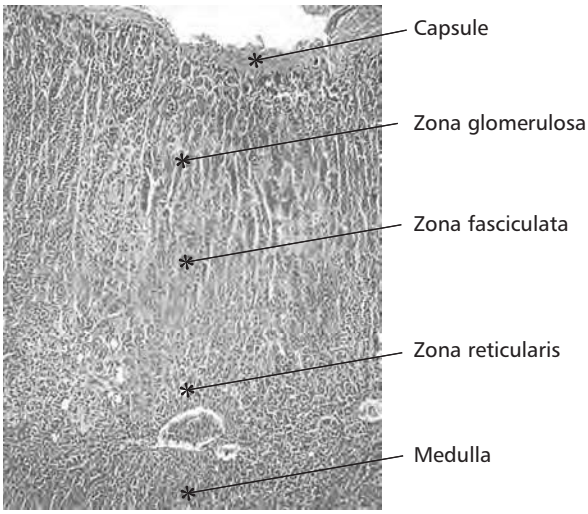


Figure 7.27 The histological structure of the adrenal cortex. Courtesy of Dr A.L. Bell, University of New England, College of Osteopathic Medicine, USA.

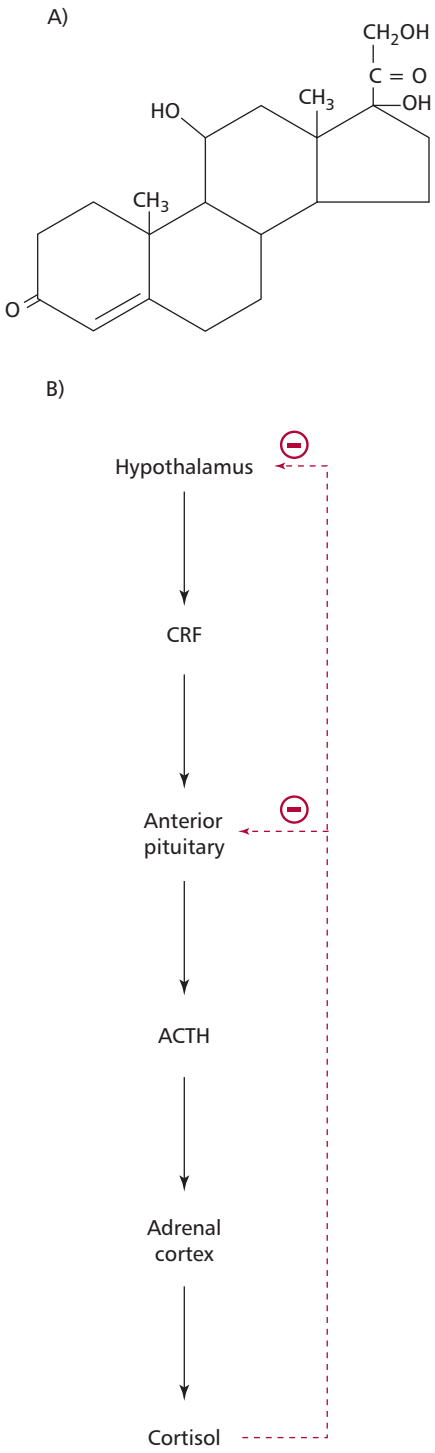


Figure 7.28 (A) Structure of cortisol and (B) the regulation of its secretion.

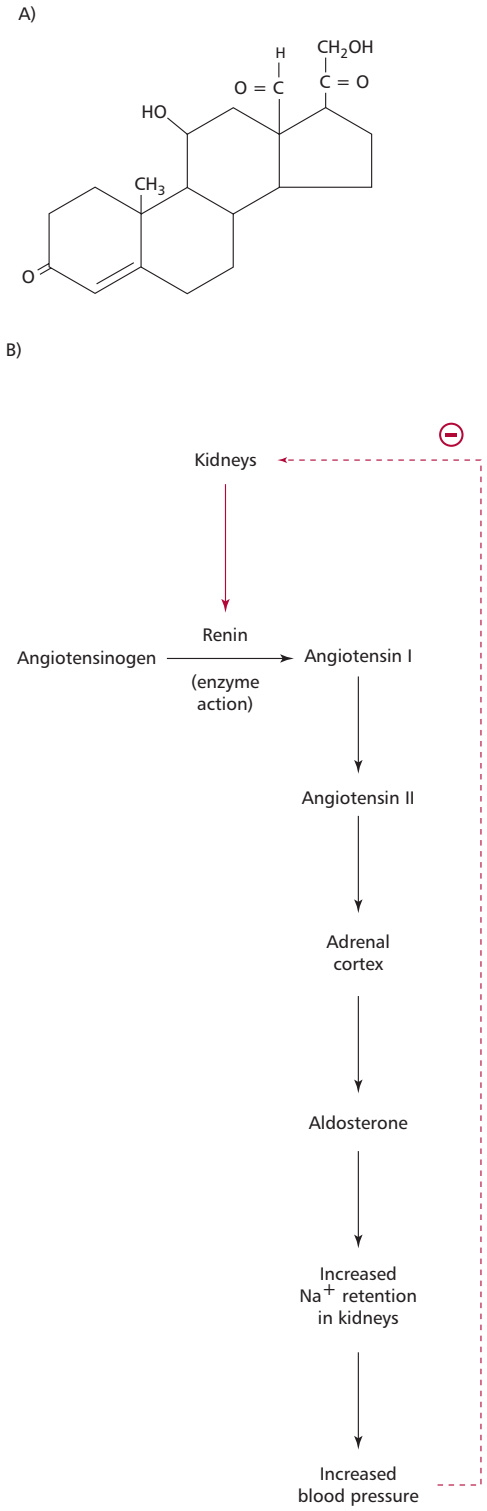


Figure 7.29 (A) Structure of aldosterone and (B) the regulation of its secretion.

physiological values. Angiotensin II also stimulates thirst that helps to increase blood pressure. The adrenal cortex secretes androgens, such as testosterone, dehydroepiandrosterone sulfate (DHEAS) and androstenedione. Testosterone is the hormone that stimulates the growth and development of the male characteristics (*Section 7.10*).

ADDISON'S DISEASE

Adrenal hypofunction or Addison's disease is a rare condition but is simple to treat once diagnosed. It can arise from one of a number of causes: an autoimmune destruction of the adrenal cortex, as a response to tuberculosis (TB), amyloidosis, hemochromatosis, following adrenalectomy or hypothalamic or pituitary diseases referred to as secondary adrenal insufficiency. Addison's disease is characterized by a deficiency of glucocorticoids and mineralocorticoids. Its clinical features include weakness, lethargy, anorexia, nausea, vomiting, weight loss, hypotension, skin pigmentation, hypoglycemia and depression (*Figure 7.30*). In the first few months, symptoms are usually vague with only lethargy, weakness and weight loss presenting as a result of glucocorticoid deficiency. Later, patients start to vomit and have abdominal pain. The lack of mineralocorticoids leads to an excessive loss of Na^+ and therefore hypotension is common in these patients. Plasma ACTH is increased because of pituitary response to low levels of cortisol given the lack of a negative feedback mechanism. Adrenocorticotrophic hormone can stimulate melanocytes in skin to produce the melanin, hence pigmentation is a common feature in Addison's disease.

Diagnosis and treatment of Addison's disease

A clinical suspicion of Addison's disease can be confirmed by demonstrating hyperkalemia with hyponatremia (*Chapter 8*). The plasma cortisol is usually, but not always, low in these patients. A high concentration of ACTH coupled with a low concentration of cortisol is indicative of Addison's disease whereas low cortisol and ACTH values are suggestive of secondary adrenal insufficiency. The situation can be resolved using complex biochemical tests with the analog of ACTH, synacthen. The short synacthen test involves an intramuscular injection of 0.25 mg of synacthen. The concentration of plasma cortisol is measured within 30 min. If it rises by at least 200 or to a value greater than 550 nmol dm^{-3}, then Addison's disease is unlikely. If this is not the case, then it is appropriate to proceed to the long synacthen test which involves an intramuscular injection of 1 mg of ACTH daily for three days. On the fourth day, the short synacthen test is performed and the serum concentration of cortisol is measured. If this is less than 200 nmol dm^{-3} with no increase following administration of synacthen there is primary adrenal failure and the patient is suffering from Addison's disease. If, however, there is an incremental increase of at least 200 nmol dm^{-3} above the baseline, then the decreased output of cortisol from adrenal gland is secondary and due to a deficiency of ACTH caused by a hypothalamic or pituitary disorder. Once Addison's disease is diagnosed, it is necessary to ascertain its cause. A number of laboratories test for the presence of antibodies against the adrenal glands to see if there is an autoimmune cause. A plain abdominal X-ray may be useful in that it can detect calcification of adrenal glands as a result of TB (*Chapter 3*).

The conventional therapy for Addison's disease involves treatment with steroids, such as hydrocortisone and fludrocortisone, which possess glucocorticoid and mineralocorticoid activities respectively. If a patient is left untreated he or she will eventually experience an adrenal crisis precipitated by stress, bacterial infection, trauma or surgery, which is a medical emergency. Typical clinical features of a crisis are abdominal pain, vomiting, hypotension together with hyponatremia, hypoglycemia and hyperkalemia. Its treatment involves administering saline infusions to correct the hypotension, fluid

and salt losses and intravenous steroids to correct glucocorticoid and mineralocorticoid deficiencies. The precipitating factors, such as bacterial infections, require identification and appropriate treatment.

CUSHING'S SYNDROME

Adrenal hyperfunction can cause Cushing's syndrome and arise from a number of causes. The commonest cause is a pituitary lesion secreting high levels of ACTH (referred to as Cushing's *disease*). Other causes include ectopic production of ACTH from a carcinoma of the lungs, or excessive production of cortisol from an adrenal adenoma or carcinoma and iatrogenic causes, such as corticosteroid or ACTH treatment. The major clinical features (*Figure 7.31*) include truncal obesity, thinning of skin, excessive bruising, poor wound healing, purple striae on the abdomen and thighs, muscle weakness and wasting, **hirsutism**, the development of increased body hair on the face, chest upper back and abdomen in females (especially in adrenal carcinoma), hypertension, amenorrhea and psychiatric disturbances. Excess of cortisol has a mineralocorticoid effect leading to the retention of Na^+ and water producing hypertension. Hypokalemia may also occur because of an excessive loss of K^+ (*Chapter 8*). Excess cortisol increases blood glucose levels and some of these patients may have diabetes mellitus. The clinical features are due to increased cortisol production and, partly, to excessive androgen release.

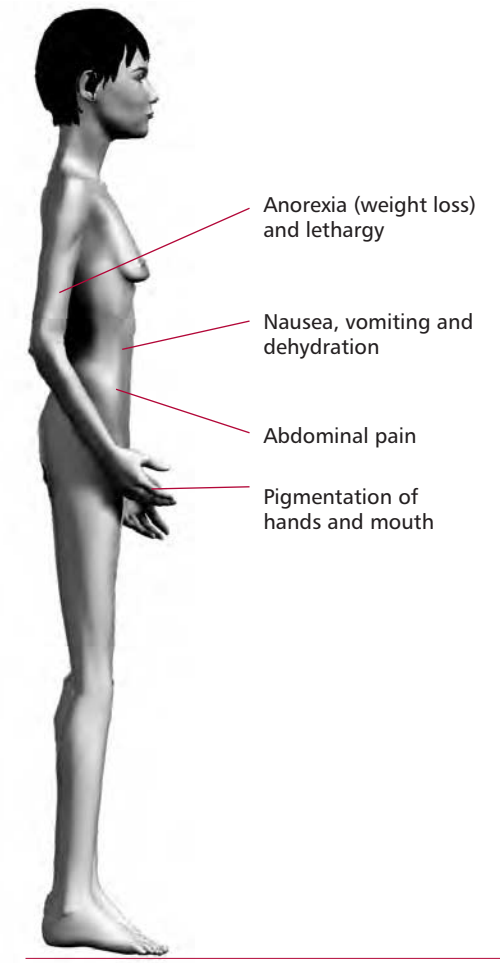


Figure 7.30 Schematic to show the clinical features of Addison's disease.

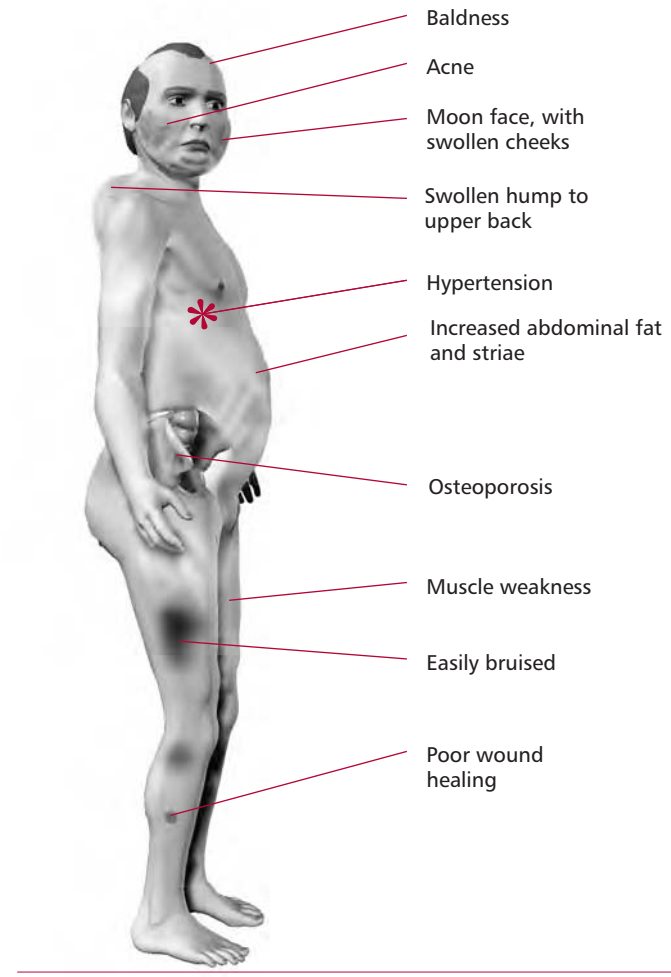


Figure 7.31 Schematic to show the clinical features of Cushing's syndrome.

Diagnosis and treatment of Cushing's syndrome

A clinical suspicion of the syndrome is supported by hypokalemia and alkalosis, high urinary free cortisol, which is normally less than 300 nmol per 24 h, and loss of the usual diurnal rhythm of cortisol secretion. Initial screening criteria are followed by tests using the cortisol analog, dexamethasone, which is not detected by the usual methods of measuring cortisol. Dexamethasone, however, suppresses ACTH production and cortisol secretion in normal people. The low dose dexamethasone test involves giving 1 mg of dexamethasone at night. A blood specimen is taken for cortisol measurement the following morning. A failure of dexamethasone to suppress cortisol release is suggestive of Cushing's syndrome or disease. To distinguish between the two, a high dose dexamethasone test may be used or the concentration of ACTH in plasma measured. The high dose dexamethasone test consists of administering 2 mg of dexamethasone every 6 h for a period of 48 h. The concentration of cortisol in the plasma is then measured at 09.00 h on the morning following the last dose. In Cushing's syndrome, due to excessive secretion of cortisol by an adrenal tumor or in response to an ectopic source of ACTH, suppression of cortisol does not occur. In Cushing's disease, caused by a pituitary lesion secreting ACTH, the concentration of cortisol is suppressed to less than 50% of its value prior to the test. Plasma ACTH levels are raised in patients with Cushing's disease and ectopic ACTH production, but are low in patients who have an adrenal tumor that secretes cortisol.

The management and treatment of Cushing's syndrome depends upon its cause. Drugs, such as metyrapone, that inhibit the synthesis of cortisol may be used. Tumors can be removed surgically.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition (*Chapter 15*) characterized by an abnormal biosynthesis of steroid hormones in the adrenal glands. The clinical features depend on whether cortisol and/or aldosterone or androgens are involved. The commonest cause of CAH is a complete or partial deficiency of 21-hydroxylase activity (*Figure 7.32*) that accounts for 95% of all cases, and occurs with an incidence of 1 in 12 000 newborn babies in the UK. A deficiency of 21-hydroxylase activity blocks the synthesis of cortisol and, as a consequence, negative feedback to the anterior pituitary is diminished. The anterior pituitary increases its secretion of ACTH, which causes hyperplasia of the adrenal glands. The substrate, 17α-hydroxyprogesterone accumulates and stimulates the production of adrenal androgens. A deficiency in 21-hydroxylase activity is complete in approximately one-third of CAH patients. Less common forms of CAH are characterized by deficiencies of other enzymes in the synthetic pathway.

Females affected with CAH are born with ambiguous genitalia, although in cases of partial enzyme deficiency this may not be apparent until early adulthood where the female presents with hirsutism, amenorrhea and infertility. Males with CAH present with premature development of the male secondary sexual characteristics called pseudoprecocious puberty. In individuals with a complete deficiency of 21-hydroxylase activity, aldosterone production is also inhibited and these individuals usually present shortly after birth with a life-threatening condition characterized by excessive salt and water loss.

Diagnosis and treatment of congenital adrenal hyperplasia

Diagnosis of CAH due to 21-hydroxylase deficiency is made by detecting increased concentrations of 17α-hydroxyprogesterone in the baby's blood at least two days following birth. Maternal 17α-hydroxyprogesterone may still be present at two days postparturition, hence the need for the delay. The affected

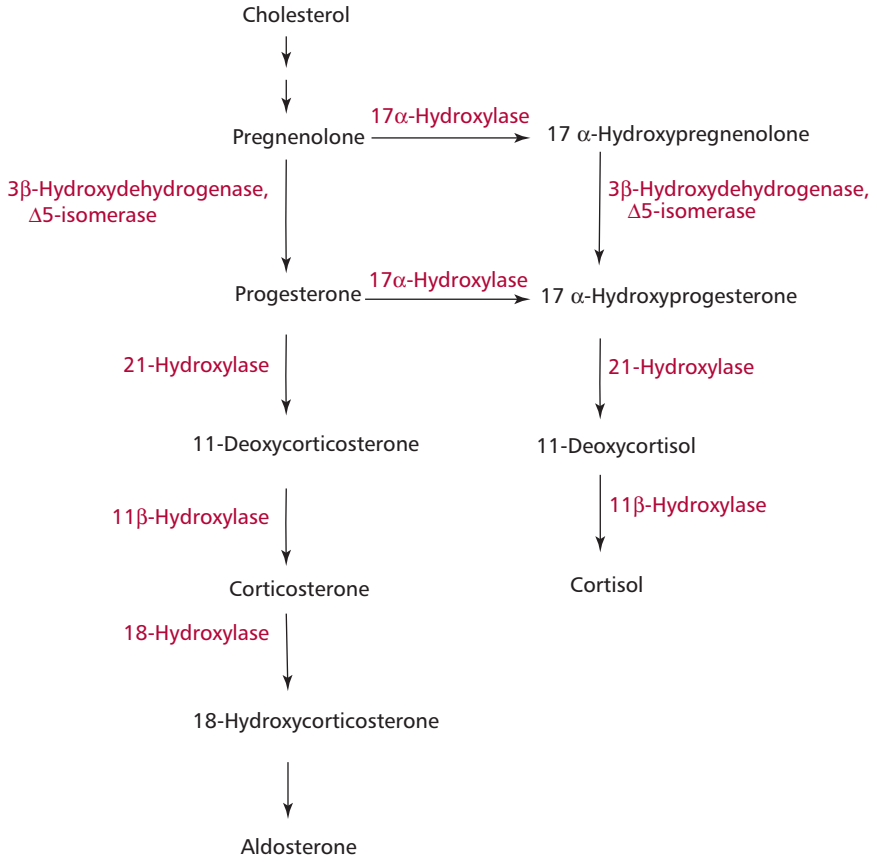


Figure 7.32 The synthesis of cortisol and aldosterone.

individuals are treated with cortisol and, if necessary, aldosterone. The treatment should reduce ACTH secretion and therefore excessive androgen production. The treatment requires monitoring by regular measurements of plasma 17α-hydroxyprogesterone.

CONN'S SYNDROME

Conn's syndrome, also called primary hyperaldosteronism, is characterized by an increased production of aldosterone. In 80% of cases this is due to an adrenal adenoma. Other causes include hypertrophy of the zona glomerulosa of the adrenal cortex and adrenal carcinoma, although the latter is extremely rare. The excessive secretion of aldosterone leads to the increased retention of Na^+ and loss of K^+ by the kidneys. Most of the clinical features, muscle weakness, tetany, paresthesiae, polydipsia and polyuria, are due to the hypokalemia (*Chapter 8*) whereas the excessive Na^+ retention causes hypertension.

Diagnosis and treatment of Conn's syndrome

Investigating the possibility of Conn's syndrome involves determining the concentrations of Na^+ and K^+ in the serum and urine of the patient. Plasma Na^+ can be high, slightly increased or normal, whereas that of K^+ is always reduced. Measurements of plasma aldosterone and renin in patients with Conn's syndrome often show a high aldosterone concentration and a low renin activity. Conn's syndrome is managed by treating its underlying cause. Often this is a tumor that must be removed surgically. Other approaches involve using diuretics, such as spironolactone, an antagonist to aldosterone that helps to control hypertension. This is particularly useful when the cause of Conn's syndrome is adrenal hyperplasia.

BOX 7.2 Pheochromocytoma

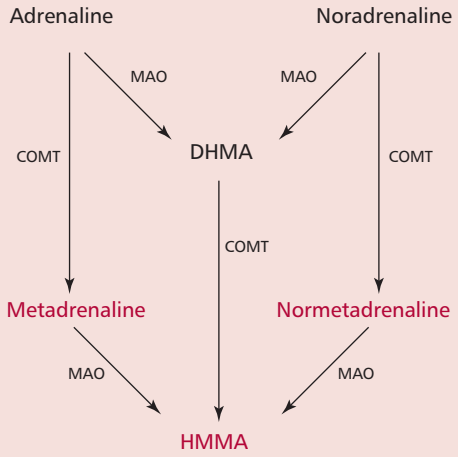
Adrenaline (epinephrine) and noradrenaline (norepinephrine) are catecholamine hormones secreted by the adrenal medulla. They stimulate increases in heart, metabolic and breathing rates, the depth of breathing and dilate blood vessels to muscles and increase the metabolism of carbohydrate stores to prepare the body for 'fright, flight or fight'.

Pheochromocytomas are tumors of the adrenal medulla that cause uncontrolled and irregular secretion of adrenaline and noradrenaline. Such tumors are usually benign, that is they do not metastasize (*Chapter 17*), and are rare causes of hypertension (*Chapter 14*) accounting for some 0.5% of such cases.

Adrenaline and noradrenaline are metabolized to metadrenaline and normetadrenaline respectively by catechol-*O*-methyl-transferase (COMT). Metadrenaline and normetadrenaline are converted to 4-hydroxy-3-methoxymandelic acid (HMMA), also known as vanillylmandelic acid (VMA), by monoamine oxidase (MAO). Metadrenaline and normetadrenaline and HMMA are all excreted in the urine (*Figure 7.33*).

Patients affected by pheochromocytomas present with headaches, pallor, tremors, increased heart rate and palpitations, sweating and abdominal discomfort. Pheochromocytoma leads to high levels of catecholamines in the plasma. However, a diagnosis based on measurement of plasma levels is difficult, as they are subject to variation by a number of factors including posture. Screening tests include measuring and demonstrating increased concentrations of urinary HMMA or metadrenaline and normetadrenaline (*Figure 7.33*). The reference range for urine HMMA is less than 35 µmol per 24 h whereas those for metadrenaline and normetadrenaline are less than 0.1 and less than 0.57 µmol per 24 h respectively. In cases where the results are equivocal, the pentolinium test is conducted. Patients are given 2.5 mg of pentolinium by intravenous injection. A blood specimen is collected before and 15 min after the injection. Pentolinium is a drug that inhibits release of catecholamines in normal individuals but not in those suffering from pheochromocytoma.

The treatment of pheochromocytoma involves surgical removal of the tumor. However, it is necessary to block the action of excess adrenaline and noradrenaline before any surgery by administration of phenoxybenzamine. This is because during the operation, the sudden release of large amounts of catecholamines results in high blood pressure which, in turn, could cause a heart attack or brain hemorrhage.



COMT	catechol-O-methyltransferase
MAO	monoamine oxidase
DHMA	dihydroxymandelate
HMMA	4-hydroxy-3-methoxymandelate

Figure 7.33 Metabolism of adrenaline and noradrenaline.

7.10 REPRODUCTIVE HORMONES

The male and female reproductive systems (*Figure 7.34 (A)* and *(B)*) produce and secrete a number of sex hormones and are responsible for the maturation of germ cells, the production of gametes and, in the female, the fertilization of the ovum and its subsequent growth and development. The testes produce male gametes or spermatozoa ('sperms') that mature and are stored in the epididymis and vas deferens. Testes are composed of lobules with up to three seminiferous tubules containing cells undergoing spermatogenesis. These cells are supported and nourished by Sertoli cells. Spermatogenesis involves meiosis and produces haploid sperm (*Chapter 15*) as outlined in *Figure 7.35*. Each sperm has a head and a tail consisting of a midpiece and flagellum. The midpiece contains mitochondria that provide energy for the locomotory movements of the flagellum. The head contains a nucleus and

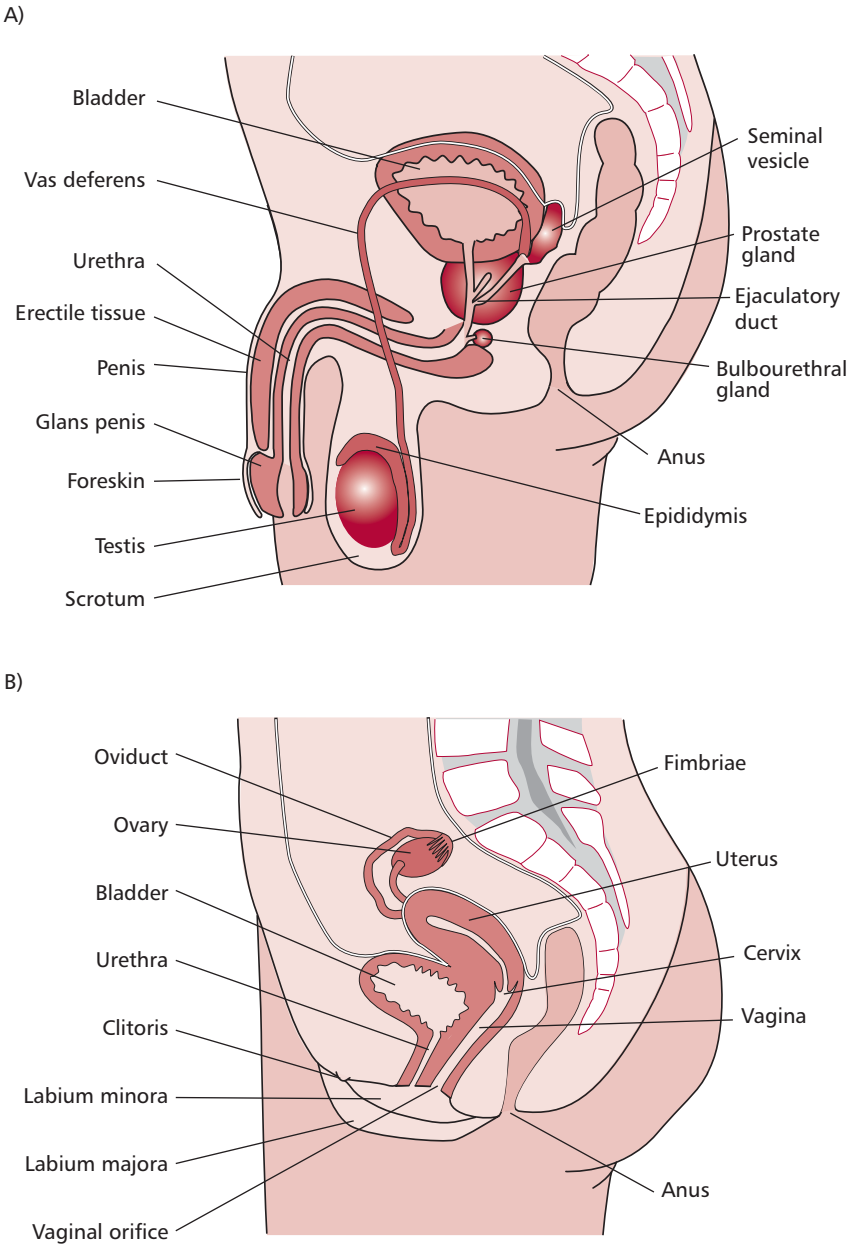


Figure 7.34 Overviews of the (A) male and (B) female reproductive systems.

is covered by a cap called an acrosome, which contains enzymes required to penetrate the ovum or egg. The production of ova, female gametes, begins in the ovaries by a process called oogenesis (*Figure 7.36*). Primordial germ cells in the outer germinal epithelium divide by mitosis to form a diploid primary oocyte that becomes surrounded by follicle cells to produce primary follicles. These migrate into the center of the ovary. As many as two million primary follicles are present at birth and remain dormant until puberty. Approximately 400 primary follicles mature over the lifetime of a female until follicle development ceases at the menopause. The primary follicle matures to form a secondary follicle. During this development, the primary oocyte divides by meiosis but this is arrested and forms a haploid secondary oocyte, which is the precursor of the ovum, and a small polar body. In an adult fertile female, the nucleus of a secondary oocyte begins the second meiotic division at each monthly ovulation but progresses only to metaphase, when

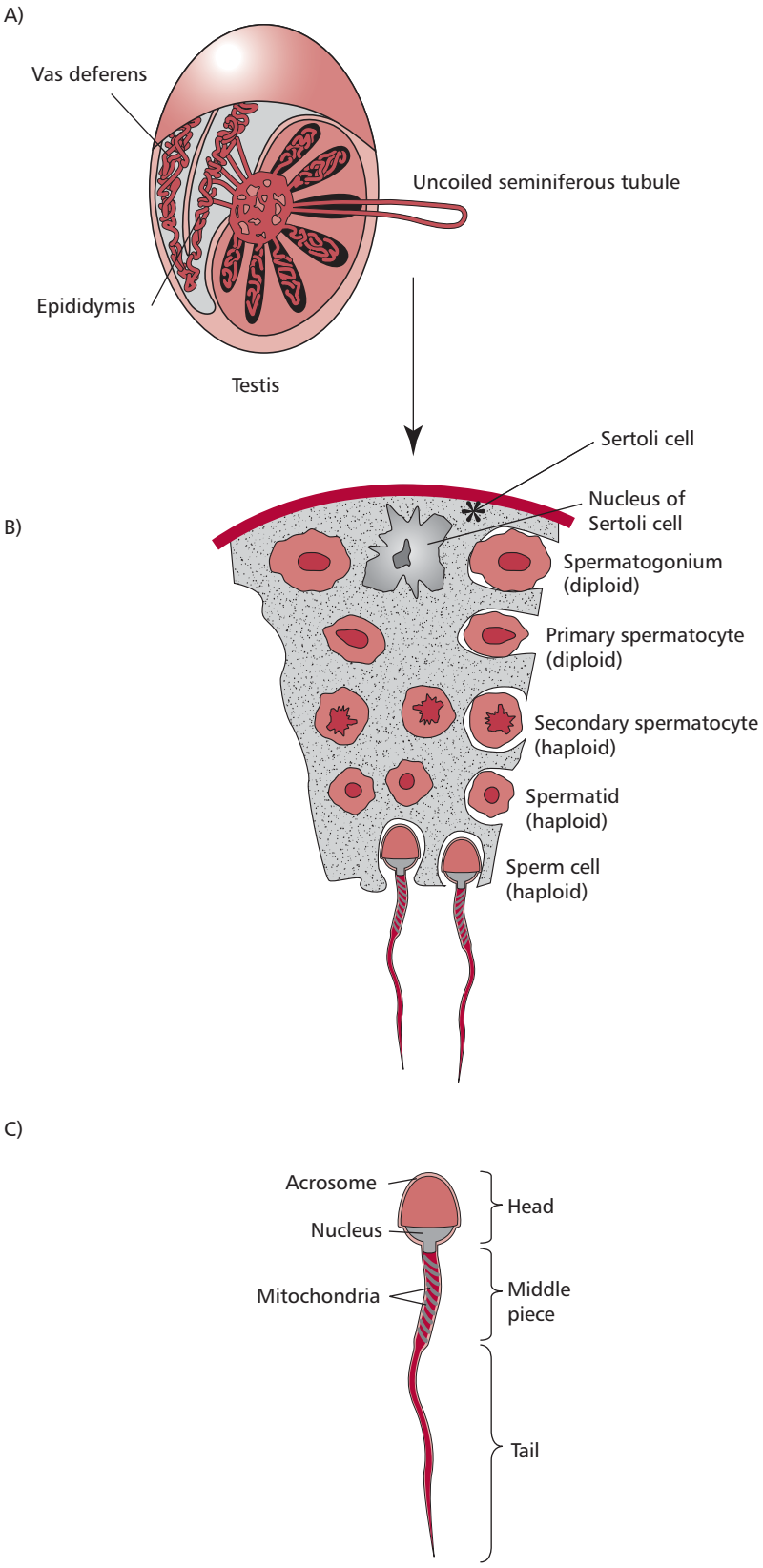


Figure 7.35 (A) Schematic of a testis. (B) Overview of spermatogenensis. (C) Schematic of a sperm. See text for details.

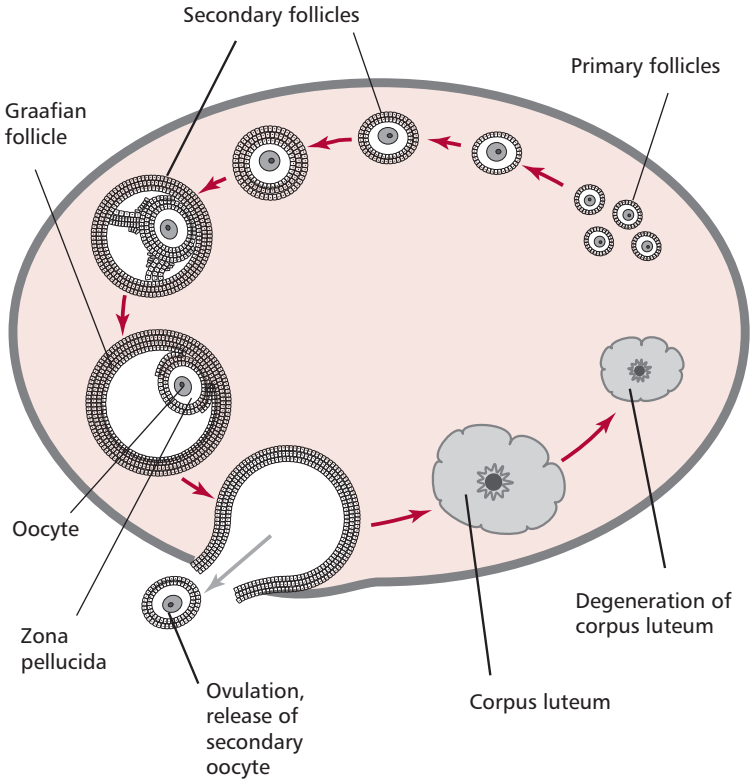


Figure 7.36 Overview of oogenesis and release of oocyte. See text for details.

division again ceases. The second meiotic division of the secondary oocyte is completed at fertilization.

In males and females, the hypothalamus secretes gonadotrophin releasing hormone (GnRH) which regulates secretion of LH and FSH from the basophil cells of the anterior pituitary. Secretion of GnRH, LH and FSH occurs in pulses. Follicle stimulating hormone and LH act cooperatively to stimulate the ovaries and testes to secrete sex hormones and to develop germ cells.

The testes are stimulated by LH to release testosterone from their Leydig cells (*Figure 7.37*). Testosterone is the principal androgen and its secretion inhibits further release of LH by a negative feedback mechanism. Follicle stimulating hormone and testosterone are required by Sertoli cells in the basement membrane of the seminiferous tubules to produce inhibin that, in turn, inhibits the secretion of FSH by negative feedback (*Figure 7.37*). Testosterone is also required for sexual differentiation, the development of secondary sexual characteristics and spermatogenesis. It is transported in the blood, bound to sex hormone binding globulin, SHBG (*Figure 7.38 (A)*) and to a lesser extent albumin. Typically, only its free fraction is metabolically active. Testosterone enters target cells and is converted to the potent androgen, dihydrotestosterone by the enzyme 5α-reductase. Testosterone is also found in the plasma of normal females, half of which is secreted by the ovaries, the remainder arising from the peripheral conversion of androstenedione and DHEAS, both of which are secreted by the adrenal cortex.

The ovaries produce estrogens, of which estradiol is required for the development of female secondary sexual characteristics and normal menstruation. Circulating estradiol is bound mostly to SHBG (*Figure 7.38 (B)*), although the blood concentration of estradiol varies widely with the menstrual cycle.

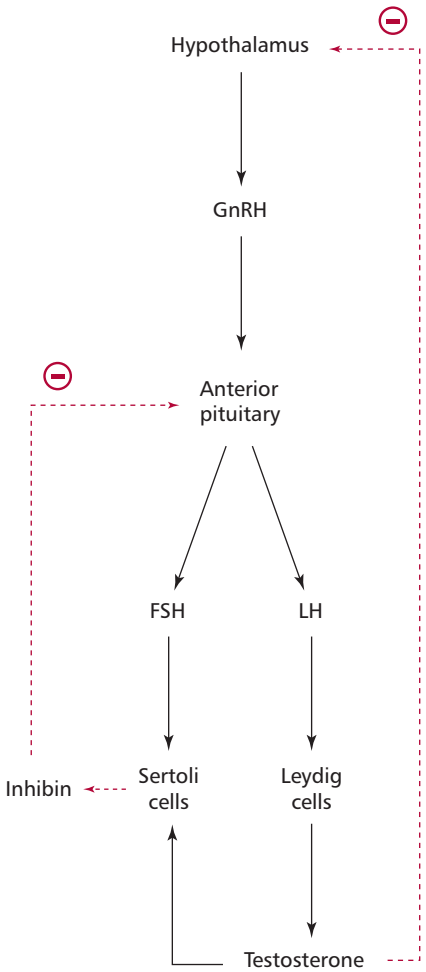


Figure 7.37 The regulation of testosterone (*Figure 7.3 (C)*) secretion.

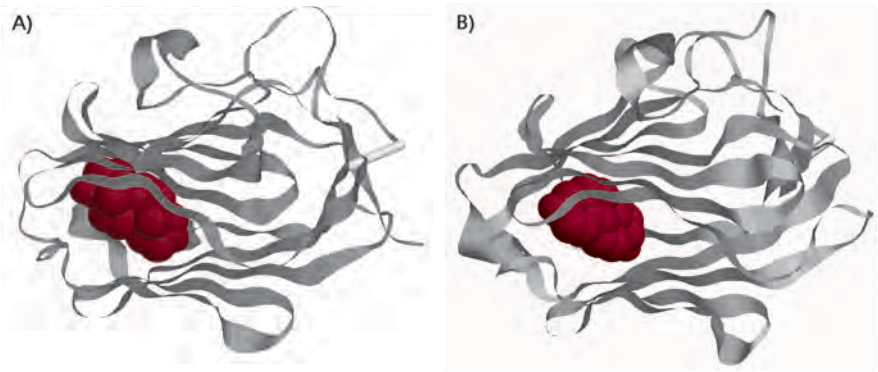


Figure 7.38 Molecular models of (A) the active form of testosterone and (B) estradiol shown in red bound to SHBG. PDB files 1KDM and 1LHU respectively.

The plasma concentration of estradiol is low before puberty but increases rapidly and fluctuates during the menstrual cycle, a series of cyclical changes in the ovary, uterus and pituitary that occur approximately every 28 days until the menopause. Variations in plasma hormones in the menstrual cycle (*Figure 7.40*) depend on interactions between the hypothalamus, anterior pituitary and ovaries. Follicle stimulating hormone is released at the beginning of the cycle and increases growth of the follicles in the ovaries. Estradiol production increases the sensitivity of the pituitary to GnRH but decreases its secretion by the hypothalamus. The release of estradiol gradually increases and a follicle matures during the first half of the cycle. At the start of each cycle, about 20 secondary follicles enlarge and begin to secrete estrogen and the hormone inhibin, and a cavity filled with follicular fluid forms around their ova. This is referred to as antrum formation. By about the sixth day, one of the secondary follicles in an ovary has outgrown the others and becomes the dominant follicle. Its secretion of estrogen and inhibin decreases the secretion of FSH

BOX 7.3 Oral contraceptive pill

Oral contraceptives (*Figure 7.39*) known colloquially as *the pill*, contain a synthetic version of estrogen, called ethinylestradiol and the synthetic version of progesterone, progestogen. The estrogen prevents ovulation taking place, whereas progestogen acts on the pituitary gland to block the normal physiological control of the menstrual cycle. Progestogen alters the lining of the uterus so that it is unsuitable for implantation and increases the viscosity of the mucus in the cervix, so that conception is less likely even if ovulation does occur. Oral contraceptive pills are taken daily for three weeks and then stopped for a week during menstruation.

Pincus (1903–1967) began development of the contraceptive pill in 1950. Within a few years, clinical trials on 6000 women began in Puerto Rico and Haiti. The first commercially available contraceptive pill was introduced in 1960 after it was discovered that Mexican yam (*Pachyrhizus erosus*) was a cheap natural source of the hormone precursors required to make the pill. Over 60 million women worldwide use the pill with about three million in the UK. Early contraceptive pills contained between 100–175 μg of estrogen and 100 mg of progestogen. However, shortly after introduction of the pill, some concern was expressed about their side effects. These included an increased disposition to blood clots, heart attacks and strokes, although the risks involved were still relatively small. Studies by 1969 showed that the increased

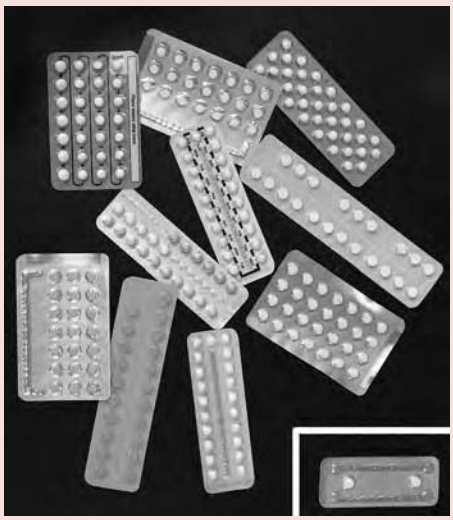


Figure 7.39 Examples of some types of oral contraceptive pills. The inset shows a packet of morning after pills. Courtesy of the Young Person's Sexual Health Clinic, Brook Advisory Center, Manchester, UK.

(*Figures 7.36* and *7.40*), leading to the regression of the other follicles in an apoptotic process to form atretic follicles. It is uncertain how only the one follicle becomes dominant, but appears to be related to its ability to secrete the estrogen, needed for its maturation under the influence of LH. Maturation involves the dominant secondary follicle accumulating fluid filled cavities that eventually enlarge to the point where they are called a Graafian follicle. Ovulation occurs each month when a Graafian follicle ruptures to release the oocyte, now usually called an ovum, into the Fallopian tube. The ovum is transported along the tube by ciliary action. The portion of the follicle remaining in the ovary develops into a corpus luteum. If fertilization does not occur, this degenerates within 10 days or so.

Following copulation, the sperm are propelled through the vas deferens by muscular contractions into the urethra. The sperm are suspended in liquid semen produced by the seminal vesicles, prostate and bulbourethral glands. Semen contains nutrients, which activates and increases the motility of sperm, and is alkaline to counteract the acidity of the vagina. The ruptured follicle develops into the corpus luteum, which secretes progesterone and estradiol and stimulates the development of the endometrium for implantation. Fertilization of the egg to form a zygote usually takes place in the Fallopian tubes and the developing embryo is transported to the uterus by ciliary action and muscular contractions. The zygote begins a series of mitotic divisions to form a developing embryo that embeds into the endometrium lining the uterus and undergoes further development to produce a fetus and eventually a neonate in 9 months. Fertilization ensures that the corpus luteum does not degenerate but begins to produce a number of sex hormones, together with those produced by the gonads and anterior pituitary.

Following the menopause, plasma levels of estradiol decline despite the high levels of gonadotrophins and ovulation ceases.

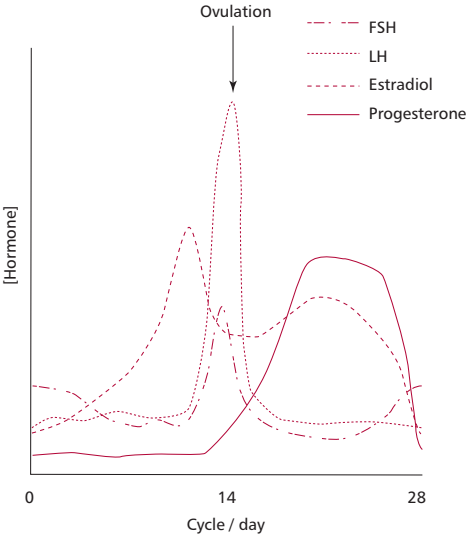


Figure 7.40 Hormonal changes in the menstrual cycle. See text for details.

risks of heart attacks and stroke were related to the amounts of estrogen in the pills. As a consequence, the amounts of estrogens used have decreased over the years and by 2006 contained less than one third of that in earlier contraceptive pills. Indeed, a reduction in the risk of heart disease and stroke has been detected in females on modern versions of the pill. Initially, there was some concern that usage of the pill increased the likelihood of cancers of the breast and cervix, but clinical data have cast doubt on this. Using the pill is still associated with some side effects, such as nausea, bleeding between menstrual periods and depression. The pill does increase the chance of blood clot in the legs (deep vein thrombosis, DVT, *Chapter 14*) although the risk for most pill users is very low. It is now known that usage of the pill may have many benefits, for example protection against pelvic infection because the thickened cervical mucus acts as a barrier to bacteria. Also, long-term usage of the pill has been reported to reduce the risk of certain ovarian cancers and can prevent ectopic pregnancies.

The development of the contraceptive pill has been a remarkable achievement as it allows women to control their fertility in a safe and effective manner. Since its introduction, the pill has had a tremendous impact on female liberty and has aided the process of making pregnancy and motherhood a choice for women. This, particularly in the developed world, has given them greater choices in marriage, work, love and lifestyle.

There is also a 'morning after pill', also known as the 'postcoital pill'. This pill is used by women to reduce the chances of pregnancy following unprotected sexual intercourse. It contains the active ingredient levonorgestrel, which is a synthetic derivative of progesterone. The precise mechanism of action of this pill is still unclear but it is believed to act by preventing ovulation, fertilization and implantation of the fetus. The whole process from fertilization to implantation in the womb can take up to three days, so the morning after pill can prevent pregnancy occurring for up to 72 h after intercourse. This pill is more effective the earlier it is taken after intercourse and it is estimated that 85% of pregnancies would be prevented if the morning after pill was taken within 72 h of sexual intercourse.

There is considerable interest in a contraceptive pill designed for use by men. This pill contains desogestrel as well as testosterone. This combination blocks the production of sperm while maintaining male characteristics and sex drive. As with the female contraceptive pill, it must be taken daily. In preliminary studies, the male pill reduced sperm counts to zero and is expected to be more effective than the female pill or the condom. According to the Food and Drug Administration (FDA) of the USA, the condom has a failure rate of about 14% under typical conditions, while the failure rate of the female pill is less than 1%. The male pill appears to be 100% effective.

DISORDERS OF SEX HORMONES

Disorders associated with male sex hormones include **hypogonadism** and gynecomastia. In the former, there is deficient sperm production and decreased testosterone secretion. Hypogonadism can occur because of testicular disease, referred to as primary or hypergonadotrophic hypogonadism, or to a defect in the hypothalamus or pituitary gland leading to secondary or hypogonadotrophic hypogonadism. In the latter, there may be a deficiency of both gonadotrophins or only of LH. The causes of primary hypogonadism are varied. They include congenital defects, such as Klinefelter syndrome (*Chapter 15*), a deficiency of 5α-reductase activity, testicular agenesis (failure of the testes to develop), acquired defects due to testicular infections, for example mumps or cytotoxic drugs, trauma or irradiation. The causes of secondary hypogonadism include pituitary tumors and hypothalamic disorders such as Kallmann's syndrome. The treatment of hypogonadism is usually directed at the underlying cause. Testosterone is given in cases of testosterone deficiency. However, if fertility is required then gonadotrophins may have to be administered.

Gynecomastia, or breast development in males, is usually related to a disturbance in the balance of estrogens to androgens. In puberty, it occurs in approximately 50% of normal boys due to a temporary increase in the secretion of estrogens. Other than at puberty, the condition is pathological. It may arise because of decreased androgen activity in hypogonadism or because of increased estrogen production from various endocrine tumors. Such tumors may secrete large quantities of estrogens or may secrete hCG that stimulates estrogen production. Some drugs possess estrogen or antiandrogen activity and their use can lead to gynecomastia.

Disorders associated with female sex hormones include amenorrhea, **oligomenorrhea**, infrequent menstruation, and **virilism**, with the development of hirsutism, muscle mass, deepening of the voice and male psychological characteristics. Amenorrhea can be primary where menstruation fails to occur by the age of 16 years, or secondary, where menstruation stops for three months or more after normal menstruation has been established and before menopause. The other clinical features of amenorrhea include hirsutism, acne, menstrual cycle disturbances and obesity, although these features vary in their severity and prevalence. A common reason for secondary amenorrhea in females is pregnancy. This condition must be excluded before other possible causes, for example stress, severe weight loss, polycystic ovary syndrome (PCOS, *see below*), gonad dysgenesis, such as in Turner syndrome (*Chapter 15*), the decrease in gonadotrophin secretion associated with some tumors, hyperprolactinemia and congenital adrenal hyperplasia, are investigated. The causes of amenorrhea are investigated by measuring the concentrations of FSH, LH and prolactin in plasma as outlined in *Figure 7.41*. A high value for FSH indicates ovarian failure. One for prolactin suggests hyperprolactinemia and requires further investigations to confirm this diagnosis. If, however, the values for FSH, LH and prolactin are normal, further tests to investigate pituitary or hypothalamic diseases are necessary. The management of amenorrhea is aimed at treating its underlying cause.

Patients with virilism present with enlargement of the clitoris, deepening of the voice, atrophy of the breasts and hirsutism. Hair growth is not only excessive but shows a male-like distribution. The cause of virilism is increased androgen secretion although abnormally low levels of SHBG can also increase the free testosterone fraction. In some cases virilism occurs because of an increased sensitivity to androgens by target cells. Its causes include PCOS, androgen secreting tumors, congenital adrenal hyperplasia, Cushing's syndrome and may be iatrogenic following treatment with androgens and progesterone. Its commonest cause is PCOS, characterized by multiple cysts in the ovaries that arise from follicles that have failed to ovulate. The ovaries secrete large amounts of androgens although why this is so is unclear. Many

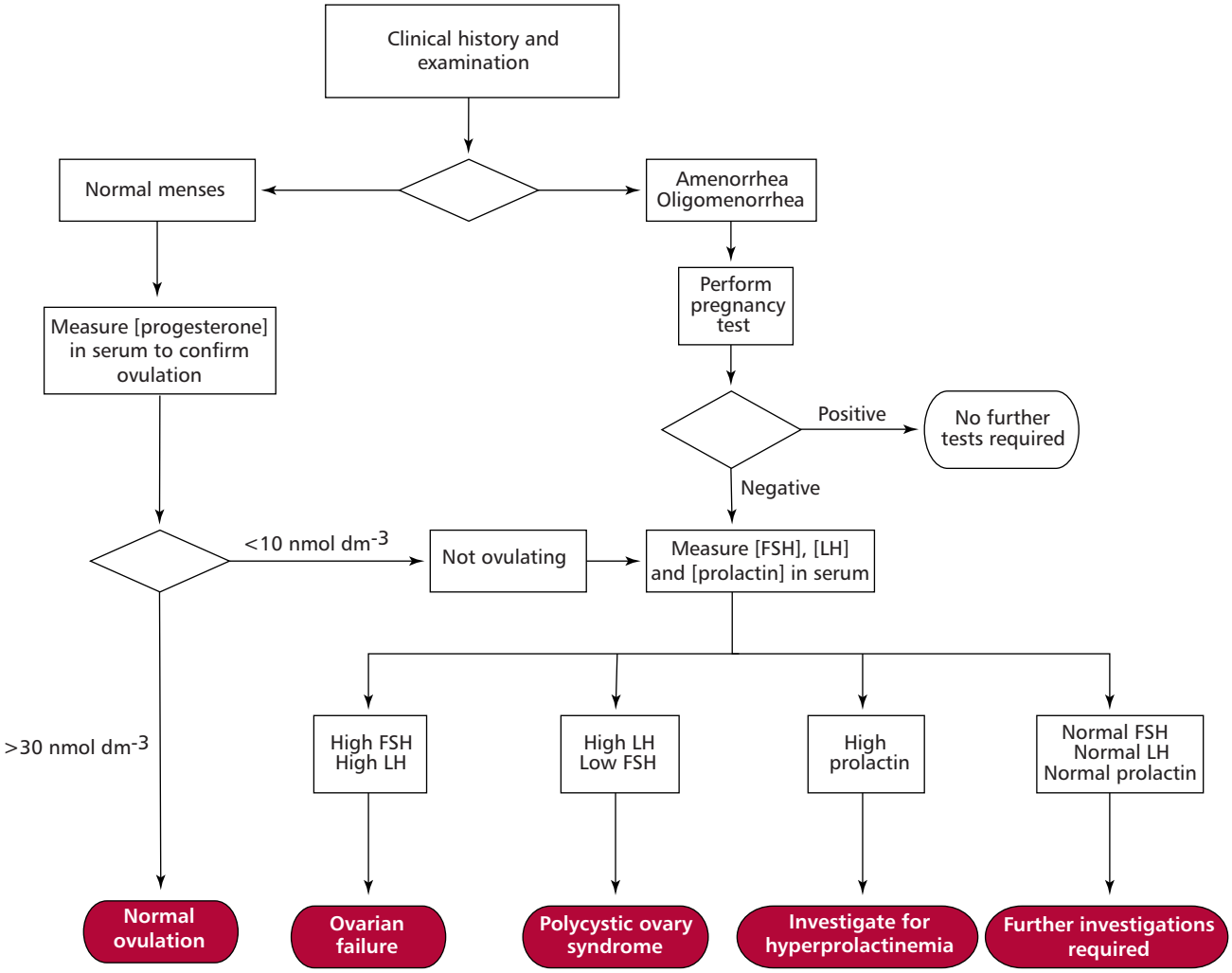


Figure 7.41 Overview of the investigation of amenorrhea.

patients with PCOS suffer from acne, obesity, type 2 diabetes mellitus and may be infertile. A diagnosis of PCOS is made on clinical grounds and assisted by ultrasonography. Plasma LH is often increased in these patients but may be normal, whereas the concentration of testosterone is increased. Treatment of severe PCOS may involve using the antiandrogen drug, cyproterone but this leads to infertility. If fertility is required, then clomiphene, an antiestrogen drug, may be used and can induce ovulation in 75% of cases.

Infertility

Infertility is defined as a failure to conceive despite regular unprotected sexual intercourse for one year. Female infertility may be due to failure to ovulate, obstruction of the Fallopian tubes or to diseases of the uterine lining. In females, failures to ovulate due to hyperprolactinemia or to hypothalamic-pituitary dysfunction are responsible for 20% of cases of infertility. Damage to the Fallopian tubes may also be a cause of female infertility. Male infertility is usually due to decreased numbers or motility of sperm (oligospermia) or complete absence of sperm (azoospermia). Infertility due to endocrine dysfunction occurs only rarely in males. The normal volume of ejaculate is

2 to 5 cm^3 and contains 40 to 500 million sperm. A sperm count of less than 20 million per cm^3 is believed to be subnormal and causes 25% of infertility cases. In general, the lower the total sperm number the greater the chances of infertility although men with low counts have been known to father children. The motility of sperm is also necessary for fertilization to take place and at least 60% of sperm should have a normal shape and be mobile with beating flagella.

Investigating infertility involves a clinical and laboratory evaluation of both partners. Women should be investigated for regular menstruation. If it is regular, then ovulation is probably occurring. The concentration of progesterone in plasma is also indicative and should exceed 30 nmol dm^{-3} on day 21 of the menstrual cycle, values below 10 nmol dm^{-3} are suggestive of abnormal ovulation. If ovulation is confirmed then it may be necessary to examine cervical mucus following intercourse to determine the presence of motile, normal shaped sperm.

Microscopic examination of samples of ejaculate will indicate whether the sperm produced are motile and normal in shape or show abnormalities, such as malformed heads and twin sperm formed by a failure in development. Sperm counts will show if adequate numbers of sperm are produced. A low sperm count may be further investigated by measuring the concentrations of testosterone, FSH and LH in the plasma to compare with their reference ranges of 9–30 nmol dm^{-3}, 2–10 U dm^{-3} and 2–10 U dm^{-3} respectively. In some cases, a biopsy of the testes may by necessary. Investigation of infertility in males is outlined in *Figure 7.42*.

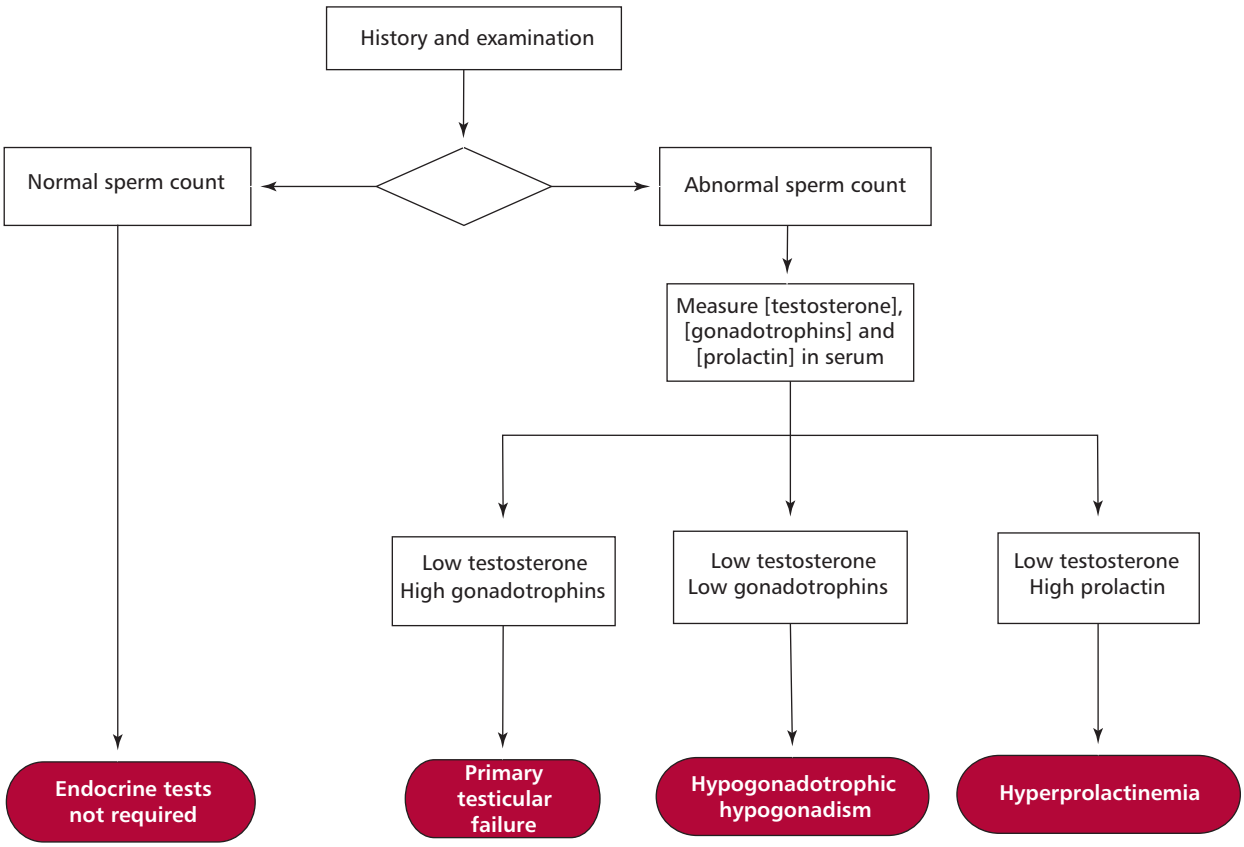


Figure 7.42 Overview of the investigation of infertility in males.

CASE STUDY 7.1

Sarah, a 46-year-old woman, was referred to hospital because of her excessive thirst and frequent urination over the preceding two months. Her thirst was severe and she had to drink water every few hours. An analysis of her plasma and urine yielded the following results (reference ranges are given in parentheses):

Plasma:	Na^+	139	(136–146 mmol dm^{-3})
	K^+	4.2	(3.7–5.1 mmol dm^{-3})
	Creatinine	105	(65–121 µmol dm^{-3})
	Osmolality	296	(282–296 mmol kg^{-1})
Urine:	Glucose		negative
	Osmolality	90	(up to 1400 mmol/kg)

A fluid deprivation test was performed and the following results were obtained for the plasma and urine osmolality:

Plasma:	Osmolality	310	(282–296 mmol kg^{-1})
Urine:	Osmolality	225	(up to 1400 mmol kg^{-1})

She was allowed to drink water on completion of the test and given a dose of desmopressin after which her urine osmolality increased to 620 mmol kg^{-1}.

Questions

(a) What could be the causes of Sarah's symptoms?

(b) Account for the plasma and urine data.

(c) Discuss the need for and results of the fluid deprivation test.

CASE STUDY 7.2

Ian, a 53-year-old man went to see his family doctor complaining of weakness. Thyroid function tests were requested to exclude the possibility of hypothyroidism. These tests showed the following results (reference ranges are given in parentheses):

TSH	7.5 mU dm^{-3}	(0.2–4.0 mU dm^{-3})
Free T_4	14.5 pmol dm^{-3}	(12–25 pmol dm^{-3})

Questions

(a) What is the most appropriate clinical explanation of these results?

(b) What other signs and symptoms should be looked for?

(c) How should Ian's progress be monitored?

CASE STUDY 7.3

Amelia, a 20-year-old student, had not been feeling well for three weeks. She was admitted to her local hospital with a history of weakness and vomiting over the previous three days. On admission she was unconscious. Clinical tests on serum yielded the following data (reference ranges are given in parentheses):

Na^+	113 mmol dm^{-3}	(137–144 mmol dm^{-3})
K^+	5.8 mmol dm^{-3}	(3.3–4.2 mmol dm^{-3})
Urea	30 mmol dm^{-3}	(2.6–6.5 mmol dm^{-3})
pH	7.3	(7.35–7.45)

Questions

(a) What is the most likely explanation of these results?

(b) What is the probable cause of Amelia's condition?

(c) Having identified her condition, how should Amelia be treated?

CASE STUDY 7.4

An 18-year-old girl, Jaclyn, was admitted to hospital in a coma. She presented with a deep sighing respiration and her breath smelt of acetone. She had vomited earlier. On presentation, she had a low blood pressure and a high pulse rate of 120 per min. The following results were obtained (reference ranges are given in parentheses):

Plasma:

Na^+	136 mmol dm^{-3}	(132–144 mmol dm^{-3})
K^+	5.7 mmol dm^{-3}	(3.2–4.8 mmol dm^{-3})
Urea	15 mmol dm^{-3}	(3.0–8.0 mmol dm^{-3})
Glucose	31.0 mmol dm^{-3}	(3.0–5.5 mmol dm^{-3})
Osmolality	371 mmol dm^{-3}	(282–295 mmol dm^{-3})

Arterial blood:

pH	7.09	(7.35–7.45)
PCO_2	2.7 KPa	(4.7–6.0 KPa)
HCO_3^-	11 mmol dm^{-3}	(24–34 mmol dm^{-3})

Urine:

Ketones	positive	negative

Questions

(a) Explain these results.

(b) How should Jaclyn be treated?

CASE STUDY 7.5

Rachel, a 32-year-old teacher, was suffering from irregular periods and acne. She was examined by her doctor and found to be overweight and hirsute. She was referred for hospital tests, which yielded the following data (reference ranges are given in parentheses):

Plasma:

Testosterone	3.9	(1.1–3.3 nmol dm^{-3})
LH	14	(2.0–10 U dm^{-3})
FSH	5.3	(2.0–8.0 U dm^{-3})

Questions

(a) What can be inferred from Rachel's symptoms?

(b) What is the most likely diagnosis?

7.11 SUMMARY

The endocrine glands and the hormones they produce control many of the activities of the body. Hormones are released into the blood and travel to their sites of action where they bind to cell surface or intracellular receptors to initiate activities. Hormones belong to several categories of molecules including amines, peptides, proteins and steroids. Endocrine disorders may arise from damage to the endocrine gland, causing hypo- or hypersecretion of the hormone, or some failure of the hormone–receptor interactions. Disorders of the pituitary gland may arise from pituitary tumors, such as prolactinomas, with excessive secretion of hormones. Abnormal GH secretion leads to dwarfism or acromegaly. Several thyroid disorders arise as a consequence of autoimmune conditions which can cause hypo- or hyperactivities. However, the commonest endocrine disorders involve insulin resistance or its absence leading to dysregulation of blood glucose concentrations. Disorders of the adrenal gland can result in Addison's disease or Cushing's syndrome. Dysfunctions associated with reproductive hormones can cause a number of clinical conditions, including gynecomastia in men and disruption of menstruation, infertility, and virilism in women.

The diagnosis of endocrine disorders usually involves measurement of the hormone in question and replacement for deficiencies. Disorders due to hypersecretion from endocrine tumors may be treated by surgical excision of the tumor.

QUESTIONS

1. Pituitary tumors can secrete various hormones. Which of the following hormones is the most commonly secreted?
   a) thyroid stimulating hormone;
   b) follicle stimulating hormone;
   c) luteinizing hormone;
   d) prolactin;
   e) growth hormone.

2. Which of the following may cause hyperthyroidism?
   a) Grave's disease;
   b) Hashimoto's thyroiditis;
   c) thyroidectomy;
   d) antithyroid drugs;
   e) diabetes insipidus.

3. Which of the following can cause acromegaly?
   a) diabetes mellitus;
   b) pituitary adenoma;
   c) excessive ingestion of growth hormone;
   d) bronchial carcinoma;
   e) excessive secretion of prolactin.

4. Which one of the following is **NOT** a cause of Cushing's syndrome?
   a) ectopic ACTH production;
   b) adrenal adenoma;
   c) corticosteroid therapy;
   d) autoimmune destruction of the thyroid gland;
   e) all of the above.

5. Ketone bodies are produced during diabetic ketoacidosis as a result of an increase in which of the following?
   a) protein breakdown;
   b) urea production;
   c) insulin release;
   d) lipolysis;
   e) K^+.

6. Estradiol is required for?
   a) the development of male secondary sexual characteristics;
   b) spermatogenesis;
   c) the development of female secondary sexual characteristics;
   d) the secretion of breast milk;
   e) stimulating the endometrium to receive fertilized egg.

7. Sajida, a 27-year-old, found over a 2-month period that she was expressing breast milk. She was not pregnant and, indeed, had not had any children. She was on medication with analgesic and antidopaminergic drugs for migraines attacks. An analysis of her serum gave a prolactin value of 1200 (reference range: 70–395 mU dm^{-3}).
   a) What is the most likely diagnosis?
   b) What could have caused such a condition?
   c) What should her doctor recommend?

8. Graham, a 50-year-old man, visited his doctor for the first time in many years complaining of blurred vision and frequent headaches. The doctor noticed changes in the facial features characteristic of acromegaly. An oral glucose tolerance test including measurements of GH was performed.

Time / min	[Glucose] / mmol dm^{-3}	[GH] / mU dm^{-3}
0	6.3	47
30	7.3	55
60	8.6	52
90	9.5	64
120	8.8	53
150	7.5	49
180	6.8	49

   Reference range for fasting glucose 3.0–5.5 mmol dm^{-3}
   Reference range for GH following glucose load < 2 mU dm^{-3}
   Plot a graph to illustrate these data. Do these findings support the diagnosis of acromegaly?

9. Tabulate the differences between types 1 and 2 diabetes mellitus.

10. Give four functions of human GH.

11. Why is it necessary to screen newborn babies to detect congenital hypothyroidism?

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