CHAPTER 9

The endocrine system

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The endocrine system consists of glands widely separated from each other with no physical connections (Fig. 9.1). Endocrine glands are groups of secretory cells surrounded by an extensive network of capillaries that facilitates diffusion of *hormones* (chemical messengers) from the secretory cells into the bloodstream. They are also referred to as *ductless glands* because hormones diffuse directly into the bloodstream. Hormones are then carried in the bloodstream to *target tissues* and *organs* that may be quite distant, where they influence cell growth and metabolism.

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

Although the hypothalamus is classified as a part of the brain rather than an endocrine gland, it controls the pituitary gland and indirectly influences many others.

The ovaries and the testes secrete hormones associated with the reproductive system after puberty; their functions are described in Chapter 18. The placenta that develops to nourish the developing fetus during pregnancy also has an endocrine function, which is outlined in Chapter 5. In addition to the main endocrine glands shown in Figure 9.1 many other organs and tissues also secrete hormones as a secondary function e.g. adipose tissue produces leptin (p. 284), involved in the regulation of appetite; the heart secretes atrial natriuretic peptide (ANP, p. 99) that acts on the kidneys. Other hormones do not travel to remote organs but act locally e.g. prostaglandins.

The endocrine glands are explored in the early sections of the chapter. Some local hormones are considered briefly on page 229. Changes in endocrine functions that accompany ageing are explored. Problems that arise when abnormalities occur are usually caused by the over- or under-activity of endocrine glands and are explained in the final sections of this chapter.

Overview of hormone action

When a hormone arrives at its target cell, it binds to a specific *receptor*, where it acts as a switch influencing chemical or metabolic reactions inside the cell. Receptors for peptide hormones are situated on the cell membrane and those for lipid-based hormones are located inside cells. Examples are shown in Box 9.1. **9.1**

The level of a hormone in the blood is variable and self-regulating within its normal range. A hormone is released in response to a specific stimulus and usually its action reverses or negates the stimulus through a *negative*

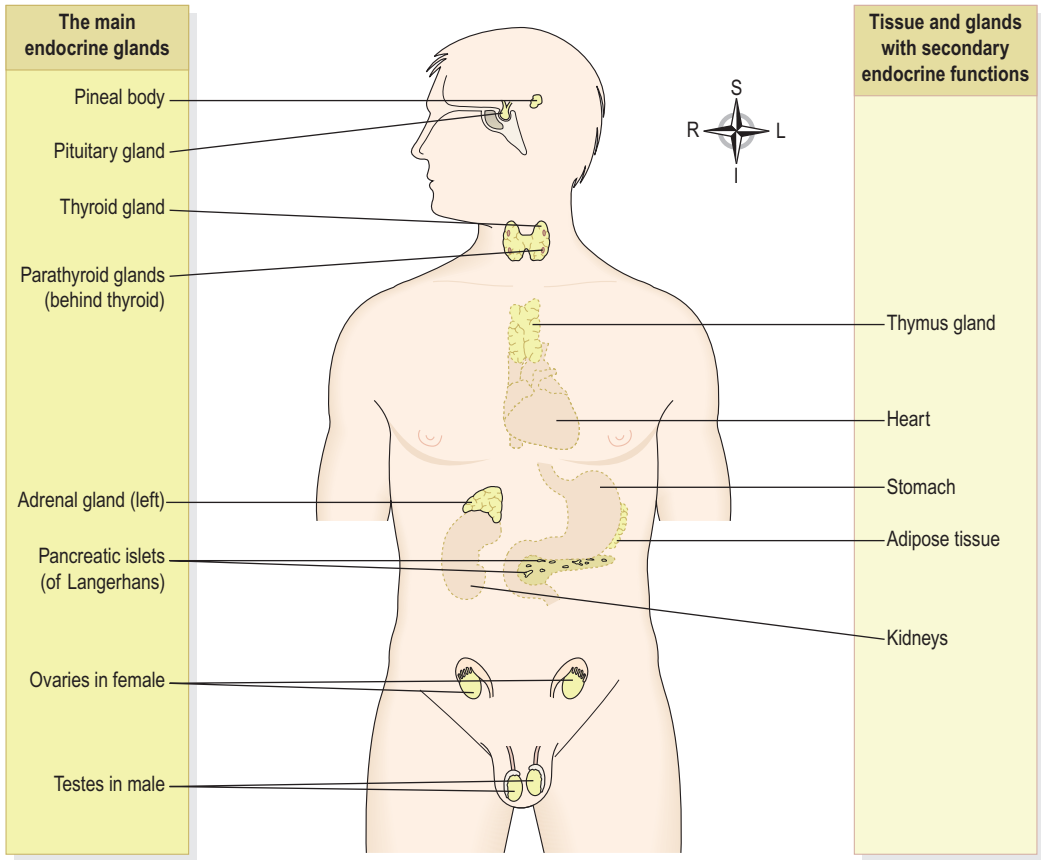

Figure 9.1 Positions of the endocrine glands.

Box 9.1 Examples of lipid-based and peptide hormones

Lipid-based hormones	Peptide hormones
Steroids e.g. glucocorticoids, mineralocorticoids	Adrenaline (epinephrine), noradrenaline (norepinephrine)
Thyroid hormones	Insulin
	Glucagon

feedback mechanism (see p. 6). This may be controlled either indirectly through the release of hormones by the hypothalamus and the anterior pituitary gland, e.g. steroid and thyroid hormones, or directly by blood levels of the stimulus, e.g. insulin and glucagon and determined by plasma glucose levels.

The effect of a *positive feedback mechanism* is amplification of the stimulus and increasing release of the hormone until a particular process is complete and the stimulus ceases, e.g. release of oxytocin during labour (p. 7).

Pituitary gland and hypothalamus

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the hypothalamus and the pituitary gland
- explain the influence of the hypothalamus on the lobes of the pituitary gland
- outline the actions of the hormones secreted by the anterior and posterior lobes of the pituitary gland.

The pituitary gland and the hypothalamus act as a unit, regulating the activity of most of the other endocrine glands. The pituitary gland lies in the hypophyseal fossa of the sphenoid bone below the hypothalamus, to which it is attached by a *stalk* (Fig. 9.2). It is the size of a pea, weighs about 500 mg and consists of two main parts that originate from different types of cells. The *anterior pituitary* (adenohypophysis) is an upgrowth of glandular epithelium from the pharynx and the *posterior pituitary* (neurohypophysis) a downgrowth of nervous tissue from the brain. There is a network of nerve fibres between the hypothalamus and the posterior pituitary.

Blood supply

Arterial blood. This is from branches of the internal carotid artery. The anterior lobe is supplied indirectly by blood that has already passed through a capillary bed in the hypothalamus but the posterior lobe is supplied directly.

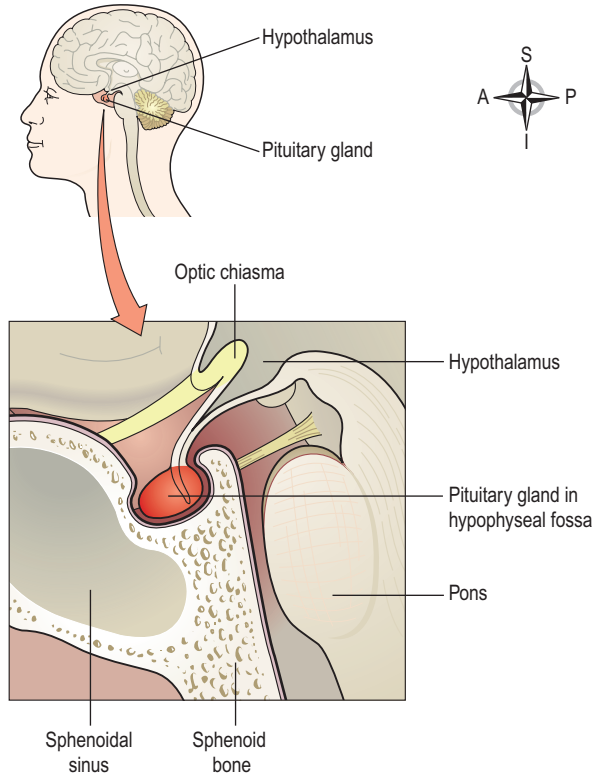

Figure 9.2 Median section showing the position of the pituitary gland and its associated structures.

Venous drainage. Containing hormones from both lobes, venous blood leaves the gland in short veins that enter the venous sinuses between the layers of dura mater.

The influence of the hypothalamus on the pituitary gland

The hypothalamus controls release of hormones from both the anterior and posterior pituitary but in different ways (see below).

Anterior pituitary

The anterior pituitary is supplied indirectly with arterial blood that has already passed through a capillary bed in the hypothalamus (Fig. 9.3A). This network of blood vessels forms part of the *pituitary portal system*, which transports blood from the hypothalamus to the anterior pituitary where it enters thin-walled sinusoids that are in close contact with the secretory cells. As well as providing oxygen and nutrients, this blood transports *releasing* and *inhibiting hormones* secreted by the hypothalamus.

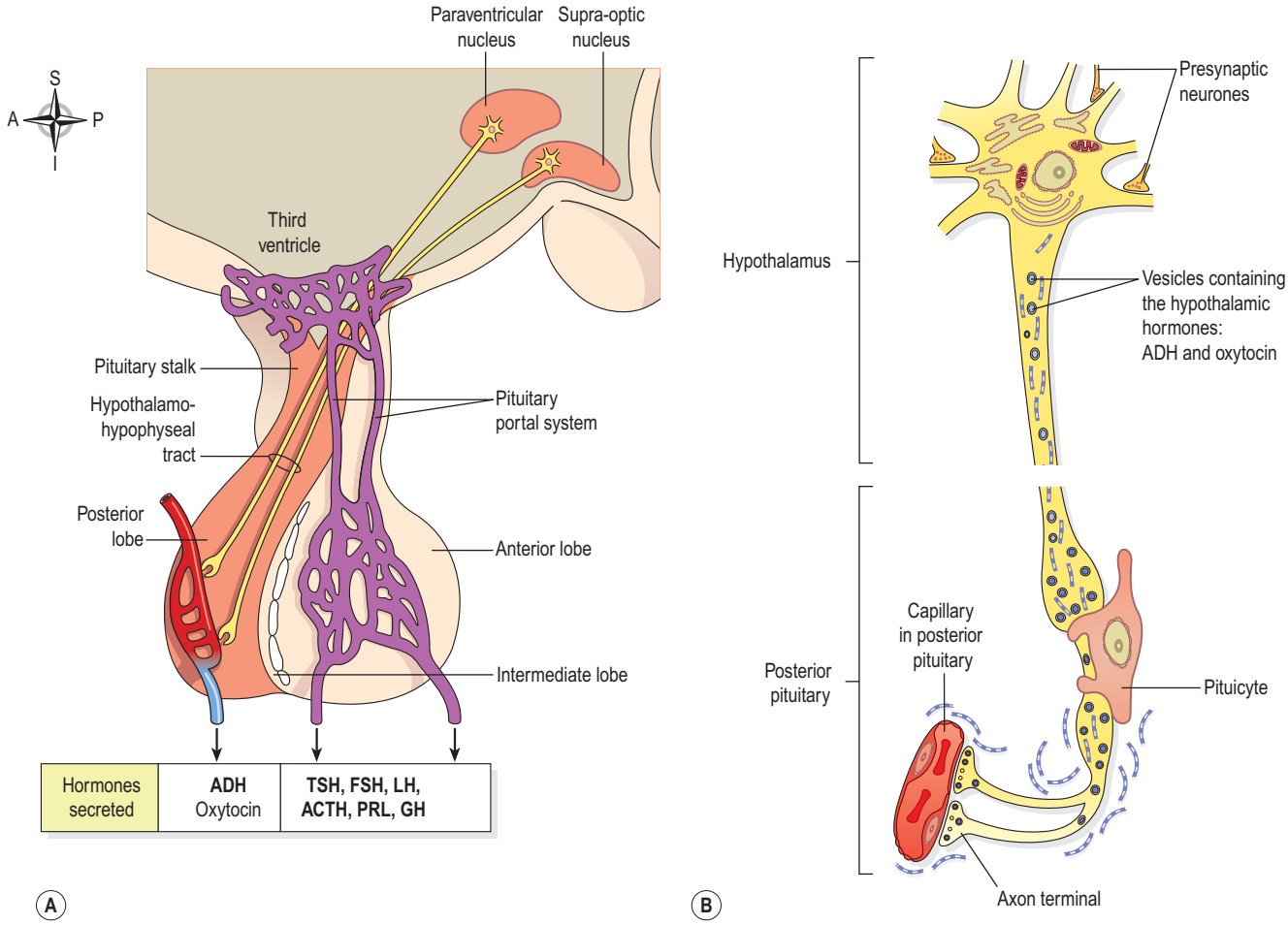

Figure 9.3 The pituitary gland. A. The lobes of the pituitary gland and their relationship with the hypothalamus. **B.** Synthesis and storage of antidiuretic hormone and oxytocin.

These hormones specifically influence secretion and release of other hormones formed in the anterior pituitary (Table 9.1).

Some of the hormones secreted by the anterior lobe stimulate or inhibit secretion by other endocrine glands (target glands) while others have a direct effect on target tissues. Table 9.1 summarises the main relationships between the hormones of the hypothalamus, the anterior pituitary and target glands or tissues.

Secretion of an anterior pituitary hormone follows stimulation of the gland by a specific *releasing hormone* produced by the hypothalamus and carried to the gland through the pituitary portal system (see above). The whole system is controlled by a *negative feedback mechanism* (Ch. 1). That is, when the level of a hormone in the blood supplying the hypothalamus is low it produces the appropriate releasing hormone that stimulates release of a *trophic hormone* by the anterior pituitary. This in turn stimulates the target gland to produce and release its hormone. As a result the blood level of that hormone rises and inhibits secretion of its releasing factor by the hypothalamus (Fig. 9.4).

Growth hormone (GH)

This is the most abundant hormone synthesised by the anterior pituitary. It stimulates growth and division of most body cells but especially those in the bones and skeletal muscles. Body growth in response to the secretion of GH is evident during childhood and adolescence, and thereafter secretion of GH maintains the mass of bones and skeletal muscles. It also regulates aspects of metabolism in many organs, e.g. liver, intestines and pancreas; stimulates protein synthesis, especially tissue growth and repair; promotes breakdown of fats and increases blood glucose levels (see Ch. 12).

Its release is stimulated by *growth hormone releasing hormone* (GHRH) and suppressed by *growth hormone release inhibiting hormone* (GHRIH), also known as *somatostatin*, both of which are secreted by the hypothalamus. Secretion of GH is greater at night during sleep and is also stimulated by hypoglycaemia (low blood sugar), exercise and anxiety. Secretion peaks in adolescence and then declines with age.

GH secretion is controlled by a negative feedback system; it is inhibited when the blood level rises and also

Table 9.1 Hormones of the hypothalamus, anterior pituitary and their target tissues

Hypothalamus	Anterior pituitary	Target gland or tissue
GHRH	GH	Most tissues Many organs
GHRIH	GH inhibition TSH inhibition	Thyroid gland Pancreatic islets Most tissues
TRH	TSH	Thyroid gland
CRH	ACTH	Adrenal cortex
PRH	PRL	Breast
PIH	PRL inhibition	Breast
LHRH or	FSH	Ovaries and testes
GnRH	LH	Ovaries and testes

GHRH = growth hormone releasing hormone
GH = growth hormone (somatotrophin)
GHRIH = growth hormone release inhibiting hormone (somatostatin)
TRH = thyrotrophin releasing hormone
TSH = thyroid stimulating hormone
CRH = corticotrophin releasing hormone
ACTH = adrenocorticotrophic hormone
PRH = prolactin releasing hormone
PRL = prolactin (lactogenic hormone)
PIH = prolactin inhibiting hormone (dopamine)
LHRH = luteinising hormone releasing hormone
GnRH = gonadotrophin releasing hormone
FSH = follicle stimulating hormone
LH = luteinising hormone

when GHRIH is released by the hypothalamus. GHRIH also suppresses secretion of TSH and gastrointestinal secretions, e.g. gastric juice, gastrin and cholecystokinin (see Ch. 12).

Thyroid stimulating hormone (TSH)

The release of this hormone is stimulated by *thyrotrophin releasing hormone* (TRH) from the hypothalamus. It stimulates growth and activity of the thyroid gland, which secretes the hormones *thyroxine* (T_4) and *tri-iodothyronine* (T_3). Release is lowest in the early evening and highest during the night. Secretion is regulated by a negative feedback mechanism, i.e. when the blood level of thyroid hormones is high, secretion of TSH is reduced, and vice versa (Fig. 9.4).

Adrenocorticotrophic hormone (ACTH, corticotrophin)

Corticotrophin releasing hormone (CRH) from the hypothalamus promotes the synthesis and release of ACTH by the anterior pituitary. This increases the concentration of

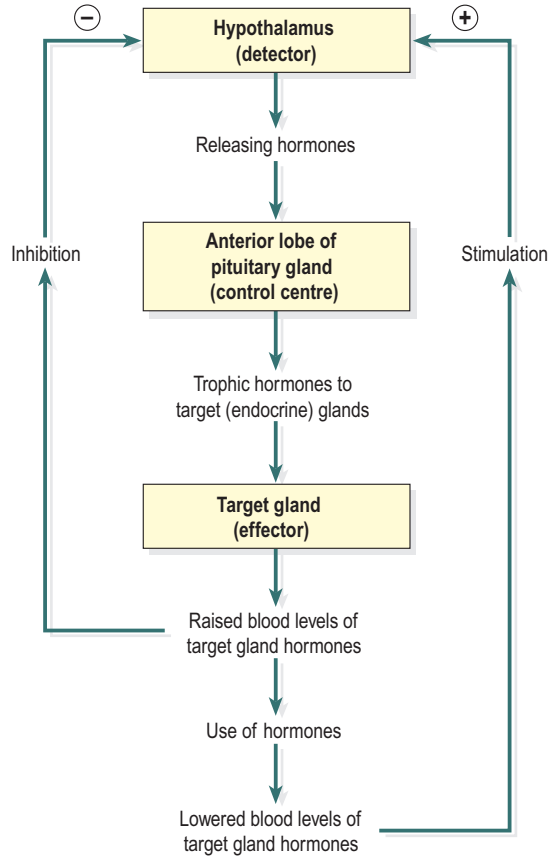

Figure 9.4 Negative feedback regulation of secretion of hormones by the anterior lobe of the pituitary gland.

cholesterol and steroids within the adrenal cortex and the output of steroid hormones, especially *cortisol*.

ACTH levels are highest at about 8 a.m. and fall to their lowest about midnight, although high levels sometimes occur at midday and 6 p.m. This circadian rhythm is maintained throughout life. It is associated with the sleep pattern and adjustment to changes takes several days, e.g. following changing work shifts, travelling to a different time zone (jet lag).

Secretion is also regulated by a negative feedback mechanism, being suppressed when the blood level of ACTH rises (Fig. 9.4). Other factors that stimulate secretion include hypoglycaemia, exercise and other stressors, e.g. emotional states and fever.

Prolactin

This hormone is secreted during pregnancy to prepare the breasts for *lactation* (milk production) after childbirth. The blood level of prolactin is stimulated by *prolactin releasing hormone* (PRH) released from the hypothalamus and it is lowered by *prolactin inhibiting hormone* (PIH, *dopamine*) and by an increased blood level of prolactin. Immediately after birth, suckling stimulates prolactin secretion and lactation. The resultant high blood level is a factor in reducing the incidence of conception during lactation.

Prolactin, together with oestrogens, corticosteroids, insulin and thyroxine, is involved in initiating and maintaining lactation. Prolactin secretion is related to sleep, rising during any period of sleep, night or day.

Gonadotrophins

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

- follicle stimulating hormone (FSH)
- luteinising hormone (LH).

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

In females. LH and FSH are involved in secretion of the hormones *oestrogen* and *progesterone* during the menstrual cycle (see Figs 18.9 and 18.10, pp. 456 and 457). As the levels of oestrogen and progesterone rise, secretion of LH and FSH is suppressed.

In males. LH, also called interstitial cell stimulating hormone (ICSH) stimulates the interstitial cells of the testes to secrete the hormone *testosterone* (see Ch. 18).

Table 9.2 summarises the hormonal secretions of the anterior pituitary.

Posterior pituitary

The posterior pituitary is formed from nervous tissue and consists of nerve cells surrounded by supporting glial cells called *pituicytes*. These neurones have their cell bodies in the supraoptic and paraventricular nuclei of the hypothalamus and their axons form a bundle known as the *hypothalamohypophyseal tract* (Fig. 9.3A). Posterior pituitary hormones are synthesised in the nerve cell bodies, transported along the axons and stored in vesicles within the axon terminals in the posterior pituitary (Fig. 9.3B).

Nerve impulses from the hypothalamus trigger exocytosis of the vesicles, releasing their hormones into the bloodstream.

The structure of the posterior pituitary gland and its relationship with the hypothalamus is explained on page 217. *Oxytocin* and *antidiuretic hormone* (ADH, *vasopressin*) are the hormones released from axon terminals within the posterior pituitary (Fig. 9.3B). These hormones act directly on non-endocrine tissue.

Oxytocin

Oxytocin stimulates two target tissues during and after childbirth (parturition): uterine smooth muscle and the muscle cells of the lactating breast.

During childbirth increasing amounts of oxytocin are released from the posterior pituitary into the bloodstream in response to increasing stimulation of sensory stretch receptors in the uterine cervix as the baby's head progressively dilates it. Sensory impulses are generated and travel to the control centre in the hypothalamus, stimulating the posterior pituitary to release more oxytocin. In turn this stimulates more forceful uterine contractions and greater stretching of the uterine cervix as the baby's head is forced further downwards. This is an example of a *positive feedback mechanism* which stops soon after the baby is delivered when distension of the uterine cervix is greatly reduced (Fig. 9.5).

The process of milk ejection also involves a positive feedback mechanism. Suckling generates sensory impulses that are transmitted from the breast to the hypothalamus. The impulses trigger release of oxytocin from the posterior pituitary. On reaching the lactating breast, oxytocin stimulates contraction of the milk ducts

Table 9.2 Summary of the hormones secreted by the anterior pituitary gland and their functions

Hormone	Function
Growth hormone (GH)	Regulates metabolism, promotes tissue growth especially of bones and muscles
Thyroid stimulating hormone (TSH)	Stimulates growth and activity of thyroid gland and secretion of T_3 and T_4
Adrenocorticotrophic hormone (ACTH)	Stimulates the adrenal cortex to secrete glucocorticoids
Prolactin (PRL)	Stimulates growth of breast tissue and milk production
Follicle stimulating hormone (FSH)	Stimulates production of sperm in the testes, stimulates secretion of oestrogen by the ovaries, maturation of ovarian follicles, ovulation
Luteinising hormone (LH)	Stimulates secretion of testosterone by the testes, stimulates secretion of progesterone by the corpus luteum

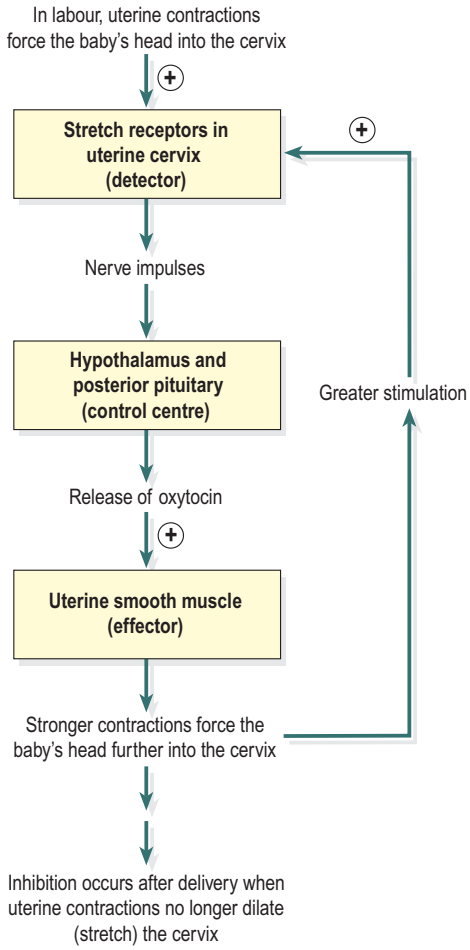

Figure 9.5 Regulation of secretion of oxytocin through a positive feedback mechanism.

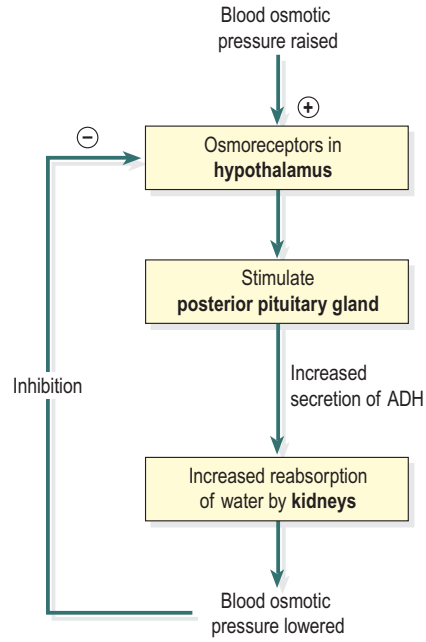

Figure 9.6 Negative feedback regulation of secretion of antidiuretic hormone (ADH).

and myoepithelial cells around the glandular cells, ejecting milk. Suckling also inhibits the release of *prolactin inhibiting hormone* (PIH), prolonging prolactin secretion and lactation.

Oxytocin levels rise during sexual arousal in both males and females. This increases smooth muscle contraction which is associated with glandular secretion and ejaculation in males. In females, contraction of smooth muscle in the vagina and uterus promotes movement of sperm towards the uterine tubes. It is believed that the smell of oxytocin may be involved in social recognition and bonding (between mother and newborn baby).

Antidiuretic hormone (ADH, vasopressin)

The main effect of antidiuretic hormone is to reduce urine output (diuresis is the production of a large volume of urine). ADH acts on the distal convoluted tubules and collecting ducts of the nephrons of the kidneys (Ch. 13). It increases their permeability to water and more of the glomerular filtrate is reabsorbed. ADH secretion is determined by the osmotic pressure of the blood circulating to the *osmoreceptors* in the hypothalamus.

As osmotic pressure rises, for example as a result of dehydration, secretion of ADH increases. More water is therefore reabsorbed and the urine output is reduced. This means that the body retains more water and the rise in osmotic pressure is reversed. Conversely, when the osmotic pressure of the blood is low, for example after a large fluid intake, secretion of ADH is reduced, less water is reabsorbed and more urine is produced (Fig. 9.6).

At high concentrations, for example after severe blood loss, ADH causes smooth muscle contraction, especially vasoconstriction in small arteries. This has a *pressor effect*, raising systemic blood pressure; the alternative name of this hormone, vasopressin, reflects this effect.

Thyroid gland (Fig. 9.7)

Learning outcomes

After studying this section, you should be able to:

- describe the position of the thyroid gland and its related structures
- describe the microscopic structure of the thyroid gland
- outline the actions of the thyroid hormones
- explain how blood levels of the thyroid hormones T_3 and T_4 are regulated.

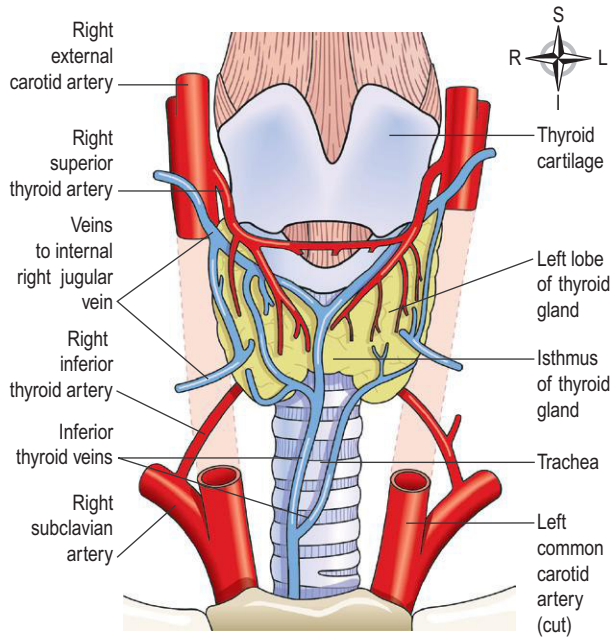

Figure 9.7 The position of the thyroid gland and its associated structures. Anterior view.

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

The lobes are roughly cone shaped, about 5 cm long and 3 cm wide.

The *arterial blood supply* to the gland is through the superior and inferior thyroid arteries. The superior thyroid artery is a branch of the external carotid artery and the inferior thyroid artery is a branch of the subclavian artery.

The *venous return* is by the thyroid veins, which drain into the internal jugular veins.

The recurrent laryngeal nerves pass upwards close to the lobes of the gland and, especially on the right side, lie near the inferior thyroid artery (see Fig. 9.10).

The gland is composed of largely spherical follicles formed from cuboidal epithelium (Fig. 9.9). These secrete and store *colloid*, a thick sticky protein material. Between the follicles are other cells found singly or in small groups: *parafollicular cells*, also called C-cells, which secrete the hormone *calcitonin*.

Thyroxine and tri-iodothyronine

Iodine is essential for the formation of the thyroid hormones, thyroxine (T_4) and tri-iodothyronine (T_3), so numbered as these molecules contain four and three atoms of the element iodine respectively. The main dietary sources of iodine are seafood, vegetables grown in iodine-rich soil and iodinated table salt. The thyroid gland selectively takes up iodine from the blood, a process called *iodine trapping*.

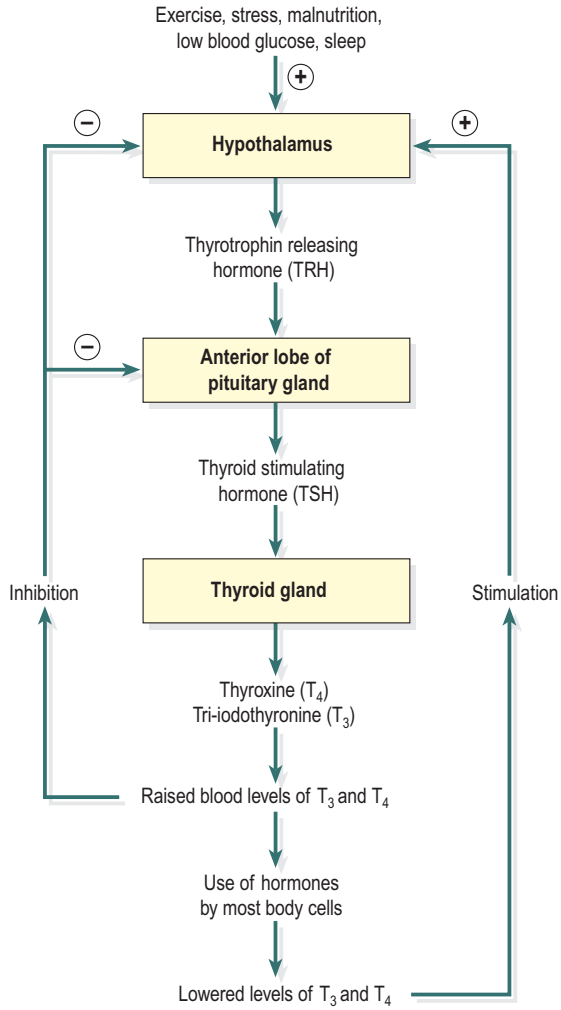

Figure 9.8 Negative feedback regulation of the secretion of thyroxine (T_4) and tri-iodothyronine (T_3).

Thyroid hormones are synthesised as large precursor molecules called *thyroglobulin*, the major constituent of colloid. The release of T_3 and T_4 into the blood is stimulated by *thyroid stimulating hormone* (TSH) from the anterior pituitary.

Secretion of TSH is stimulated by *thyrotrophin releasing hormone* (TRH) from the hypothalamus and secretion of TRH is stimulated by exercise, stress, malnutrition, low plasma glucose levels and sleep. TSH secretion depends on the plasma levels of T_3 and T_4 because it is these hormones that control the sensitivity of the anterior pituitary to TRH. Through the negative feedback mechanism, increased levels of T_3 and T_4 decrease TSH secretion and vice versa (Fig. 9.8). Dietary iodine deficiency greatly increases TSH secretion causing proliferation of thyroid

Table 9.3 Common effects of abnormal secretion of thyroid hormones

Hyperthyroidism: increased T_3 and T_4 secretion	Hypothyroidism: decreased T_3 and T_4 secretion
Increased basal metabolic rate	Decreased basal metabolic rate
Weight loss, good appetite	Weight gain, anorexia
Anxiety, physical restlessness, mental excitability	Depression, psychosis, mental slowness, lethargy
Hair loss	Dry skin, brittle hair
Tachycardia, palpitations, atrial fibrillation	Bradycardia
Warm sweaty skin, heat intolerance	Dry cold skin, prone to hypothermia
Diarrhoea	Constipation
Exophthalmos in Graves' disease (see Fig. 9.17)	

gland cells and enlargement of the gland (goitre, see Fig. 9.16). Secretion of T_3 and T_4 begins about the third month of fetal life and increases at puberty and in women during the reproductive years, especially during pregnancy. Otherwise, it remains fairly constant throughout life. Of the two thyroid hormones, T_4 is much more abundant. However it is less potent than T_3, which is more physiologically important. Most T_4 is converted into T_3 inside target cells. **9.2**

Thyroid hormones enter the cell nucleus and regulate gene expression, i.e. they increase or decrease protein synthesis (see Ch. 17). They enhance the effects of other hormones, e.g. adrenaline (epinephrine) and noradrenaline (norepinephrine). T_3 and T_4 affect most cells of the body by:

- increasing the basal metabolic rate and heat production
- regulating metabolism of carbohydrates, proteins and fats.

T_3 and T_4 are essential for normal growth and development, especially of the skeleton and nervous system. Most other organs and systems are also influenced by thyroid hormones. Physiological effects of T_3 and T_4 on the heart, skeletal muscles, skin, digestive and reproductive systems are more evident when there is underactivity or overactivity of the thyroid gland and can be profound in childhood (Table 9.3).

Calcitonin

This hormone is secreted by the parafollicular or C-cells in the thyroid gland (Fig. 9.9). Calcitonin lowers raised blood calcium (Ca^{2+}) levels. It does this by acting on:

- bone cells promoting their storage of calcium
- kidney tubules inhibiting the reabsorption of calcium.

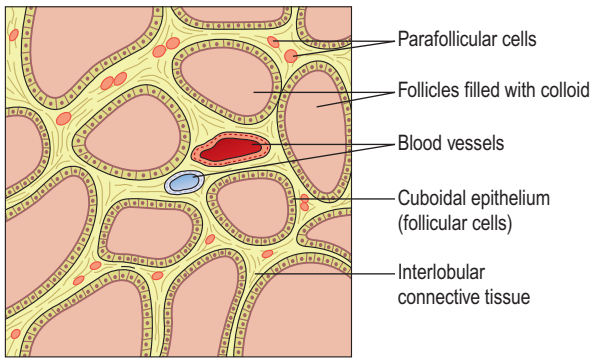

Figure 9.9 The microscopic structure of the thyroid gland.

Its effect is opposite to that of parathyroid hormone, the hormone secreted by the parathyroid glands. Release of calcitonin is stimulated by increased blood calcium levels.

This hormone is important during childhood when bones undergo considerable changes in size and shape.

Parathyroid glands

Learning outcomes

After studying this section, you should be able to:

- describe the position and gross structure of the parathyroid glands
- outline the functions of parathyroid hormone and calcitonin
- explain how blood levels of parathyroid hormone and calcitonin are regulated.

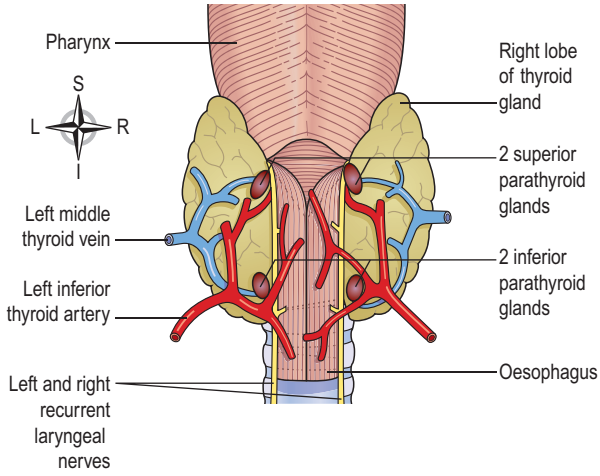

Figure 9.10 The positions of the parathyroid glands and their related structures, viewed from behind.

There are four small parathyroid glands, each weighing around 50 g, two embedded in the posterior surface of each lobe of the thyroid gland (Fig. 9.10). They are surrounded by fine connective tissue capsules that contain spherical cells arranged in columns with sinusoids containing blood in between them.

Function

These glands secrete *parathyroid hormone* (PTH, parathormone). Secretion is regulated by blood calcium levels. When they fall, secretion of PTH is increased and vice versa.

The main function of PTH is to increase blood calcium levels. This is achieved by increasing the calcium absorption from the small intestine and reabsorption from the renal tubules. If these sources provide inadequate supplies then PTH stimulates osteoclasts (bone-destroying cells) and calcium is released from bones into the blood.

Parathormone and calcitonin from the thyroid gland act in a complementary manner to maintain blood calcium levels within the normal range. This is needed for:

- muscle contraction
- transmission of nerve impulses
- blood clotting
- normal action of many enzymes.

Adrenal glands

Learning outcomes

After studying this section, you should be able to:

- describe the structure of the adrenal glands
- describe the actions of each of the three groups of adrenocorticoid hormones
- explain how blood levels of glucocorticoids are regulated
- describe the actions of adrenaline (epinephrine) and noradrenaline (norepinephrine)
- outline how the adrenal glands respond to stress.

The two adrenal (suprarenal) glands are situated on the upper pole of each kidney enclosed within the renal fascia (Fig. 9.1). They are about 4 cm long and 3 cm thick.

The *arterial blood supply* is by branches from the abdominal aorta and renal arteries.

The *venous return* is by suprarenal veins. The right gland drains into the inferior vena cava and the left into the left renal vein.

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

Adrenal cortex

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

- glucocorticoids
- mineralocorticoids
- sex hormones (androgens).

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

Glucocorticoids

Cortisol (hydrocortisone) is the main glucocorticoid but small amounts of *corticosterone* and *cortisone* are also produced. Commonly these are collectively known as 'steroids'; they are essential for life, regulating metabolism and responses to stress (see Fig. 9.13). Secretion is controlled through a negative feedback system involving the hypothalamus and anterior pituitary. It is stimulated by ACTH from the anterior pituitary and by stress (Fig. 9.11). Cortisol secretion shows marked circadian variation peaking between 4 a.m. and 8 a.m. and being lowest between midnight and 3 a.m. When the sleeping waking

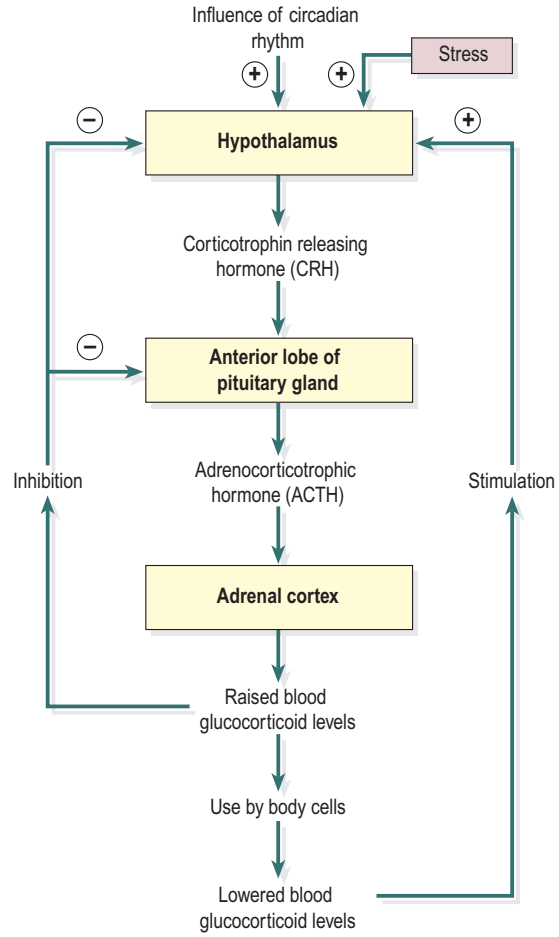

Figure 9.11 Negative feedback regulation of glucocorticoid secretion.

pattern is changed, e.g. night shift working, it takes several days for ACTH/cortisol secretion to readjust (p. 219). Glucocorticoid secretion increases in response to stress (Fig. 9.11), including infection and surgery.

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

- hyperglycaemia (raised blood glucose levels) caused by breakdown of glycogen and *gluconeogenesis* (formation of new sugar from, for example, protein)
- *lipolysis* (breakdown of triglycerides into fatty acids and glycerol for energy production) raising circulating levels of free fatty acids
- stimulating breakdown of protein, releasing amino acids, and increasing blood levels. Amino acids are then used for synthesis of other proteins, e.g. enzymes, or for energy production (Ch. 12)
- promoting absorption of sodium and water from renal tubules (a weak mineralocorticoid effect).

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

- anti-inflammatory actions
- suppression of immune responses
- delayed wound healing.

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

Mineralocorticoids (aldosterone)

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

Blood potassium levels regulate aldosterone secretion by the adrenal cortex. When blood potassium levels rise, more aldosterone is secreted (Fig. 9.12). Low blood potassium has the opposite effect. *Angiotensin* (see below) also stimulates the release of aldosterone.

Renin–angiotensin–aldosterone system. When renal blood flow is reduced or blood sodium levels fall, the enzyme *renin* is secreted by kidney cells. Renin converts the plasma protein *angiotensinogen*, produced by the liver, to *angiotensin 1*. *Angiotensin converting enzyme* (ACE), formed in small quantities in the lungs, proximal kidney tubules and other tissues, converts angiotensin 1 to *angiotensin 2*, which stimulates secretion of aldosterone. Angiotensin 2 causes vasoconstriction and increases blood pressure closing the negative feedback loop (Fig. 9.12).

Sex hormones

Sex hormones secreted by the adrenal cortex are mainly *androgens* (male sex hormones) although the amounts produced are insignificant compared with those secreted by the testes and ovaries in late puberty and adulthood (see Ch. 18).

Adrenal medulla 9.3

The medulla is completely surrounded by the adrenal cortex. It develops from nervous tissue in the embryo and is part of the sympathetic nervous system (Ch. 7). When stimulated by extensive sympathetic nerve supply, the glands release the hormones *adrenaline* (epinephrine, 80%) and *noradrenaline* (norepinephrine, 20%).

Adrenaline (epinephrine) and noradrenaline (norepinephrine)

Noradrenaline is the postganglionic neurotransmitter of the sympathetic division of the autonomic nervous system (see Fig. 7.43, p. 174). Adrenaline and some noradrenaline

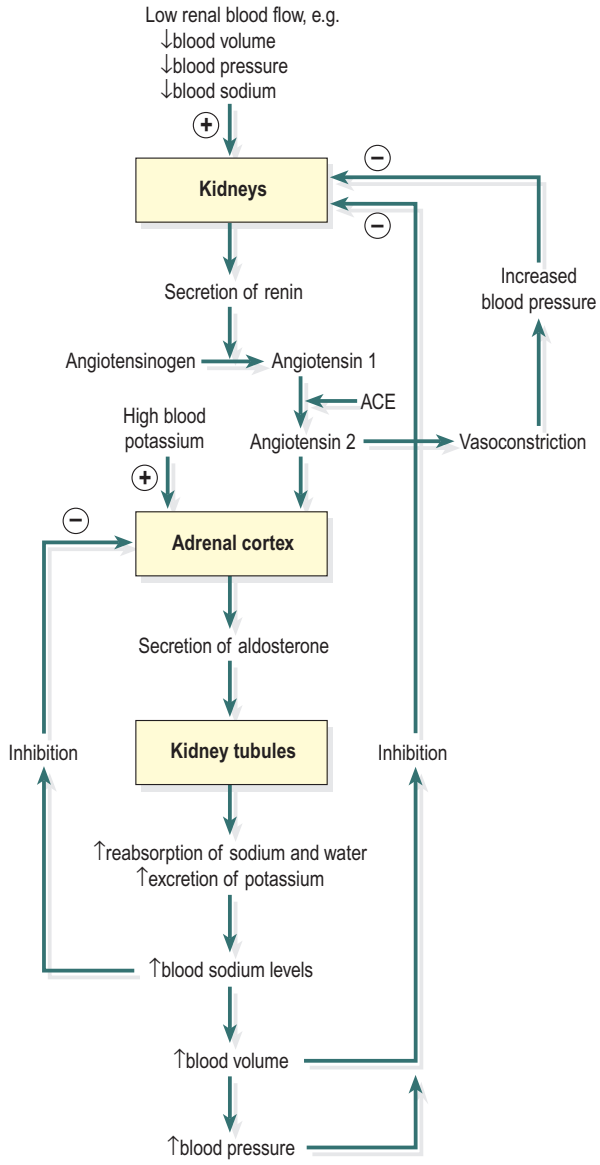

Figure 9.12 Negative feedback regulation of aldosterone secretion.

are released into the blood from the adrenal medulla during stimulation of the sympathetic nervous system (see Fig. 7.44, p. 175). The action of these hormones prolongs and augments stimulation of the sympathetic nervous system. Structurally they are very similar, which explains their similar effects. Together they potentiate the fight or flight response by:

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

Adrenaline has a greater effect on the heart and metabolic processes whereas noradrenaline has more influence on blood vessel diameter.

Response to stress

When the body is under stress homeostasis is disturbed. To restore it and, in some cases, to maintain life there are immediate and, if necessary, longer-term responses. Stressors include exercise, fasting, fright, temperature changes, infection, disease and emotional situations.

The *immediate response* is sometimes described as preparing for 'fight or flight' (p. 176). This is mediated by the sympathetic nervous system and the principal effects are shown in Figure 9.13.

In the *longer term*, ACTH from the anterior pituitary stimulates the release of glucocorticoids and mineralocorticoids from the adrenal cortex providing a more prolonged response to stress (Fig. 9.13).

Pancreatic islets

Learning outcomes

After studying this section, you should be able to:

- list the hormones secreted by the endocrine pancreas
- describe the actions of insulin and glucagon
- explain how blood glucose levels are regulated.

The gross structure of the pancreas is described in Chapter 12. The endocrine pancreas consists of clusters of cells, known as the pancreatic islets (islets of Langerhans), scattered throughout the gland. Pancreatic hormones are secreted directly into the bloodstream and circulate throughout the body. This is in contrast to the exocrine pancreas and its associated ducts (p. 308).

There are three main types of cells in the pancreatic islets:

- α (alpha) cells, which secrete *glucagon*
- β (beta) cells, which are the most numerous, secrete *insulin*
- δ (delta) cells, which secrete *somatostatin* (GHRIH, pp. 218 and 228).

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

- glucagon increases blood glucose levels
- insulin reduces blood glucose levels.

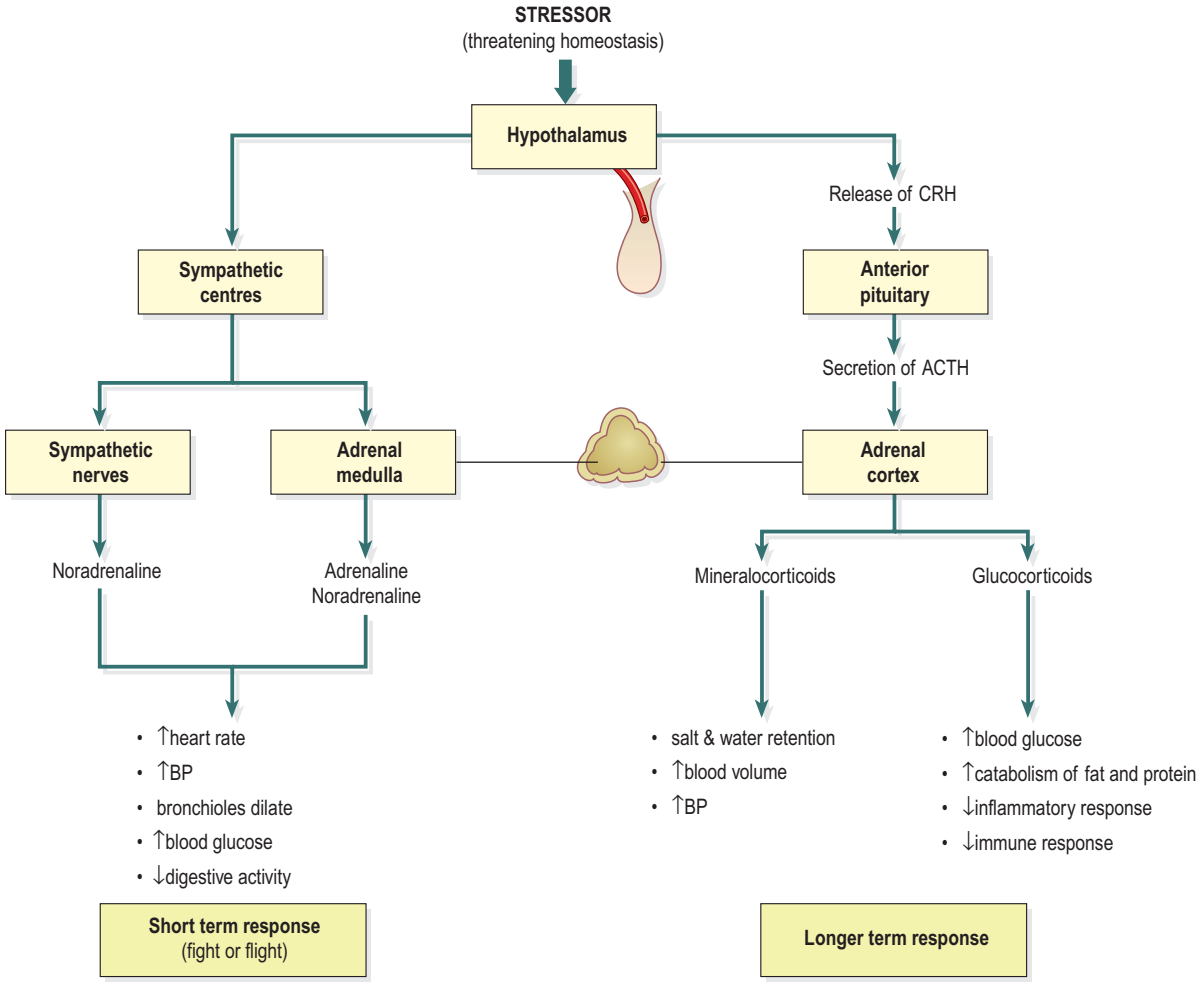

Figure 9.13 Responses to stressors that threaten homeostasis. CRH = corticotrophin releasing hormone. ACTH = adrenocorticotrophic hormone.

Insulin

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

- acting on cell membranes and stimulating uptake and use of glucose by muscle and connective tissue cells
- increasing conversion of glucose to glycogen (*glycogenesis*), especially in the liver and skeletal muscles
- accelerating uptake of amino acids by cells, and the synthesis of protein
- promoting synthesis of fatty acids and storage of fat in adipose tissue (*lipogenesis*)
- decreasing *glycogenolysis* (breakdown of glycogen into glucose)
- preventing the breakdown of protein and fat, and *gluconeogenesis* (formation of new sugar from, e.g., protein).

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

Glucagon

Glucagon increases blood glucose levels by stimulating:

- conversion of glycogen to glucose in the liver and skeletal muscles (glycogenolysis)
- gluconeogenesis.

Secretion of glucagon is stimulated by low blood glucose levels and exercise, and decreased by somatostatin and insulin.

Somatostatin (GHRIH)

This hormone, also produced by the hypothalamus, inhibits the secretion of both insulin and glucagon in addition to inhibiting the secretion of GH from the anterior pituitary (p. 218).

Pineal gland

Learning outcomes

After studying this section, you should be able to:

- state the position of the pineal gland
- outline the actions of melatonin.

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

Melatonin

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

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

Organs with secondary endocrine functions

Learning outcome

After studying this section, you should be able to:

- Outline the functions of some other hormones.

In addition to the glands with primary endocrine functions described above, many other organs and tissues secrete hormones as a secondary function (see Fig. 9.1). Examples of such organs and the hormones they secrete are shown in Table 9.4.

Table 9.4 Organs with secondary endocrine functions

Organ	Hormone	Site of action	Function
Kidney	Erythropoietin	Red bone marrow	Stimulation of red blood cell production (Ch. 4)
Gastrointestinal tract			
Gastric mucosa	Gastrin	Gastric glands	Stimulates secretion of gastric juice (Ch. 12)
Intestinal mucosa	Secretin	Stomach and pancreas	Stimulates secretion of pancreatic juice, slows emptying of the stomach (Ch. 12)
Intestinal mucosa	Cholecystokinin (CCK)	Gallbladder and pancreas	Stimulates release of bile and pancreatic juice (Ch. 12)
Adipose tissue	Leptin	Hypothalamus and other tissues	Provides a feeling of fullness ('satiety') after eating (Ch. 11); needed for GnRH and gonadotrophin synthesis (Ch. 18)
Ovary and testis	Inhibin	Anterior pituitary	Inhibits secretion of FSH
Heart (atria)	Atrial natriuretic peptide (ANP)	Kidney tubules	Decreases reabsorption of sodium and water in renal tubules (Ch. 13)
Placenta	hCG	Ovary	Stimulates secretion of oestrogen and progesterone during pregnancy (Ch. 5)
Thymus	Thymosin	White blood cells (T-lymphocytes)	Development of T-lymphocytes (Ch. 15)

Local hormones

Learning outcome

After studying this section, you should be able to:

- outline the actions of local hormones.

A number of body tissues not normally described as endocrine glands secrete substances that act in tissues nearby (locally). Some of these are described below.

Histamine

This is synthesised and stored by mast cells in the tissues and basophils in blood. It is released as part of the inflammatory responses, especially when caused by allergy (p. 386), increasing capillary permeability and causing vasodilation. It also acts as a neurotransmitter, causes contraction of smooth muscle of the bronchi and alimentary tract, and stimulates the secretion of gastric juice.

Serotonin (5-hydroxytryptamine, 5-HT)

This is present in platelets, in the brain and in the intestinal wall. It causes intestinal secretion and contraction of smooth muscle and its role in haemostasis (blood clotting) is outlined in Chapter 4. It is a neurotransmitter in the CNS and is known to influence mood.

Prostaglandins (PGs)

These are lipid substances found in most tissues. They act on neighbouring cells but their actions are short-lived as they are quickly metabolized. Prostaglandins have potent and wide-ranging physiological effects in:

- the inflammatory response
- potentiating pain
- fever
- regulating blood pressure
- blood clotting
- uterine contractions during labour.

Other chemically similar compounds include *leukotrienes*, which are involved in inflammatory responses, and *thromboxanes*, e.g. thromboxane A_2, which is a potent aggregator of platelets. All of these active substances are found in only small amounts, as they are rapidly degraded.

The effects of ageing on endocrine function

Learning outcome

After studying this section, you should be able to:

- Describe the effects of ageing on the endocrine system.

Adrenal cortex

Osteoporosis caused by oestrogen deficiency in postmenopausal women is reviewed in Chapter 16. Reduced secretion of androgens in women after the menopause may be accompanied by changing hair patterns, e.g. increased facial hair and thinning of hair on the scalp.

Pancreatic islets

In the pancreatic islets, β-cell function declines with age. Especially when associated with weight gain in middle life and older age, this predisposes to type 2 diabetes mellitus (p. 236).

Endocrine disorders are commonly caused by tumours or autoimmune diseases and their effects are usually the result of:

- hypersecretion (overproduction) of hormones, or
- hyposecretion (underproduction) of hormones.

The effects of many conditions explained in this section can therefore be readily linked to the underlying abnormality.

Disorders of the pituitary gland

Learning outcomes

After studying this section, you should be able to:

- list the causes of diseases in this section
- relate the features of conditions affecting the anterior pituitary to the actions of the hormones involved
- relate the features of diabetes insipidus to abnormal secretion of antidiuretic hormone.

Hypersecretion of anterior pituitary hormones

Gigantism and acromegaly

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

- excessive growth of bones
- enlargement of internal organs
- formation of excess connective tissue
- enlargement of the heart and raised blood pressure
- reduced glucose tolerance and a predisposition to diabetes mellitus.

Gigantism. This occurs in children when there is excess GH while epiphyseal cartilages of long bones are still growing, i.e. before ossification of bones is complete. It is evident mainly in the bones of the limbs, and affected individuals may grow to heights of 2.1 to 2.4 m, although body proportions remain normal (Fig. 9.14).

Acromegaly. This means 'large extremities' and occurs in adults when there is excess GH after ossification is complete. The bones become abnormally thick and there is also thickening of the soft tissues. These changes are most noticeable as coarse facial features (especially excessive growth of the lower jaw), an enlarged tongue and excessively large hands and feet (Fig. 9.15).

Figure 9.14 Historical artwork showing effects of normal and abnormal growth hormone secretion. From left to right: normal stature, gigantism (2.3 m tall) and dwarfism (0.9 m tall).

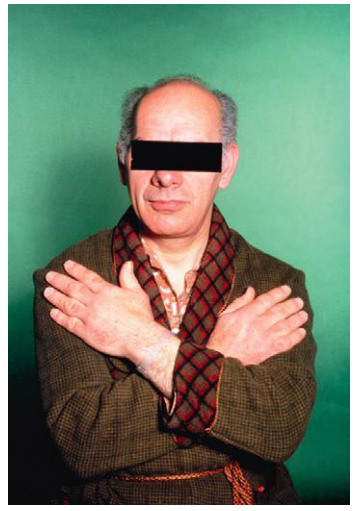

Figure 9.15 Facial features and large hands in acromegaly.

Hyperprolactinaemia

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

Hyposecretion of anterior pituitary hormones

The number of hormones involved and the extent of hyposecretion varies. *Panhypopituitarism* is the absence of all anterior pituitary hormones. Causes of hyposecretion include:

- tumours of the hypothalamus or pituitary
- trauma, usually caused by fractured base of skull, or surgery

- pressure caused by a tumour adjacent to the pituitary gland, e.g. glioma, meningioma
- infection, e.g. meningitis, encephalitis, syphilis
- ischaemic necrosis
- ionising radiation or cytotoxic drugs.

Ischaemic necrosis

Simmond's disease is hypofunction of the anterior pituitary gland, which only rarely affects the posterior lobe. The arrangement of the blood supply makes the gland unusually susceptible to a fall in systemic BP. Severe hypotensive shock may cause ischaemic necrosis. The effects include deficient stimulation of target glands and hypofunction of all or some of the thyroid, adrenal cortex and gonads. The outcome depends on the extent of pituitary necrosis and hormone deficiency. In severe cases, glucocorticoid deficiency may be life threatening or fatal. When this condition is associated with severe haemorrhage during or after childbirth it is known as *postpartum necrosis* (Sheehan's syndrome), and in this situation the other effects are preceded by failure of lactation.

Pituitary dwarfism (Lorain–Lévi syndrome)

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

Fröhlich's syndrome

In this condition there is panhypopituitarism but the main features are associated with deficiency of GH, FSH and LH. In children the effects are diminished growth, lack of sexual development, obesity with female distribution of fat and learning disabilities. Obesity and sterility are the main features in a similar condition in adults. It may arise from a tumour of the anterior pituitary and/or the hypothalamus but in most cases the cause is unknown.

Disorders of the posterior pituitary

Diabetes insipidus

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

Disorders of the thyroid gland

Learning outcome

After studying this section, you should be able to:

- compare and contrast the effects of hyperthyroidism and hypothyroidism, relating them to the actions of T_3 and T_4.

These fall into three main categories:

- abnormal secretion of thyroid hormones (T3 and T4) causing hyperthyroidism or hypothyroidism
- goitre – enlargement of the thyroid gland
- tumours.

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

Hyperthyroidism

This syndrome, also known as *thyrotoxicosis*, arises as the body tissues are exposed to excessive levels of T_3 and T_4. The main effects are due to increased basal metabolic rate (see Table 9.3).

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

- Graves' disease
- toxic nodular goitre
- adenoma (a benign tumour, p. 232).

Graves' disease

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

- increased release of T_3 and T_4 and signs of hyperthyroidism (see Table 9.3)
- goitre (visible enlargement of the gland, Fig. 9.16) as the antibody stimulates thyroid growth
- exophthalmos in many cases.

Exophthalmos. This is protrusion of the eyeballs that gives the appearance of staring, which is due to the deposition of excess fat and fibrous tissue behind the eyes (Fig. 9.17); it is often present in Graves' disease. Effective treatment of hyperthyroidism does not completely reverse

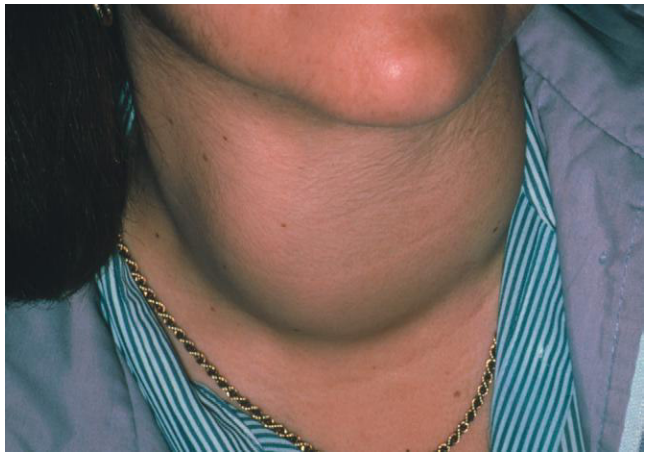

Figure 9.16 Enlarged thyroid gland in goitre.

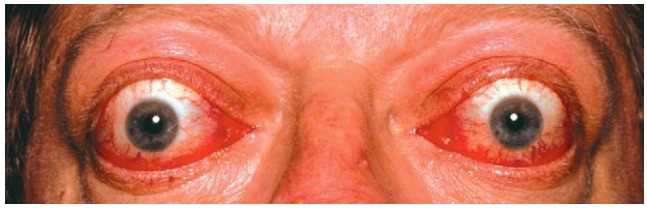

Figure 9.17 Abnormally bulging eyes in exophthalmos.

exophthalmos, although it may lessen after 2–3 years. In severe cases the eyelids become retracted and may not completely cover the eyes during blinking and sleep, leading to drying of the conjunctiva and predisposing to infection. It does not occur in other forms of hyperthyroidism.

Toxic nodular goitre

In this condition one or two nodules of a gland that is already affected by goitre (see Fig. 9.16) become active and secrete excess T_3 and T_4 causing the effects of hyperthyroidism (Table 9.3). It is more common in women than men and after middle age. As this condition affects an older age group than Graves' disease, arrhythmias and cardiac failure are more common. Exophthalmos does not occur in this condition.

Hypothyroidism

This condition is prevalent in older adults and is five times more common in females than males. Deficiency of T_3 and T_4 in adults results in an abnormally low metabolic rate and other effects shown in Table 9.3. There may be accumulation of mucopolysaccharides in the subcutaneous tissues causing swelling (non-pitting oedema), especially of the face, hands, feet and eyelids (myxoedema). The commonest causes are autoimmune thyroiditis, severe iodine deficiency (see goitre) and healthcare interventions, e.g. antithyroid drugs, surgical removal of thyroid tissue or ionising radiation.

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

Congenital hypothyroidism. This is a profound deficiency or absence of thyroid hormones that becomes evident a few weeks or months after birth. Hypothyroidism is endemic in parts of the world where the diet is severely deficient in iodine and contains insufficient for synthesis of T_3 and T_4. Absence of thyroid hormones results in profound impairment of growth and cognitive development. Unless treatment begins early in life, cognitive impairment is permanent and the individual typically has disproportionately short limbs, a large protruding tongue, coarse dry skin, poor abdominal muscle tone and, often, an umbilical hernia.

Simple goitre 9.4

This is enlargement of the thyroid gland without signs of hyperthyroidism. It is caused by a relative lack of T_3 and T_4 and the low levels stimulate secretion of TSH resulting in hyperplasia of the thyroid gland (Fig. 9.16). Sometimes the extra thyroid tissue is able to maintain normal hormone levels but if not, hypothyroidism develops. Causes are:

- persistent iodine deficiency. In parts of the world where there is dietary iodine deficiency, this is a common condition known as *endemic goitre*
- genetic abnormality affecting synthesis of T_3 and T_4
- iatrogenic, e.g. antithyroid drugs, surgical removal of excess thyroid tissue.

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

Tumours of the thyroid gland

Malignant tumours are rare.

Benign tumours

Single adenomas are fairly common and may become cystic. Sometimes the adenoma secretes hormones and hyperthyroidism may develop. The tumours may become malignant, especially in older adults.

Disorders of the parathyroid glands

Learning outcome

After studying this section, you should be able to:

- explain how the diseases in this section are related to abnormal secretion of parathyroid hormone.

Hyperparathyroidism

This condition is characterised by high blood calcium levels (hypercalcaemia) and is usually caused by a benign parathyroid tumour which secretes high levels of parathormone (PTH). This results in release of calcium from bones, raising blood calcium levels. The effects may include:

- polyuria and polydipsia
- formation of renal calculi
- anorexia and constipation
- muscle weakness
- general fatigue.

Hypoparathyroidism

Parathyroid hormone (PTH) deficiency causes hypocalcaemia, i.e. abnormally low blood calcium levels, and is much rarer than hyperparathyroidism. There is reduced absorption of calcium from the small intestine and less reabsorption from bones and glomerular filtrate. Low blood calcium causes:

- *tetany* (Fig. 9.18)
- anxiety
- paraesthesia
- grand mal seizures
- in some cases, cataracts (opacity of the lens, Fig. 8.25, p. 207) and brittle nails.

Causes of hypoparathyroidism include damage to or removal of the glands during thyroidectomy, ionising radiation, development of autoantibodies to PTH and parathyroid cells, and congenital abnormalities.

Tetany

This is caused by hypocalcaemia because low blood calcium levels increase excitability of peripheral nerves. There are very strong painful spasms of skeletal muscles, causing characteristic bending inwards of the hands, forearms and feet (Fig. 9.18). In children there may also be laryngeal spasm and seizures.

Figure 9.18 Characteristic positions adopted during tetanic spasms.

Hypocalcaemia

In addition to hyperthyroidism, this may be associated with:

- chronic renal failure when there is excessive excretion of excess calcium in the urine
- deficiency of vitamin D or dietary deficiency of calcium
- alkalosis; metabolic or respiratory
- acute pancreatitis.

Disorders of the adrenal cortex

Learning outcomes

After studying this section, you should be able to:

- relate the features of Cushing's syndrome to the physiological actions of adrenocorticoids
- relate the features of Addison's disease to the physiological actions of adrenocorticoids.

Hypersecretion of glucocorticoids (Cushing's syndrome)

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

- hormone-secreting adrenal tumours
- hypersecretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary
- abnormal secretion of ACTH by a non-pituitary tumour, e.g. bronchial or pancreatic tumour.

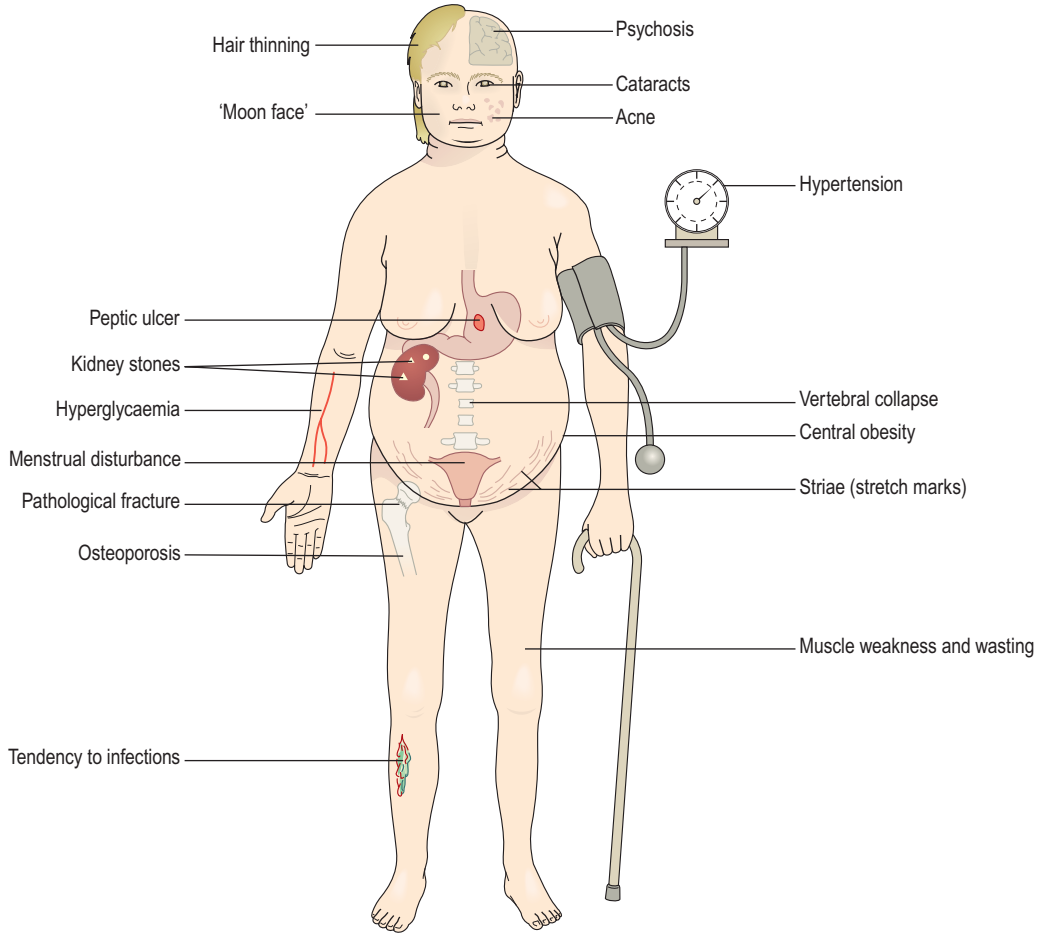

Figure 9.19 The systemic features of Cushing's syndrome.

Prolonged therapeutic use of systemic ACTH or glucocorticoids is another cause of Cushing's syndrome where high blood levels arise from drug therapy. Any of the features shown in Figure 9.19 may occur as side effects of this treatment.

Hypersecretion of cortisol exaggerates its physiological effects (Fig. 9.19). These include:

- adiposity of the face (*moon face*), neck and abdomen
- excessive tissue protein breakdown, causing thinning of subcutaneous tissue and muscle wasting, especially of the limbs
- diminished protein synthesis
- suppression of growth hormone secretion preventing normal growth in children
- osteoporosis (p. 431), and kyphosis if vertebral bodies are involved
- pathological fractures caused by calcium loss from bones
- excessive gluconeogenesis resulting in hyperglycaemia and glycosuria which can precipitate diabetes mellitus (p. 236)
- atrophy of lymphoid tissue and depression of the immune response
- susceptibility to infection due to reduced febrile response, depressed immune and inflammatory responses
- impaired collagen production, leading to capillary fragility, cataract and striae
- insomnia, excitability, euphoria, depression or psychosis
- hypertension due to salt and water retention
- menstrual disturbances
- formation of renal calculi
- peptic ulceration.

Hyposecretion of glucocorticoids

Inadequate cortisol secretion causes diminished gluconeogenesis, low blood glucose levels, muscle weakness and pallor. This may be primary, i.e. due to disease of the adrenal cortex, or secondary due to deficiency of ACTH from the anterior pituitary. In primary deficiency there is also hyposecretion of aldosterone (see below) but in secondary deficiency, aldosterone secretion is not usually affected because aldosterone release is controlled by the renin–angiotensin–aldosterone system (p. 225).

Hypersecretion of mineralocorticoids

Excess aldosterone affects kidney function, with consequences elsewhere:

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

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

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

Hyposecretion of mineralocorticoids

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

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

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

Chronic adrenocortical insufficiency (Addison's disease)

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

- muscle weakness and wasting
- gastrointestinal disturbances, e.g. vomiting, diarrhoea, anorexia
- increased skin pigmentation, especially of exposed areas
- listlessness and tiredness
- hypoglycaemia
- confusion
- menstrual disturbances and loss of body hair in women
- electrolyte imbalance, including hyponatraemia, low blood chloride levels and hyperkalaemia
- chronic dehydration, low blood volume and hypotension.

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

Acute adrenocortical insufficiency (Addisonian crisis)

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

Disorders of the adrenal medulla

Learning outcome

After studying this section, you should be able to:

- explain how the features of the diseases in this section are related to excessive secretion of adrenaline (epinephrine) and noradrenaline (norepinephrine).

Tumours

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

- hypertension
- weight loss
- nervousness and anxiety
- headache
- excessive sweating and alternate flushing and blanching of the skin
- hyperglycaemia and glycosuria
- constipation.

Phaeochromocytoma

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

Neuroblastoma

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

Disorders of the pancreatic islets

Learning outcomes

After studying this section, you should be able to:

- compare and contrast the onset and features of types 1 and 2 diabetes mellitus
- relate the signs and symptoms of diabetes mellitus to deficiency of insulin
- explain how the causes and effects of the following conditions occur: diabetic ketoacidosis and hypoglycaemic coma
- describe the long-term complications of diabetes mellitus.

Diabetes mellitus (DM)

This is the most common endocrine disorder; the primary sign is hyperglycaemia which is accompanied by varying degrees of disruption of carbohydrate and fat metabolism. DM is caused by complete absence of, relative deficiency of or resistance to the hormone insulin. Box 9.2 shows the classification of diabetes. *Primary DM* is categorised as type 1 or type 2. In *secondary DM*, the disorder arises as a result of other conditions, and *gestational diabetes* develops in pregnancy. The incidence of types 1 and 2 DM, especially type 2, is rapidly increasing worldwide. Table 9.5 shows some distinguishing features of types 1 and 2 DM.

Type 1 diabetes mellitus

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

Box 9.2 Classification of diabetes mellitus

Primary

Type 1 diabetes mellitus
Type 2 diabetes mellitus

Secondary

Due to other situations, e.g.:

- acute or chronic pancreatitis (p. 331)
- some drug therapy, e.g. corticosteroids
- other endocrine disorders involving hormones that increase plasma glucose levels, e.g. growth hormone, thyroid hormones, cortisol (Cushing's syndrome, p. 233)

Gestational diabetes

This develops during pregnancy and may disappear after delivery but often recurs in later life. It is associated with birth of heavier than normal and stillborn babies, and deaths shortly after birth.

Type 2 diabetes mellitus

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

- obesity
- sedentary lifestyle
- increasing age: predominantly affecting middle-aged and older adults
- genetic factors.

Its onset is gradual, often over many years, and it frequently goes undetected until signs are found on routine investigation or a complication occurs. Insulin secretion may be below or above normal. Deficiency of glucose inside body cells occurs despite hyperglycaemia and a high insulin level. This may be due to insulin resistance, i.e. changes in cell membranes that block the insulin-assisted movement of glucose into cells. Treatment involves diet and/or drugs, although sometimes insulin injections are required.  **9.5**

Pathophysiology of DM

Raised plasma glucose level

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

Table 9.5 Features of type1 and type 2 diabetes mellitus

	Type 1 DM	Type 2 DM
Age of onset	Usually childhood	Adulthood and later life
Body weight at onset	Normal or low	Obese
Onset of symptoms	Weeks	Months/years
Main cause(s)	Autoimmune	Obesity, lack of exercise
Insulin requirement	100% of cases	Up to 20% of cases
Ketonuria	Yes	No
Complications at diagnosis	No	Up to 25%
Family history	Rare	Common

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

Glycosuria and polyuria

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

Weight loss

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

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

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

Ketosis and ketoacidosis

This nearly always affects people with type 1 DM.

In the absence of insulin to promote normal intracellular glucose metabolism, alternative energy sources must be used instead and increased breakdown of fat occurs (see Fig. 12.43, p. 317). This leads to excessive production of weakly acidic ketone bodies, which can be used for metabolism by the liver. Normal buffering systems maintain pH balance so long as the levels of ketone bodies are not excessive. *Ketosis* (see p. 318) develops as ketone bodies accumulate. Excretion of ketones is via the urine (ketonuria) and/or the lungs giving the breath a characteristic smell of acetone or 'pear drops'.

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

- increasing acidosis (↓ blood pH) due to accumulation of ketoacids
- increasing hyperglycaemia
- hyperventilation as the lungs excrete excess hydrogen ions as CO_2
- acidification of urine – the result of kidney buffering
- polyuria as the renal threshold for glucose is exceeded
- dehydration and hypovolaemia (↓ BP and ↑ pulse) – caused by polyuria
- disturbances of electrolyte balance accompanying fluid loss, hyponatraemia (↓ plasma sodium) and hypokalaemia (↓ plasma potassium)
- confusion, coma and death.

Acute complications of diabetes mellitus

Diabetic ketoacidosis

The effects and consequences of diabetic ketoacidosis are outlined above.

Hypoglycaemic coma

This occurs when insulin administered is in excess of that needed to balance the food intake and expenditure of energy. Hypoglycaemia is of sudden onset and may be the result of:

- accidental overdose of insulin
- delay in eating after insulin administration
- drinking alcohol on an empty stomach
- strenuous exercise.

It may also arise from an insulin-secreting tumour, especially if it produces irregular bursts of secretion. Because neurones are more dependent on glucose for their energy needs than are other cells, glucose deprivation causes disturbed neurological function, leading to coma and, if prolonged, irreversible damage.

Common signs and symptoms of hypoglycaemia include drowsiness, confusion, speech difficulty, sweating, trembling, anxiety and a rapid pulse. This can progress rapidly to coma without treatment, which usually enables rapid recovery. Most people can readily recognize the symptoms of hypoglycaemia and can take appropriate action.

Long-term complications of diabetes mellitus

These increase with the severity and duration of hyperglycaemia and represent significant causes of morbidity (poor health) and mortality (death) in people with both type 1 and type 2 diabetes.

Cardiovascular disturbances

Diabetes mellitus is a significant risk factor for cardiovascular disorders. Blood vessel abnormalities (angiopathies) may still occur even when the disease is well controlled.

Diabetic macroangiopathy. The most common lesions are atheroma and calcification of the tunica media of the large arteries. In type 1 diabetes these changes may occur at a relatively early age. The most common consequences are serious and often fatal:

- ischaemic heart disease, i.e. angina and myocardial infarction (p. 127)
- stroke (p. 181)
- peripheral vascular disease.

Diabetic microangiopathy. This affects small blood vessels and there is thickening of the epithelial basement membrane of arterioles, capillaries and, sometimes, venules. These changes may lead to:

- peripheral vascular disease, progressing to gangrene and 'diabetic foot'
- diabetic retinopathy and visual impairment (see p. 212)
- diabetic nephropathy and chronic renal failure (p. 352)
- peripheral neuropathy causing sensory deficits and motor weakness (p. 188), especially when myelination is affected.

Infection

DM predisposes to infection, especially by bacteria and fungi, possibly because phagocyte activity is depressed by insufficient intracellular glucose. Infection may cause:

- boils and carbuncles
- vaginal candidiasis (thrush, p. 466)
- pyelonephritis (p. 352)
- diabetic foot.

Renal failure

This is due to diabetic nephropathy (p. 352) and is a common cause of death.

Visual impairment and blindness

Diabetic retinopathy (p. 212) is the commonest cause of blindness in adults between 30 and 65 years in developed countries. Diabetes also increases the risk of early development of cataracts (p. 211) and other visual disorders.

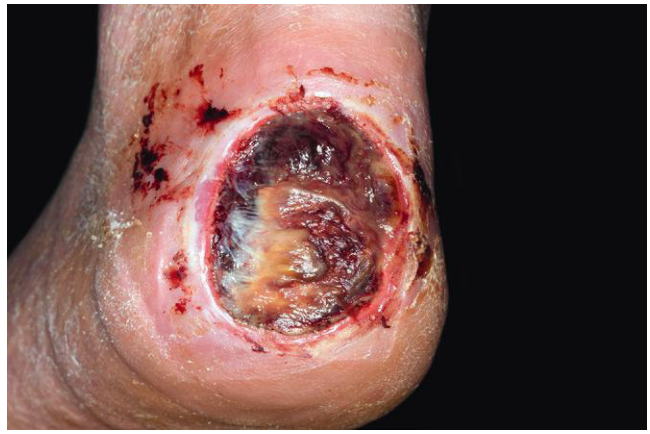

Figure 9.20 Diabetic foot: a large heel ulcer.

Diabetic foot

Many factors commonly present in DM contribute to the development of this serious situation. Disease of large and small blood vessels impairs blood supply to and around the extremities. If peripheral neuropathy is present, sensation is reduced. A small injury to the foot may go unnoticed, especially when there is visual impairment. In DM healing is slower and injuries easily worsen if aggravated, e.g. by chafing shoes, and often become infected. An ulcer may form (Fig. 9.20) and the healing process is lengthy, if at all. In severe cases the injured area ulcerates and enlarges, and may become gangrenous, sometimes to the extent that amputation is required.

For a range of self-assessment exercises on the topics in this chapter, visit Evolve online resources: https://evolve.elsevier.com/Waugh/anatomy/