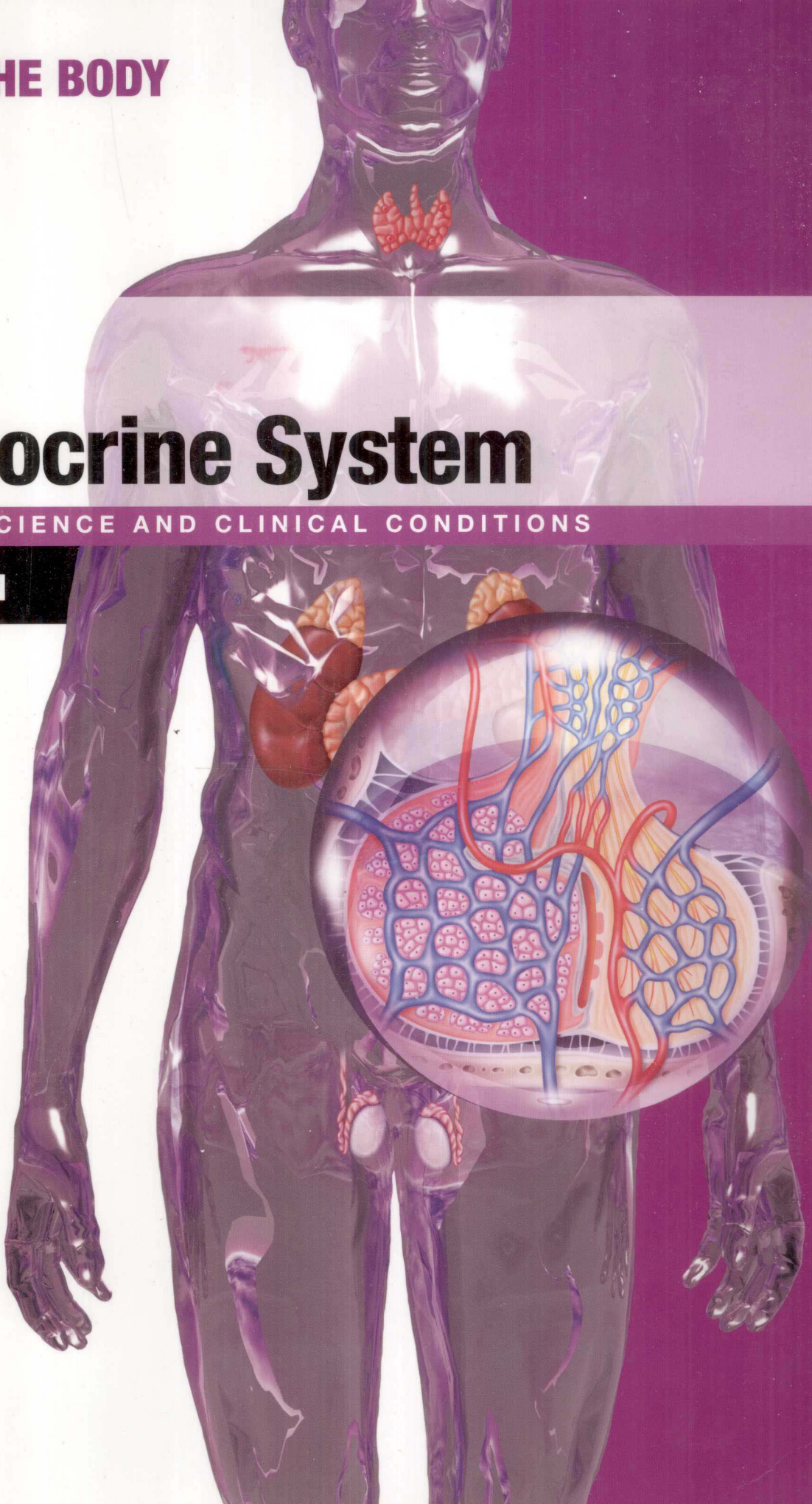
SYSTEMS OF THE BODY

The Endocrine System

BASIC SCIENCE AND CLINICAL CONDITIONS

SECOND EDITION

Joy **Hinson**
Peter **Raven**
Shern **Chew**



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Endocrinology is really very simple. You can either have too much of a hormone ... or too little.

(Professor John Landon's traditional and reassuring introduction to his endocrinology teaching.)

The first edition of this book was aimed primarily at medical students, particularly those taking a modern, integrated course. This second edition is enlarged and expanded to include more detail of physiological and biochemical mechanisms, and has a whole chapter on mechanisms of hormone action. We hope that this edition will be used by students of the biomedical sciences as well as medical students.

The book is intended as a broad general introduction to the Endocrine System, although we hope that you will be sufficiently enthused after reading it to wish to take your studies further in this exciting and fast-moving area.

Each chapter is structured around clinical cases. Endocrinology is at its most interesting when considered in the context of what happens when things go wrong. These cases have been chosen to illustrate important points about either the biochemistry of hormone synthesis or the physiology of endocrine regulation. This will allow medical students early in their studies to understand the clinical relevance of the basic science. However, we hope that the book will also allow clinical students to understand the basic science underlying endocrine disease.

In the clinical cases featured in this book we have tried to show common presentations of the different disorders, but endocrine problems present in such a wide variety of ways that students should not be misled into thinking that these are the only presentations!

The 'Interesting fact' we included in the first edition have been added to. These are snippets of information that particularly interested us and that we wanted to share with you. We hope that you will find them interesting too.

The first two chapters are not case-based: these contain details of the basic concepts needed to understand hormones and their actions. The final chapter describes a mixture of hormones and other signalling molecules with varying degrees of clinical importance. This chapter illustrates perfectly the idea that endocrinology is rather more than a stand-alone speciality but rather it is a subject which impinges on the cardiovascular system, the immune system and all other systems of the body.

We do hope that we have managed to convey to you our enthusiasm for this most fascinating subject.

We are most grateful to all our colleagues for their help and advice in the preparation of this book. In particular, we would like to thank: Dr Dan Berney for providing the histology, Dr Norbert Avril for the whole-body glucose image and Dr Alistair Chesser for the EPO case. Thanks also to Dr Antonia Brooke, Derek and Niloufar (you know why), Dr John Patterson and Mrs Jacqualyn Conner. Although many colleagues have helped and advised us, all errors remain our own.

Thanks are due also to the team at Elsevier led by Timothy Horne, and especially to our editor, Lulu Stader.

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1

INTRODUCTION

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.

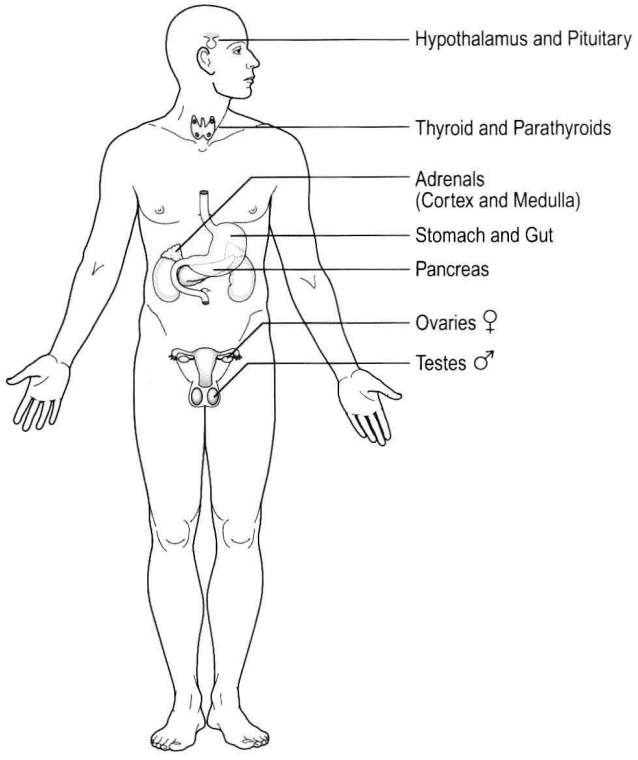

Figure 1.1 Major endocrine glands of the body. In addition, the gut, heart and skin have all been shown to produce hormones.

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.

Figure 1.2 In 2005, The Society for Endocrinology celebrated the centenary of Endocrinology as a recognized science.

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

Table 1.1 Major endocrine glands and the hormones they secrete

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

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.

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.

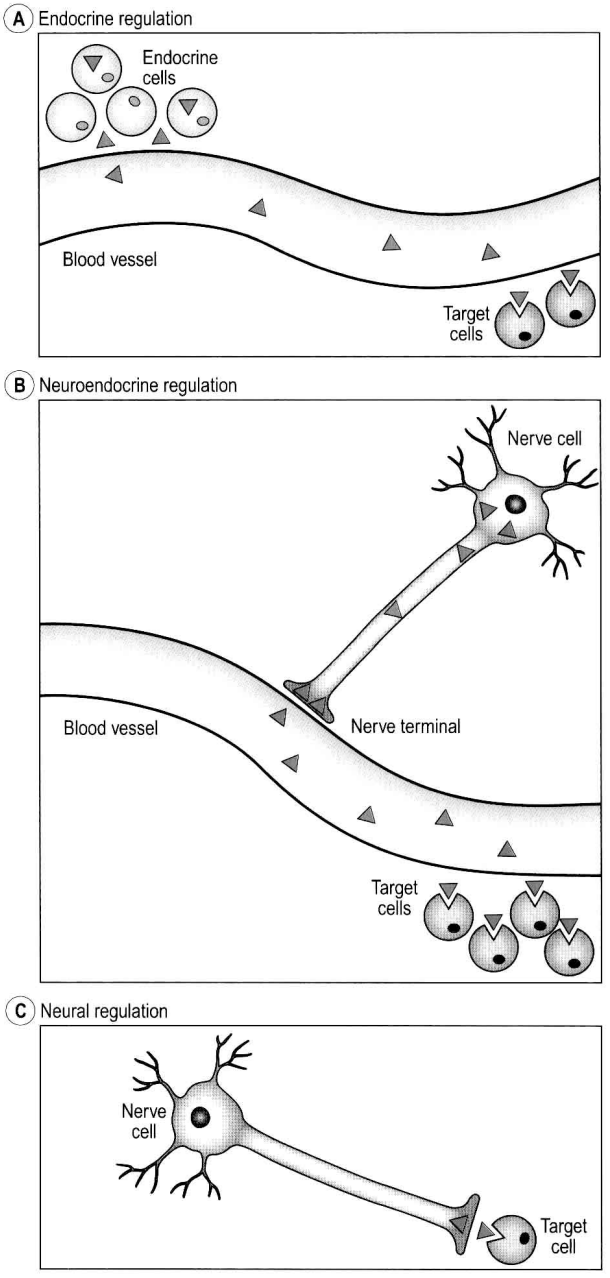

Figure 1.3 Comparison of (A) endocrine, (B) neuroendocrine and (C) neural regulation. In endocrine regulation, the hormone is released from the cells of an endocrine or 'ductless' gland into the bloodstream where the hormones travel to target cells often at some distance from the endocrine gland. In neural regulation, the neurotransmitter is released, in response to an action potential, from a nerve ending into the synaptic cleft, directly onto the surface of the target cell. In neuroendocrine regulation, the hormone is secreted by a nerve cell in response to an action potential, but is released into the bloodstream, not a synaptic cleft, and then acts as a hormone.

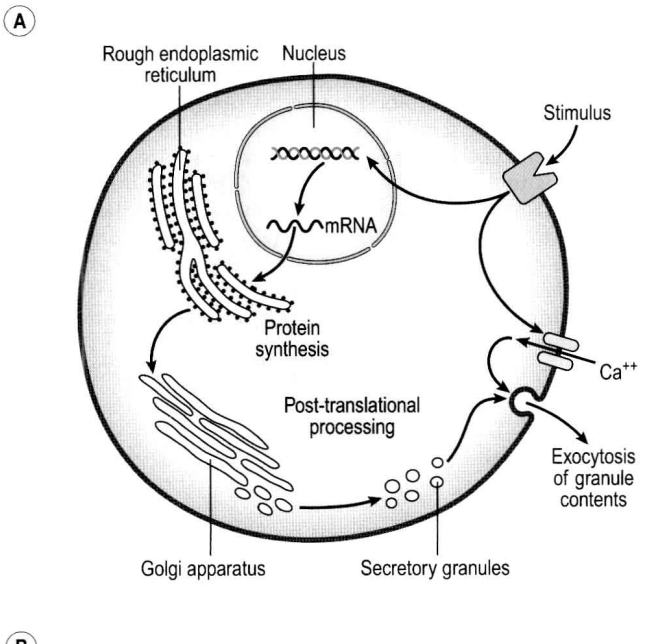

Figure 1.4 Synthesis and secretion of (A) peptide hormones and (B) steroid hormones. The cells that synthesize peptide hormones have abundant rough endoplasmic reticulum and Golgi apparatus. Secretory granules are often visible. Peptides require a specific secretory mechanism, exocytosis, which is usually triggered by an increase in intracellular calcium levels, or depolarization of the cell. The entire contents of the secretory granule are released. Steroid-secreting cells, on the other hand, have lipid droplets visible in the cytoplasm. They have abundant mitochondria and smooth endoplasmic reticulum. The steroid hormones, once made, simply diffuse out of the cell and do not require a specific secretory mechanism.

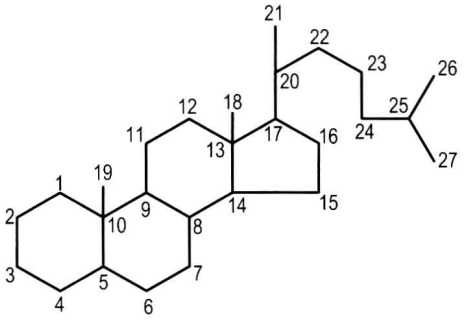

Figure 1.5 Structure of cholesterol, the parent compound for all steroid hormones and vitamin D. The classical steroid system for numbering carbon atoms is shown.

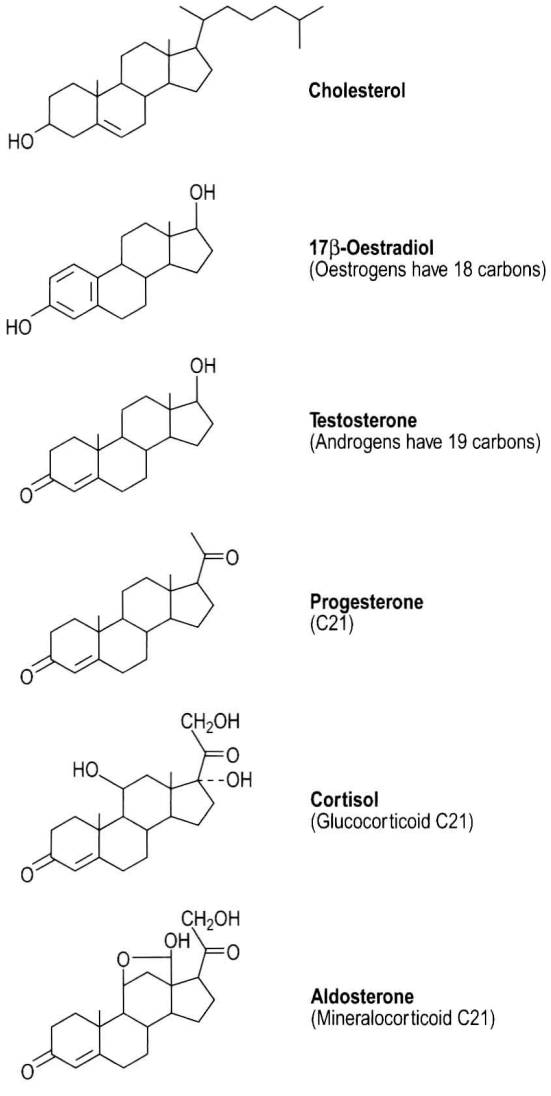

Figure 1.6 The major families of steroid hormones.

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.

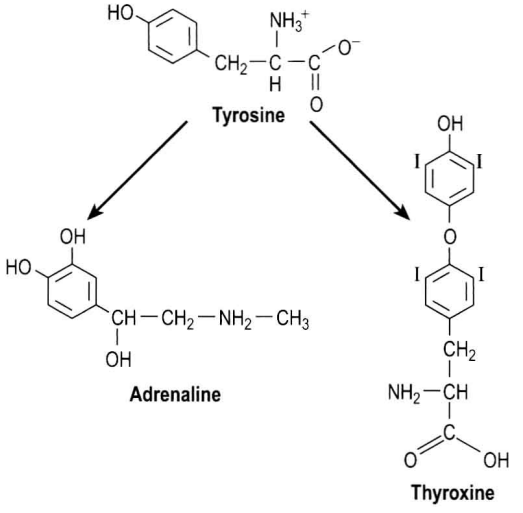

Figure 1.7 Metabolism of the amino acid tyrosine produces both thyroid hormones (thyroxine) and catecholamines (adrenaline).

Interesting fact

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.

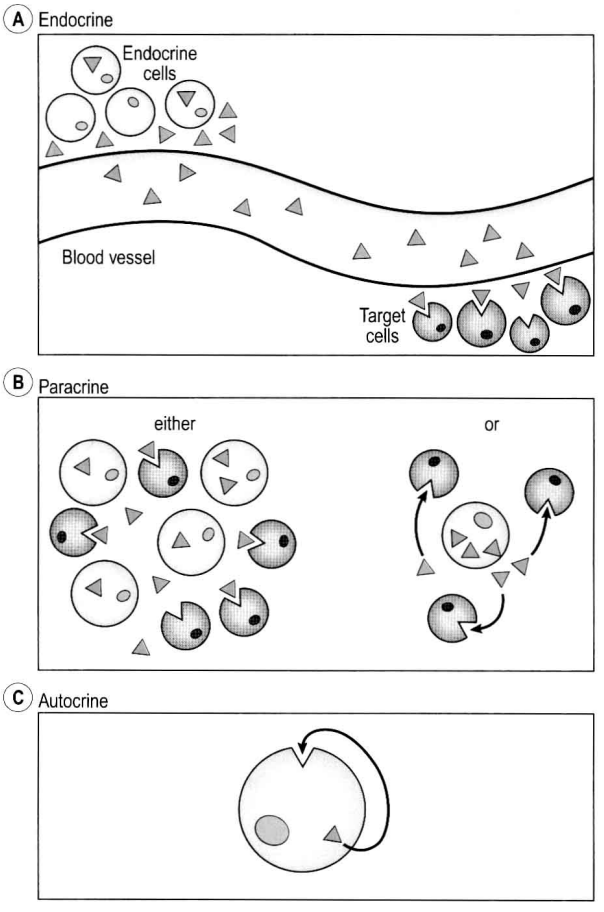

Figure 1.8 (A) Endocrine, (B) paracrine and (C) autocrine regulation.

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

	Location of receptors	*Carrier protein*	*Active if administered orally?*	*Storage*
Peptides	Cell membrane	No	Not usually	Hormone stored
Steroids	Cytoplasm/nucleus	Yes	Yes, mostly	Precursor stored
Thyroid hormone	Nucleus	Yes	Yes	Precursor stored
Catecholamines	Cell membrane	No	No	Hormone stored

The transport and metabolism of hormones

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. Mostly,

Table 1.4 Hormones and their binding proteins

Hormone	*Binding protein*
Thyroid hormone	Thyroid hormone binding globulin (THBG)
Testosterone/oestradiol	Sex hormone binding globulin (SHBG)
Cortisol	Cortisol binding globulin (CBG, also called transcortin)
Vitamin D	Vitamin D binding protein (DBP)

Table 1.3 Concentrations of various substances in blood

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

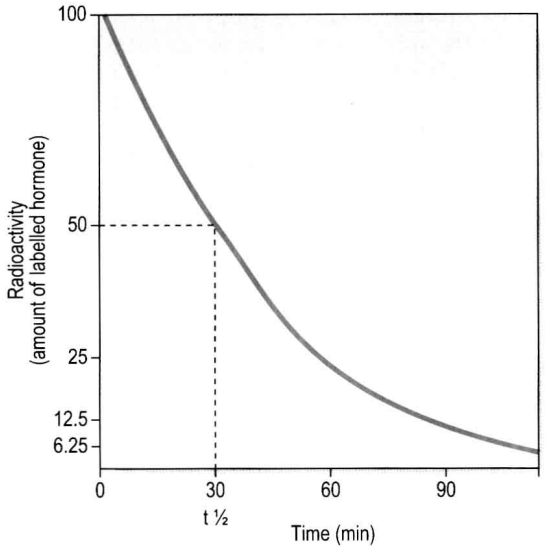

Figure 1.9 Measurement of the half-life of a hormone in blood. A labelled (radioactive) hormone is injected into the blood at time 0. Blood is sampled regularly and the radioactive content measured. When there is half the original level, the interval between time 0 and this time is called the half-life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

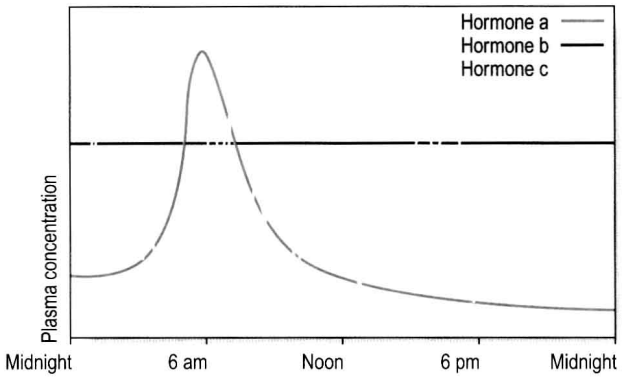

Figure 1.10 Diurnal variation and episodic secretion. Some hormones, such as hormone a, have a pronounced diurnal variation in their secretion. An example of such a hormone would be cortisol. Other hormones such as hormone b, which could be thyroxine, show very little diurnal variation. Hormone c shows episodic secretion; this pattern is common to many different hormones. It means that taking a single-point blood measurement of the hormone is of little value in diagnosing endocrine disorder because there is so much variation during the day.

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)

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

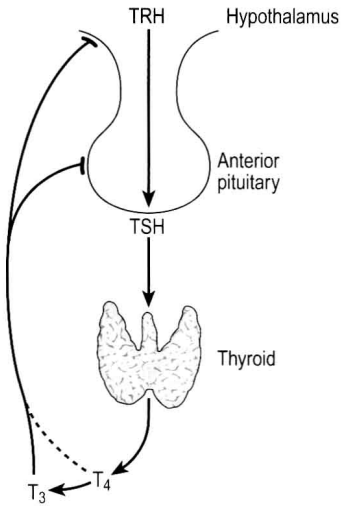

Figure 1.11 An endocrine axis and negative feedback. The axis shown is the hypothalamo–pituitary–thyroid axis. Thyrotropin releasing hormone (TRH), from the hypothalamus, stimulates the release of thyroid stimulating hormone (TSH) from the anterior pituitary. The TSH stimulates the thyroid gland to release T_4 and T_3, which exert a negative feedback inhibitory effect on the hypothalamus and pituitary glands.

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 thyroxine but one of the effects of thyroxine is to act on both the hypothalamus and anterior pituitary to decrease the production of TRH and TSH, respectively. This pattern, of the final product of a cascade system exerting negative feedback higher up the endocrine axis, is one which you will see repeated throughout this book.

Negative feedback does not mean that hormone production is switched on and off like a light switch. There is a basal or residual rate of hormone secretion which can be increased by a variety of stimuli and decreased by negative feedback. This means that all endocrine systems are dynamic, in other words they are responsive to change and with a tendency to return to the basal or residual state of activity.

Most negative feedback operates through a genomic mechanism resulting in a decrease in the production of hormones higher up the endocrine axis. This process takes place over a relatively long time period, hours to days, and so it is known as 'delayed feedback'. An example of this would be the action of thyroxine on the production of TRH and TSH. This type of feedback is determined by both the amplitude of the original increase in hormone secretion and its duration.

Some systems also have a more rapid negative feedback response called 'fast feedback', which is clearly not

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 tend 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. Glycosuria 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