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Chapter objectives

After studying this chapter you should be able to:

1. Explain what is meant by a hormone and name the major endocrine organs.

2. Categorize common hormones by their basic chemical structures.

3. Understand the role of plasma binding proteins for some hormones.

4. Understand the different forms of endocrine regulation, including set point, diurnal variation, endocrine axis and negative feedback.

5. Understand the basis of endocrine disease.

6. Appreciate the purpose and types of endocrine testing.
What is endocrinology?

Endocrinology is the study of hormones and their actions. Hormones are chemical messengers, released into the blood, that act through receptors to cause a change in the target cell. The glands that release hormones are ductless, giving the term ‘endocrine’ from the Greek for ‘internal secretion’. The thyroid gland is an example of a classical endocrine gland. Its only function is to synthesize and release hormones into the bloodstream. Some organs, such as the pancreas, have endocrine as well as other functions. So the hormones released by the pancreas are released directly into the blood, whereas the other (exocrine) secretions of the pancreas are released into a duct.

The major, or ‘classical’, endocrine glands are shown in Figure 1.1 and the hormones they secrete are listed in Table 1.1. It has been suggested that the vascular endothelium, the whole gastrointestinal tract, and even the skin, should also be considered to be endocrine organs as they all release hormones or their precursors into the blood. Such tissues form the extensive ‘diffuse endocrine system’, which is located throughout the body. This system consists of scattered endocrine cells, located in various different tissues, that secrete hormones but do not form a discrete endocrine gland.

Endocrinology is a relatively young branch of medical science and is, by definition, exciting. The term ‘hormone’ was coined by Starling in the early 1900s. It derives from the Greek hormon, meaning ‘exciting’ or ‘setting in motion’. Ernest Starling (1866–1927) is perhaps best known for his eponymous law of the cardiovascular system, but is also regarded as the founder of endocrinology. Working at University College, London, with Sir William Bayliss, he isolated and described the actions of secretin, the first known hormone. Starling built on the theoretical work of Edward Schafer and developed the concept of ‘an endocrine system’ in 1905, in a series of lectures called ‘On the chemical correlations of the functions of the body’.

Endocrine disorders are very common in Western society and it has been estimated that more than half the population will suffer from an endocrine disease during their lifetime. There are several examples of common endocrine diseases: osteoporosis, the bone-weakening disease, affects one-third of older women. Around one in six women has polycystic ovarian disease. In addition, an increasing number of the population has type 2 diabetes, a disease of insulin resistance, as a result of obesity.

Interesting fact

The year 2005 saw the centenary of ‘Endocrinology’ as a recognized science and branch of medicine. Learned societies, such as the Society for Endocrinology, celebrated this with a series of special published articles, papers, lectures, events and poster campaigns (Fig. 1.2). To put this into perspective, surgery and pharmacology have been around for thousands of years.

What do hormones do?

There are two major regulatory systems in the body: the neural system and the endocrine system. Although both use chemical messengers, they are set up very differently and have quite different functions. Neural regulation is very rapid, while endocrine control is generally slower and acts over a longer period of time. These differences arise because the neural system is designed to deliver its messenger directly to the surface of its target cell, while the endocrine system puts its messengers into the blood and allows for diffusion from the
blood to the target cell. Thus, the endocrine system is not designed for the same speed of communication as the neural system, but instead has the ability to deliver its messengers to a wider range of targets throughout the body.

Hormones usually control regulatory systems in the body, including homeostasis, metabolism and reproduction. Homeostasis means ‘keeping the same’ and is a term used to describe the regulation of any of the large physiological systems in the body, including levels of glucose in blood and body temperature. Hormones are particularly important in making sure that blood levels of sodium, potassium, calcium and glucose stay within set limits.

<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone</th>
<th>Type of hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>Corticotropin releasing hormone (CRH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Dopamine (DA)</td>
<td>Modified amino acid</td>
</tr>
<tr>
<td></td>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Growth hormone releasing hormone (GHRH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Somatostatin</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Thyrotrpin-releasing hormone (TRH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Vasopressin (AVP, anti-diuretic hormone, ADH)</td>
<td>Peptide</td>
</tr>
<tr>
<td>Anterior pituitary</td>
<td>Adrenocorticotropic (ACTH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Follicle stimulating hormone (FSH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Growth hormone (GH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Luteinizing hormone (LH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Prolactin (Prl)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Thyroid stimulating hormone (TSH; thyrotropin)</td>
<td>Peptide</td>
</tr>
<tr>
<td>Posterior pituitary</td>
<td>Oxytoxin</td>
<td>Peptide</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroxine (T4)</td>
<td>Modified amino acid</td>
</tr>
<tr>
<td></td>
<td>Tri-iodothyronine (T3)</td>
<td>Modified amino acid</td>
</tr>
<tr>
<td></td>
<td>Calcitonin</td>
<td>Peptide</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Parathyroid hormone (PTH)</td>
<td>Peptide</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>Aldosterone</td>
<td>Steroid</td>
</tr>
<tr>
<td></td>
<td>Cortisol</td>
<td>Steroid</td>
</tr>
<tr>
<td></td>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>Steroid</td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Adrenaline (epinephrine)</td>
<td>Modified amino acid</td>
</tr>
<tr>
<td></td>
<td>Noradrenaline (norepinephrine)</td>
<td>Modified amino acid</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Insulin</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>Peptide</td>
</tr>
<tr>
<td>Stomach and gut</td>
<td>Gastrin</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>And many other peptides, see Ch. 13</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>17 beta oestradiol</td>
<td>Steroid</td>
</tr>
<tr>
<td></td>
<td>Progesterone</td>
<td>Steroid</td>
</tr>
<tr>
<td>Testes</td>
<td>Testosterone</td>
<td>Steroid</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Erythropoietin (EPO)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Calcitriol</td>
<td>Modified steroid</td>
</tr>
</tbody>
</table>

Table 1.1 Major endocrine glands and the hormones they secrete
The boundaries between the endocrine system and the neural system are quite fuzzy (Fig. 1.3), because some hormones are released from nerve endings, ‘neurohormones’, while other hormones, such as adrenaline, are perhaps better known as neurotransmitters.

**Types of hormone: their synthesis and secretion**

In terms of their chemical structure, hormones are a varied group of substances. There are, however, three major basic types. The first and most numerous are the peptide hormones, made of chains of amino acids. Some of these are very small indeed: the hypothalamic hormone thyrotropin releasing hormone (TRH) is only three amino acids long, whereas the pituitary hormone whose release it stimulates (thyroid stimulating hormone, TSH) is a large glycoprotein with a molecular weight of around 30,000 Daltons. Usually, peptide hormones are pre-formed and stored in granules within the endocrine cell, ready for release in response to the appropriate signal. The synthesis and secretion of peptide hormones is shown in Figure 1.4A.

Many peptide hormones, particularly the larger ones, undergo modification of the basic peptide sequence before being secreted. This post-translational processing, which occurs in the Golgi apparatus and the secretory granules, can include the linking of peptide chains by disulphide bridges, and the addition of carbohydrate residues (glycosylation). Peptide hormone-secreting cells are distinguished by the large amounts of rough endoplasmic reticulum, prominent Golgi apparatus and by the presence of secretory granules, containing the finished hormone ready for secretion.

The second major group of hormones consists of the steroids. These are all made from cholesterol (Fig. 1.4B) and have a common core structure (Fig. 1.5). Quite small chemical changes to this core structure cause significant differences in their biological effects (Fig. 1.6). The steroids are formed by metabolism of cholesterol by enzymes within the steroid-secreting cell, located either within the mitochondria or the smooth endoplasmic reticulum. Cells which are involved in steroid hormone production are distinctive under microscopy because of the presence of unusually large amounts of smooth endoplasmic reticulum and mitochondria. They also usually contain significant lipid droplets, containing cholesterol esters, as steroid-secreting cells store the precursor to hormone synthesis rather than the finished product. The pathways of steroid hormone biosynthesis are shown in the adrenal chapter and the chapters on reproduction.

The third group of hormones are those derived from amino acids. For example, tyrosine residues can be iodinated to give thyroid hormones, or hydroxylated as the first step on the biosynthetic pathway of the catecholamines: dopamine, adrenaline and noradrenaline (Fig. 1.7). A detailed account of the synthesis of thyroid hormones in given in Chapter 7 and for the catecholamines, in Chapter 5.
The differences in chemical structure of hormones have implications for the way in which these hormones are stored, released, transported in blood, their mechanism of action and, of course, their route of administration when they are used therapeutically (Table 1.2). Peptide hormones and catecholamines, being generally quite water-soluble, dissolve readily in plasma, the fluid component of the blood, but cannot enter the target cell, so interact with receptors on the cell surface. The lipophilic...
steroid and thyroid hormones, on the other hand, dissolve poorly in plasma and are mostly transported in blood bound to carrier proteins, but readily enter cells to interact with cytoplasmic or nuclear receptors. While peptide hormones and catecholamines are synthesized then stored in granules in the cells to be released as soon as they are needed (see Fig. 1.4A), steroid-secreting cells keep a store of cholesterol, the substrate for steroid biosynthesis, rather than the final steroid product (see Fig. 1.4B). This is largely a matter of practicality as the steroid hormones, being lipid soluble, are difficult to store, whereas cholesterol can be esterified and stored easily. Similarly, in the thyroid gland, a store of precursor is maintained, from which thyroid hormones may be readily released.

As a consequence of their small and lipophilic nature, steroid hormones do not require a specific secretory mechanism: they simply diffuse across the plasma membrane and out of the cell down a concentration gradient. Peptide hormones, on the other hand, need a specific secretory mechanism (see Fig. 1.4).

Finally, when they are used therapeutically, steroid hormones and thyroid hormones are orally active, whereas most peptide hormones (such as insulin) must be injected, to avoid being inactivated by digestive enzymes.

Classically, hormones travel from the cells where they are made, in the bloodstream, to reach the cells where they act. But some hormones also act locally, on different cell types in the tissue where they are produced. This is termed a 'paracrine' effect. Other hormones act directly on the same type of cell that secretes them. This is termed an 'autocrine' action (Fig. 1.8). Hormones may have a mixture of different types of action. An example of this is testosterone, which exerts a paracrine effect on spermatogenesis in the testis, but an endocrine effect on other tissues.

**Figure 1.7** Metabolism of the amino acid tyrosine produces both thyroid hormones (thyroxine) and catecholamines (adrenaline).

**Figure 1.8** (A) Endocrine, (B) paracrine and (C) autocrine regulation.

**Table 1.2** Comparison of steroids, peptides, thyroid hormones and catecholamines

<table>
<thead>
<tr>
<th></th>
<th>Location of receptors</th>
<th>Carrier protein</th>
<th>Active if administered orally?</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptides</td>
<td>Cell membrane</td>
<td>No</td>
<td>Not usually</td>
<td>Hormone stored</td>
</tr>
<tr>
<td>Steroids</td>
<td>Cytoplasm/nucleus</td>
<td>Yes</td>
<td>Yes, mostly</td>
<td>Precursor stored</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>Nucleus</td>
<td>Yes</td>
<td>Yes</td>
<td>Precursor stored</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Cell membrane</td>
<td>No</td>
<td>No</td>
<td>Hormone stored</td>
</tr>
</tbody>
</table>
Hormones circulate in blood in very low concentrations indeed, and for this reason they are measured in units that are unfamiliar to many people (Table 1.3). Although some hormones, mostly the peptide hormones, are freely water-soluble, the steroid and thyroid hormones are not so soluble, and need to be transported in blood bound to a carrier or binding protein (Table 1.4). Not all steroids have a specific binding protein: aldosterone, for example, does not have a specific carrier protein, and circulates in blood mostly bound loosely to albumin. The binding proteins have three main functions. First, they increase the solubility of the hormone in blood. Second, they create a readily accessible reserve of the hormone in blood. Only the fraction of hormone that is not bound to the carrier protein is considered to be biologically active. When we describe a hormone as ‘biologically active’ we mean that it is available to exert its physiological effects but is also susceptible to metabolism or excretion. The biologically active hormone is ‘seen’ by the body but the bound hormone is effectively hidden. This is one factor that must be considered when measuring circulating concentrations of hormones: some assays measure total hormone (bound and free) while others measure only the biologically active hormone. You really need to know what it is that you are measuring. It is particularly important because levels of binding proteins can be altered in some clinical conditions and by some drugs.

The third function is to increase the biological half-life of the hormone. The biological half-life of a hormone is the time taken for half the hormone present in blood to be metabolized or excreted. It can be measured by injecting somebody with a ‘tagged’ hormone that can be easily distinguished from the normal hormone, then seeing how quickly it disappears from the circulation by measuring the amount present in samples taken at different times after the injection (Fig. 1.9). Binding proteins increase the biological half-life of a hormone by protecting it from metabolism and excretion, so that aldosterone, which does not have a specific carrier protein, has a half-life of around 15 min, whereas cortisol, which is bound to cortisol binding globulin (CBG), has a half-life of 90 min.

Different types of hormones are metabolized and excreted in different ways: Peptide hormones are mainly metabolized following binding to a receptor in the target cell. The hormone–receptor complex is internalized (that is taken up into the cell), and the hormone undergoes degradation in a lysosome. Most peptide hormones have a short half-life of just a few minutes, although the larger glycosylated peptide hormones such as thyroid stimulating hormone and luteinizing hormone have a longer half-life.

Steroid hormones are small and lipophilic and may be excreted by the kidney in an unchanged form.

---

**Table 1.3** Concentrations of various substances in blood

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration in SI units (using conventional abbreviations)</th>
<th>Log mol/L and equivalent SI unit (per litre) in full</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140 mmol/L</td>
<td>10^−1 100 millimoles</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>21–26 mmol/L</td>
<td>10^−2 10 millimoles</td>
</tr>
<tr>
<td>Glucose</td>
<td>3–5 mmol/L</td>
<td>10^−3 1 millimole</td>
</tr>
<tr>
<td>Uric acid</td>
<td>150–500 μmol/L</td>
<td>10^−4 100 micromoles</td>
</tr>
<tr>
<td>Iron</td>
<td>10–30 μmol/L</td>
<td>10^−5 10 micromoles</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>0.5–2 μmol/L</td>
<td>10^−6 1 micromole</td>
</tr>
<tr>
<td>Cortisol (0900 h)</td>
<td>200–650 nmol/L</td>
<td>10^−7 100 nanomoles</td>
</tr>
<tr>
<td>Testosterone (men)</td>
<td>10–35 nmol/L</td>
<td>10^−8 10 nanomoles</td>
</tr>
<tr>
<td>Tri-iodothyronine</td>
<td>1–3.5 nmol/L</td>
<td>10^−9 1 nanomole</td>
</tr>
<tr>
<td>Adrenaline (resting)</td>
<td>170–500 pmol/L</td>
<td>10^−10 100 picomoles</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>10–30 pmol/L</td>
<td>10^−11 10 picomoles</td>
</tr>
<tr>
<td>Oxytocin (basal)</td>
<td>1–4 pmol/L</td>
<td>10^−12 1 picomole</td>
</tr>
</tbody>
</table>

**Table 1.4** Hormones and their binding proteins

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Binding protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid hormone</td>
<td>Thyroid hormone binding globulin (THBG)</td>
</tr>
<tr>
<td>Testosterone/oestradiol</td>
<td>Sex hormone binding globulin (SHBG)</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Cortisol binding globulin (CBG, also called transcortin)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Vitamin D binding protein (DBP)</td>
</tr>
</tbody>
</table>
however, they undergo metabolism in the liver into more water-soluble forms which are then excreted in bile and in the urine. Catecholamines are metabolized rapidly by the action of an enzyme called catechol-O-methyltransferase (COMT) which is found in most tissues but especially blood vessels, and by monoamine oxidase (MAO) in neural tissues.

Metabolism of hormones does not only result in their inactivation, however. There are examples of the principal secreted hormone being inactive and requiring metabolism in peripheral tissues to produce the active version. Testosterone is a good example of this: it needs to be metabolized to 5-alpha dihydrotestosterone in order to have its effects in its target tissues. Similarly, metabolism of Vitamin D3 is absolutely essential to produce the active calcitriol.

The metabolism of thyroxine is by the removal of one of the iodine residues of the hormone. Depending on which particular iodine residue is removed this either increases the activity of the hormone by producing T3, or decreases the activity by producing reverse T3. So we can see that metabolism, as well as providing a way of excreting hormones more efficiently, can also provide a way of regulating the activity of the hormone.

**Important concepts in endocrine regulation**

There are several concepts which are important for the understanding of endocrinology. These include the understanding of different patterns of hormone secretion, the concept of an ‘endocrine axis’, the idea of negative feedback regulation, and the concepts of hormone antagonism and synergy.

**Patterns of hormone secretion (Fig. 1.10)**

**Figure 1.9** Measurement of the half-life of a hormone in blood. A labelled (radioactive) hormone is injected into the blood at time 0. Blood is sampled regularly and the radioactive content measured. When there is half the original level, the interval between time 0 and this time is called the half-life (t½) of the hormone. In the example shown, the plasma half-life of the hormone is 30 min.

---

**Episodic secretion**

The endocrine system is involved in a variety of homeostatic mechanisms in the body. In many cases regulation involves the maintenance of a ‘set point’ by correction of any deviation from this point. One example is the regulation of plasma calcium concentration, which is tightly controlled within closely set limits. In this case, any deviation from the set point triggers a hormonal response which acts to correct the calcium level (see Ch. 12). This results in the episodic secretion of the regulatory hormone. Other hormones are also secreted episodically, not because they are responding to physiological changes but because they are always secreted episodically or in bursts. These bursts can be quite frequent. For example, if you took very frequent blood samples to measure levels of GnRH (gonadotropin releasing hormone) you would see that levels went up and down in a saw-tooth manner over short periods of time. Overall, the pattern of secretion for hormones which are secreted episodically depends on other factors such as the half-life of the hormone and the frequency and amplitude of secretory episodes.

**Diurnal variation**

The secretion of many hormones has a predictable daily pattern which is known as diurnal variation (see Fig. 1.10). Growth hormone concentrations, for example, are usually so low that they are undetectable during the
day, but increase during the early part of sleep. In contrast, corticotropin concentrations are at their lowest at midnight and reach a peak at around 0800 h each day. It is clearly important to be aware of diurnal variation when circulating hormone levels are being measured.

The main regulator of the 24-h periodicity of hormone secretion is the ‘body clock’, principally the suprachiasmatic nucleus (SCN) in the hypothalamus. However, other factors can influence the diurnal pattern of secretion. For example, cortisol, which increases in response to food intake, also increases in anticipation shortly before the times when we normally eat. Melatonin is one of the most obviously day–night related hormones. Its secretion is suppressed by light so it is produced during the hours of darkness (see Ch. 13). There is also evidence from cell culture experiments which suggests that some endocrine cells may even have their own inbuilt 24-h clock to help control their diurnal secretion.

**Set point regulation**

It is quite unusual for a hormone to be maintained at a set level. However, thyroxine concentrations in blood vary very little from day to day and are constant within a 24-h period. Changes in thyroxine concentrations occur only over weeks or months. One reason for this is the very long half-life of thyroxine in blood.

Different hormones clearly have markedly different patterns of secretion. However, most have some diurnal pattern but with episodic secretion on top of this underlying rhythm. Thus, there is a daily rhythm plus an element of response to physiological demand in the final pattern of secretion of most hormones.

**Endocrine axis**

Many hormones function as part of a cascade, so that the target tissue of one hormone is another endocrine gland. For example, thyrotropin releasing hormone (TRH) from the hypothalamus stimulates the release of pituitary TSH, which in turn stimulates release of thyroxine from the thyroid. The cascade allows amplifications of signal, flexibility of response to a variety of physiological stimuli and fine regulation of levels of the end hormonal product. This functional grouping is called an endocrine axis (Fig. 1.11) and, in the example we have used is called the hypothalamo–pituitary–thyroid axis. There are examples of endocrine axes in most of the following chapters.

**Negative feedback**

One of the most important principles of endocrine regulation is the concept of negative feedback. We have seen that one of the functions of hormones is to regulate homeostatic mechanisms in the body. However, there is also a homeostatic process that regulates levels of hormones. Basically, the body has systems which are designed to ‘damp-down’ excess of any kind. The simplest form of negative feedback is where the final product of an endocrine cascade acts to inhibit release of hormones higher up the cascade (see Fig. 1.11). In the example shown, a stimulus such as exercise causes an increase in thyrotropin releasing hormone (TRH) from the hypothalamus, which in turn acts to increase the secretion of thyroid stimulating hormone (TSH) from the anterior pituitary. The increased TSH stimulates the thyroid gland to produce T4 and T3, which exert a negative feedback inhibitory effect on the hypothalamus and pituitary glands.

![Figure 1.11 An endocrine axis and negative feedback. The axis shown is the hypothalamo–pituitary–thyroid axis. Thyrotropin releasing hormone (TRH), from the hypothalamus, stimulates the release of thyroid stimulating hormone (TSH) from the anterior pituitary. The TSH stimulates the thyroid gland to release T4 and T3, which exert a negative feedback inhibitory effect on the hypothalamus and pituitary glands.](image-url)
mediated by a genomic mechanism as it can take place within ten minutes. For example, in the hypothalamo-pituitary-adrenal axis, the hormonal end-product is cortisol. If cortisol levels rise rapidly, this triggers a fast feedback mechanism which reduces activity of the axis at higher levels. The speed of this response suggests that cortisol exerts its fast feedback effect through a different mechanism than the conventional genomic mechanism of steroid action. So in general, fast feedback kicks in when hormone levels rise rapidly and is triggered by the gradient of the increase. Delayed feedback, in contrast, is determined by the amplitude and duration of the end-product response and takes place over longer time periods.

So far, we have only considered those feedback loops from the end-products of an endocrine cascade. The hormones that exert this form of negative feedback effect are usually small molecules that can readily cross the blood–brain barrier, as the hypothalamus is an important site of negative feedback in many hormone systems. Some systems also have short feedback loops which allow intermediate products of an endocrine axis to exert negative feedback at higher levels. For example pituitary corticotropin (ACTH), which stimulates cortisol secretion, also inhibits hypothalamic corticotropin releasing hormone (CRH). This suggests that there are specific mechanisms to allow transport of certain peptide hormones across the blood–brain barrier.

So, in summary, the CRH–ACTH–cortisol cascade is regulated by both classical negative feedback from cortisol (the end-product) and by short-loop feedback from ACTH (the intermediate product).

The principle of negative feedback is the basis of several dynamic tests of endocrine function. The general principle is that failure of high levels of a hormone to be suppressed by its negative feedback regulator suggests that there is a pathological abnormality in the system. Specific examples are given throughout this book.

**Hormone antagonism and synergy**

When a hormone has an effect, it is called an agonist. A hormone which has the opposite effect is said to be an antagonist of the first hormone (see Ch. 2 for details of agonists and antagonists).

In cases where it is really important to maintain the levels of a substance within narrow limits, the body takes a ‘belt and braces’ approach and uses more than one hormone to achieve the control. Very often, the hormones will act in opposition: one or more will act to increase the level of the substance, while one or more will act to decrease it. This might seem wasteful, but it has two very important consequences. One is that it allows considerable fine control and responsiveness to a changing environment. The second is that it can afford protection against a potentially devastating change in the level of the substance. For example, there are many hormones involved in glucose homeostasis. However, only one of these, insulin, acts to decrease blood glucose levels, while all the rest act as insulin antagonists and increase blood glucose levels. The interactions between them allow fine control and the number of hormones which increase glucose helps to protect against potentially fatal hypoglycaemia.

Sometimes, hormones which exert the same effect have much greater action when the two act together than either of them can have individually. This is called synergy and is rare in endocrine systems. The best example is the synergy between CRH and AVP in stimulating ACTH secretion (see Ch. 4).

**Endocrine disorders**

As a general rule, endocrine disorders are the result of either excessive secretion of a hormone or of insufficient secretion. The terminology used to describe these disorders can be confusing. Too much hormone is indicated by the prefix hyper-, while too little hormone is indicated by the prefix hypo- (from the Greek meaning ‘over’ and ‘below’, respectively). So hypercortisolism is the state of excess cortisol production. The suffix can also change to indicate where the excess occurs, so hypercortisolaemia is too much cortisol in the blood. Glicosurial means that there is glucose in the urine. In this case we do not need to use hypo- or hyper-, because glucose is not normally found in urine, so the fact of its presence is all that needs reporting.

The effects of either hormone excess or relative absence of hormone are exaggerations of the normal physiological effects of the hormone and serve as a very useful illustration of endocrine physiology. Historically, endocrine disease states were used to gain an understanding of the actions of different hormones. The cases used in this book have been chosen to illustrate important points about either the biochemistry of hormone synthesis or the physiology of endocrine regulation. The common endocrine disorders are listed in Table 1.5 according to the chapter in which you will find them described.

The endocrine axes described above mean that a deficiency in the final hormone of the cascade may be due to a defect at one of several points in the axis. Looking at the example of an endocrine axis shown in Figure 1.11, a defect in the thyroid gland itself would result in primary thyroid failure, a problem with pituitary secretion of TSH would be called secondary thyroid failure, and a deficiency of TRH from the hypothalamus would be called tertiary thyroid failure. This categorization of primary, secondary and tertiary defect is generally used in describing disorders of an endocrine axis. Another generalizable feature is that very often the symptoms of the disorder may be similar for each of the primary, secondary and tertiary causes because they all result in abnormal secretion of the final hormone in the axis.

We started the Preface to this book with Professor John Landon’s quote about clinical endocrinology being about either too much or too little of a hormone. As you may have guessed however, endocrinology is a bit more...
Table 1.5  Endocrine disorders described in this book: their major features and the chapter where you can read about them

<table>
<thead>
<tr>
<th>Name</th>
<th>Cause</th>
<th>Ch.</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common, likely to be seen in a GP surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>Excess glucocorticoid (any cause)</td>
<td>6</td>
<td>Central obesity, hypertension, IGT, ‘moon-face’, bruising, osteoporosis</td>
</tr>
<tr>
<td>Goitre</td>
<td>Growth of thyroid gland</td>
<td>7</td>
<td>Thyroid hormone secretion may be high, low or normal</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Increased T3/T4 any cause</td>
<td>7</td>
<td>Weight loss, heat intolerance, increased heart rate, tremor, anxiety</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Decreased T3/T4 any cause</td>
<td>7</td>
<td>Weight gain, cold intolerance, muscle weakness, decreased heart rate, depression</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Any cause: men decreased testosterone</td>
<td>8</td>
<td>Infertility, impotence, decreased secondary sex characteristics</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome (PCOS)</td>
<td>Women decreased oestrogen</td>
<td>9</td>
<td>Absent periods. Infertility, osteoporosis</td>
</tr>
<tr>
<td>Menopause</td>
<td>↓ Oestrogen at end of reproductive life</td>
<td>10</td>
<td>Periods stop, infertile, flushes, sweats, osteoporosis</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Type 1 lack of insulin secretion</td>
<td>11</td>
<td>Weight loss, thirst, ↑ urine production, ketoacidosis, long term organ damage</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Type 2 insulin receptor insensitivity</td>
<td>11</td>
<td>Obesity, thirst, ↑ urine production, cardiovascular disease</td>
</tr>
<tr>
<td><strong>Commonly seen in a specialist endocrine clinic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic hormone secretion</td>
<td>Hormone secretion by tumour cells</td>
<td>1</td>
<td>Depends on hormone secreted</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Cranial, failure of AVP secretion</td>
<td>3</td>
<td>Failure to concentrate urine, dehydration</td>
</tr>
<tr>
<td>SIADH</td>
<td>↑ AVP</td>
<td>3</td>
<td>Inappropriate water retention, low plasma sodium</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>↑ Growth hormone in adult</td>
<td>4</td>
<td>Growth of soft tissues and viscera, IGT</td>
</tr>
<tr>
<td>Hyperprolactinaemia</td>
<td>↑ Prolactin</td>
<td>4</td>
<td>Women, stop periods, lactation</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>↓ In anterior pituitary hormones</td>
<td>4</td>
<td>Features of ↓ GH, LH/FSH, ACTH and TSH.</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>↑ Adrenaline and noradrenaline</td>
<td>5</td>
<td>Raised blood pressure, ↑ heart rate, anxiety</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Abnormal adrenal steroid secretion</td>
<td>6</td>
<td>Children: failure to thrive, virilization of girls</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>Primary adrenal insufficiency ↓ cortisol</td>
<td>6</td>
<td>Weakness, hypotension, dehydration, ↓ sodium ↑ potassium</td>
</tr>
<tr>
<td>Grave's disease</td>
<td>Autoimmune cause of ↑ T3/T4</td>
<td>7</td>
<td>As hypothyroid with exophthalmos and myxoedema</td>
</tr>
<tr>
<td>Hashimoto's thyroiditis</td>
<td>Autoimmune cause of ↓ T3/T4</td>
<td>7</td>
<td>As hypothyroid</td>
</tr>
<tr>
<td>Klinefelter's syndrome</td>
<td>Chromosomal abnormality XXY</td>
<td>8, 10</td>
<td>Male hypogonadism</td>
</tr>
<tr>
<td>Turner's syndrome</td>
<td>Chromosomal abnormality X0</td>
<td>10</td>
<td>Female absent puberty, periods do not start, infertility, cardiovascular abnormalities</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>↓ Oestrogen, menopause before 40</td>
<td>10</td>
<td>As menopause</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Primary ↑ PTH</td>
<td>12</td>
<td>Hypercalcaemia, (stones, moans, groans), dehydration</td>
</tr>
<tr>
<td>Osteomalacia</td>
<td>Vitamin D deficiency in adults</td>
<td>12</td>
<td>↓ Bone density, pathological fractures</td>
</tr>
<tr>
<td><strong>Rarely seen, even in a specialist endocrine clinic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giantism</td>
<td>↑ Growth hormone in children</td>
<td>4</td>
<td>Increased growth, especially height in childhood</td>
</tr>
<tr>
<td>Laron syndrome</td>
<td>Abnormal growth hormone receptor</td>
<td>4</td>
<td>Decreased growth in childhood</td>
</tr>
</tbody>
</table>

(Continued)
complicated than that. While most endocrine disorders are the result of either excessive secretion of a hormone or of insufficient secretion, there are also a number of clinical conditions which result from receptor insensitivity to a hormone. A good example of this is non-insulin dependent diabetes (see Ch. 11), which can be considered to be a condition of insulin resistance. In other words, although there is circulating insulin and there are insulin receptors on the target cells, it does not have the same effectiveness.

Endocrine investigations: general principles

The investigation of endocrine disorders usually starts with a simple single-point measurement of plasma hormone concentrations. In some cases, this measurement may be sufficient to determine whether there is a disorder, but when the hormone under investigation is secreted episodically (such as growth hormone or cortisol), a single-point measurement is often of very limited value. In this case, a dynamic test of the endocrine system is used. The principle of dynamic testing is really quite simple: when an excess of hormone is suspected, the aim of the dynamic test is to suppress hormone levels. If, on the other hand, insufficient secretion is suspected, then the aim of the test is to stimulate secretion. As far as possible the tests aim to check the whole system.

There are two general reasons for performing endocrine investigations (Box 1.1). The first is to confirm a diagnosis and the second is to monitor the progress of a disease. There are a large number of possible tests aimed at confirming a diagnosis, and so a degree of selection and judgement has to be introduced. The selection of tests to perform must be guided by the clinical situation, and here the clinician may use two types of approach. One approach is to make a clinical diagnosis based on pattern recognition. For example, a classical combination of symptoms in endocrine disease is weight loss despite a good appetite (seen in thyrotoxicosis), which will lead an experienced clinician into testing the thyroid gland. A second approach is to use the basic principles of physiology and anatomy in guiding diagnostic testing. This is needed if the clinical pattern is unclear or a surprising result is found. For example, a patient may be found to have atrial fibrillation (an irregular heart rhythm) when undergoing a routine examination before an operation. As high thyroid hormone levels stimulate the heart, and in particular the atrial chambers, this should lead to thyroid function testing, even in the absence of other classical symptoms.

The most commonly used tests in endocrinology measure hormones and minerals in blood samples (Box 1.2). The levels of most hormones vary through the day and
The normal ranges are very dependent on the time a sample is taken; thus, normal ranges are usually based on samples taken at 0900 hours and in a fasted state. It is vital to the correct interpretation of a blood test result that the time of the sample is recorded. These samples are also known as basal samples as they represent the base, or unstimulated, state. Samples are also tested at specific times after stimulation or suppression and these are called dynamic tests. An example is the stimulation of the steroid hormone cortisol from the adrenal gland 30 and 60 min after an injection of synthetic adrenocorticotropicin.

The maximum information is obtained when a hormone and its regulator are measured together. For example, if thyroxine and TSH are measured together then it is immediately clear whether the disease process is in the thyroid or the pituitary.

**Interesting fact**

In clinical endocrinology, as in other branches of medicine, it is fairly unusual for a patient to present with every single classical symptom and sign of a particular condition (with no red herrings). Such a case is called ‘textbook’ or a ‘textbook example’ because they are rarely encountered outside the pages of books.

**Biological samples**

All blood, urine and biopsy samples need to be collected in the correct containers. Some hormones have a very short life and a falsely low value may occur if the procedure is not done properly. For example, adrenocorticotropicin has a half-life in the blood of about 10 min, so the blood must be taken in a chilled syringe and bottle, and then the plasma has to be separated immediately from blood by centrifugation.

Urine testing is very important in endocrinology. A simple stick can be dipped into urine and chemical pads will detect the presence of glucose (suggesting diabetes), blood, protein, white cells, ketones, acidity and even hormones (e.g. hCG, indicating pregnancy). This yields a tremendous amount of clinical information and a dip-stick test should be performed in all new patients. Hormones and minerals are usually best measured in accurately timed 24-h urine samples. All urine produced over this time is placed in a bottle and the total excretion of a hormone can be measured.

**Imaging**

Radiological imaging is vital to the assessment of endocrine glands. The type of test selected depends on the gland (Table 1.6). For example, the pituitary is surrounded by a bony cup and is not well seen by radiography. The best image is obtained with magnetic resonance imaging.
Ectopic hormone secretion

It is not only the well-defined endocrine tissues that can secrete hormones. All cells retain the genetic capacity for hormone secretion and it is increasingly recognized that malignant cells may express the genes encoding hormonally active peptides. As the usual mechanism for hormone processing is not usually present in these malignancies, the peptide secreted may be a fragment or a precursor of the normal mature hormone. The inappropriate secretion of hormones by tissues that do not usually produce that hormone is called ‘ectopic’ hormone secretion. Often ectopic hormone secretion is seen as a feature of endocrine tumours; for example, pancreatic islet cell carcinomas have occasionally been found to secrete adrenocorticotrophic hormone (ACTH), which usually comes from the pituitary gland. Non-endocrine tissues may also secrete hormones; for example, inappropriate ACTH secretion is a recognized feature of some small cell carcinomas of the lung.

The most common example of ectopic hormone secretion is a peptide hormone called parathyroid hormone-related peptide (PTHrp), which is secreted by around 10% of malignant tumours and causes hypercalcaemia, termed ‘hypercalcaemia of malignancy’.

Ectopic hormone secretion is diagnosed through a combined approach of imaging, together with arteriovenous sampling to measure a hormone concentration gradient across a tissue and so establish the source of the hormone.

### Interesting fact

Endocrine disorders can have such profound effects on the body that many disorders are ‘foot of the bed’ diagnoses. You will read about the characteristic changes of acromegaly, Cushing’s syndrome, Graves’ disease and hypothyroidism later. All of these disorders of hormone secretion result in changes to the appearance that makes it possible to recognize them from a distance. Keep your eyes open on the bus!